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Review Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A METHOD FOR BIOAVAILABILITY ENHANCEMENT

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ABSTRACT

Oral route is preferred for drug administration. More than 40% of New Chemical Entities exhibit poor aqueous solubility resulting in unsatisfactory oral drug delivery. Low aqueous solubility and thereby low oral bioavailability is a major concern for formulation scientist as many recent drugs are lipophilic 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 lipophilic drugs. SEDDS are ideally isotropic mixtures of drug, oil, surfactant and/or co surfactant. Following their administration, these systems rapidly disperse in gastrointestinal fluid, yielding micro-/nano-emulsions containing solubilized dug .This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect. This article gives an overview of SEDDS with emphasis on need of SEDDS, mechanism of SEDDS, various formulation approaches, methods of formulation of SEDDS and evaluation of SEDDS.

Keywords: solubility, bioavailability, lipophilic, solid dispersion, solubilization.

INTRODUCTION

Nowadays, nearly 35-40% of new drug candidates have poor water solubility; oral delivery of such drugs is associated with the problem of lowbioavailability. To overcome these issues various formulation strategies have been exploited like complexation, particle size reduction, use of lipids, surfactants, cyclodextrins and micelles. Advanced approaches include self-micro emulsifying drug delivery system and self-microemulsifying nanoparticles.

Self-emulsifying drug delivery systems are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic cosolvents or coemulsifier with droplet size ranging from few nanometers to several microns. Self-micro emulsifying drug delivery system is mixture of natural or synthetic oils, solid or liquid surfactants with a droplet size in a range of 10-100 nm (Sapra K et al., 2012).

Properties of SEDDS

1. SEDDS can incorporate hydrophobic or hydrophilic drug within the oil surfactant mixture.
2. Used for solid as well as liquid dosage form.
3. It require low dose of drug as compare to conventional dosage form.

Advantages

1. High drug solubilization capacity.
2. Good thermodynamic stability.
3. Protect the drug from enzymatic hydrolysis.
4. Improvement in oral bioavailability.
5. Improve drug loading capacity.
6. Reduce the intrasubject and intersubject variability and food effects.
7. Useful for drug targeting toward specific absorption window.
8. Control of delivery profile.

Disadvantages

1. Lack of in vitro model for assessment of the formulations.
2. Chemical instabilities of drugs and high surfactant concentrations.
3. Moreover, volatile co solvents in the conventional self-emulsifying formulation s are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drugs.
4. These formulations potentially are dependent on digestion prior to release the drug.

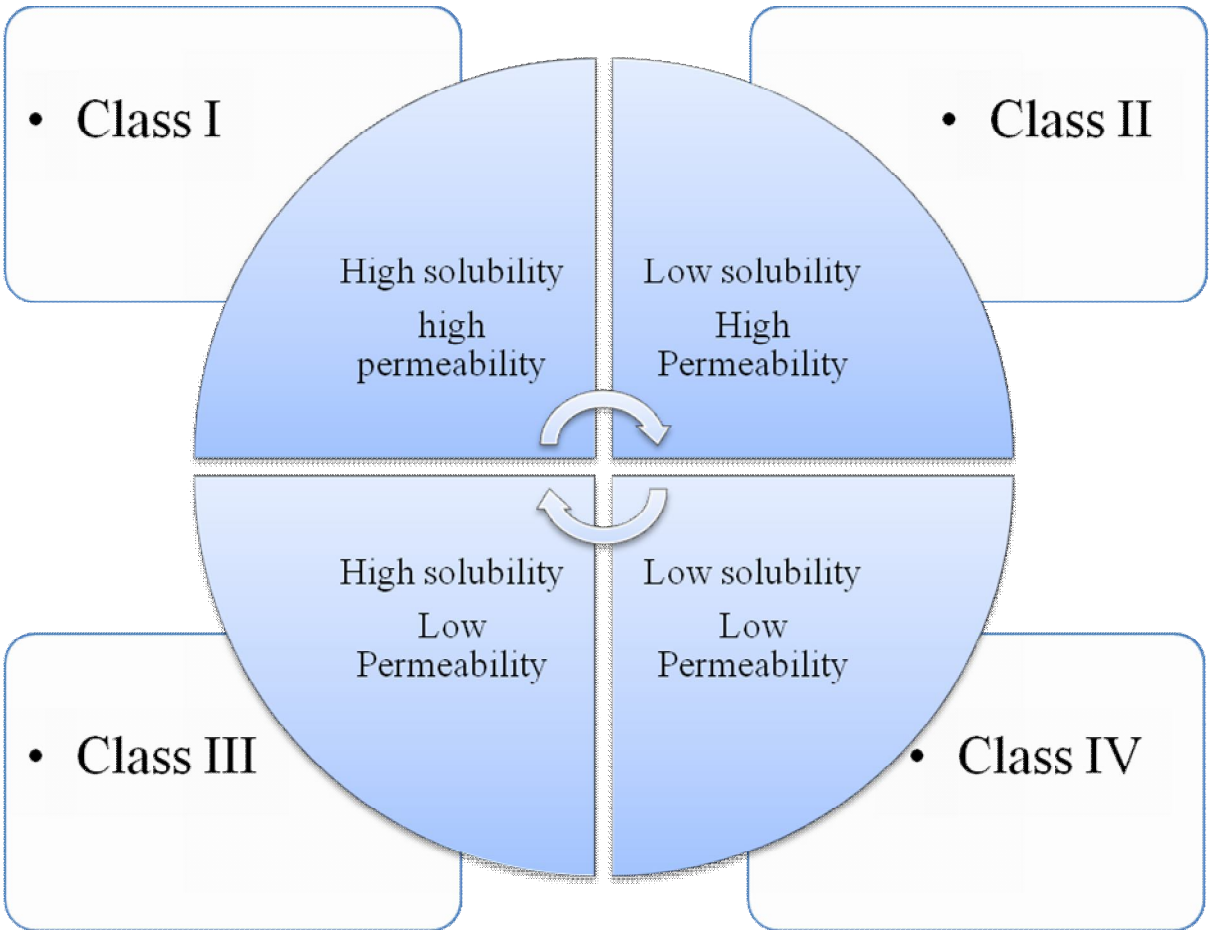

Fig. 1: Biological Classification System (BCS)

BCS class II and Class III are suitable candidates for SEDDS.(Kohli K et al., 2010; Wadhwa J & Nair A 2011)

Lipid Formulation Classification system: lipid formulation classification system was introduced by Pouton in 2000 and updated in 2006.According to this classification lipid based formulation classified into four categories(Sapra K et al.,2012).

Need of SEDDS

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets.(Meinzer A, Mueller E &Vonderscher,1995)Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

Potential advantages of these systems

1. Enhanced oral bioavailability enabling reduction in dose,
2. More consistent temporal profiles of drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Protective of sensitive drug substances
8. High drug payloads
9. Liquid or solid dosage forms

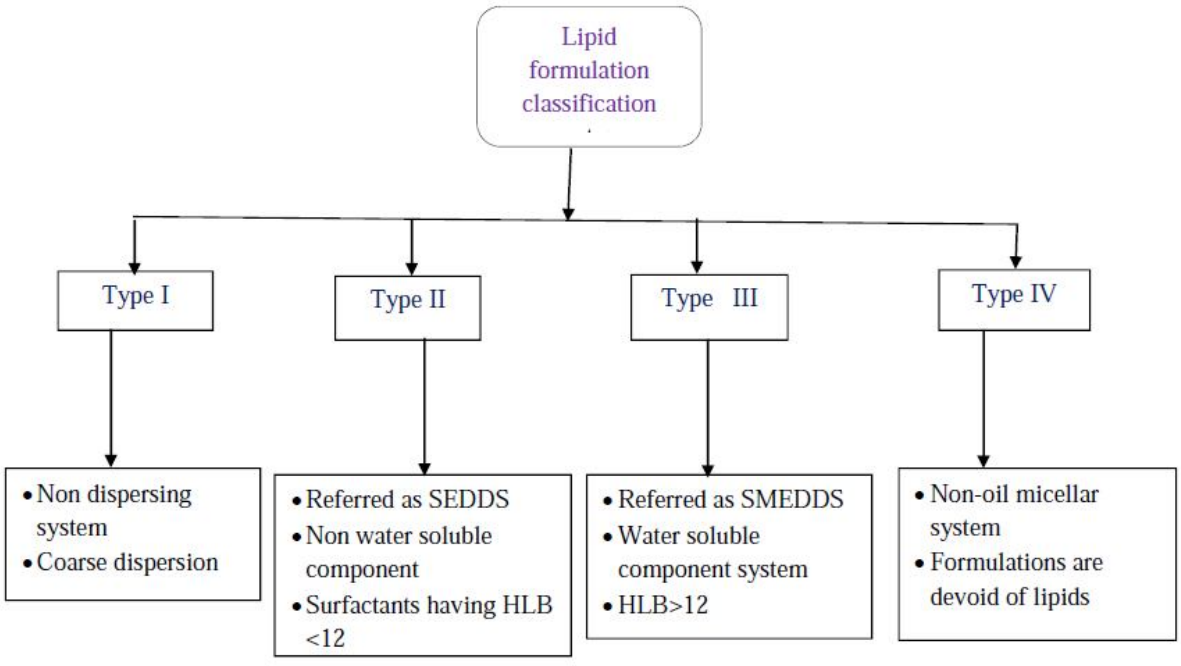

Fig.2: Classification of Lipid Based Formulation

Mechanism of Self-Emulsification

The process of self-emulsification takes place is not well understood. However, according to Reiss (Vonderscher J &Meinzer A, 1994), 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 addition, the free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by following equation

$$\Delta G = \sum_{i} N_i \pi r_i^2 \sigma$$

Where, G is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and s represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing (Karim A et al., 1994).In earlier work, it was suggested that the ease of emulsification could be associated with the ease bywhich water penetrates into the various LC or gel phases formed on the surface of the droplet. According to Wakerly et al., the addition of a binary mixture (oil/non-ionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will is LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The involvement of the LC phase in the emulsion formation process was extensively studied by Pouton et al. (Groves M J et al., 1974; Rang M J & Millar C A, 1999; Pouton et al., 1987). Later, Craig et al. used the combination of particle size analysis and low frequency dielectric spectroscopy (LFDS) to examine the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic acids)/Tween 80 systems. The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the relationship was clearly complex (Pouton CW, 1985). The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase (Craig DQM 1993). However, the correlation between the spontaneous emulsification and LC formation is still not definitely established (Craig DQM, 1995; Pouton CW, 1985; Craig DQM 1993).

General Formulation Approach

Preliminary studies are performed for selection of oil, which is an important and critical requisite for formulation of SEDDS. . SEDDS consisted of oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oils and surfactants. Prepare a series of SEDDS system containing drug in various oil and surfactant. Then, in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions is studied. Pseudo-ternary phase diagram is constructed, identifying the efficient self-emulsification region. From these studies, an optimized formulation is selected and its bio-availability is compared with a reference formulation. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. SMEDDS are distinguished from SEDDS by the much smaller emulsion droplets produced on dilution, resulting in a transparent or translucent solution. SMEDDS

generally contain relatively high concentrations of surfactant (typically 40-60% w/w), and regularly contain hydrophilic co-solvents (e.g. propylene glycol, polyethylene glycols). They are often described as microemulsion pre-concentrates, as the micro-emulsion is formed on dilution in aqueous media When developing lipid based formulations the following parameters are believed to be important; (Patel PA, Chaulang&Mutha SS,2008).

- The solubility of drug in the formulation as such and upon dispersion (for SEDDS),
- The rate of digestion (for formulations susceptible to digestion) and possibly
- The solubilization capacity of the digested formulation.

1. Oils

Both long- and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. Unmodified edible oils provide the most `natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SEDDS. In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems. Since they exhibit formulative and physiological advantages. These excipients form good emulsification systems, with a large number of non-ionic surfactants approved for oral administration, while their degradation products resemble the end products of intestinal digestion. MCTs were preferred in the earlier self-emulsifying formulations(Charman, 1992). Because of higher Fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium chain derivatives(Constantinides PP, 1995) which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation (Constantinides PP, 1995; Shaha NH, 1994). Solvent capacity for lesshydrophobic drugs can be improved by blendingtriglycerides with mono- and di-glycerides (Pouton CW &Charman WN, 1997).

2. Surfactants

Non-ionic surfactants with a relatively high hydrophilic± lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylatedpolyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80) are the most frequently used excipients. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF (self-dispersedlipidformulation) use (Patel PA, 2008; Yuasa H, 1994; Georgakapoulos et al, 1992)despite their limited ability to self-emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability (Patel PA, 2008).Amemiya et al. proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration. The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. A large quantity of surfactant may irritate the GI tract. Thus, the safety aspect of the surfactant vehicle should be carefully considered in each case. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-emulsifying performance. The surfaceactive agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of the hydrophobic drug. The latter is of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying formulations (SMEDDS) (VonderscherJ,Meinzer A, 1994; Karim A, 1994). Formulations consisting only of the surfactant mixture may form emulsions or microemulsions (when surfactants exhibit different low and high HLB), micelle solution or, in some particular cases, neosomes, which are non-ionic, surfactant-based bilayer vehicles[40].

3. Co-solvents

Relatively high surfactant concentrations (usually more than 30% w/w) are needed in order to produce an effective self-emulsifying system. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large

amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimesplay the role of the co-surfactant in the micro emulsion systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile cosolventscomprised in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Drug release from the formulation increased with increasing amount of cosurfactant.

Dosage form of SEDDS

1. 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 (Patel A et al 2008;Charman SA,1992;Constantinides PP, 1995). 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. Dry emulsions can be used for further preparation of tablets & capsules. Thistechnique has been applied for poorly water soluble drug amlodipine (Sapra et al., 2012; Jang DJ et al., 2006).

2. Self-emulsifying capsule

After administration of capsules containing conventional liquidSE formulations, microemulsion droplets form and subsequentlydisperse in the GI tract to reach sites of absorption. However, ifirreversible phase separation of the microemulsion occurs, an Improvement of drug absorption cannot be expected. For handlingthis problem, sodium dodecyl sulfate was added into the SEformulation(Itoh K, 2008). With the similar purpose, the supersaturatableSEDDS was designed, using a small quantity of HPMC (or otherpolymers) in the formulation to prevent precipitation of the drugby generating and maintaining a supersaturated state in vivo. Thissystem contains a reduced amount of a surfactant, thereby minimizingGI side effects (Gao P &Morozowich W,2006; Gao P,2003).

Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteralroute. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinicallyavailable only via the parenteral route. So, oral LMWH therapywas investigated by formulating it in hard capsules. LMWH wasdispersed in SMEDDS and thereafter the mixture was solidified topowders using three kinds of adsorbents: micro porous calciumsilicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320). Eventually these solidswere filled into hard capsules (Ito Y, 2006). In another study, such adsorbentswere also applied to prepare SE tablets of gentamicin that, inclinical use, was limited to administration as injectable or topicaldosage forms (Ito Y, 2005).

3. Self-emulsifying sustained release tablet

To minimize significantly the amount of solidifying excipients required 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 (Sapra K et al., 2012;Vasanthavada M &Serajuddin A T,2007).

A newer advancement in the SE tablet is the osmotic pump tablet ofcarvediol. In which osmotic pump was chosen as the carrier for SES

4. Self-emulsifying sustained /controlled release pellets

Pellets having several advantages over conventional solid dosage forms like minimizing the intersubject and intra subject variability of plasma profiles and also minimize the GI irritation without lowering the bioavailability of drug. These are the multiple unit dosage forms.(Tang Bo et al, 2008).

5. Self-emulsifying beads

These are prepared as a solid dosage form using less amount of excipient. Paradkar and Patil formulated an isotropic formulation of loratidine consisting Cremophore EL, Capmul MCM and

Captex 200. By using solvent evaporation technique the SE mixture loaded into poly propylene beads. Formulations were optimized and evaluated. The results indicated that self-emulsifying beads can be formulated as a solid dosage form with less amount of solidifying agents(Wadhwa J et al., 2011).

6. Self-emulsifying nanoparticles

Self-emulsifying nanoparticles are prepared by using nanoparticles technology. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise 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 was obtained.

7. Self-emulsifying solid dispersion

To overcome the difficulties related to manufacturing and stability SE solid dispersion was formulated. It also increases the dissolution rate and bioavailability of water soluble drugs. For the preparation of SE solid dispersion hot melt granulation is widely used 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 usedas surface adsorbent and gelucire 50/13 was used as dispersion carrier(Tang Bo et al, 2008).

8. Self-emulsifying suppositories

Some investigators proved that solid SEDDS can not only increase GI adsorption but can also are used to improve rectal and vaginal absorption.By using self-emulsifying technique suppositories of Indomethacin have been prepared (KimJY&Ku YS, 2000).

9. Self-emulsifying implants

Research in the field of SE implants has greatly enhance the utility and application of solid self-emulsifying formulation for example Carmustin is a therapeutic agent used in the treatment of malignant brain tumors but it has short biological half-life. To increase its stability compared with that released from poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). Then the self-emulsifiedBCNU was fabricated into wafers with flat and smooth surface by compression molding. Ultimately, SES increased in vitro half-life of BCNUup to 130 min contrastedwith 45 min of intact BCNU. In vitro release of BCNU from SE PLGA wafers were prolonged up to 7 days. Such wafers had higher in vitro antitumor activity and were less susceptible to hydrolysis than those wafers devoid of SES.

10. Self-emulsifying Powder formulation

Lipids and surfactants have been widely used for the preparation of self-emulsifying tablets.

For minimizing the amount of solidifying excipients required 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(Tang Bo et al., 2008;Patil P,2004).To enhance the dissolution and absorption of the poorly water-soluble drug griseofulvinArida*etal* prepared an SE powder formulation. In which Capmul GMO-50, poloxamer and myvacet were used as surfactants and co-surfactants. A major enhancement in dissolution and bioavailability of griseofulvin was observed (Wadhwa et al.,2011).

Table 1: Commercially available SEDDS

S.No.	Drug	Formulation type
1	Astaxanthin	SE Capsules
2	Amlodipine	SE Dry emulsion
3	Diclofenac	SE tablets
4	Nitendipine	Pellets
5	Loratidine	SEF(Beads)
6	Paclitaxel	SE nanoparticles
7	Phenacetin	Solid Dispersion
8	Indomethacin	Suppositories
9	Carmustine	Implants
10	Halofantrine	SEF powder

Methods of preparation

I. Spray drying

A process in which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction, i.e. the organic solvent or the water contained in an emulsion is known as spray drying. This process produces solid particles.

Before spray drying, the formulation is prepared by forming a mixture of excipients with drug, followed by solubilization of the mixture in an organic solvent. The solubilized formulation then spray dried to remove the solvent.

Dry emulsion also prepared by this method. Instead of dissolving the excipients in an organic solvent, an oil-in-water emulsion can be formulated and spray dried in same equipment to remove the aqueous phase (Goyal U et al., 2012).

II. Spray congealing

Spray congealing also referred as spray cooling, where the molten formulation is sprayed into a cooling chamber. When the molten mixture comes in contact with cooling air, the molten droplets congeal and recrystallize into spherical solid particles which collect at the bottom of the chamber as fine powder. The fine powder then used for the development of solid dosage forms like, tablets and capsules.

For spray cooling the main parameter is the melting point of the excipients that should be in the range of 50-80^{0}C.

This technique can be used for enhancement of bioavailability and for sustained release formulation depending on the drug behavior and lipid matrix (Jannin et al., 2008).

III. Melt extrusion

It is also known as extrusion spheronization. It is a solvent free process. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions.

This approach has been successfully tied on 17β-estradiol and methyl and propyl paraben by using surfactant such as sucrosemonopalmitate, lauroylpolyoxyglycerides and polysorbate 80 (Tang Bo et al., 2008).

IV. Melt granulation

Melt granulation also known as thermoplastic pelletization. It is the one step process in which the transformation of a powder mixture into granules or spheronized pellets. This technique requires high shear mixing in presence of a meltable binder which may be sprayed in the molten state onto the powder mixture likewise wet granulation process. This referred to as pump on technique. Otherwise the binder may be blended with the powder mixture in its solid or semi-solid state and allowed to melt by the heat generated from the friction of particles during high shear mixing. This is referred as melt-in process. The melted binder forms liquid bridges with the particles and shape into small granules which is transformed to spheronized pellets by further mixing under controlled conditions (Jannin et al., 2008).

V. Supercritical fluid technology

The lipids may be used in supercritical fluid technology for preparing solid dispersions or for coating of drug particles. The coating process involves dispersion of the drug particles in a supercritical fluid containing one or more coating materials in it. 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 glyceryltrimyristate (dynasan 114) and stearoyl poly oxyl glycerides (gelucire 50/02) (Santosh I et al., 2003; Sethia, E &Squilliante, 2002).

The following factors considered during this formulation technique.

- Solubility of the formulation components in the supercritical fluid.
- The energy or environmental conditions relating to the evaporation of solvents.
- The integrity and stability of the active substance under the process conditions.
-

VI. Solid lipid nanoparticles and nanostructure lipid carriers

Solid lipid nanoparticles and nano structured lipid carriers 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, (Hu L et al., 2005) I.V. (Wang Y et al., 2005) or topical Route (Puglia C et al., 2005).

Solid lipid nanoparticlesof clozapine have been prepared by using soya lecithin 95%, triglycerides,Poloxamers 188 and Stearylamine as

a positive charge inducer by hot homogenization followed by ultrasonication (Sapra K et al., 2012).

VII. Adsorption on solid carriers

Free flowing powders may be obtained from liquid lipid formulations by adsorption onto solid carriers. The adsorption process involves addition of the liquid formulation onto the carrier of choice by mixing in a blender. Calcium silicate, magnesium alumino silicate, silicon dioxide used as carrier for these preparations. This technique has benefit like good content uniformity, require minimum investment in equipment and facilitates formulation of tablets.

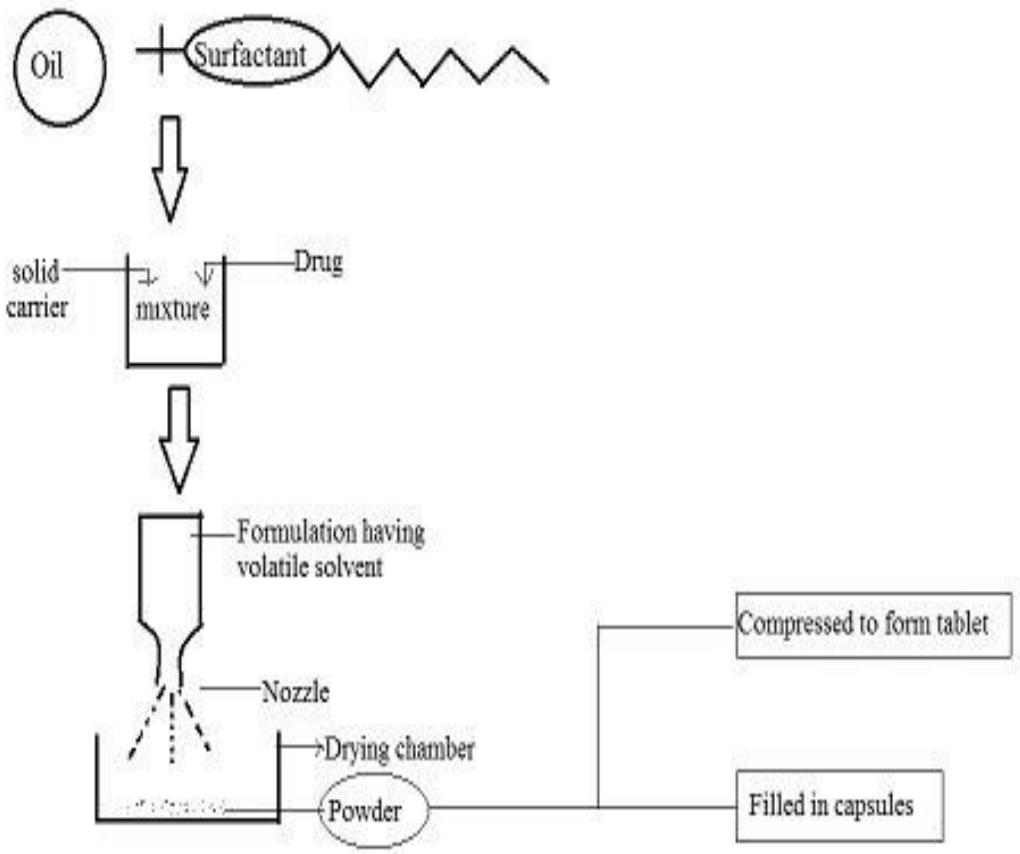

Fig.3: Spray drying technique to prepare SEDDS

Table 2: Commercially Available SMEDDS

Drug	Indications	Brand Name	Manufacturer
Cyclosporine A	Immunosuppressant	Sandimmune Neural	Biochem, Cipla, Novartis
Ritonavir	Anti-HIV	Norvir	Abbott Laboratories
Amprenavir	Anti-HIV	Agenerase	Glaxosmithkline
Saqunavir	Anti-HIV	Fortavase	Hoffman-La Roche inc
Valproic Acid	Anti-epileptic	Convulex	Pharmacia

Evaluation parameters of self-emulsifying drug delivery system

1) Turbidity measurement

It is a relatively crude parameter for estimation of droplet size as well as emulsification time. It is used to determine the rapid equilibrium reached by the dispersion and the reproducibility of this process (Nazzal Set al., 2002) Turbidity measurements are carried out on turbidity meters,(Gursoy N et al.,2003; Taha EI et al.,2004) with the instrument connected to a dissolution apparatus. The optical density of the formulation is recorded periodically (say every 15 sec) to determine the clarity of microemulsion formed as well as the emulsification time, i.e., time required by the formulation to emulsify completely. Turbidity can also be observed in terms of spectroscopic characterization of optical clarity, i.e., the absorbance of suitably diluted aqueous dispersion (Singh B &Bandopadhyay, 2009; Gursoy N et al., 2003).

2) Droplet size

Droplet size measured by dynamic light scattering technique andproperly diluted samples of self-emulsifying systems are used for droplet size analysis using Photon Correlation Spectroscopy. Average droplet size and polydispersity index are determined and the data obtained are further treated with regression analysis. Measurements are obtained in duplicate at an angle of 90°. The diluted emulsions arealso allowed standing for 12 h at room temperature to assess dilution stability (Kale AA&Patravale VB, 2008).

3) Zeta potential measurement

It determines the charge on droplets. Zeta potential helps to predict the stability and flocculation effect in emulsion system. If the zeta potential falls below a certain level, colloid will aggregate due to attractive forces. High zeta potential maintains a stable system(Sarpal K et al.,2013;Boonme P et al.,2006).

4) Liquefaction time

This test is designed to estimate the time required by solid SEDDS to melt *in vivo* in the absence of agitation in the simulated GI tract conditions. One dosage form is wrapped in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread (Singh B et al., 2009; Attama AA et al., 2003).The thermometer with attached tablets is placed in a round bottom flask containing simulated gastric fluid without pepsin maintained at 37±1°C, by means of thermo-regulated heating mantle.

5) Electron Microscopic Studies

Freeze-fracture electron microscopy has been used to study the surface characteristics of the SEDDS. However, due to the high labiality of the samples and the possibility of artifacts, electron microscopy is, at times, considered as a somewhat misleading technique. Particle size analysis and low frequency dielectric spectroscopy have been utilized to examine the self-emulsifying properties of a series of Imwitor 742 (i.e., a mixture of mono- and diglycerides of capric and caprylic acids) and Tween 80 systems(Singh B et al., 2009; Craig DQM et al., 1995; Craig DQM et al., 1993).

6) Dispersibility test

The efficiency of self-emulsification of oral micro/nanoemulsion is assessed using a standard USP dissolution apparatus II (Pouton CW, 1985; Shefiq et al., 2007; Tuleu et al., 2004).One milliliter of each formulation is added to 500 mL of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm tends to provide gentle agitation. The *in vitro* performance of the formulations is visually assessed from such dispersion, using a suitable grading system (Shefiq et al., 2007). A grading system has been reported to be based upon the formation of a microemulsion (o/w or w/o), microemulsion gel, emulsion or emulgel. The schematic flow chart in Figure 5 illustrates the mode to characterize the type of formulation on the basis of this grading system and the type of dispersion formed on water dilution.

***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 (Gupta AK et al., 2011).

8) Robustness to dilution

Emulsions upon dilution with various dissolution media should not show any phase separations or precipitation of drug even after12 hrs of storage, that formulation is considered as robust to dilution (Gupta AK et al., 2011; PatelD&Sawant K,2007;Date AA &Nagarsenkar S,2007).

9) Refractive Index and Percent Transmittance

The refractive index of the system was measured by an Abbe refractometer by placing 1 drop of solution on the slide. The percent transmittance of the system was measured at 650 nm using UV spectrophotometer keeping distilled water as a blank. Ghosh et.al30 measured the refractive index of acyclovir system and it was found similar to the water (1.333). In addition, the developed system showed percent transmittance > 99%. The refractive index and percent transmittance data prove the transparency of the system.

10) Thermodynamic stability studies

The physical stability of a lipid –based formulation is alsocrucial to its performance, which can be adversely affectedby precipitation of the drug in the excipient matrix. Inaddition, poor formulation physical stability can lead tophase separation of the excipient, affecting not onlyformulation performance, but visual appearance as well. Inaddition, incompatibilities between the formulation and thegelatin capsules shell can lead to brittleness or deformation,delayed disintegration, or incomplete release of drug.

i. Heating cooling cycle: Six cycles between refrigerator temperature (4°C) and 45°C with storage at eachtemperature of not less than 48 h is studied. Thoseformulations, which are stable at these temperatures, aresubjected to centrifugation test.

ii. Centrifugation: Passed formulations are centrifugedthaw cycles between 21°C and +25°C with storage at eachtemperature for not less than 48 h is done at 3500 rpm for30 min. Those formulations that do not show any phaseseparation are taken for the freeze thaw stress test.

iii. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stabilitywith no phase separation, creaming, or cracking (Makadia HA et al., 2013).

11) In vitro diffusion study

In vitro diffusion studies were performed for all the formulations developed, using a dialysis technique. The dialyzing medium was phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread, and then 1 ml of self nano-emulsifying formulation was placed in it along with 0.5 ml of dialyzing medium. The other end of the tubing was also secured with thread and was allowed to rotate freely in 200 ml of dialyzing medium and stirred continuously at 100 rpm with magnetic bead on magnetic plate at 37°C. Aliquots of 1 ml were removed at different time intervals and diluted further. Volume of aliquots was replaced with fresh dialyzing medium each time. These samples were analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer (Makadia HA et al., 2013).

12) Drugcontent

Drug from pre-weighed SEDDs is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

13) Equilibrium phase diagram

Pseudo-ternary phase diagrams are often constructed for, that help in determining the optimum concentrations of different excipients necessary to obtain homogenous pre-concentrate, self-emulsification ability and drug loading. Each corner of pseudo-ternary diagram represents 100% of a particular component and when more than three components are used, closely related ones are grouped together as one component and treated as such in the diagram. They are generally generated by titration method (SarpalKet al., 2013).

14) Conductivity measurement

Conductivity measurement are able to determine the point of aqueous phase addition where the system changes from oil continuous to a water continuous phase. It also helps in monitoring percolation or phase inversion phenomenon (SarpalKet al., 2013).

15) Cryo-TEM studies

For Cryo-Transmission Electron Microscopy (TEM), samples wereprepared in a controlled environment verification system. A smallamount of sample is put on carbon film supported by a copper gridand blotted by filter paper to obtain thin liquid film on the grid.The grid is quenched in liquid ethane at _1808C and transferred toliquid nitrogen at -----196^{0}C. The samples were characterized with aTEM microscope.

16) Small-angle neutron scattering

Small-angle neutron scattering can be used to obtain informationon the size and shape of the droplets. The term ‘droplet’ is used todescribe micelles, mixed micelles and oil-swollen

micellesthroughout the present work. Small-angle neutron scatteringexperiments use the interference effect of wavelets scattered fromdifferent materials in a sample (different scattering-length densities) (Kohli K et al., 2010).

17) Small-angle X-ray scattering

It is a small-angle scattering technique in which the elastic scatteringof X-rays by a sample that has inhomogeneities in the nmrange is recorded at very low angles (typically 0.1–108). Thisangular range contains information about the shape and size ofmacromolecules, characteristic distances of partially orderedmaterials, pore sizes and other data. Small-angle X-ray scatteringis capable of delivering structural information ofmacromoleculesbetween 5 and 25 nm, of repeat distances in partially orderedsystems of up to 150 nm. Small-angle X-ray scattering is usedor the determination of the microscale or nanoscalestructure of particle systems in terms of such parameters as averaged particlesizes, shapes, distribution and surface-to-volume ratio. The materialscan be solid or liquid and they can contain solid, liquid orgaseous domains (so-called 'particles') of the same or another material in any combination(Kohli K et al.,2010).

18) 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 IIdissolution apparatus using 500 ml of simulated gastric fluid containing 0.5% w/v of SLS (Sodium Lauryl Sulphate) at 50 r/ min andmaintaining the temperature at 37 + 0.5 ^{o}C. Aliquots of samples are withdrawn at regular intervals of time and volume withdrawn isreplaced with fresh medium. Samples taken are then analyzed by using UV spectrophotometer or any other suitable technique (Sapra K et al., 2012; Singh B et al., 2011).

19) Permeation studies

For information about oral bioavailability enhancement of a formulation, one must have to perform *in vitro* or *ex vivo* studies. Forthese studies, isolated and perfused organ systems have been developed (Singh B et al., 2009). These organ systems have the advantage that researchscientist works with an intact organ, where physiological cells remain in contacts intracellular matrices are preserved (Level-Trafit B et al., 1996). A numberof techniques are available for such *in vitro* studies First is In Situ Single Pass Perfusion Technique (SPIP) in which perfusion solutionis passed through the jejunum(a part of intestine) and the experimental conditions provided are closer to the *in vivo* conditions. Thistechnique is also able to determine exact absorption mechanism that is passive or active or carrier mediated absorption (Sharma P et al.,2005).Permeability parameters are determined by calculating the amount of drug which is not absorbed from intestine (Yao J et al.,2008).

20) Solubility studies

The solubility of drug in various oils, surfactants and co surfactants is determinedby using shake flask method. An excessamount of drug is added to each vial containing 1 ml of the selected vehicle i.e. oil, surfactant or solubilizer. After sealing, the mixture is vortexes using a cyclomixer for 10min in order to facilitate proper mixing of drug with the vehicles. Mixtures are then shaken for 72 h in an isothermal shakermaintained at 37 }1°C for equilibration.Equilibrated samples are centrifuged at5, 000 rpm for 15 min, followed by filtrationthrough membrane filter (0.22 μm). Theconcentrations of drug are then determinedby high-performance liquid chromatography (HPLC) method (Kale AA &Patravale VB, 2008).

Applications

A. Solidself-emulsifying drug systems

Solid self-emulsifying drug delivery used for the development of tablets using a liquid SEDDS for a poorly water-soluble drug. A high content of liquid SEDDS can be loaded (up to 70%) onto a carrier, which not only maintains good flowability but also enables the production of tablets with good cohesive properties and good content uniformity in both capsules and tablets. This clearly expands the options available to the formulator (Kohli K et al., 2010).

B. Enhancement of solubility

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-II drug (Low solubility/highpermeability). A SMEDDS formulation of a poorly water soluble drug, candesartancilexetil was formulated for directly filling in hard gelatin capsules for oral administration. The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan (Mehta K et al., 2011; Shukla JB & Patel SJ, 2010).

C. Protection against biodegradation

SEDDS have ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and protect these from enzymatic degradation (SarpalKet al., 2013).

D. Supersaturable SEDDS (S-SEDDS)

The high surfactant level typically present in SEDDSformulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developedto reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs (Fregonezi-Nery MM,2001; Borhade V et al.,2008). The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturationis intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier (Mukherjee T &Plakogiannis FM,2010). The S-SEDDS formulations contain a reducedlevel of surfactant and a polymeric precipitation inhibitorto yield and stabilize a drug in a temporarily supersaturatedstate. Hydroxypropyl methylcellulose (HPMC) andrelated cellulose polymers are well recognized for their propensityto inhibit crystallization and, thereby, generate andmaintain the supersaturated state for prolonged time periods (Patrik H et al., 2004; Martin A, 1999; Patil P et al., 2004; Patil P et al., 2007).

Future Trend

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being usedto convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasinginterest in using inert adsorbents, such as the Neusilin(Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders – which can then be processed into powder fill capsules or tablets. But to obtain solids with suitable processing properties,the ratio of SEDDS to solidifying excipients must be veryhigh, which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) is selected as a gelling agent for the oil based systems, which may serve the dual purpose of reducing the amount ofsolidifying excipients required and aiding in slowing drugrelease.

REFERENCES

1. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU and Onugu CO. The use of solid self-emulsifying systems in the delivery of diclofenac. Int J Pharm. 2003; 262(1-2): 23-8.
2. Boonme P, Krauel K, Graf A, Rades T and Junyaprasert VB, Characterization of Microemulsion Structures in the Pseudoternary Phase Diagram of Isopropyl Palmitate/Water/Brij 97:1-Butanol. AAPS Pharm Sci Tech. 2006; 7(2)
3. Borhade V, Nair H and Hegde D: Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS PharmSciTechnol. 2008; 9:13–21.
4. Charman SA, Self-emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm Res. 1992; 9: 87-93.
5. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects, Pharm. Res. 1995; 12: 1561-1572.
6. Craig DQM. The use of self-emulsifying systems as a means of improving drug delivery, B.T. Gattefosse. 1993; 86; 21-31.
7. Craig DQM. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy, Int. J. Pharm. 1995; 114:103-110
8. Craig DQM, Lievens HSR, Pitt KG and Storey DE. An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int J Pharm. 1993; 96(1-3): 147-55.

9. Craig DQM, Barker SA, Banning D and Booth SW. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int J Pharm. 1995; 114(1): 103-10.
10. Date AA, Nagarsenker MS. Design and evaluation of self-nan emulsifying drug delivery systems (SNEDDS) for cefpodoximeproxetil. Int. J. Pharm. 2007; 329: 166-172.
11. Fregonezi-Nery MM: Determination of albendazole in oral suspension. Analytical Letters. 2001; 34:1255–1263.
12. Gao, P. and Morozowich, W. Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert. Opin. Drug. Discov. 3. 2006; 97–110.
13. Gao, P. Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. J. Pharm. Sci.2003;92: 2386–2398.
14. Georgakopoulos E, Farah N, Vergnault G. Oral anhydrous non-ionic microemulsions administrated in softgel capsules, B.T. Gattefosse 1992; 85:11-20.
15. Goyal U, Gupta A, Rana AC, Agrawal G. Self microemulsifying drug delivery system:A method for enhancement of bioavailability. Int J Pharm SciReserch. 2012;3(1): 66-79.
16. Groves MJ, Mustafa RMA, Carless JE. Phase studies of mixed phosphated surfactants n-hexane and water, J. Pharm. Pharmacol. 1974; 26: 616-623.
17. Gupta AK, Mishra DK, Mahajan SC. Preparation and in vitro evaluation of SEDDS of anti-hypertensive drug valsartan. Int. J. Pharm.life Sci. 2011; 2: 633-639.
18. Gursoy N, Garrigue JS, Razafindratsita A, Lambert G and Benita S. Excipient effects on in vitro cytotoxicity of a novel paclitaxel self-emulsifying drug delivery system. J Pharm Sci. 2003; 92(12): 2411-8.
19. Hu L, Tang X, Cui F. Solid Lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs. J. Pharm. Pharmacol. 2004; 56: 1527-1535.
20. Ito, Y. Preparation and evaluation of oral solid heparin using emulsifierand adsorbent for in vitro and in vivo studies. Int. J. Pharm. 2006.
21. Ito, Y. Oral solid gentamicin preparation using emulsifier and adsorbent.J. Control Release. 2005 105, 23–31
22. Itoh, K. Improvement of physicochemical properties of N-4472 part I: formulation design by using self-microemulsifying system. Int. J. Pharm. 2002; 238: 153–160.
23. Jang DJ, Jeong EJ, LeeHM. Improvement of bioavailability & photo stability of amlodipine using redispersible dry emulsion.Eur.J. Pharm. Sci. 2006; 28:405-411.
24. Jannin ,Musakhanian J, Marchaud D. Approaches for Development of solid and semi-solid lipid-based formulations. Advanced drug delivery reviews. 2008; 60: 734-746.
25. Kale AA and Patravale VB, Design and Evaluation of Self-Emulsifying Drug Delivery Systems (SEDDS) of Nimodipine. AAPS Pharm Sci Tech. 2008; 9(1).
26. Karim A. HIV protease inhibitor SC-52151: a novel method of optimizing bioavailability profile via a microemulsion drug delivery system, Pharm. Res. 1994; 11:S368
27. Kim J & Ku YS. 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.
28. Kohli K, Chopra S, Dhar D, AroraS.Self-emulsifying drug delivery systems: an Approach to enhance oral bioavailability. Drug Discovery Today.2010; 15:
29. Levet-Trafit B, Gruyer MS, Marjanovic M. Estimation of oral drug absorption in man based on intestine permeability in rats. Life Sci. 1996; 58: PL359-363.
30. Makadia HA, Bhatt AY, Parmar RB. Self-Nan emulsifying Drug Delivery System (SNEDDS): Future Aspect. Asian J Pharm. Res. 2013; 3(1):21-27.
31. Martin A, “A book on physical pharmaceutical sciences”, Lippincott Williams, Fourth Edition. UK, 156-71.
32. Mehta K, Borade G, Rasve G, Bendre A. Self-emulsifying drug delivery system: Formulation and Evaluation. Int J Pharm BioSci. 2011; 2(4).

33. Meinzer A, Mueller E, Vonderscher J. Microemulsion a suitable galenical approach for the absorption enhancement of low soluble compounds. B.T. Gattefosse 1995; 88: 21- 26.
34. Mukherjee T and Plakogiannis FM: Development and oral bioavailability assessment of a supersaturated self-microemulsifying drug delivery system of albendazole. J Pharm Pharmacol. 2010; 62:1112-1120.
35. Nazzal S, Nutan M, Palamakula A, Shah R, Zaghloul AA and Khan MA. Optimization of a self-nanoemulsified tablet dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm. 2002; 240(1-2): 103-14
36. Nigde P, Patil S, Tiwari S. Self-emulsifying drug delivery system (SEDDS): A review. Int J Pharm Bio Sci. 2012; 2(2): 42-52.
37. Patel PA ,Chaulang , Mutha SS. Self-emulsifying drug delivery system: A Review.Research J Pharm and Tech. 2008; 1(4).
38. Patel D, Sawant K. Oral bioavailability enhancement of acyclovir by self-micro emulsifying drug delivery systems (SMEDDS). Drug Dev. Ind. Pharm. 2007; 33: 1318-1326.
39. Patil P, Joshi J and Paradkar P: Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. AAPS Pharm Sci Technol. 2004; 5:34-42.
40. Patil P, Vandana P and Paradkar P: Formulation of self-emulsifying drug delivery system for oral delivery of simvastatin: In vitro and in vivo evaluation. ActaPharmaceuticals. 2007; 57:111-122.
41. Patil, P. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen.AAPS Pharm. Sci. Tech. 2004; 10
42. Patrick H, Nigel MD and Uwe V: Pseudo-ternary phase diagram of aqueous mixtures of Quil A cholesterol and phospholipids prepared the lipid film hydration method. Int J PharmSci. 2004; 270:229-39.
43. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification, Int. J. Pharm. 1985; 27: 335-348
44. Pouton CW, Charman WN. The potential of oily formulations for drug delivery to the gastro-intestinaltract. Adv Drug Deliv Rev. 1997; 25:1-2.
45. Pouton CW, Meakin BJ, Wakerly MG. Evaluation of the self-emulsifying performance of a non-ionic surfactantvegetable oil mixture, J. Pharm. Pharmacol. 1987; 39: 6P
46. Puglia C, Ricici M, Bonina F. Evaluation of indomethacin percutaneous absorption from nanostructured lipid carriers (NLC): In vitro and in vivo studies. J. Pharm. Sci. 2005; 94: 1149-1159.
47. Rang MJ, Miller CA. Spontaneous emulsification of oils containing hydrocarbon, non-ionic surfactant, and oleyl alcohol,J. Colloids Interface Sci. 1999; 209: 179-192.
48. Reza J. Self-emulsifying drug delivery system: A review. Int J Pharm Life Sci. 2013; 2(2):80-84.
49. Santos I, Thies C, Richard. A Supercritical fluid bases coating technology 2: solubility considerations. J. Microencapsul. 2003; 20: 97-109.
50. Sapra K, Sapra A, Singh S, Kakkar S. Self-emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs.Indo Global J Pharm Sci, 2012;2(3):313-332.
51. Sarpal K, Pawar Y B, Bansal AK. Self-emulsifying drug delivery system: A Strategy to improve oral bioavailability. Current research and information on Pharm Sci. 2013; 13 (3): 42-49.
52. 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.
53. Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK and Ali M. Development and bioavailability assessment of ramiprilnanoemulsion formulation. Eur J PharmBiopharm. 2007; 66(2): 227-43.
54. Shah NH, Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of

lipophilicdrugs. Int J Pharm. 1994; 106:15-23.
55. Shukla JB and Patel SJ, Formulation and Evaluation of Self micro Emulsifying System of Candesartan cilexetil. Int. J. Pharm. Pharm. Sci. 2010; 2(4).
56. Singh b., Bandopadhyay, Kapil R. Self-emulsifying drug delivery system (SEDDS): Formulation development, characterization and Application. Critical Reviews. Therapeutic Drug Carrier Systems. 2009; 26(5): 427–521.
57. Singh B, Khurana L, Kapil R. Development of optimized self nano emulsifying drug delivery systems of carvedilol with enhanced bioavailability potential. Drug Del. 2011; 18:599-612.
58. Taha EI, Al-Saidan S, Samy AM and Khan MA. Preparation and in vitro characterization of self-nanoemulsified drug delivery system (SNEDDS) of all-trans-retinol acetate. Int J Pharm. 2004; 285(1-2): 109-19
59. Tang BC: Development of Self emulsifying drug delivery system: Preparation techniques and dosage forms. Drug Discovery Today. 2008, 13:13-14.
60. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A and Booth S. Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. J Pharm Sci. 2004; 93(6): 1495-502.
61. Vasanthavada M &Serajuddin AT. Lipid based self-emulsifying solid dispersions. In Oral lipid based formulations: Enhancing bioavailability of Poorly Water Soluble drugs (Hauss DJ. ed.) *ppinforma Healthcare.* 2007; 149-184.
62. Vonderscher J, Meinzer A. Rationale for the development of Sand immune Neoral. Transplant. Proc. 1994; 26: 2925-2927.
63. Wadhwa J, Nair A, Kumria R. Self-emulsifying therapeutic systems: A potential approach for delivery of lipophilic drugs.Brazillian J Pharm Sci. 2011; 47
64. Wang Y, Deng Y, Mao S. Characterization and body distribution of beta-elemene solid lipid nanoparticles (SLN). Drug Dev. Ind. Pharm. 2005; 31: 769-778.
65. Yao J, Lu Y, Zhou JP. Preparation of nobiletin in self-micro emulsifying systems and its intestinal permeability in rats. J. Pharm. Pharm.Sci. 2008; 11: 22-29.
66. Yuasa H. Evaluation of milk fat globule membrane (MFGM) emulsion for oral administration: absorption of linolenic acid in rats and the effect of emulsion droplet size, Biol. Pharm. Bull. 1994; 17:756-758.