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Review Article

Self Emulsified Drug Delivery System for the Enhancement of Oral Bioavailability of Poorly Water Soluble Drugs

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ABSTRACT

Oral route still remains the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. But the major problem is that oral delivery is not possible for 50% of currently marketed drug compounds due to low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. The improvement of bioavailability of drugs with such properties presents one of the greatest challenges in drug formulations. Among the approaches to improve the oral bioavailability of these molecules, the use of self-emulsified drug delivery systems (SEDDS) has been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs. The present review examines the recent advances in Solid SEDDS (S-SEDDS) with regard to the selection of lipid systems for current formulations, solidification techniques and the development of solid SE (self-emulsifying) dosage forms and their related problems and possible future research directions.

Keywords: self-emulsified drug delivery systems (SEDDS), poor aqueous solubility, lipophilic drugs.

INTRODUCTION

According to an FDA survey conducted between 1995 and 2002, only 9% of the new drug entities belonged to BCS class-I category (high solubility-high permeability), majority of new drug candidates (approximately more than 40%) have poor aqueous solubility because of their low bioavailability[1]. So, in recent years, much attention has turned to lipid-based formulations with the aim of improving the oral bioavailability of poorly water soluble drugs. Lipid-based formulations encompass a diverse group of formulations, very different in physical appearance, ranging from a simple tri-glyceride vehicle to more sophisticated formulations such as Self emulsifying drug delivery systems (SEDDS)[2]. Self emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water micro (SMEDDS) and nano (SNEDDS)-emulsions, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the GIT. The spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from emulsion in a reproducible manner[3-4]. Both system, SEDDS (droplet sizes of 200 nm-5 mm) and SMEDDS (droplet size <100 nm) are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs[5-9].

WHY SEDDS ARE NEEDED

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug

delivery of hydrophobic drugs can be made possible by SEDDS. 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 favor the drug remaining in the lipid droplets[10].

POTENTIAL ADVANTAGES OF SELF EMULSIFING DRUG DELIVERY SYSTEM[11]

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.

ADVANTAGES OF SEDDS OVER CONVENTIONAL DRUG DELIVERY SYSTEM (DDS)[11]

1. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these system can form fine oil in water (o/w) emulsion or microemulsion (S(M)EDDS).Fine oil droplets would pass rapidly wide distribution of the drug throught the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
2. Emulsion are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation those are easy to manufacture.
3. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.

COMPOSITION OF SEDDS AND SMEDDS

Surfactant

The choice of surfactants is limited as very few surfactants are orally acceptable. Non-ionic surfactants with high HLB value are used in formulation of SMEDDS including: Ethoxylated polyglycolysed glyceride, Tween 80, LABRFAC CM1O-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides and other long chain alkyl sulfonate sulfate surfactants, such as sodium dodecyl benzene sulfonate, sodium lauryl sulfate and dialkyl sulfo succinate and quaternary ammonium salts, fatty alcohols such as lauryl, cetyl and stearyl, glyceryl esters, fatty acid esters and polyoxyethylene derivatives are also, employed. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SMEDDS use despite their limited ability to selfemulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents. 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-micro emulsifying performance[12]

Oils

Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride . Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation are also valuable in designing of SEDDS.[13]

Co-surfactant

In SMEDDS, generally co-surfactant of HLB value (10-14) is used. Hydrophilic co-surfactant preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion are used in formulation of SMEDDS.[13]

Cosolvents

Cosolvents may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base which are as follows diethylene glycol, monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, Etc[13]

Consistency builder

Materials such as tragacanth, cetyl alcohol, stearic acids and /or beeswax are added to alter the consistency of emulsion.[14]

Table 1 : Examples of oils,surfactant,co-surfactant and co-solvent used[15]

Oils	Surfactant	Co-surfactant/Co-solvent
Cotton seed oil	Polysorbate 20[Tween 20]	Span 20
Soybean oil	Polysorbate 80[Tween 80]	Span 80
Corn oil	D-alpha Tocopheryl glycol 1000 succinate	Capryol 90
Sunflower oil	Polyoxy-35-castor oil [Cremophor RH40]	Lauroglycol
Castor oil	Polyoxy-40-hydrogenated castor oil	Transcutol
Sesame oil	Labrasol	Capmul
Peanut oil	Ethanol	
Labrafac	polypylene glycol	
Labrafil	polypylene glycol	

Table 2: Some Patented formulation of SEDDS and SMEDDS[16]

U.S.Patent No	Date	Active	Information Ingredient
7,749,540	july 6,2010	Modafinil	particle-forming composition of modafinil Compound and aqueous composition of Particles comprise a modafinil compound Are disclosed along with method of their Prepration,uses and treatment of diseases.
7,736,666	june 15,2010	Naproxan	The present invention claims and disclose a pharmaceutical composition suitable for oral administration, in form of emulsion pre- concentrate, comprising a compound of formula one or more surfactant, optionally an oil or semi- solid fat, said composition forming an in-situ oil-in-water emulsion Upon contact with aqueous media such as Gastrointestinal fluid.
6,652,865	November 25,2003	simvastatin	A pharmaceutical composition of oral use is disclosed. The carrier include : therapeutically effective amount of active principle ; a lipophilic phase, which is a mixture of glycerol. A method of decreasing the effect of intestinal metabolism on a drug using the composition is also disclosed.
6,555,558	April 29, 2003	pyranone Protease Inhibitors	A microemulsion of pyranone protease inhibitors compound that is substantially free of alcohol and propylene glycol comprising a pyranone protease inhibitors,one or more pharmaceutically acceptable surfactant, polyethylene glycol,di-glycerieds and optionally are basic amine.

MECHANISM OF SELF-EMUSLIFICATION

The process by which self-emulsification takes place is not yet well understood. However, 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 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 equation.

$$\Delta G = \sum N_i \pi r_i^2 \sigma$$

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. 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. 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)[17].

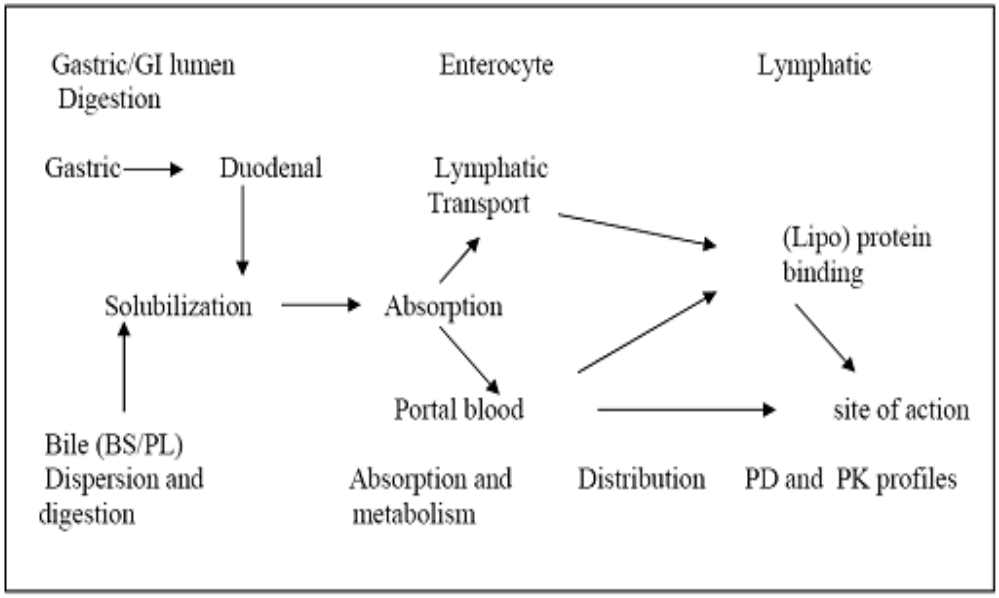

Fig. 1: Fate of SEDDS and SMEDDS following oral administration and mechanisms proposed for bioavailability enhancement of drug[18]

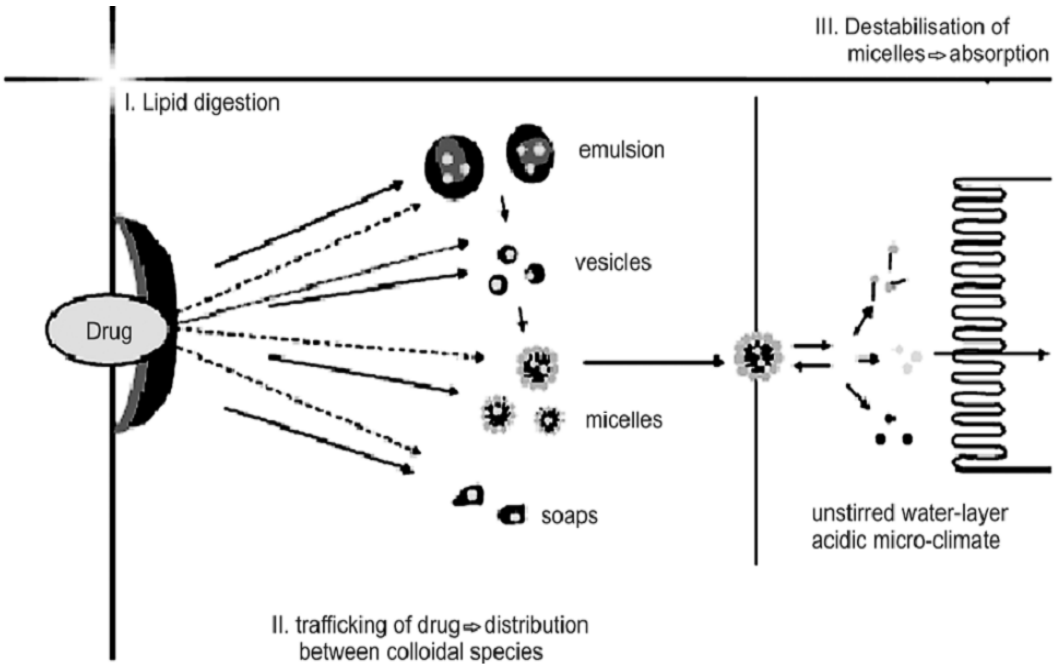

Fig. 2: Intestinal pre-absorptive processes[18]

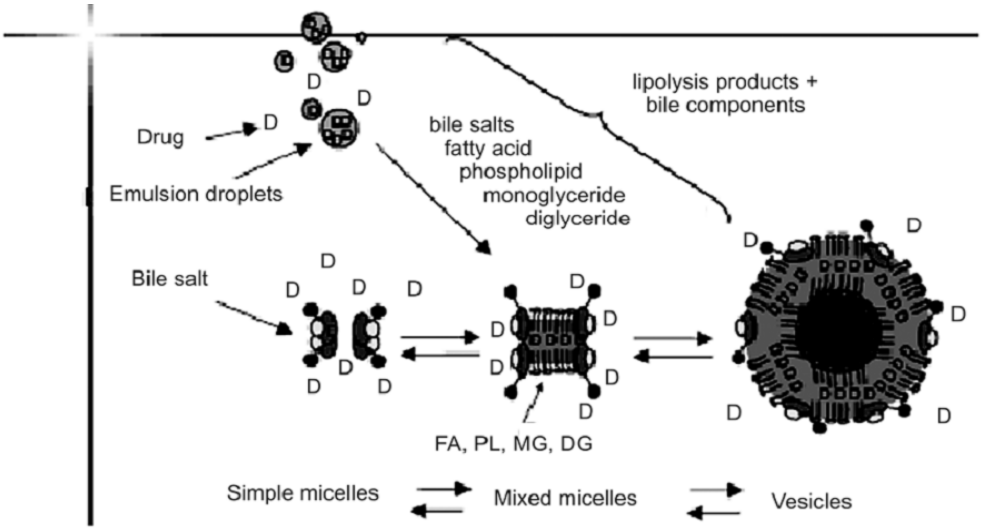

Fig. 3: Distribution of drug solubilized in an emulsion[18]

EVALUATION OF SEDDS

1) Thermodynamic stability studies

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

Centrifugation: Passed formulations are centrifuged thaw cycles between 21°C and 25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test[19].

2) Dispersibility test

The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP dissolution apparatus 2. 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 provides gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

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

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

Grade C: Fine milky emulsion that formed within 2 min.

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

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

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation[19].

3) Viscosity Determination

The rheological properties of the micro emulsionare evaluated by Brookfield viscometer. Thisviscosities determination conform whether thesystem is w/o or o/w. If system has low viscositythen it is o/w type of the system and if highviscosities then it are w/o type of the system[19].

4) Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter[20].

5) Droplet Size Analysis Particle Size

Measurements The droplet size of the emulsions is determined by photon correlation spectroscopy using a Zetasizer able to measure sizes between 10 and 5000 nm[20].

6) Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at particular

wavelength using UV-spectrophotometer keeping distilled water as blank[21]

7) Drug content

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method against the standard solvent solution of drug[21].

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SMEDDS TO S-SMEDDS: Various solidification techniques are as listed below;

1) Capsule filling with liquid and semisolid self-emulsifying formulations:

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process: (i) heating of the semisolid excipient to at least 20˚C above its melting point; (ii) incorporation of the activesubstances (with stirring); (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: filling of theformulation into the capsules followed by sealing of the body and cap of the capsule,either by banding or by micro spray sealing. The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading potential (up to 50% (w/w)).[22]

2) Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the
temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.[22]

3) Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a 'one-step' operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent.[22]

4) Adsorption to solid carriers

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS/SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carrier[23]

5) Melt extrusion/extrusion spheronization:

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.[24]

Table 3: Examples of Marketed SEDDS Formulations[25]

Drug name	compound	Dosage form	company	Indication
Neoral	Cyclosporine A/I	Soft gelatin capsules	Novartis	Immune suppresant
Norvir	Ritonavir	Soft gelatin capsules	Abbott laboratories	HIV antiviral
Fortovase	Saquinavir	Soft gelatin capsules	Hoffmann-la Roche inc.	HIV antiviral
Agenerase	Amprenavir	Soft gelatin capsules	Glaxo smithkline	HIV antiviral
Convulex	Valporic acid	Soft gelatin capsules	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Hard gelatin capsules	Genus	Antihyper-lipoproteinemic
Sandimmune	Cyclosporine A/I	Soft gelatin capsules	Novartis	Immune suppresent
Targretin	Bexarotene	Soft gelatin capsules	Ligand	Antineoplastic

RECENT ADVANCEMENTS IN SEDDS

1) Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing self emulsifying tablets that have been widely researched. After evaluation the effect of some processing parameters (colloidal silicates X1, magnesium stearate mixing time X2, and compression force X3) on hardness and coenzyme Q10 (CoQ10)dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved bya face-centered cubic design [26]. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS onto solid dosage forms, a gelled SEDDS has been developed. 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 excipeints and aiding in slowing down of the drug release[27].

2) Self-emulsifying capsules

After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation[28]. With the similar purpose, the super saturatable SEDDS was de-signed, using a small quantity of hydroxyl propyl methyl cellulose (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo.This system contains a reduced amount of a surfactant, thereby mini-mizing GI side effects[29-30]. The SEDDS formulations, empty soft gelatin capsules were filled with the formulation using a syringe and sealed with hot gelatin. The optimized self-emulsifying formulation contained 30% (w/w) Tagat TO, 67.1°/,) (w/w) Miglyol 812 and 2.9 %(w/w) cyclosporin, and each capsule was filled to contain 25 mg of cyclosporine. The limited drug loading capacity and incomplete emulsification characteristics of the EG formulation were improved by developing a surfactant enhanced system (SEEG). Although thedrug loading capacity of these systems is still relatively low, for potent, lipophilic compounds, solid SEEG formulations may provide advantages in administration and chemical stability over traditional formulation alternatives such as emulsions and liquid fill soft gels[31].

3) Self-emulsifying suppositories

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption[32]. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester[33].

4) Micro emulsion Drug Delivery

Dioctyl sodium sulfosuccinate (aerosol OT) has proved to increase the intestinal absorption of many drugs[34-35] While the number of publications on the possible application of aerosol OT micro emulsions for topical drug delivery is already extensive, aerosol OT applicability for oral micro emulsion drug delivery still needs to be studied.[36-37] Recently, a patent cooperation treaty (PCT) provided a stable, self-emulsifying water/oil micro emulsion in which the surfactant with high Hydrophilic Lipophilic Balance (HLB) comprises a medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt dissolved in a polyhydric alcohol to improve the delivery characteristics of a therapeutic peptide drug[38].

5) Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%[39]. More recently, a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an

efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like PTX[40]. The purpose of the present study was to formulate a self-nanoemulsifying system (SNES) containing model lipophilic drug,felodipine (FLD), to improve its solubility. The SNES was formulated using varying amounts of Miglyol 840 (as an oil), Cremophor EL (as asurfactant), and Capmul MCM (as a co-surfactant). The SNES were characterized for turbidity, droplet size and in vitro FLD release. TheSNES containing oil, surfactant, and co-surfactant in the weight ratio of 3.5:1.0:1.0, respectively, showed good emulsification, median droplesize (of 421 nm), and rapid FLD release (more than 90% release in 15min)[41].

6) Self-emulsifying sustained/controlled-release pellets

To formulate and prepare SEDDS, there were some basic guidelines needed to conform: safety, compatibility, drug solubility, efficient self-emulsification efficiency and droplet size, etc.[42]. Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reduction of intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pelletswith those of SEDDS by SE pellets. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs[43]. Formulation of SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rateof drug release are also very useful. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs(methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80[44]. The combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution[45].

CONCLUSION

From the above review we can conclude that Self-em ulsifying drug delivery systems are appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. Self emulsifying drug delivery system has improved solubility/dissolution, absorption and bioavailability for poorly water soluble drug. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. SEDDS is superior to other colloidal vehicle in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance.

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