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Recent Updates on Self Micro Emulsifying Drug Delivery Systems

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ABSTRACT

Solubility plays a vital role in achieving the therapeutic efficacy of a drug from a dosage form. Advances in molecular screening techniques for identification of potential drug molecules investigated an increased number of new pharmacologically active lipophilic compounds that are poorly water soluble. About 40% of new chemical entities have been discovered as poorly water soluble. Numbers of technical strategies have been investigated for improving bioavailability like solid dispersions, cyclodextrins, micronization, surfactants, nanoparticles, lipids, permeation enhancers etc. It is a great task for pharmaceutical scientist to formulate oral dosage forms of these drug candidates with sufficient bioavailability. Among the various approaches to improve oral bioavailability of these drug candidates, Self- dispersing lipid formulations (SDLF's) is one of the approaches used to improve the bioavailability of lipophilic drugs. SDLF's is very broad area which covers Self-emulsifying drug delivery systems (SEDDS), Self-microemulsifying drug delivery systems (SMEDDS) and Self-nanoemulsifying drug delivery systems (SNEDDS) as carrier systems that have been developed. This review article covers basics of SDLF's particularly SMEDDS and recent research updates in SDLF's i.e. the research carried out and most recent solid SDLF's.

Keywords: self-dispersing lipid formulations, self-micro emulsifying drug delivery system, solubility, bioavailability, lipophilic.

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INTRODUCTION

Oral route is the easiest and most convenient route of administration, being non invasive and cost effective but the major problem encountered is 50% of drug candidates have poor solubility and low bioavailability, giving rise to high inter and intra subject variability, lack of dose uniformity and finally therapeutic failure.[1] Numbers of technical strategies are investigated for improving bioavailability like solid dispersions, cyclodextrins, micronization, surfactants, nanoparticles, lipids, permeation enhancers etc.[2] Indeed, in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical / thermal stability. Many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray drying method requires particular facilities and processes, leading to high production cost. Though, traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous organic solvents.[3] Considering the fact that oral bioavailability of poor water soluble drugs may be enhanced when co-administered with meal rich in fat, the formulation of poorly water soluble drugs in lipids became the prime area of research. Various lipid based formulations such as suspensions, solutions and emulsions have been used to enhance the oral bioavailability.[4] Initially emulsions have been used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs.[5] The poor stability of these systems led to development of micro emulsions which has various advantages like excellent thermodynamic stability, high drug solubilization capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis. The only problem with micro emulsion is poor palatability due to the lipid content leading to poor patient compliance, more over due to their water content, micro emulsions cannot be encapsulated into soft gelatin or hard gelatin capsule. Self-microemulsifying drug delivery systems (SMEDDS) are a viable alternate to traditional dosage forms as they tend to self -emulsify in the aqueous contents of the stomach. These systems may offer an improvement in the rate and extent of absorption, and more reproducible blood-time profiles of lipophilic drugs. The poorly soluble drugs are marketed as self-emulsifying formulations (with improved oral absorption). These are i) Sand immune R

(cyclosporine), ii) Neoral R (cyclosporine), iii) NorvirR (ritonavir), iv) Fortovase (saquinavir) and v) Aptivus R(tipranavir).[6]

Types of Self Dispersing Lipid Formulations

Lipid based formulations have been classified on the basis of particle size of oil droplets of the system. Figure 1 shows different self dispersing lipid formulations and Table 1 depicts their features.

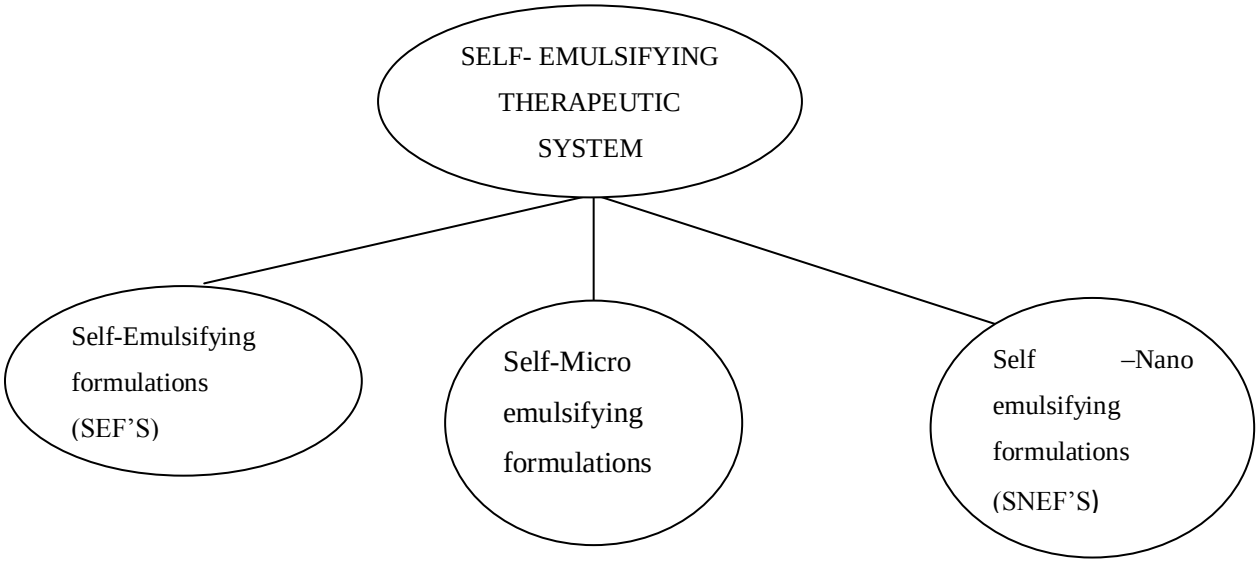

Figure 1: Different self-emulsifying lipid formulations

Table 1: Features of different self-emulsifying formulations

SEF's	SMEF's	SNEF's
Oil droplet size 200nm-5µm	Oil droplet size 100-250nm	Droplet size >100nm
Appearance is turbid	Appearance clear to translucent	Optically clear
Use surfactants of HLB<12	Use surfactants of HLB>12	Use surfactants of HLB >12
Concentration of oil is 40-80%	Concentration of oil is less than 20%	--

Self-Micro emulsifying Drug Delivery Systems (SMEDDS)

Self micro-emulsifying drug delivery system (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. [7, 8] SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for Self- emulsification.[9, 10, 11] When compared with emulsions, which are sensitive and metastable dispersed forms while SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-

limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. The SMEDDS mixture can be filled in either soft or hard gelatin capsules.[1]

Benefits of SMEDDS

1. They led to enhanced oral bioavailability of drugs e.g. ketoprofen
2. They decrease inter-subject and intra subject variability and food effects. e.g. cyclosporine.
3. SMEDDS are used to deliver peptides which are prone to enzymatic hydrolysis in GIT.
4. SMEDDS are used for both liquid and solid dosage forms.e.g.progesterone.
5. They can be produced at large scale.

Limitations of SMEDDS

1. They are not used for drugs which are chemically unstable and have high stability concentrations.
2. The large amount of surfactant in formulations (30-60%) causes irritation in GIT
3. Self emulsifying formulations which contain volatile co-solvents are incorporated in soft or hard gelatin capsules resulting in the precipitation of the lipophilic drug.

Excipients used in SMEDDS

Various excipients which have been used in preparation of SMEDDS[12] are as follows:

a) Oils: Oils are the most important excipients because oils can solubilize the lipophilic drug in a specific amount and it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, increasing absorption from GIT. Both long chains triglycerides and medium-chain triglycerides oils with different degree of saturation can be used for the formulation of SEDDS.

b) Surfactant: Non-ionic surfactant with high hydrophilic-lipophilic balance (HLB) value is used in the formulation of SEDDS (e.g. Tween, Labrasol, Labrafac CH 10, Cremophore etc). High HLB and hydrophilicity of surfactant assists the immediate formulation of o/w droplets and rapid spreading of formulation in the aqueous media.

c) Co-solvents: Co-solvents like ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate tetrahydrofurfuryl alcohol, Glycofurol etc. help in dissolving large amount of hydrophilic surfactant or hydrophobic drugs in lipid phase. Example of surfactant, co-surfactant and co-solvent used in commercial formulations are given below.

d) Surfactant/co-surfactants: Polysorbate 20C (Tween 20), Polyoxy-40 hydrogenated castor oil (Cremophor RH 40), Polyoxy ethylated glycerides (Labrafil M 2125cs)

e) **Lipid ingredients:** Corn oil, mono, di, tri-glycerides, D2- alpha-tocopheryl, Olive oil, Oleic acid, Sesame oil, Beeswax.

Recent Advancements and Future Prospects:

Dry emulsions:

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, malto dextrin, and so on) in the aqueous phase by rotary evaporation,[13] freeze-drying[14] or spray drying.[15,16] Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. Cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects. The technique of spray drying is more frequently used in preparation of dry emulsions.[17] The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of surfactant; a vegetable oil, and a pH-responsive polymer, with lyophilisation used. Recently prepared dry emulsions by spreading liquid O/W emulsions on a flat glass then dried and triturated to powders.

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 microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulphate was added into the SE formulation.[18] With the similar purpose, the super saturable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects.[19, 20] Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solider semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on) as an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self micro emulsification upon mixing with water.[21, 22] Oral administrations of SE

capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules.[23] LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: micro porous calcium silicate (FloriteTM RE); magnesium aluminium silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320). Eventually these solids were filled into hard capsules. In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as inject able or topical dosage form.

Self-emulsifying sustained/controlled release tablets:

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal and Khan evaluated the effect of some processing parameters (colloidal silicates-X_1, magnesium stearate mixing time X_2, and compression force-X_3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X_1 = 1.06%, X_2 = 2 min, X_3 = 1670 kg) were achieved by a face-centered cubic design. In order to reduce significantly the amount of solidifying excipients required for transformation of SMEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosol 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. SE tablets are of great utility in obviating adverse effect e.g. SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet.[24] The newest advance in the research field of SME tablet is the which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol TM (a copolymerof alkyl phenol and formaldehyde.[25]

Self-emulsifying sustained/controlled release pellets:

Pellets as a multiple unit dosage form, possess many advantages over conventional solid dosage

forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability.[26] Thus, it is very appealing to combine the advantages of pelletwiththose of SEDDS by SE pellets. Serratoni et al. prepared 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 rate of drug release. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80. There is another report that SEsustained-release matrix pellets could be successfully formulated with glyceryl palmito-stearate (Gelucire 54/02) and glyceryl behenate (Gelucire 70/02).

Self-emulsifying solid dispersions:

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling. SE excipients like Gelucire144/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field.[27-30]

Self-emulsifying beads:

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, solvent evaporation method was used for loading of SES into the micro-channels of porous polystyrene beads (PPB). PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pores architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES loaded PPB.

Self-emulsifying sustained release microspheres:

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumour suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, prepared solid SE sustained-release microspheres using the quasi emulsion–Solvent

diffusion method of the spherical crystallization technique. ZTO release behaviour could be controlled by the ratio of hydroxylpropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration– time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.

Self-emulsifying nanoparticles:

Nanoparticles techniques have been useful in the production of SE nanoparticles. Solvent injections are one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stir red non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. These approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%.

Self–emulsifying suppositories:

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption.[31] 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 aC6–C18 fatty acid macrogol ester.

Self-emulsifying implants:

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl) -1-nitroso urea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. Loomis invented copolymers having bio restorable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.

Self-emulsifying fast dissolving tablets:

The IR-SETS were prepared by powderization of liquid SMEDDS by adsorbing it to porous solid carriers and blending of powdered SMEDDS with pharmaceutical excipients, and then tablets are prepared by compression of tablet mixture. Various examples of bioavailability enhancement using SEDDS as carriers are Halofantrine tend to higher bioavailability from LCT SMEDDS, Vitamin E bioavailability 3-folds higher from SEDDS, Coenzyme Q10 bioavailability 2-folds higher from SEDDS, Progesterone bioavailability-9 folds higher from SEDDS.

Solid Self-Micro emulsifying Drug Delivery System (S-SMEDDS)

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. S-SMEDDS focus on the incorporation of liquid/semisolid SME ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms.

Advantages of S-SMEDDS:

- Spontaneous formation
- Ease of manufacture
- Thermodynamic stability
- Improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- Greater bioavailability
- Less drug need to be used
- These systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles

Solidification Techniques for transforming Liquid/Semisolid SMEDDS to S-SMEDDS

Liquid SEDDS can be filled in soft or hard gelatin capsule. Recently, there have been efforts by research groups working on SEDDS to convert liquid SEDDS to solid state SEDDS. The primary reason to formulate SEDDS in a solid form is to consolidate the advantages of Liquid SEDDS with convenience of solid oral dosage forms. Researchers have adopted various techniques to obtain this conversion. The following description elaborates various Liquid to Solid SMEDDS conversion techniques.

1. Spray drying

Spray drying is the most widely used technique to convert Liquid SEDDS into solid state. In this method the Liquid SEDDS is mixed with a solid carrier in a suitable solvent. The solvent is then atomized into a spray of fine droplets. These droplets are introduced into a drying chamber, where the solvent gets evaporated forming dry particles under a controlled temperature and

airflow conditions.[32] Various solid carriers that have been used for this purpose are: Aerosil 200 [33] suspended in ethanol and aqueous solution of Dextran 40.[34]

2. Adsorption to solid carriers

The Liquid SEDDS can be made to adsorb onto free flowing powders that possess very large surface area and are capable of adsorbing high quantities of oil material. The adsorbents are capable of adsorbing Liquid SEDDS up to 70 %w/w of its own weight. Categories of solid adsorbents used are: silicates, magnesium trisilicate, talcum, cros povidone, cross-linked sodium carboxy methyl cellulose and cross-linked polymethylmethacrylate.[35] Oral solid heparin and gentamicin SMEDDS were prepared using three kinds of adsorbents: microporous calcium silicate (Florite RE), magnesium aluminometa silicate (Neusilin US2) and silicon dioxide (Sylysia 320).[36, 37]

3. Encapsulation of Liquid and Semisolid SEDDS

It is one of the simplest techniques for conversion of Liquid SEDDS to solid oral dosage form. For a semisolid SEDDS, it is a four step process: heating the semisolid excipients to at least 20°C above its melting point; adding the drug in the molten mixture while stirring; filling the drug loaded molten mixture into the capsule shell and cooling the product to room temperature. The compatibility of the excipients used with the capsule shell should be well investigated. Capsule filling of SEDDS is suitable for low dose highly potent drugs and allows high drug incorporation.

4. Extrusion Spheronization

This is a solvent free technique that converts Liquid SEDDS into pellets using extrusion and spheronization processes. In this method the Liquid SEDDS is first mixed with a binder, followed by addition of water until the mass is suitable for extrusion. The extruded mass is then spheronized to form uniform sized pellets. The pellets are then dried and size separated. High drug incorporation can be achieved by using this technique. A mixture of silicon dioxide, glyceryl behenate, pre gelatinized starch, sodium cross carmellose, and MCC were used in the preparation curcumin loaded SMEDDS pellets.[38]

5. Melt Granulation

Melt Granulation is another solvent free technique for converting Liquid SEDDS. In this method, Liquid SEDDS is mixed with a binder that melts or softens at relatively low temperature. This melted mixture can be granulated. This technique is advantageous since it does not require addition of a liquid binder and subsequent drying unlike conventional wet granulation. The variables to be controlled in this process are impeller speed, mixing time, binder particle size,

and the viscosity of the binder. A mixture of mono-, di- and triglycerides and esters of polyethylene glycol (PEG) called as Gelucire are used as binders to prepare immediate release pellets by melt granulation and as a self-emulsifying drug delivery system by capsule moulding or as powder obtained by cryogenic grinding.[39]

RESEARCH CARRIED OUT ON SMEDDS:

This section comprises the research reported on various self-dispersing lipid formulations (SEDDS, SMEDDS and SNEDDS).

SEDDS as carriers:

A novel Liquid SEDDS of curcumin consisted of Lauroglycol FCC, Labrasol, Transcutol HP as oil phase, surfactant and co-surfactant at a weight ratio (15:70.8: 14.2)(w/w/w) was formulated by simple mixing method and further developed into solid SEDDS by spray drying technique using aerosil 200 as solid carrier to enhance oral bioavailability. Solid SEDDS were quickly and completely dissolved within 5 min both in 0.1 N HCl and phosphate buffer pH 6.8 whereas crude curcumin was less dissoluble.[39]

SEDDS of Spironolactone were formulated using oils (arachis oil, oleic acid, castor oil, soybean oil, Neobee oil M5, Miglyol, and capmul), surfactants (Tween 80, cremophor RH40, cremophor EL) and absorbents (Aerosil-200, Avicel-PH101, Lactose, Dextrose, Mannitol, and Talc) by simple agitation method. The release pattern from arachis oil is 92.95%, oleic acid 90.21% and castor oil 97.54% which was better in comparison to other oils. The release rate of all three oils was rapid in Tween 80 (above 85%) due to its better emulsifying propery than Cremophor RH40, Cremophor EL.[40]

SEDDS of fenofibrate were developed using lipophilic Labrafac WL 1349 as the oil, Cremophor RH 40 as surfactant and Transcutol HP as co-surfactant by simple agitation method. The SEDDS ensured maximum solubilisation of the drug thereby enhanced drug bioavailability.[41]

Immediate release self-emulsifying tablets of ibuprofen was prepared with solidified SEDDS of ibuprofen using capryol 90, Cremophor EL, Labrasol and IBU at a ratio 3:4:3:3. The liquid SEDDS were solidified with various carriers like Fujicalin, Neusilin and Neosyl. The powderized SEDDS were tableted by direct compression. Fulicalin based SEDDS tablets shows higher dissolution rate as compared with Neusilin and Neosyl based SEDDS. The immediate release formula of IBU prepared with Fujicalin as an adsorbent, Polyplasdone as a disintegrant and Sodium bicarbonate as a co-disintegrant showed over 90% of initially loaded dose of IBU released within 5min in a simulated gastric juice (pH 1.2) which is equivalent to that shown by liquid SEDDS.[8]

SEDDS of Atorvastatin were developed by emulsification method using Sefso. It is l218 and oleic acid (oil phase), Tween 20, Tween 80 (surfactants) and Carbitol (co-surfactants). SEDDS led to improvement of the dissolution rate and there by oral bioavailability of poorly water-soluble drugs like ATV without incompatibility between the ingredients.[42]

Atorvastatin self-emulsifying drug delivery system (SEDDS) with high drug load (10% w/w) was achieved with combination of oleic acid, Tween 80, and polyethylene glycol 400 ensuring maximum dissolution.[43]

SEDDS of Loratadine using Liquid paraffin and Labrafil as oil, Span 20 as surfactant, Capryol as co-surfactant and Transcutol P (liquid) as solubilizer were formulated by simple admixing the components. In this we used two –phase liquid paraffin oil and Labrafil (liquid). Thus, two series of formula was obtained, which in both surfactant Span 20 and Cosurfactant Capryol (liquid) were used. The percentage of drug release after 6hrs for Labrafil and liquid paraffin were 30.87%- 54.26% and 31.99-61.34 respectively. Formulations prepared with liquid paraffin and Labrafil demonstrated drug permeability through rat intestine 2.72 and 2.25 folds compared to control. SEDDS prepared with liquid paraffin provide perfect solubility in acidic condition and increased intestine permeability.[44]

Solid form of lipid-based self emulsifying drug delivery System (SEDDS) was prepared by spray drying liquid SEDDS with an inert solid carrier Aerosil 200 to improve the oral bioavailability of poorly water-soluble drug Dexibuprofen. The liquid SEDDS consisted of Dexibuprofen, Labrasol, Capryol 90 and Labrafil M 1944 CS prepared by simple agitation method. Solid SEDDS proved as an effective oral solid dosage form to improve the bioavailability of poorly water-soluble drug Dexibuprofen.[45]

Self-emulsifying drug delivery system (SEDDS) composed of oil, surfactant and cosurfactants were reported for oral administration of CoQ10.The formulations were prepared using two oils (Labrafil M 1944 and Labrafil M 2125), surfactant (Labrasol) and co-surfactants (Lauroglycol FCC and Capryol 90) by simple agitation method. In all the formulations, the level of CoQ10 was fixed at 6% (w/v) of the vehicle. The SEDDS lead to improved oral bioavailability of lipophilic drug, CoQ10.[46]

Metronidazole loaded SEDDS were formulated using two vegetable oils (Palm Kernel oil and Palm oil) and surfactant by simple mixing method in different ratios. The *in vitro* release profile showed that most of the formulations released within 50% of drug in less than 8min and 85% of drug in less than 30 min.[47]

SEDDS of Nimodipine were formulated with varying ratio of oil to surfactant: co-surfactant mixture. The ratio of oil (Gelucire 44/14) to surfactant + Co-surfactant (Labrasol containing 80% Transcutol P + Plurol Oleique CC 497) was varied from 9:1 to 1:9.The ratio of surfactant to co-surfactant was maintained at 5:1 and the concentration of drug was also kept constant in all formulations (30mg) by gentle stirring method. The SEDDS proved as effective and commercially viable alternate to the currently existing Nimodipine formulations.[48]

Self-emulsifying drug delivery system (SEDDS) of Phenytoin were developed using Labrasol®, Plurol® Oleique, Transcutol®, Lauroglycol ®FCC, Labrafac® CC as lipophilic excipients. Sigma Stat software was used to analyze the data. Two-way ANOVA test was used to compare the dissolution profile. A stable SEDDS formulation of Phenytoin was obtained that showed significantly improved *in vitro* release when compared to a commercially available Phenytoin suspension.[49]

An optimized formulation of SEDDS containing Puerarin using Oleic acid as oil(17.5%), Tween -80 (34.5%) as Surfactant and Propylene glycol (34.5%) as Co-surfactant was prepared by gentle stirring. The absolute bioavailability of optimized SEDDS in beagle dogs after oral administration was found to be about 24.8%.[50]

SEDDS incorporating Simvastatin using 1:1(v/v) mixture of Captex and Lauroglycol as oil phase and Cremophor EL/ Capmul MCM as co-surfactant was formulated by mixing method. Among oils Lauroglycol showed the maximum solubility (around 90mg/ml-1) while Captex 60mg/ml-1.[51, 52]

In vivo performance of a gelled self-emulsifying Ketoprofen formulation using oil (Captex 200), surfactant (Tween80), co-surfactant (Capmul MCM) and colloidal silicon dioxide (A200) was evaluated.[53]

Itraconazole loaded self-emulsifying drug delivery system (SEDDS) composed of Transcutol, Pluronic L64 and tocopherol acetate were developed. The prepared SEDDS showed much higher absorption and less affected by food intake than Sporanox capsule (marketed formulation of Itraconazole).[54]

Self-emulsifying tablets of Diclofenac using Goat fat and Tween 65 were formulated by pour moulding using a plastic mould. The tablets exhibited improved *in vitro* release profiles and acceptable tablet properties. It is best suited for lipophilic drugs where the resulting emulsification gives faster dissolution and absorption rates.[55]

SMEDDS as carriers:

SMEDDS of olmesartan (OLM) were developed to enhance the solubility and bioavailability of

poorly water soluble drug using oils, surfactant and co-surfactants by gentle stirring and mixing. The optimized liquid SMEDDS were further used for the preparation of solid –SMEDDS by using Neusilin U52 and fujacilin as adsorbent carriers. Neusilin U52 showed highest drug release (99.02%) and also good hardness (3.8kg/cm2) as compared to other formulations. The optimized formulation of OLM-loaded S-SMEDDS exhibited complete release in 60 min as compared to liquid SMEDDS and it can be regarded as novel and commercially feasible alternative to current olmesartan formulations.[56]

SMEDDS with *a* composition of 25% lipid, 48%surfactant and 27% co-surfactant was developed and evaluated with regard to bioavailability and chemical stability using the vitamin analogue, Seocalcitol, as model compound. There was no improvement in bioavailability by the use of SMEDDS as compared to the bioavailability achieved from simple MCT and LCT solutions (22–24%). Simple lipid solutions seem to be a better choice compared with the developed SMEDDS due to a slightly higher bioavailability and a better chemical stability of Seocalcitol.[57]

SMEDDS were developed to achieve faster onset of action of Celecoxib. The optimized SMEDDS formulation consisted of 49.5% PEG-8 caprylic/capric glycerides, 40.5%mixture of Tween 20 and Propylene glycol monocaprylic ester (3:1) and 10% Celecoxib, which showed significantly higher rate and extent of absorption than conventional capsule. SMEDDS formulation has the potential to minimize the variability in absorption and to provide rapid onset of action of Celecoxib.[58]

Vinpocetine (VIP) incorporated self-microemulsifying drug delivery system (SMEDDS) were reported to increase the solubility, dissolution rate and oral bioavailability. The optimal formulation of SMEDDS (Labrafac: oleic acid: Cremophor EL: Transcutol P = 40: 10: 40: 10) (w/w) was prepared by simple agitation method. The formulations of VIP-SMEDDS were optimized by solubility assay, compatibility tests, and pseudo-ternary phase diagrams analysis. This study highlighted the potential of using SMEDDS as efficient strategy for the oral delivery of hydrophobic compounds such as vinpocetine.[59]

SMEDDS of Olmesartan Medoxomil were prepared and characterized using oil phase (Acrysol EL 135), surfactant (Tween 80), co-surfactant (Transcutol P) in different ratios by simple mixing method. *In vitro* release showed complete drug release within 15 min. SMEDDS formulations containing Olmesartan Medoxomil showed significant increase in dissolution rate and *in vitro* diffusion rate compared to plain Olmesartan Medoxomil.[60]

Folate modified self-microemulsifying drug delivery system (FSMEDDS) using 57.5% Cremophor® EL, 32.5% Transcutol® HP, 10% Capryol™ 90, and a small amount of Folate-

polyethylene glycol-cholesteryl hemisuccinate (the weight ratio of Folate materials to Cremophor EL was 1:100) were developed with the aim to improve the solubility of cur cumin and its delivery to the colon, facilitating endocytosis of FSMEDDS mediated by Folate receptors on colon cancer cells. Curcumin loaded FSMEDDS was then filled into colon targeted capsules and *in vitro* release was investigated. *In vitro* release indicated that the obtained formulation of curcumin could reach the colon efficiently and release the drug immediately.[61]

Self-microemulsifying drug delivery System (SMEDDS) was developed to improve the bioavailability of Probucol. SMEDDS was composed of Probucol, olive oil, Lauroglycol FCC, Cremophor EL, Tween-80, and PEG-40 by simple agitation method. Improved solubility and lymphatic transport of SMEDDS contributed to the enhancement of bioavailability of the drug.[62]

Curcumin loaded SMEDDS using various oils (Isopropyl myristate, Aethylis oleas, and Soybean oil), surfactants (Tween 80, Cremophor EL, Cremophor RH40) and co-surfactants (Ethanol, PEG 400, 1, 2 Propylene Glycol) by agitation method. Curcumin release was complete from SMEDDS within 10 min.[63]

SMEDDS containing Flutamide were reported by simple agitation method. The optimized formulation's study was composed of Capryol PGMC (50%), Cremophore RH 40 (37.5%) and PEG-300 (12.5%). SMEDDS can be explored as a potential drug carrier for dissolution enhancement of Flutamide.[64]

Solid self-microemulsifying drug delivery system (S-SMEDDS) to improve drug dissolution profile of poorly aqueous soluble drug, Ramipril. SMEDDS composed of Ramipril (10 mg), Tween 80(160 mg), Cremophor EL (640 mg) and Capmul MCM (CAP) as oily phase (200 mg).proved an effective oral solid dosage form with improved dissolution profile of poorly aqueous soluble drug.[65]

SMEDDS of Rapamycin were prepared with different co-solvents including PEG 400/ethanol (F1), glycerol/ethanol (F2), propylene glycol (F3), glycerol (F4), Transcutol P (F5) by simple agitation method. The study highlighted the importance of co-solvents on the stability and bioavailability of rapamycin formulated in SMEDDS. The results demonstrated that co-solvent can effectively improve the absorption rate and extent of drug from SMEDDS formulations and illustrate the potential use of SMEDDS for the delivery of rapamycin by the oral route.[66]

SMEDDS of Atorvastatin were reported by simple agitation method. The optimized formulation composed of sunflower oil and surfactants Cremophore 40 and capmul MCM C8. SMEDDS can be used as a possible alternative to conventional oral formulation of Atorvastatin based on the results of dissolution enhancement of drug by SMEDDS.[67]

Solid -SMEDDS of candesartan cilexetil in various non aqueous excipients like oils (Miglyol 812), surfactant (Tween 80, Cremophor EL), co-surfactant (Labrasol, Transcutol) were developed and characterized. The Optimized liquid SMEDDS formulation was converted into free flowing powder by adsorbing onto solid carriers (Microcrystalline cellulose and colloidal silicon dioxide) for encapsulation. The rate and extent of drug dissolution for solid intermediates was significantly higher than commercial tablet formulation.[68]

Domperidone SMEDDS for improving the oral bioavailability were developed with oleic acid, Tween 80 and PEG 400 by simple agitation method with surfactant co-surfactant ratio (3:1). And SMEDDS proved as promising carriers to improve the solubility and dissolution rate of domperidone.[69]

Valsartan bioavailability was improved by developing SMEDDS. The valsartan SMEDDS was prepared by simple agitation method using Capmul MCM (oil), Tween 80(surfactant), and polyethylene glycol 400 (cosurfactants). The optimized SMEDDS showed improved *in vitro* release which is increased more than 90% when compared with marketed formulation and drug suspension.[70]

Stable self-microemulsifying drug delivery system (SMEDDS) of Valproic acid (VPA) were prepared and evaluated for *in vitro* release. The optimized formulation used for *in vitro* dissolution was composed of castor oil (38.4 %), Cremophor RH 40 (42.4 %), PEG 400 (14.4 %) and was prepared by simple agitation method. SMEDDS proved as commercially feasible alternative to currently marketed sodium valproate.[71]

Lovastatin SMEDDS formulations were prepared in sunflower oil (oil), Acrysol K140 (surfactant), Capmul MCM C8 (co-surfactant) and PEG400 (co-solvent) by simple mixing at 40˚C. Lovastatin SMEDDS provide excellent drug solubilization, drug stability in water and 0.1 N HCl and improved *in vitro* release of lovastatin compare to marketed product.[72]

SMEDDS of Exemestane using various oils (Castor oil, Capryol 90), surfactant (Cremophor ELP, Labrasol,) and Co-surfactant (Lauroglycol FCC, Transcutol P) were developed and characterized. Liquid SMEDDS converted into solid SMEDDS by using adsorbent carriers. The optimized formulation of Exemstane SMEDDS consisted of Capryol 90, Cremophor ELP; Transcutol P had sufficient drug loading, rapid self-emulsification in aqueous media and produce small droplet size in the range of microemulsion. *In vitro* release of drug from solid SMEDDS capsules was significantly higher than the conventional marketed formulation and the relative bioavailability was enhanced by 287.32% .[73]

SMEDDS of antidiabetic agent Glyburide were formulated and evaluated for improving drug

delivery. The solubility of Glyburide in oil (Capryol 90), Surfactant (Tween 20) and Co-Surfactant (Transcutol P) was evaluated to identify the components of microemulsion. The area of microemulsion existence increased with the increase in the Co-surfactant (Transcutol P) concentration .The Glyburide microemulsion exhibited globule size 133.5nm and polydispersity index of 0.94.[74]

Nobiletin self-microemulsifying drug delivery systems (SMEDDS) were formulated and investigate its intestinal transport behaviour using the single-pass intestinal perfusion (SPIP) method in rat. A mixture of the surfactants, co-surfactant and oils were prepared at a fixed ratio of 7:2:1 (g/g). Polyoxyethylene 35 castor oil and polysorbate 80 were used as the surfactants because of the higher solubility of Nobiletin in polyoxyethylene 35 castor oil and polysorbate 80 observed. Caprylic/capric triglyceride (GTCC), medium-chain triglyceride, was selected as the oil phase for formulation development because it provided higher solubility than other oils and might influence the tight junctions of the epithelial cells. This study concluded that the Nobiletin SMEDDS and its dilutions were more stable than the Nobiletin micelles.[75]

Self-microemulsifying drug delivery systems (SMEDDS) were reported for Tacrolimus (FK 506) (an immunosuppressant with low and erratic bioavailability). Capmul MCM as oily phase and Cremophore -EL+ Carbitol as surfactant and co-surfactant was used as lipophilic carriers. FK 506 SMEDDS exhibited significantly higher immunosuppressant activity in mice as compared to Pangraf capsules.[76]

Stable self-microemulsifying drug delivery systems (SMEDDS) were prepared for poorly soluble drug, Silymarin. Silymarin SMEDDS containing a mixed oil phase (Ethyl oleate/MCT, 1: 1, w/w) of 40%, Cremophor EL of 45% and Transcutol P of 15% were evaluated for drug solubility in various solvents and a detailed study of pseudo ternary phase behaviour.[77]

SNEDDS as carriers

Self-Nanoemulsifying drug delivery systems (SNEDDS) of ezetimibe was formulated using long chain triglycerides (LCT's) and medium chain triglycerides (MCT's) in which Maisine 35-1 and Capryol 90 used as lipids, and Labrasol and Tween 80 as emulgents. The nano meter size range and high negative values of zeta potential depicted non-coalescent nature of the optimized SNEDDS. Thermodynamic studies, cloud point determination and accelerated stability studies ascertained the stability of optimized formulations. In situ perfusion (SPIP) studies in rats construed remarkable enhancement in the absorptivity and permeability parameters of SNEDDS as compared to the conventional marketed product. In vivo pharmacodynamic studies in SD rats indicated significantly superior modification in plasma lipid levels of optimized SNEDDS over

marketed product, inclusion complex and pure drug.[78]

Irbesartan (IRB) incorporated self-nanoemulsifying drug delivery carriers were developed. The optimized SNEDDS formulation containing IRB (75mg), cremophor EL (43.33%), Carbitol (21.67%) and capryol 90(32%) exhibited complete *in vitro* release in 15min as compared with plain drug, which had limited dissolution rate.[79]

Self- nano emulsifying drug delivery system (SNEDDS) of poorly water soluble Telmisartan (TEL) were developed containing TEL (20mg), Tween 20(43.33%w/w), Carbitol (21.67%w/w) and acrysol EL135(32%w/w) by simple agitation method. The optimized SNEDDS formulation of TEL showed significant increase in dissolution rate and oral absorption compared to the aqueous drug suspension.[80]

Cinnarizine loaded self-nanoemulsifying drug delivery system using Oleic acid as oil, Tween 80 as surfactant and Capmul MCM C-8 as co-surfactant by gentle stirring. The SNEDDS exhibited good efficiency for self-emulsification. The in vitro dissolution profile was studied in 0.1 N HCl and phosphate buffer (pH 6.8). SNEDDS with surfactant: cosurfactant ratio (2:1) and oil ratio (6:1) showed the highest drug release.[81]

Self- nanoemulsifying drug delivery systems (SNEDDS) for the delivery of indomethacin based on either melon oil alone, or its admixture with cow fat by utilizing varying ratios of oil, surfactant (Tween 65 and Tween 80) and co-surfactants (span 65) with or without carbosil, a glidant by simple agitation method. SNEDDS of Indomethacin not only preserved the activity of the drug, but also maintained its anti-inflammatory activity at a level comparable to that of indomethacin injection.[82]

SNEDDS and SMEDDS incorporating Carbamazepine have been developed. SNEDDS showed faster absorption into the systemic circulation than SMEDDS, conventional tablet and suspension formulation indicating less retention time of CBZ in the GIT thereby enhancing solubility and minimizing erratic absorption.[83]

Olanzapine loaded self- nanoemulsifying drug delivery system has been prepared and evaluated using various oils, surfactants and co-surfactants by simple mixing method. [84]

RECENT PATENTS:

Panayiotis P. Constantinides Gurnee, IL (US) published a patent (US006479540B1, NOV 12, 2002) entitled as compositions of Tocol soluble therapeutics. The patent describes tocol based compositions of charged amphillic and water soluble pharmaceutically active compounds which are useful as ion-pair forming compounds.[85]

Dong Won Lee,Seoul (KR) published a patent(US2004/0248901A1, DEC 9,2004) entitled as compositions containing itraconazole which is a sparingly soluble drug, fatty acid or fatty alcohol and surfactant and their preparation methods.[86]

Jean Sebastien Garrigue (FR) published a patent (US2005/0232952A, OCT 20, 2005) entitled as Self emulsifying drug delivery system for poorly soluble drugs. The present invention includes pharmaceutical composition comprising one or more theraupeutic agent which have low solubility in water or are water insoluble, vitamin E, PEG and ethanol, TPGS and hydrogenated castor oil.[87]

Groves, Michael J. (Deerfield, IL) published a patent (US006960563, NOV 1, 2005) entitled Spontaneous emulsions containing cyclosporine. The invention relates to pharmaceutical compositions containing cyclosporine as the active ingredient. More specifically, the invention relates to orally administered pharmaceutical compositions in the form of a spontaneous emulsion comprising cyclosporine.[88]

Jinglin, Victoria (AU) published a patent (US2006/O275358A1, DEC 7, 2006) entitled Self microemulsifying dosage forms of low solubility active ingredients such as coenzyme Q10. The present invention includes a self microemulsifying mixture that comprises a combination of a hydrophillic surfactant and a lipophillic cosurfactant.[89]

Diana Shu-Lian Chow (Houston, TX, US) Pranav Gupta (Short Hills, NJ, US) Yulan Qi (Houston, TX, US) Dong Liang (Pearland, TX, US) published a patent (US20090048322, 19 JAN, 2009) entitled Parenteral and oral formulations of benzimidazoles. The Present invention comprises a benzimidazole derivative (mebendazole), oil, surfactant, co-surfactant and a dipolar aprotic solvent in a microemulsion formulation. Also provided are methods for improving the bioavailability of a benzimidazoles derivative during treatment of a pathophysiological condition by using a formulation combining a particular emulsion droplet diameter and ratio of the surfactant: cosurfactant.[90]

Girish Kumar Jain, Delhi (IN), Munish Talwar, Haryana (IN) published a patent (US2010/O303902A1, DEC 2, 2010) entitled Self emulsifying pharmaceutical compositions of Rhein or Diacerin. The invention relates to self emulsifying drug delivery system based compositions of Rhein or Diacerin or salts or Prodrugs which are bioequivalent to 50 mg Diacerin. [91]

Christina Holmberg published a patent (USOO7815933132, OCT 19, 2010) entitled Self emulsifying drug delivery system. The present invention include pharmaceutical composition comprising one or more NSAIDS,surfactants of which atleast one is phospholipid forming oil in

water emulsions upon contact with GI fluids.[92]

Sure Chem published a patent (US20101362, JAN 12, 2010) entitled. self-microemulsifying mitotane composition. The invention provides a mitotane oily formulation which comprises mitotane in a matrix comprising propylene glycol monocaprylate; from 10 to 30% of the total weight of the mitotane oily formulation (w/w)propylene glycol di-caprate; from 20 to 60% of the total weight of the mitotane oily formulation(w/w) & polyoxyethylene sorbitan from 10 to 30% of the total weight of the mitotane oily formulation (w/w).[93]

Table 2: List of marketed products based on self-emulsifying drug delivery systems

Generic name	brand name	Dosage form	Lipidic components
Amprenavir	Agenerase/GlaxoSmithKline	SG capsule	D-alpha TPGS
Bexarotene	Targretin/Ligand	SG capsule	Polysorbate 80
Calcitriol	Rocaltrol/Roche	SGcapsule,solution	Fractionated medium chain TG of coconut oil and palm seed oil
Carvedilol Phosphate	CoregCR/GlaxoSmithKline	CR HG capsule	Hydrogenated castor oil, Hydrogenated vegetable oil
Ciprofloxacin	Cipro/Bayer	Microcapsules for suspension	Medium-chain TG
Cyclosporin A	Neoral/Novartis	SG capsules,Oral suspensions	dl-alpha tocopherol,corn oil-mono-dl-TG,CremophorRH 40
Dronabiol	Marino/roxane and Unimed	SG capsule	Sesame oil
Dutasteride	Avodart/GSK	SG capsule	Mixture of mono-and diglycerides of caprylic/capric acid
Fenofibrate	Lipofen/Kowa pharmaceuticals America.Inc	HG capsule	Gelucire44/14
Isotretinoin	Accutane/Roche	SG capsule	Bees wax, Hydrogenated oil flaxes, Hydrogenated vegetable oils, soyabean oil
Lopinavir and Ritonavir	Kaletra/Abbott	Tablet, SG capsule	Span 20
Mesalamine	Pentasa/ShireUS inc.	CR capsules	Acetylated monoglyceride, castor oil
Omega-3-acid esters	Lovaza/GSK	HG capsule	Alpha-tocopherol
Paricalcitol	Zemplar/Abbott	SG capsule	Fractionated medium chainTG of coconut oil or palm Kernel oil
Saquinavir	Fortovase/Roche	SG capsule	Medium-chain mono- and diglycerides,dl-alpha tocopherol
Sirolimus	Rapamune/Wyeth-Ayerst	Oral solution	Phosal 50, PG, Polysorbate 80
Tipranavir	Aptivus/boehringer/Ingelheim	SG Capsule	Cremophor EL, Medieum-chain mono-and diglycerides
Tolterodine tartrate	DetrolLA/Pharmacia	ER HG capsule	Medium-chain triglycerides, oleic acid
Tretinon	Vesaniod/Roche	SG capsule	Bees wax

Kanchan Kohli, New Delhi (IN), Sunny Chopra,Chandigarh(IN) published a patent(US2011/0294900A1, DEC 1,2011) entitled Self emulsifying drug delivery system for a curcuminoid based composition. The present invention comprises of a pharmaceutically effective amount of curcuminoid, an oil phase, a surfactant and a co-surfactant.The pharmaceutical composition shows an enhanced drug loading capacity, better stability and improved bioavailaibility.[94]

CONCLUSION

SMEDDS are promising approach for the formulation of drugs with poor aqueous solubility. In future sight, novel development technology will enable SMEDDS to solve more problems with other routes of administration along with oral route. This study explores the possibilities of loading a wide variety of hydrophobic drugs and plant actives as their scale up is as well as economical too. Thus this field requires further exploration and research to bring out a wide range of commercially available self emulsifying formulations

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