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Review Article

A VIEW ON "ADVANCED SELF EMULSIFYING LIPID FORMULATIONS (SELFs)" IN ENHANCING THE AQUEOUS SOLUBILITY OF HYDROPHOBIC DRUGS

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ABSTRACT

It has been estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble and not well absorbed after oral administration which can distract from the drugs inherent efficacy. Various techniques have been developed for the improvement of solubility of poorly aqueous soluble drugs. Recently, self emulsifying lipid formulations (SELFs) are considered a relatively newer strategy. SELFs is a drug delivery system that uses micro emulsion achieved by chemical rather than mechanical means. SELFs consist of lipids, surfactants, co solvents. The unique properties of lipids and their proven ability to formulate poorly-water soluble molecules may have a remarkable impact on enhancing bioavailability of drugs eliminating food effects, allowing for dose escalation and thereby improving efficacy and safety. This article focused on the advanced formulations of SELFs with recent literature reports and some patented formulations have also been highlighted.

Key words: Micro emulsion, Self emulsifying lipid formulations, advanced formulations of SELFs, enhanced bioavailability.

INTRODUCTION: The lipid based formulation approach is considered a relatively newer strategy for enhancing the solubility of poorly water soluble drugs. The value, utility and commercial viability of this approach for compounds with a low aqueous solubility has been demonstrated in recent years.

Lipid-based drug delivery systems (LBDDS) cover a wide array of formulation types, which include lipid solution, suspensions, emulsions, dry emulsions, micro emulsions, mixed micelles, Self Emulsifying Lipid Formulations (SELFs), thixotropic vehicles, thermo softening matrices and liposomes.[1]

Classification of Lipid Formulations: A particular classification system has been established called as 'lipid formulation classification system' to get a clear picture of all the lipid based formulations[2] and to understand the fate of different lipid formulation *in vivo*. According to the composition and the effect of dilution and digestion on the ability to prevent precipitation of drug, lipid based formulations are classified into four groups.[3]

Table.1.LFCS: characteristic features, pros and cons of the four essential types of lipid formulations.[4]

Formulation	Excipients	Properties	Pros	Cons
Type I	Oils without surfactants (e.g. tri-, di- and monoglycerides)	Nondispersing, requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 μm)
Type III	Oils, surfactants cosolvents (both water insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IV	Water-soluble surfactants and co solvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; might not be digestible

Type III formulations consists of SELFs (SEDDS and SMEDDS). SELF-systems act as carriers for drugs by forming fine emulsions, or micro-emulsions, under gentle stirring when diluted in water or physiological media with physiological motion. Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption.[5] It is classified as SEDDS, SMEDDS and

SNEDDS based upon emulsion particle size and the composition of the system.[6]

Table.2. Characteristics Features of SEDDS and SMEDDS [5, 7, 8]

Parameter	SEDDS	SMEDDS
Formulation aspect	Can be a simple binary formulation with drug and lipidic excipient or surfactant to self emulsify in contact with GI fluids.	Composed of drug, surfactant, co-surfactant and oil.
Appearance	Translucent	Transparent
Type of emulsion formed	Forms milky emulsion upon dispersion with water	Forms micro-emulsion upon dispersion with water
Droplet size	100-300 nm	<50 nm
Concentration of oil used	30-80 %	< 20%
Concentration of surfactant used	Low	High (40-60%)
Surfactants of HLB used	< 12	>12
Thermodynamic stability	Not stable in water or physiological conditions	Thermodynamically stable in water and physiological conditions.
For development or optimization	SEDDS requires ternary phase diagrams	SMEDDS requires pseudo-ternary phase diagrams.

Need of SELFs: Poorly soluble drugs can be formulated in a solid solution using a water soluble polymer like PEG 6000 and PVP to aid solubility of the drug. But the problem with this formulation is that drug may favor a more thermodynamically stable state, which can result in the drug crystallizing in the polymer matrix. In this case, SELFs can be advantageous.[6] for oral delivery, class 2 and class 3 drugs are pre-dissolved in a suitable solvent to overcome the initial rate limiting step of particulate dissolution in the aqueous environment within the GIT. But the problem is drug may precipitate in the solution when formulation disperses in the GIT, particularly when hydrophilic solvent like PEG is used. In this case, SMEDDS can be a good approach as the drug is dissolved in the lipid vehicle, so there will be less potential for drug precipitation on dilution in the GIT, because partitioning kinetics will favor the drug remaining in the lipid droplets.[9] Micro emulsion helps in the improvement of bioavailability, protection against enzymatic hydrolysis and decrease toxicity. But the only problem with micro emulsion is poor palatability and moreover due to their water content, micro emulsions cannot be encapsulated in soft and hard gelatin capsules. Hence there is a need for drug delivery of hydrophobic drug

that is Self-micro emulsifying Drug delivery system (SMEDDS).[8]

Benefits of SELFs: [6,10,8]

- It acts as substitute for traditional oral formulations of lipophilic drugs.
- The formulation has low viscosity.
- It enhances the dissolution rate and hence, bioavailability of hydrophobic drugs enabling reduction in dose, e.g., Ketoprofen
- It provides better consistent temporal profiles of drug absorption.
- It helps in selective drug targeting toward a specific site in the GI tract.
- It protects drug molecule from the hostile environment of GIT.
- It reduces inter-subject and intra-subject variability and food effects e.g., cyclosporine
- Possess great ability as drug delivery vehicles.
- High drug payloads
- They are comprised of aqueous and oily components and therefore can accommodate both hydrophilic as well as lipophilic drugs.
- It can be formulated in both liquid and solid dosage forms. E.g., Progesterone
- Ease of manufacture and scale-up, does not require much energy and the use of special equipments;

Table.3.Application of SELFs in various BCS category of drugs[11]

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by SELFs
I	High	High	Enzymatic degradation, Gut wall efflux
II	Low	High	Solubilization, Bioavailability
III	High	Low	Enzymatic degradation, Gut wall efflux, Bioavailability
IV	Low	Low	Solubilization, Enzymatic degradation, Gut wall efflux, Bioavailability

Properties of Drug Suitable for Loading in SELFs: [3,10]

- Active pharmaceutical agent should be soluble in oil phase as this influence the ability of SELFs to maintain the API in solubilised form.
- Ideal log p value of drug candidate suitable for SELFs should be above 2 (log p>2).
- The active pharmaceutical agent should have low melting point.
- Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SELFs, preferably oil phase.
- Lipid based formulations offer a potential platform for improving oral bioavailability of drugs especially those belonging to BCS class II and class IV .
- Drugs with high melting point and low log P value are not suitable for this formulation.[18,23]

ROLE OF SELFs IN DRUG DELIVERY

Postolache *et al.* (2002) compared the bioavailability of two cyclosporine capsule products with different pharmaceutical formulations. Results showed that the test cyclosporine non-SMEDDS formulation was not bioequivalent to the cyclosporine SMEDDS formulation due to a statistically significantly lower absorption rate. These authors demonstrated that the non-self micro emulsifying capsules are not totally interchangeable with the self micro emulsifying capsules unless validated clinical and laboratory conversion protocols for each kind of organ transplantation are enforced.[12]

Advanced formulations of SELFs:

Once the formulator succeeds in addressing the challenges of drug solubility and absorption, the next major challenge they face is the delivery of drug in an acceptable dosage form. It is an undisputed fact that oral dosage forms are the most preferred. Further, lipid formulations offer versatility for oral dosage forms, as these can be formulated into various formulations such as solutions, semi-solids and solid forms.[1]

Super saturable SELFs: Super saturation represents a potent technique for enhancing absorption by generating and maintaining a supersaturated state of drug in the intestine.[1] Surpersaturation is intended to increase the thermodynamic activity of the drug beyond its solubility limit and, therefore, resulting in an increased driving force for transit into and across the biological barrier.[3] Super saturable SELFs are SELFs having reduced amount of surfactant and a crystal growth inhibitor such as HPMC which prolongs the supersaturated state of drugs in GIT.[1] This is due to the formation of widely spaced cellulosic-polymer network that is formed by the HPMC chains in water. This HPMC chain will

inhibit nucleation as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei, or onto the surface of crystals. SS-SELFs have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs.[11] Recently, Gao *et al.* (2008) investigated the mechanism responsible for the enhanced intestinal absorption of hydrophobic drugs from supersaturable SEDDS containing HPMC is due to enhanced permeation of drug to the enterocyte brush border region through the aqueous pathway by mimicking, or equilibrating with, the bile acid /bile acid mixed micelle pathway.[13] As the literature suggested, directly supersaturating a system with a drug during manufacture adds to the risk of recrystallization of the product. Various ways of inhibiting recrystallization have been identified. Thermodynamic "freezing" inside a polymer is one such option. Under storage conditions, the drug is mobilized by thermodynamic changes in the polymeric structure. To avoid risk of direct super saturation, several strategies can be employed, for example: • Evaporation of a solvent from the system, Activation of thermodynamically "frozen" drug-supersaturated islands by hydration.[1]

Solid SELFs: Traditionally, lipid-based formulations are prepared as liquids and administered orally in either soft or hard gelatin capsules which possess several limitations. These include drug incompatibility, instability, drug leakage, precipitation and capsule ageing. An alternative method is Solid-SELFs , which is prepared by solidification of liquid self-emulsifying (SE) components into powder form which can then be used for formulating tablets, capsules, etc.[14,15] Solid SELFs means solid dosage forms with self emulsification properties. This approach focus on the incorporation of liquid/semi liquid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion and nanoparticle technology). They combine the advantages of SELFs (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance).[16]

Table.4.Solidification techniques for transforming liquid/semisolid SELFs to S- SELFs [10, 16, 17]

Technique	Description	Benefits
Capsule filling with liquid and semisolid self-emulsifying formulations	Liquids and semisolid self emulsifying systems are filled into the capsules	simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading potential (up to 50% (w/w)).
Spray drying	Spray drying of mixture containing lipids, surfactants, drug, solid carriers in drying chamber forming dry powders.	Simple
Spray Cooling	The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder.	Simple
Direct adsorption onto solid carrier	Liquid SEDDS adsorbed onto solid carrier by mixing liquid formulation with carriers.yhe resulting powder is filled into capsules or compressed	high levels (up to 70% (w/w)) of drug can be adsorbed onto suitable inert adsorbent carriers and provide good content uniformity.
Melt granulation	A binder is added that melts or softens at relatively low temperatures to form powder agglomeration	offers several advantages compared with conventional wet granulation, liquid addition and the subsequent drying phase are omitted. It is a good alternative to the use of solvent.
Melt extrusion/extrusion spheronization	Raw materials with plastic properties are forced through a die under controlled temperature, product flow and pressure conditions to form a product of uniform shape and density	It's a solvent-free process, allows high drug loading (60%), as well as content uniformity.

DOSAGE FORM DEVELOPMENT OF S-SELFs:

Dryemulsions: Dry emulsions are powders from which emulsion spontaneously occurs in-vivo or when exposed to an aqueous solution. Dry emulsion formulations are typically prepared from oil/water emulsions containing a solid carrier(lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation,

freeze-drying or spray drying. Myers and Shively obtained solid state glass emulsions in the form of dry foam by rotary evaporation with heavy mineral oil and sucrose. Here surfactant is not required. Enteric coated dry emulsion formulation has been developed for delivery of peptide and protein drugs. These formulations consisted of surfactant, vegetable oil and pH responsive polymer.[17]

Self-emulsifying tablets (SE tablets): Incorporation of lipid formulation into a solid dosage form combines the advantages of lipid-based drug delivery systems with those of solid dosage forms. Nazzal and Khan (2006), evaluated the effect of some parameters (colloidal silicates-X_1, magnesium stearate mixing time X_2, and compression force X_3) on coenzyme Q $_{10}$ (CoQ $_{10}$) dissolution from tablets of eutectic-based SMEFs. The optimized conditions (X_1 = 1.06%, X_2 = 2 min, X_3 = 1670 kg) were achieved by a face centred cubic design.[18] In order to significantly reduce the amount of solidifying excipients required for transformation of SEFs into solid dosage forms, gelled SEFs have been developed by Patil et al.,2004 In this study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems. Colloidal silicon dioxide served a dual purpose: (i) - reducing the amount of solidifying excipients required; and (ii) aiding in reducing drug release.[19]

Self-emulsifying pellets (SE pellets): Oral pellets are known to overcome the poor and variable GIT absorption of drugs and have shown the ability to reduce or eliminate the influence of food on bioavailability. Thus, it appears highly appealing to combine the advantages of pellets with those of SELFs by formulating SE pellets.[1]

Self- emulsifying sustained/controlled-release pellets: Formulation of SE controlled-release pellets by incorporating drugs into SELFs that enhanced their rate of release and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release are also very useful. Serratoni et al. have been developing 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.[15] Iosio et al. (2008) prepared two types of pellets containing vinpocetine (model insoluble drug) where Type I pellets contained a self-emulsifying system internally and an inert matrix externally, whereas Type II contained an inert matrix internally and a self-emulsifying system externally. Results indicated that Type I pellets released 90% of vinpocetine within 30 min while the same quantity was released within 20 min from Type II pellets. Type II pellets showed better drug solubility and *in vivo* bioavailability. The above investigations suggest that a solid dosage form containing a self-emulsifying system is

a promising approach for the formulation of drug compounds with poor aqueous solubility.[20]

Self-emulsifying powder formulation (SE powder formulation): Balakrishnan et al. (2009) developed a novel solid SEF of dexibuprofen using spray drying. Aerosil 200 was used as an inert solid carrier. Both i*n-vitro and in-vivo* studies were carried out. The study showed that optimized formulation comprising Labrafil M 1944 CS, Labrafil M 2125, Labrasol, Capryol 90 and Lauroglycol FCC could enhance the solubility of CoQ $_{10}$ and provide the desired drug loading.[21]

Self-emulsifying beads (SE beads): Self-emulsifying beads can be formulated as a solid dosage form using smaller amounts of different excipients. Patil and Paradkar formulated an isotropic formulation of loratadine consisting of Captex 200, Cremophore EL and Capmul MCM. The SE mixture was loaded onto poly propylene beads (PPB) using the solvent evaporation method. Formulations were optimized for loading efficiency and in vitro drug release by evaluating their geometrical features such as bead size and pore architecture. Results indicated that the poly propylene beads are potential carriers for solidification of SE mixture, with sufficiently high SE mixture to PPB ratios for the solid form. The results indicated that self-emulsifying beads can be formulated as a solid dosage form with a minimal amount of solidifying agents.[22]

Self-emulsifying sustained-release microspheres: You et al. (2006) prepared solid SE sustained-release microspheres of zedoary turmeric oil (oil phase) using the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The plasma concentration time profiles after oral administration in rabbits showed a bioavailability of 135.6% compared with the conventional liquid SEFs.[23]

Self-emulsifying implants (SE implants): Research into SE implants has greatly increased the use and application of S-SELFs. Carmustine (BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness is hindered by its short half life. In order to enhance its stability, the SELF of carmustine was formulated using tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). The self-emulsified BCNU was fabricated into wafers with a flat and smooth surface by compression moulding. The release profile was compared with a wafer implant fabricated using poly (d, l-lactide-co-glycolide) acetic acid. It was found that SELF increased the in vitro half-life of BCNU to 130 min compared with 45 min with intact BCNU. The in vitro release of BCNU from self-emulsifying PLGA wafers

was prolonged up to 7 days and was found to have higher in vitro anti-tumor activity.[24]

Self nanoemulsifying formulations (SNEFs): The classical lipid nanoparticles that have been proposed for drug delivery are composed of solid lipids. A distinct advantage of SNEFs over polymeric nanoparticles is that the lipid matrix is made from physiologically tolerated lipid components, which decreases potential acute and chronic toxicity.[1] Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%. These were proposed as good alternatives to liposomal preparations which pose problems in stability, sterilization, and non-reproducibility between batches. Koynova et al. (2010) suggested the use of nanosized self-emulsifying lipid vesicles as carriers for the inclusion of lipophilic dietary supplements.[25]

Self emulsifying suppositories: Kim and Ku (2000) investigated the Solid-SEDDS could increase not only GI absorption but also rectal/vaginal absorption. 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.[8, 26]

Positively Charged SEDDS: Many physiological studies have proved that the absorptive cells, as well as that of all other cells in the body, are negatively charged with respect to the mucosal solution in the lumen. A novel SEDDS containing progesterone, which results in positively charged dispersed oil droplets upon dilution with an aqueous phase, showed an increased oral bioavailability in young female rats. More recently, it has been shown that the enhanced electrostatic interactions of positively charged droplets with the mucosal surface of the everted rat intestine are mainly responsible for the preferential uptake of the model drug cyclosporine A (CsA) from positively charged droplets.[5, 27]

Table.5. Literature reports on various SELFs

Type of delivery system	Model drug	Optimized formula	Results
SEDDS	Nevirapine	8.56% of Caprylic acid oil, 74.50% of surfactant Soluphor P and 16.93% of co-surfactant Transcutol P	In vitro diffusion study showed 99.18 ± 2.85% release of nevirapine from SEDDS as compared to 65.14 ± 2.98% from the marketed suspension, approximately in 5 hours. The *ex vivo* intestinal permeability of nevirapine was 69 ± 4.58% and 57 ± 6.77%, respectively from SEDDS and marketed suspension.[28]
SMEDDS	Valsartan	Capmul MCM (oil), Tween 80 (surfactant), and polyethylene glycol 400 (co surfactant	The area under curve and time for SMEDDS were 607 ng h/mL and 1 h in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase ($p < 0.01$) in oral bioavailability of Valsartan SMEDDS.[29]
SNEDDS	Gemfibrozil	Box–Behnken experimental design was employed as statistical tool to optimize the formulation variables, X_1=32.43%, (Cremophor® EL), X_2=29.73 % (Capmul® MCM-C8), and X3=21.62%, (lemon essential oil) and (16.22% of gemfibrozil).	Optimized SNEDDS formulation of gemfibrozil showed a significant increase in dissolution rate compared to conventional tablets.[30]
Gelled SEDDS	Ketoprofen	Captex 200, Tween 80, Capmul MCM	Silicon dioxide was used for gelling agent. As the concentration of silicon dioxide increases, it causes increase in the droplet size of emulsion and slows the drug diffusion.[19]
solid-SNEDDS	Adefovir dipivoxil (ADV)	D-mannitol as cryoprotectant.	Thus, SNEDDS were found to be instrumental in reducing the effect of pH variability of ADV and improving the release performance of ADV, indicating their potential to improve the oral bioavailability and thus the therapeutic efficacy of ADV.[31]
super-saturable	Halofantrine	either medium chain lipids	two capsules of conventional

SS-SNEDDS		(Captex 300/Capmul MCM) or long chain lipids (soybean oil/Maisine), Cremophor RH40 maintaining the lipid-to-surfactant-to-co solvent ratio constant (55:35:10, w/w %). and ethanol were formulated which can be the driving force for enhanced absorption.	SNEDDS were needed to achieve similar AUC and C_{max} as obtained after dosing of a single capsule of SS-SNEDDS. SS-SNEDDS lead to precipitation of halofantrine in an amorphous form, which can be the driving force for enhanced absorption.[32]
SE pellets	nitrendipine	adsorbents (porous silicon dioxide), MCC and lactose to form fine flowable powder. Crospovidone	The AUC of nitrendipine from the SE pellets was two-fold greater than the conventional tablets and was comparable with the liquid SEFs.[33]
SE powder	Griseofulvin.	Capmul GMO-50, poloxamer and myvacet were used as surfactants and co-surfactants.	A significant enhancement in dissolution (without ultra-micronisation) and bioavailability of Griseofulvin was observed.[34]
Self-nanoemulsifying Tablets	Carvedilol	HCO-40, Transcutol® HP, and medium-chain triglyceride (Migliol® 812) granulated silicon dioxide	Prepared self-nanoemulsifying tablet produced acceptable properties of immediate-release dosage forms and expected to increase the bioavailability of carvedilol.[35]

In addition to the methods for advanced development of SEDDS, SMEDDS, SNEDDS mentioned above, another very important factor to examine is the digestibility of SELFs containing digestible excipients in the gastrointestinal tract. When excipients in SELFs are digested the solubilisation capacity may be compromised, leading to precipitation of drug, which can have implications for the bioavailability. The digestibility of SMEDDS can be assessed by the use of in-vitro lipolysis models.[36,37,38] Basically two different in-vitro lipolysis models have been described: a model where calcium chloride (Ca^{2+}) is added at the initiation of the lipolysis[36] and a model where Ca^{2+} is added continuously during the lipolysis[37,38] (the dynamic lipolysis model). However, other differences also apply between the two different models.

There are In Vitro and In Vivo Models to study these formulations include- Caco-2 cell monolayer (human, intestinal), Anaesthetized rat model, Genetically Modified Models and so on. Flemming et al., were successful in predicting the In vitro–in vivo correlations of self-emulsifying drug delivery systems of probucol combining the dynamic lipolysis model and neuro-fuzzy networks.[39]

Some technologies developed for SELFs: PORT (Programmable Oral Release Technology) Systems formulate poorly soluble drugs as preconcentrates (concentrates) that will form microemulsion in vivo leading to enhanced bioavailability of such drugs. IDD-SE® technology constitutes a SEDDS where surface stabilized sub micron sized particles or droplets are self generated when the dosage form is exposed to the aqueous environment of the GIT. Macromed developed a system for oral application ReSolv™, which will spontaneously emulsify in situ. Alpha Rx uses its proprietary BCD (Bioadhesive Colloidal Dispersion) drug delivery technology for the development of novel drug formulations for insoluble or poorly aqueous soluble drugs. BCD drug delivery technology consists of two different approaches 1. CLD (Colloidal Lipid Dispersion System) for transdermal drug delivery and 2. SECRET (Self Emulsifying Controlled Release Tablet System) for oral drug delivery.

SELFs can be delivered by different routes such as:[7,40]

1. **Oral delivery:** Three major factors solubility, dissolution and intestinal permeability will affect the oral absorption of drug. SELFs have the potential to enhance the solubilization of poorly water soluble drugs and overcome the dissolution related bioavailability problems.[3]
2. **Parenteral delivery:** Lipophilic and hydrophilic drugs formulation into parenteral dosage form proven difficult. For sparingly soluble drugs where suspension is not desirable, this o/w microemulsions could be beneficial. These systems exhibit high physical stability in plasma than liposomes and other vesicles and the internal oil phase is more resistant to drug leaching. These systems provide high concentrations of drugs and are used for fat soluble vitamins and lipids in parentrals nutrition by IV route.
3. **Topical delivery:** It has been reported that these systems enhanced the transdermal permeation of drugs significantly compared to conventional formulations such as solutions, gels or creams. They are able to incorporate both hydrophilic (S-Fluorouracil, apomorphine Hcl, diphenhydramine Hcl, tetracaine Hcl, etc) and lipophilic drugs (estradiol, fenasteride, Ketoprofen, meloxicam, felodipine, triptolide). But the skin irritation aspect must be considered if used for longer time.
4. **Ophthalmic delivery:** Microemulsions have emerged as a promising dosage form for ocular use than conventional dosage forms such as solutions, suspensions, ointments, etc.
5. **Nasal delivery:** Addition of mucoadhesive polymer to these formulations helps in prolonging the residence time on the mucosa and enhance the uptake across the nasal mucosa.
6. **Periodontal delivery:** Bordin et al. invented a novel composition in the form of microemulsion comprising local anesthetic

with a taste masking agent. This formulation had thermo reversible gelling properties. This novel formulation overcame the problem with the existing topical products(jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste.

7. **Drug targeting:** Submicron size range of these systems confers excellent opportunities to overcome the physiological barriers and enables efficient cellular uptake followed by intracellular internalization.

Table.6.Some patented formulations:[8]

US Patent No.	Inventors	Types	Active ingredient
20110160168	Dhingra 2011	SMEDDS	Testosterone
20100331356	Legen and Igor 2010	SMEDDS	Imwitor 308
7588786	Khan et al 2009	SNEDDS	Co-enzyme Q_{10}
20080319056	Liu et al 2008	SEDDS	Butyl phthalide
20060275358	Lin and Jing 2006	SMEDDS	Co-enzyme Q_{10}
20050032878	Deboek 2005	SEDDS	Fenofibrate
20040248901	Lee and Jin 2004	SMEDDS	Itraconazole
6652863	Benameur et al 2003	SMEDDS	Simvastatin
6436430	Mulye and Nirmal 2002	SEDDS	Cyclosporin
6057289	Mulye and Nirmal 2000	SEDDS	Cyclosporin

Conclusion: A brief discussion of advanced formulations of SELFs have been decsribed in the article. Advanced formulations of SMEDDS, SNEDDS will be a promising drug delivery system for the enhancement of solubility and bioavailaiblity of poorly water soluble drugs and they proved to be advantageous.There is need of proper understanding of developing and manufacturing process regarding physical and chemical stability issue which are challenging. Effective in vitro tests should be utilized which can be predict in vivo performance of this fascinating and diversifying group of formulations and distinguish between various type III formulations, because this group is likely to contain formulations which have very different performance characteristics.

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