In-vivo Self Emulsification: Tools for Bioavailability Enhancement

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Abstract

With the advancements in science and technology, a lot of new drug molecules have been added and are being added to our repertoire of drugs for fighting against diseases and ailments that trouble mankind. Each and every drug molecule is different in respect of their physico-chemical properties, thereby differing in their biotherapeutic effects. Problems like poor solubility and low permeability may render a perfectly effective drug molecule inactive *in vivo* because of low bioavailabilty. Thus the drug molecules which fall under the BCS category of Class II and Class IV represent certain specific problems regarding attainment of therapeutic drug concentrations at the required site and their bioavailability. Various techniques and drug delivery systems are being developed for such drugs. SEDDS or SELF's represent one of such efforts. SEDDS are an isotropic mixture of one or more hydrophilic solvent and co- solvent /surfactants. On mild agitation they form fine oil – in- water (o/w) microemulsion. This present study aims at studying the various formulation, classification, optimization and utilization aspects of these systems.

Keywords: self-emulsifying drug delivery system, Lipid based formulation, Application, Herbal Formulation, Surfactant.

Introduction

Most of the recently developed drugs have low aqueous solubility and fall under either category II or IV of the BCS classification due to which they show poor dissolution and low bioavailability characteristics. This problem can be overcome by formulating self emulsifying formulations like SEDDS. SEDDS are an isotropic mixture of one or more hydrophilic solvent and co- solvent /surfactants. On mild agitation they form fine oil – in- water (o/w) microemulsion. The molecular property of solubility of the given drug in water is of vital importance for successful drug development as it acts as the determining factor for drug accessibility to biological membranes. The importance of solubility in drug disposition is clear from the fact that the major pathway for absorption of drugs which is passive transport of the drug molecule across a biological membrane is dependent on two factors i.e. solubility of the drug molecule along with its permeability [1]. SEDDS are useful in enhancing bioavailability of highly lipophilic compounds by keeping the drug in the dissolved state until it gets absorbed. One of the other major advantages of this system is that it bypasses hepatic first pass effect due to the small globule size of the microemulsion being formed [2].

Mechanism of drug release in SEDDS is interfacial transfer and vehicle degradation. Interfacial transfer mechanisms take place when the drug diffuses from the formulation into the bulk medium or directly over the intestinal membrane.Vehicle degradation involves mainly lipase- catalysed lipolytic degradation of the SEDDS. This system is thermodynamically unstable. By using the oils and surfactants in different ratios and by manipulating the polarity and charge of the dispersed globules behavior of such systems can be modified [3]. While formulating SEDDS, surfactants which are used are generally having higher HLB values (>12) and they are usually selected along with cosurfactants which have moderate HLB value. Drug release from such systems largely depends on the liberation from lipid excipients on self emulsification [4].

Properties of SEDDS[5]

1-) They get emulsified themselves in GI fluid due to peristaltic movement of GI track and form o/w emulsion.

2-) Useful for both hydrophilic and hydrophobic drugs because the drug is incorporated within the oil surfactant mixture.

3-) Required dose of the drugs is lower in comparison of conventional dosage form .

4-) It can be formulated for liquid as well as solid dosage form.

Advantage[5,6,7,8,9]

1-) Protection of drug from GIT environment.

2-) Selective targeting of the drug is possible.

3-) Enhanced oral bioavailability and stability of drugs which show low bioavailability.

4-) Drug administered by using this system show consistent drug absorption profile.

5-) both Liquid and solid type of dosages form can be used in this system .

6-) Sensitive drug can be protected by this system.

7-) Easy to manufacture.

8-) Reduced irritation which occurs due to extended contact between bulk drug substance and gut wall and cause extensive distribution of the drug throughout the GI tract.

9-) Provide large interfacial area for partitioning of drug between oil and water in comparison with oily solution.

10-) Better control over drug plasma concentration profiles.

11-) Physically stable formulation.

Disadvantage of SEDDS-[10]

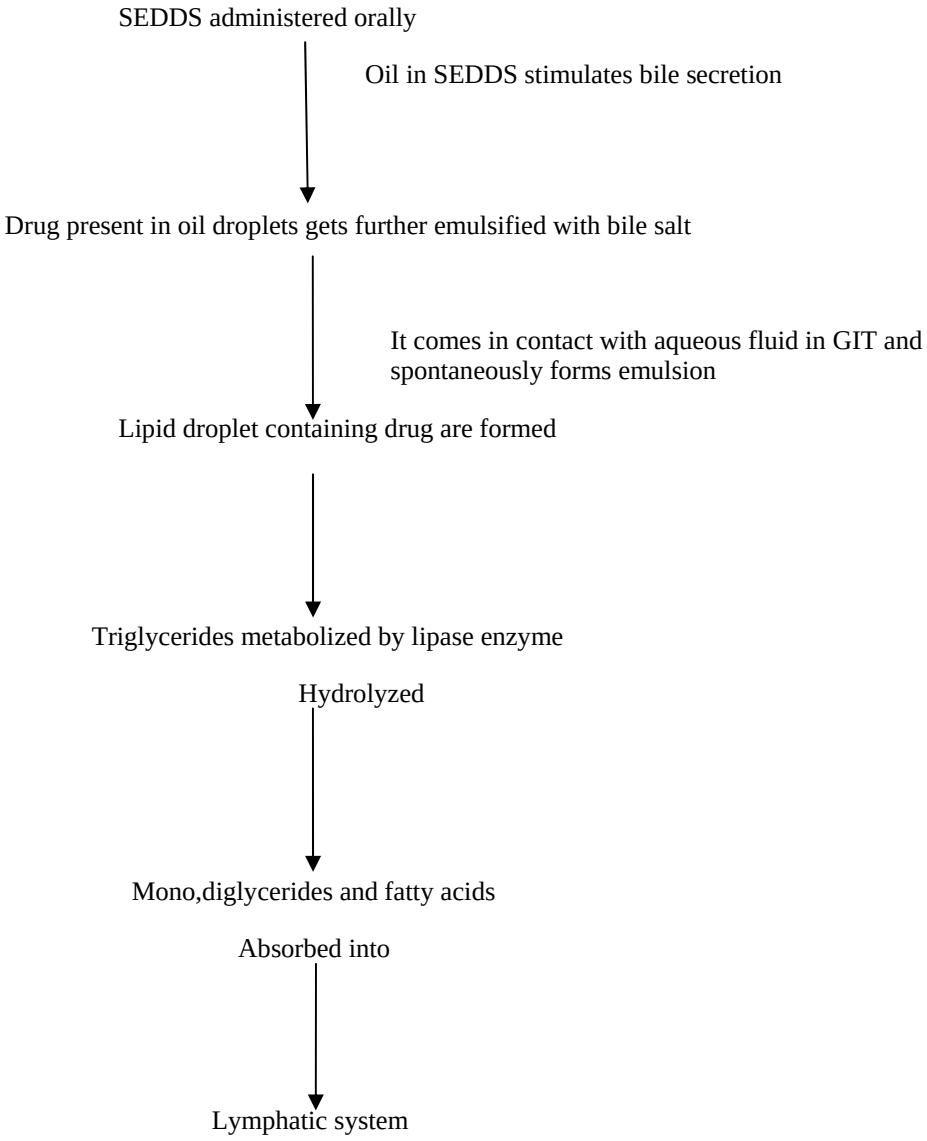
1-) SEDDS formulations potentially depend on digestion which is prior to release of drug so that's why traditional dissolution method does not work for evaluating their bioavailability.

2-) One of major drawbacks of this system is that the high concentrations of surfactant being used which may irritate the GIT.

3-) Co-solvents which are volatile in nature can migrate into the shells of soft or hard gelatin capsule.

4) Another disadvantage often associated with these systems is the chemical instability of drug in formulation.

Mechanism of Self Emulsification-[11]



Process of self emulsification related to the free energy ΔG and the equation given below:

$$\Delta G = \sum N\pi r^2\sigma$$

Where-

ΔG = Free energy

N = Number of droplet with radius r

σ = Interfacial energy

thus the above equation shows that the spontaneous formation of interface between oil and water phase is not favorable due to high energy level.

Due to their following *in vivo* properties SEDDS enhance bioavailability of drug substance[2]

a) SEDDS inhibit cellular efflux mechanisms which are responsible for keeping the drugs out of circulation.

b) First pass metabolism of drug in liver gets reduced.

c) Precipitation and recrystallization of drug compound is prevented due to formulation of fine dispersion and micellar suspension thus increasing bioavailabilty.

Table No: 1 Type of SEDDS [11,12,13]-

Characteristics/ Types	Self emulsifying	Self microemulsifying	Self nanoemulsifying formulaion
Oil droplet size	200nm to 5µm	Less than 200 nm	Less than 100nm
Appearance	Turbid	Optically clear to translucent	Optically clear
HLB value of surfactant	<12	>12	>12

Table No: 2 Difference between SEDDS and SMEDDS[10]-

SEDDS	SMEDDS
1-) SEDDS formulations may or may not contain cosurfactants. They can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug able to self-emulsify when in contact with gastrointestinal fluid	1-) In this system co-surfactant are needed to generate a microemulsion.
2-) Oil droplet size is 200 nm- 5µm	2-) In this system oil droplet size is <200nm
3-)They have turbid appearance	3-) They have optically clear to translucent appearance
4-) Thermodynamically unstable in water or physiological conditions	4-)Thermodynamically stable
5-) Require development of ternary phase diagram for formulation and optimization	5-) For the optimization of SMEDDS pseudo ternary diagrams are required
6-) The concentration of oil in SEDDS is 40 -80 %	6-) The concentration of oil required in SMEDDS is less than 20%.

Similarity between SEDDS and SMEDDS[10]-

1-) Both form fine o/w dispersions when they come in contact with gastric fluids.

2-) Both have high solubilizing and high dispersion capacity.

3-) Both formulations can be prepared as liquid and semisolid for capsule dosage forms and solid forms for tabletting.

Formulation- Various type of components are used in the formulation of SEDDS-[7,11,14,15,16,17]

Oils-Fatty acid ester or medium/long chain saturated, partally unsaturated hydrocarbon, mineral oil, vegitable oil, silicon oil, lanolin, refined animal oil, fatty alcohols and mono/di/triglycerides, coton seed oil, soyabean oil, corn oil, sunflower oil, seasame oil, captex 350 etc. Higher concentration of cremophor RH 40 is required when we used LCT to form microemulsion in compared to MCT.

Active Pharmaceutical Ingredient (API)- This system is used for those drug who have poor water solubility and for this class II drug of BCS classification are best such as itraconazole, nifedipine, vitamin E, simvastatin, danazol etc.

Surfactants- Surfactants used in SEDDS improve the bioavailability of the entrapped drugs by drug dissolution, by increasing intestinal epithelial permeability, by increasing tight junction permeability or by decreasing or inhibiting p- glycoprotein drug efflux. The concentration of surfactants used in formulating SEDDS usually ranges between 30–60%w/w of the formulation. Generally surfactants which are obtained from natural sources are preferred over the synthetic ones as safety is a critical factor in choosing a surfactant. Nonionic surfactants are less toxic than the cationic or anionic surfactants. Surfactants having high HLB values help in the instantaneous formation of o/w droplets leading to faster dispersion of the formulation in the aqueous media. Amphiphilic surfactants on the other hand, can solubilize high amounts of hydrophobic drug compounds which prevents precipitation of the drug inside the GI lumen. HLB value of nonionic surfactants is generally high for example ethoxylated polyglycolyzed glyceride and tween 80, ethanol, glycerin. The only disadvantage associated with non ionic surfactants is that over long term they may cause reversible changes in the permeability of the intestinal lumen.

Most of the times, mean droplet size tends to decrease as the concentration of surfactant is increased. It happens because the surfactant molecule gets localized at the oil water interface due to which oil droplet get stabilized. However sometimes it has also been observed that with the increase in concentration of surfactant, mean droplet size of oil also increased because of the interfacial disruption mediated by enhanced water penetration into the oil droplets caused due to the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. Hence the concentration of surfactant plays a crucial role in determining the physiological effectiveness of SEDDS.

Co- surfactant- To reduce the concentration of surfactants being used, co –surfactants are added to the SEDDS. These co- surfactants are added with the surfactant to lower the interfacial tension.

Co- solvent/ solvent- Either hydrophilic surfactant or the drug in lipid phase in large amount are generally dissolve in orgainc solvent. Ex- ethanol, Propylene glycol, PEG.

Table No. 3 Substance used in formulation of SEDDS along with drug and marketed product[11]

		Drug	Marketed Product
Oil	Corn oil Soyabean oil Peanut oil Sesame oil	Valproic acid Isotretrnoin Progestrone Dronabinol	Depakene capsule Accutane soft gelatin capsule Prometrium soft gelatin capsule Marinol soft gelatin capsule
Surfactant	Tween 80 D-alpha tocopheryl Span 80, tween 80	Bexarotene Amprenavir Cyclosporine	Targretin hard gelatin capsule Agenerase soft gelatin capusle Gengraf soft gelatin capsule

Factor affecting SEDDS[11]-

A-) Nature and dose of the drug- SEDDS are not suitable for drugs having high dose, unless they exhibit extremely good solubility in at least one of the part of the SEDDS, preferably lipophilic phase. Drug which have *log p* value of approximately 2 and exhibit limited solubility in water and lipids are the most difficult to deliver by SEDDS.

B-) Concentration of surfactant or Co-surfactant- If the concentration of surfactant being used for drug solubilization is high, then it may cause drug precipitation on coming in contact with gastric fluids.

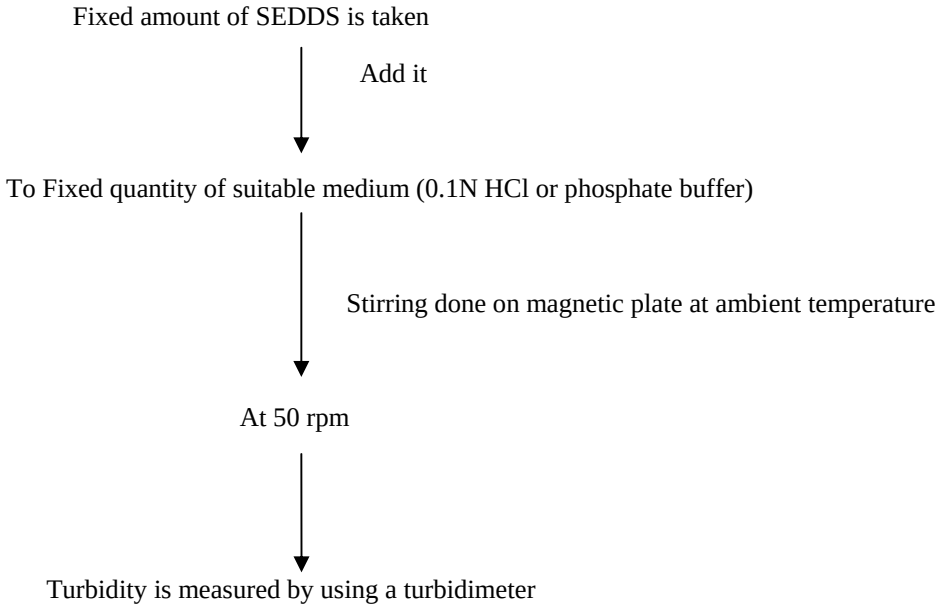
C-) Polarity of Lipophilic phase- The polarity of the droplets is dependent upon the HLB value, chain length, degree of unsaturation of fatty acid and the molecular weight of micronized drug which in turn affects rate of drug release from the microemulsion formed when SEDDS interact with body fluids.

Evaluation of SEDDS-For the evaluation and optimization of SEDDS, a number of tests are outlined-[7,16,18,19]

1-) Dispersibility test- This test is done to determine the ease of formation of an emulsion when the formulation encounters gastric fluids as well as to categorize the formulations based upon the size of the resulting globules. USPXXII dissolution apparatus is used and 1 ml of formulation is added to 500 ml of water at $37 \pm 0.50^{\circ}C$ and the steel paddles are rotated at 50 rpm. Following grades are used for assessing the results of the test-

Grade	Time	Appearance
A	Rapidly formed(within 1 min) nanoemulsion	Clear or bluish appearance
B	Rapidly formed	Slightly less clear
C	2min	Fine milky emulsion
D	Longer than 2 min	Oily appearance, Dull grayish
E	Poor or minimal emulsification	Large oil globules

Turbidometric Evaluation- Emulsion growth and droplet size can be determined by nepheloturbidimetric evaluation. The steps taken are enlisted as under:



However as the rate of change of turbidity is very high, hence time for complete emulsification is too short due to which rate of change of turbidity cannot be determined.

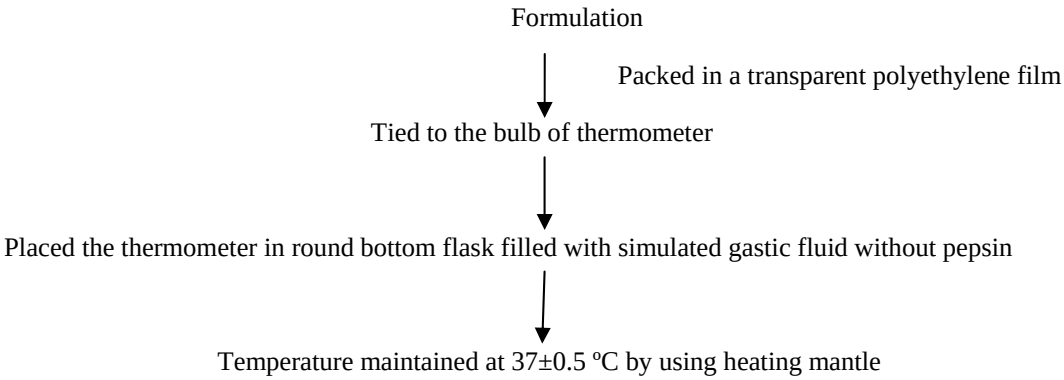
3-) Viscosity Determination- Both soft and hard gelatin capsules are used for administering SEDDS. Rheological properties of the microemulsion can be evaluated by using Brookfield viscometer or rotational viscometer. Rheological properties (viscosity) of fresh and other SEDDS formulation which are stored for longer duration of time can be determined by using rotational viscometer. Viscosity determination of liquid SEDDS indicates nature of emulsion that whether it is o/w or w/o.

4-) Drug Content-For this suitable analytical method is used. Suitable solvent is used for the extraction of drug from pre-weighed SEDDS.

5-) Droplet size analysis and particle size measurement- Droplet size of the emulsion is measured by photon correlation spectroscopy technique. For it spherical polystyrene beads are used for external standardization of light. Light scattering is monitored at 25◦C at 90◦ angle. The fluctuations in light scattering occuring due to brownian motion of the particles is analysed. Size ranging between 10-5000 nm can be measured by using a Zetasizer.

6-) Refractive index and Percent transmittance-Transparency of formulation is determined by refractive index and percent transmittance. For this purpose, a refractometer is used by placing a drop of solution on a slide and comparing it with distilled water. If refractive index of system is similar to the refractive index of water(1.333) and formulation have percent transmittance >99 percent, then formulation has a transparent nature.

7-) Liquefication time- This test is applied on solid SEDDS formulation to find out the time required by it to melt in *in vivo* in absence of agitation in simulated gastric fluid.



8-) ***In –vitro*** **dissolution technique –** USP type 2 apparatus is used for this test using 500 ml of simulated gastric fluid containing 0.5% w/v of SLS and maintaining the temperature at 37±0.5 ºC and at 50 rpm. Adequate amount of sample is withdrawn from it at regular intervals of time and the volume withdrawn is replaced with fresh medium. The samples taken are analysed by using UV spectrophotometer.

9-) ***In –vitro*** **Diffusion study-** By using different dialysis techniques we can determine the diffusive behavior of formulation. Phoshate buffer (pH 6.8) is generally used as dialyzing medium. 1ml of formulation along with 0.5 ml of dialyzing medium are filled in a membrane whose both ends are tied with a thread. Then with the help of magnetic stirrer or dissolution apparatus, the above setup is allowed to rotate at 100 rpm in a dialyzing medium and then samples are withdrawn at different time intervals and analyzed after suitable dilution. Fresh dialyzing medium ia added to mantain the volume of sample.

10-) Thermodynamic stability studies- Performance of the formulation is dependent upon the physical stability of formulation and it is adversely affected by precipitation of drug in excipient matrix. Phase separation of excipient in formulation generally occurs due to poor physical stability of formulation. Following cycles are carried out for thermodynamic stability studies-

a) Heating Cooling Cycle- In it following steps are carried out-

1) Six cycles of cooling and heating between refrigerator temperature($4C^0$) and elevated temperature($45\ C^0$) are carried out.

2) Exposure at each temperature is for not less than 48 hours.

3) Stable formulation subjected to centrifugation test.

b-) Centrifugation- It is done at 3500rpm for 30 min on those formulations which pass the heating cooling cycle. Formulation which fail to pass Heating Cooling cycle and do not show any phase separation in centrifugation are taken for the freeze thaw stress test.

c-) Freeze thaw stress cycle- It is done on those formulations which show good stability with no phase separation, cracking or creaming. 3 freeze thaw cycles done between -21 ºC and 25 ºC.

Application of SEDDS[2,11,13,20]-

1-) Increase oral bioavalbility of poorly water soluble drug.

2-) Helpful in deliver macromolecule like peptides, hormones, enzymes substrate and inhiditors and protecting them from enzymatic hydrolysis.

3-)This system is suitable for thermolabile drug such as peptides

4-)Reduce the side effect of surfactant.

List of drug with oil , surfactant and co-solvent ratio

Table No. 4 List of drug with oil, surfactant and co -solvent

Drug	Oil	Surfactant	Co-solvent	Improvement
1)Carvedilol	Labrafil M1944CS	Labrasol	Transcutol P	Bioavailability increased upto 413%
2-)Coenzyme Q 10	Labrasol	Captex 200	Lauroglycerol	Oral bioavailability increased upto 2 fold than powder formulation
3-)Diclofenac Sodium (SE Tablet)	Tween GS	Goat fat	_	Better release rate
4-)Itraconazole	Pluronic L64	Tocopherol acetate	Transcutol	Oral bioavialability increased without influence of food
5-) Ketoprofen	Tween 80	Captex 200	Capmul MCM	Increased bioavailability

6) Literature report on bioavailability enhancement using SEDDS[5,18,21,22]-

Table No. 5 Report on bioavailability enhancement using SEDDS

Drug	Bioavilbility enhancement
1-)Vitamin E	3 fold
2-) Phenytoin	2.3 fold
3-)Acyclovir	3.5 fold
4-)Simvastatin	1-5 fold
5-) Carvedilol	3-4 fold
6-)Ketoprofen	1.13 fold
7-) Vitamin A	2 fold
8-)Coenzyme Q-10	2 fold higher
9-) Progesterone	3 fold higher
10-) Win 54954	No difference in bioavailability but improve reproducibility, increased C_{max}
11-)Ontazolast	Bioavailability increase of at least 10 fold from all lipid based formulation
12-)Cyclosporin	a) Increased bioavailability and C_{max} reduce T_{max} from SMEDDS b-) Increased C_{max},AUC and dose linearity and reduced food effect from SMEDDS c) Reduce intra and inter subject variability from SMEDDS

7-) List of selected commercially available lipid based formulation for oral adminstration[2,13]-

A-)**Ritonavir**- It is a soft gelatin capsule marketed under the trade name of Norvir used as HIV antiviral by using Oliec acid,BHT, ethanol, polyonyl 3S castor oil as a excipients.

B-) **Sanquinavir**-It is used as HIVantiviral and by preparation it is a soft gelatin capsule. Markeded under the trade name of Fortovase(Roche) by using Medium- chain povidone,monodigylcerides dl- α- tocopherol as a excipients.

C-) **Lopinavir and Ritonavir**-It is soft gelatin capsule. Used as HIV-1- antiviral. For this acesulfame, potassium, alcohol, citric acid, glycerin, high fructose,corn syrup,peppermint oil, polyoryl 40 hydrogenated castor oil,povidone, propylene glyG as excipients. Marketed under the trade name of Kaletra(abbott)

D-) **Bexarotene**- Used as antineoplastic. These are soft gelatin capsules. Marketed under the trade name of Targretin (Ligand). Polyethylene glycol 400 NF, Polysorbate 20 NF, Povidone USP and Butylated hydroxyanisole NF used as excipients

E-) **Tritinion**- It is also a soft gelatin capsule. Marketed under the trade name of Vesanoid (Roche). Soybean oil, butylated hydroxyanisole, edetate disodium, methylparaben, propylparaben used as excipients. It is indicated in Acute promyelocytic leukaemia.

8-) SEDDS also used in formulation of herbal and traditional medicine[5,23,24]-

a) Iosio *et al*. increased the oral bioavailability of silymarin by formulating its self-emulsifying pellets. From their study they concluded that most viable technology to produce self-emulsifying pellets was extrusion/spheronization.They improve the *in –vivo* oral bioavailability of main components of a phytotherapeutic extract of more than 100 times. This was done by enhancing the lymphatic route of absorption.

b) Setthacheewakul *et al.* formulated and evaluated self – emulsifying liquid and pellet formulation of curcumin and rats were selected for the absorption study.Study shows that release rate of about 80% of curcumin from curcumin – SMEDDS in liquid and pellet forms was greater to only 5% in aqueous solution from unformulated curcumin. Pharmacokinetic studies shows that absorption was 14 and 10 fold greater in both liquid and pellet SMEDDS when compare with aqueous suspension of curcumin which have small oral dose.

c) You et al. formulated solid SE sustained release microsphere of Zedoary Turmaic oil. It have in tumor suppression, antibacterial and antithrombotic activity. It is prepared by quasi emulsion solvent diffusion method which involves spherical crystallization.

d-) **Silybin**- It is obtained from *Carduus marianus*. It has low oral bioavailability because of its low aqueous solubility. Protecting liver cells from harmful effect caused by drinking, smoking. It increase oral bioavailability by at least 4 folds.

e-)**Ginkgo biloba-** It have antioxidant, antischaemic, neuroprotectant,cardiovascular and cerebrovascular activites. It is generally used in congnitive deficits like alzheimer's disease and multi infarct dementia. Solubility of active compound of *Ginkgo biloba* is less. SEDDS formulation increased the dissolution and improved oral absorption and achieved the reproducible blood time profile of active compound.

f-**) Fructus Schisandral Chinensis**- Lowering abnormal serum glutamic pyruvic transaminase level in acute or chronic hepatitis.

8-) Example of marketed product with SEDDS formulation[18]-

Table No.6 Example of marketed product with SEDDS formulation

Active moity	Trade name	Dosage forms
Ritonavir	Norvir	Soft gelatin capsule,Abbott laboratories
Ibuprofen	Solufen	Hard gelatin capsule, Sanofi Aventis
Cylosporine	Neoral	Soft gelatin capsule, Novartis
Tretinoin	Vesanoid	Soft gelatin capsule, Roche
Cyclosporine	Panimum bioral	Capsule, Panacea Biotech
Fenofibrate	Liprex	Hard gelatin capsule, Sanofi Aventis
Lopinavir and Ritonavir	Kaletra	Soft gelatin capsule, Abbott
Tipranavir	Aptivus	Soft Gelatin Capsule, Boehringer Ingelhim.

Table No. 7 List of patent-

S.No.	Patent no.	Inventors	Work Done	Year	Reference
1-)	MX200700233 5(A) (2007)	Liu Zhentao, Yang Hanyu, Gao Yuqing, Shen Dongmin,Guo Wenimin, Feng Xiaolong,Zheng Jia, Yang, Liying	They worked on Butylbenzene phthalein Self Emulsifying drug Delivery System. For this 1%- 65% butyl benzene pthalein and 10-65% emulsifier are essential constituents. This SEDDS can self emulsify in GIT, increase the contact area between the GIT and drug and accordingly improve absorption	2007	25
2-)	WO200503725 1(A) 2005	Ong, Johm, Stetsko Gregg, Levy Odile Esther, Ghosh Soumitra Shankar	They all worked on novel SEDDS useful for the administration of water insoluble drug to a patent is disclosed. The SEDDS comprises a hydrophilic surfactant with HLB value greater than 10, adigestible oil comprised of medium chain fatty acid ester of propylene glycol and a non – aqueous protic solvent. Optionally a soluble chelating agent and antioxidant may be added to enhance the stability of phenolic antioxidant drug.	2005	26
3-)	WO0061744(AI) 2000	Lee Sang Soon, Choi Young Wook, Lee Sang Kil, Park Gee Bae	The present invention is related to a new solution preparation containing progstanglandin E_1 for the treatment of erectile dysfunction, which is prepared into a form of microemulsion preconcentrate.	2000	27
4-)	WO200611254 1(A1) 2006	Sakai Kenich	The invention provides an HTFS (high-through put functional screening) system by which SEEDS formulation containing viscous-liquid, semisolid or solid ingredient can be prepared and evaluated at low cost and much rapidly. The invention provides a method for the designing of SEDDS formulation.	2006	28
5-)	US0294900A1	Kanchan Kohli, Sunny chopra, Roop K. Khar, Kolapp K. Pillai	Present invention discloses a pharmaceutical composition in the form of self- nano emulsifying drug delivery formulation comprising curcuminoids. The pharmaceutical composition of the present invention shows an enhanced drug loading ability, better stability and an improved bioavilbility. The composition of the present invention comprises of a pharmaceutical effective amount of a curcuminoid , an oil phase, a surfactant and a co-surfactant		29

Conclusion: Self emulsifying lipid based formulations present an attractive approach for the delivery of drugs belonging to BCS II and IV category. These are further classifiable into SEEDS, SMEDDS or SNEDDS depending upon the type of microemulsion system being formed. Further research is required in this area for harnessing the optimum potential of this drug delivery system in development as vehicles for the delivery of pharmaceutically active principles having low solubility and permeability.

Conflict of interest:

The authors have no conflict of interest.

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