IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Impact Factor: 6.252
Volume 2, Issue 1, November 2022

Self Emulsifying Drug Delivery System a Tool for Enhancement of Solubility: A Critical Review

Tejaswini A. Dhawale[1], Shital D. Pande[2], Madhuri K. Sonawane[3], Ashwini R. Jambhale[4], Ruchita R. Giri[5]
Yashodeep Institute of Pharmacy, Aurangabad, Maharashtra, India

Abstract: *Oral drug delivery system is an oldest and most preferable form of drug admiration. The main concern regarding oral drugs are most of them are very poorly soluble which may affect directly or indirectly affect the bioavailability. SEDDS is the oldest and most preferable method to enhancing bioavailability. An ideal self-emulsifying SEDDS containing API, emulsification agents like oils and surfactant, polymers and antioxidant etc. the problem arises to researcher that all data are scattered in various places, this has been tried to resolve in this review. This review comprehensively describes literature updates containing composition, factor affecting, various emulsification processes, studied carried out on formulation, recent advancement, bioavailability enhancement, patents and marketed preparation.*

Keywords: Poorly-soluble, surfactants, lipid-based, SEDDS, bioavailability

I. INTRODUCTION

Approximately 40% of newer drugs have lowly water solubility and the oral delivery of such drugs is commonly associated with low bioavailability, great intra- and intersubject variability.[1,2] Recently, much attention has been paid to lipidbased formulations with particular emphasis on self-emulsifying drug delivery systems (SEEDS) to improve the oral bioavailability of lipophilic drugs. [3,4-5] Upon slight agitation AND THEN dilution in aqueous media , these systems can form fine oil-in-water (o/w) emulsions Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently met during extended contact amongst bulk drug ingredients and the gut wall. An extra advantage of SEEDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drugs with dissolution-limited oral absorption, these systems may offer an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles. [6]

1.1 Advantages of SEEDS

- Quick Onset of Action
- Reduction in the Drug Dose
- Ease of Manufacture & Scale-up
- Improvement in oral bioavailability
- Inter-subject and Intra-subject variability and food effects
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- No influence of lipid digestion process
- Increased drug loading capacity.[7,8]

1.2 Disadvantages of SEDDS

- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- This in vitro model needs further development and validation before its strength can be evaluated.
- Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.

- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT. [8]

1.3 Properties of SEDDS

- They are able to self-emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.
- They require lower dose of drug with respect to conventional dosage forms.[9]

1.4 Composition of Self Emulsifying Drug Delivery System

1. Active Pharmaceutical Ingredient (API): As, SEDDS are used to increase the solubility of poor water-soluble drugs, BCS class II drugs are preferred e.g. itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefanimic acid, naproxen, carbamazepine. [10, 11]

2. Excipients used in SEDDS: The self emulsification process is specific to the concentration and nature of the oil/surfactant ratio, surfactant/co-surfactant ratio and the temperature at which self- emulsification occurs.

a. Oils: Oils can solubilize the required dose of the lipophilic drug and facilitate selfemulsification and also they can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. [12,13]

So, this entire aspect must be well-thought-out through choice of excipients in SEDDS.

Table 1: Type Of Oils Used In Marketed Sedds

Type of oil	Drug	Marketed Product
Corn oil	Valproic acid	Depakene capsule
Sesame oil capsule	Dronabinol	Marinol soft gelatin
Soya bean oil	Isotretinoin	Accutane soft gelatin capsule
Peanut oil	Progesterone	Prometrium soft gelatin capsule
Hydrogenated soya bean oil	Isotretinoin	Accutane soft gelatin capsule

b. Surfactants: The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophiliclipophilic balance (HLB) and less toxicity than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. A list of surfactant used in marketed SEDDS is given in table 2

Table 2: Type Of Surfactants Used In Marketed Sedds [14]

Surfactant	Drug	Marketed Product
Span 80,Tween 80	Cyclosporine	Gengraf soft gelatin capsule
Tween 20	Bexarotene	Targretin Hard gelatin Capsule
Cremophor RH 40	Carmustine	BCNU self-emulsifying implant
D-alpha Tocopheryl Poly ethylene Glycol	Amprenavir	Agenerase Soft Gelatin capsule, Agenerase oral solution

c. Co-surfactants: The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants but it causes GI irritation. So co surfactant is used to reduce concentration of surfactant. Role of the cosurfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value.. Such systems may exhibit some advantages over the other formulations when incorporated in capsule dosage forms. A list of surfactant used in marketed SEDDS is given in table 3

d. Polymers:

Polymer matrix (inert) present in 5 to 40% w/w, which is not ionizable at physiological pH are able to form matrix. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc. [14]

e. Antioxidant Agents: Lipophilic antioxidants (E.g. α tocopherol, propyl gallate, ascorbic palmitate) stabilize the oily content of SEDDS formulations.[14]

1.5 Factors Affecting SEDDS:[14]

1: Nature and dose of the drug:

The drugs which exhibit limited solubility in water and lipids typically with log p values of approximately 2 are most difficult to deliver by SEDDS. The ability of SEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase.

2: Concentration of Surfactant or Cosurfactant:

If surfactant or co-surfactant is contributing to the greater extent in drug solubilization then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of bulk of the surfactant or co-surfactant.

3: Polarity of the Lipophilic phase:

The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of micronized drug.

1.6 The Emulsification Process

A. Mechanism of Self-emulsification:

Self emulsification occurs, when the entropy (energy) change occurs. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation. $\Delta G == \Sigma N \pi r2 \sigma$.. (i) Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r, σ is interfacial energy with period. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence .[15] In case of self-emulsifying system, the free energy requires to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously .[16]

Emulsification require very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.[17]

Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface[18]

Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase.

B. Construction of Ternary Phase Diagrams

This is the first step before starting the formulation. It is useful to identify best emulsification region of oil, surfactant and co-surfactant combinations. Ternary phase diagram of surfactant, co-surfactant and oil will plot; each of them, representing an apex of the triangle [19]

a. Dilution method: Ternary mixtures with varying compositions of surfactant, cosurfactant and oil were prepared .The area of nanoemulsion formation in Ternary phase diagram) was identified for the respective system in which nanoemulsions with desire globule size were obtain.

b. Water Titration method: The pseudoternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and cosurfactant with water at room temperature (as shown in figure 2b). Oil phase, Surfactant and the co-surfactant, at Km values 1.5 and 1 (surfactant: co-surfactant ratio), oily mixtures of oil, surfactant and co-surfactant were prepared varied from 9:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed8 .

The mixture was visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the micro-emulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SEDDS.

1.7 Evaluation of SEDDS

A number of tests are carried out for characterization and evaluation of SEDDS

1**. Drug Content:**. Drug content in the solvent extract is analyzed by suitable analytical method [20]

2. **Dispersibility Test:** The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. One ml of each formulation is added to 500 ml of water at 37 + 0.5ºC and the paddle is rotated at 50 rpm.[21]

- Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- Grade C: Fine opaque emulsion In 2 min.
- Grade D: Dull, grayish white emulsion (longer than 2 min).
- Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.
- Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation. The stability of the formulation decreases from micro emulsion to emulgel given in table 5

A. Rheological Properties Determination

The SEDDS system can also be administered in soft gelatin capsules, where, it should have appreciable flow properties for processing. The rheological properties (viscosity, flow, thixotropic, static yield, creep value) of formulation (diluted to 5 % v/v water) are determined by rotational viscometers, digital instruments coupled with either cup and bob or coaxial measuring device. [16] . Viscosity determination of liquid SEDDS also indicates whether the system is o/w or w/o, as low viscosity systems are o/w and high viscosity systems are usually w/o in nature. Viscosity of formulation is inversely proportional to dilution. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation and gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies). a. Heating cooling cycle 17: Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

B. Thermodynamic Stability Studies

The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation and gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies).

Heating Cooling Cycle

Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test. [22]

- Centrifugation: Formulations which pass the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.
- Freeze thaw stress cycle: Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than those formulations which pass this test show decent stability with no phase separation. Robustness to Dilution: Emulsions upon dilution with various dissolution media should not show any phase separations or precipitation of drug even after 12 hrs of storage, such formulation is considered as robust to dilution.[23]
- Turbid Metric Evaluation: Turbidity is a parameter for determination of droplet size and self-emulsification time. [24] Fixed quantity of SEDDS is added to fixed quantity of suitable .Since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity i.e. rate of emulsification. Turbidimetric evaluation is carried out to monitor the growth of droplet after emulsification.
- Droplet size analysis & Particle size measurements: Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizeretc
- Self-Emulsification Time: The selfemulsification time is determined by using USP dissolution apparatus 2 at 50 rpm, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS (Sodium Lauryl Sulphate) solution. The time for emulsification at room temperature is indicated as selfemulsification time for the formulion
- In vitro Diffusion study: This study is done to determine release behavior of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium [25]ne end of the dialysis membrane is tied with a thread and 1 ml of the SEDDS formulation along with 0.5 ml of dialyzing medium are filled in the membrane. Samples are withdrawn at different time intervals and then after suitable dilution are analyzed. Volume of samples withdrawn is replaced with fresh dialyzing medium.
- In vitro Dissolution technique: The quantitative in vitro dissolution studies are carried out to assess drug release from oil phase into aqueous phase by USP type 2 dissolution apparatus using 500 ml of simulated gastric fluid containing 0.5% w/v of SLS at 50 rpm and maintaining the temperature at 37±0.5ºC. Aliquots of samples are withdrawn at regular intervals of time and volume withdrawn is replaced with fresh medium. Samples taken are then analyzed by using UV spectrophotometer or any other suitable technique.
- Liquefaction Time: This test is done to determine the time required by solid SEDDS formulation to melt in vivo in the absence of agitation in simulated gastric fluid.[26]
- Refractive index (R.I.) & Percent Transmittance: Refractive Index & percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing drop of solution on slide & then comparing with water (R.I = 1.333). The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer by using distilled water as blank. If R.I. of formulation is similar to that of water & formulation having percent transmittance is greater than 99%, then the formulation are transparent in nature.

1.8 Dosage Forms of SEDDS

Table 6 shows, Studies carried out on different dosage forms.

Table 6: Studies carried out on different dosage forms.

Dosage forms	Studies carried out
Dry Emulsion	• Poorly water soluble drug- amlodipine [27] • Enteric coated dry emulsion formulations which are more appropriate for peptide & protein drugs oral delivery. These formulations are prepared by using surfactant,

	vegetable oil & pH responsive polymer followed by lyophilization[28]
Self-Emulsifying Solid Dispersion	• SE solid dispersion granules of seven drugs are prepared which includes using four carboxylic acid containing drugs, an amide containing drug (Phenacetin), a hydroxyl containing drug & a drug having no proton donating groups (Progesterone) in which Neusilin US2 was used as surface adsorbent and gelucire 50/13 was used as dispersion carrier [29]
Self-Emulsifying Tablets	• For studying effect of formulation ingredients on the release rate of drug & to evaluate an optimized self nano emulsifying tablet [30] formulation- ubiquinone • Self-emulsifying tablet using goat fat and Tween [31] – diclofenac • Biodegradable homolipid with particle size of approximately 100nm are obtained with loading efficiency of 70-75%27 -Solvent injection method • 5 Flourouracil (5–FU) and antisense Epidermal Growth Factor Receptor (EGFR) plasmid in biodegradable PLGA/o-CMC nanoparticles. This combination i.e. PLGA &ocarboxymethyl chitosan shows self-emulsifying effect without any surfactant stabilizer [31]
Self-Emulsifying Nanoparticles	• It was found that the release rate of 5-FU from self-emulsifying nanoparticles was sustained for as long as three weeks- sonication emulsion-diffusion-evaporation • Trickler et al (2008) used multiple emulsion (o/w/o) for preparation of self-emulsifying nanoparticle system with chitosan and glycerylmonooleate (GMO) for the delivery of paclitaxel. These nanoparticles possessed bioadhesive properties & increased cellular association of the drug [32] -solvent evaporation method

1.9 Recent Dosage form Development in SEDDS

1. Dry emulsions
2. Self- emulsifying capsules
3. Self- emulsifying sustained/controlled-release tablets
4. Self- emulsifying sustained/controlled-release pellets
5. Self emulsifying solid dispersions
6. Self emulsifying beads
7. Self emulsifying Sustained release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories
10. Self emulsifying implants. [33-40]

Bioavailability Enhancement

Oral drug bioavailability of a chemically stable drug is limited by its solubility and its permeability. Poor drug absorption therefore can be caused by inadequate rate and extent of drug dissolution and or low permeation. Accordingly as per the biopharmaceutical classification system, a drug on the basis of these solubility and permeability characteristics classified in to four possible categories, class I to IV. Bioavailability of poorly soluble class II drugs, on the contrary is dependent on their aqueous solubility/ dissolution rate. As these drugs tend to exhibit dissolution limited bioavailability, the in vivo physiological response is well correlated with the in vitro dissolution, resulting eventually in good in vitro/in vivo correlations (IVIVC). For accomplishing better solubility or dissolution rate of class II drugs use of techniques like micronization, co solvents, micellarsolubilization, solid dispersions and complexation has been employed with fruition.70 a report on bioavailability enhancement using self emulsifying formulation by different workers is presented in Table 7. [41-44]

Table 7 : Literature updates on various reports of bioavailability enhancement using self-emulsifying formulations.

Drug	Enhancement	With reference to	Species
Acyclovir	3.5 fold	Pure drug solution	Male albino rats
Anethole trithione	2.5 fold	Tablets	Rabbits
Atorvastatin	1.5 fold	Conventional tablet	Beagle dogs
Bicalutamide	2 fold	Suspension	Rats
Carvedilol	4.13 fold	Commercial tablet	Beagle dogs
Carvedilol	1.56 fold	Luode (a commercial tablet)	Beagle dogs
Danazold	2 fold	Pure surfactant solution	Beagle dogs
Fenofibrate	1.075 fold	Tricor tablets	Human
Gentamycin	5 fold	I.V saline	Beagle dogs
Insulin	1.15 fold	Subcutaneous injection	Beagle dogs
Itraconazole	1.9-2.5 fold	Sporanox capsules	Humans
Itraconazole	2 fold	Solid dispersion	Rats
Ketoconazole	2 fold	Pure drug	Rats
Ketoprofen	1.13 fold	Pure drug	Humans
Mitotane	3.4 fold	Lysodren	Rabbits
Nimodipine	2.6-6.6 fold	Conventional tablet	New Zealand Male rabbits
Nimodipine	4.6 fold 1.91 fold 1.53 fold	Suspension Oily solution Micellar solution	Male rabbits
Nitrendipine	1.6 fold	Conventional tablet	Beagle dogs
Silymarin	3.6 fold	Legalon capsule	Rats
Oleanolic acid	2.4 fold	Tablet	Rats
Simvastatin	1.5 fold	Zocor tablets	Beagle dogs
Tretinoin	1.67 fold	Commercial capsule formulation	Beagle dogs

Table 8: Various patents on self-emulsifying formulations for phyto-constituents**.**

Patent title	Assignee	Observation	Patent Number	References
Oral pharmaceutical composition con- taining lutein using self-micro emul- sion system	Meditip co ltd, KR	Enhance the solubility of lutein effectively delivers the lutein *in vitro* and *in vivo*	KR2011 0019327 (A)	[62]
Self emulsifying drug delivery system for a curcuminoid based composition	Jamia Hamdard University and Arbro Pharmaceutical ltd., IN	Drug loading ability, stability and bioavail-ability was improved	US2011 294900 (A1)	[63]
Rhizoma corydalis total alkaloids self emulsifying drug delivery system and preparation method and application thereof	Hongda Ma Tao Guo, CN	Formulation solve the problem of low aqueous solubility, bioavailability and dis- integration of total alkaloids of plant	CN1019 12447 (A)	[64]

Apogossypolone self emulsifying drug delivery system and preparation method thereof	Shanghai Yasheng Medical Techonology Co ltd, CN	Composition increase the intestinal perme- ability and improve the bioavailability, aqueous solubility and drug loading rate	CN1022 47321 (A)	[65]
Novel curcumin self emulsifying drug delivery system and preparation thereof	Univ Zhejiang Technology,CN	Enhance the absorption and oral bioavail-ability of curcumin	CN1016 27969 (A)	[66]
Delivery of tetrahydro cannabinol: A self-emulsifying drug delivery system to improve dissolution, stability, and bioavailability of drug compounds of dronabinol or other cannabinoids	Murty Pharmaceuticals, Inc.,US	SEDDS formulation with at least one sur- factant unexpectedly promote the targeted chylomicron delivery and optimal bioavail-ability	EP19038 66 (A1)	[67]
Hemlock parsley oil self emulsifying oral medicine delivery system and preparing method thereof	Sichuan Pearl Pharmaceutical CN	Use of plant oil as oil phase solve the prob-lem of using too much surfactant in the formulation and improves the oral bioavailability	CN1012 29205 (A)	[68]
Self emulsifying pharmaceutical com-positions of Rhein or Diacerein	Nakhat Premchand and Man- daogade Prashant IN	SEDDS formulation is bioequivalent to market formulation Art 50TM and reduces the side effect like soft stool formation with market formulation	US2010 303902 (A1)	[69]
Vinpocetine oral self microemulsifica- tion medicine releasing system and preparation method thereof	Tong ji Medical College of Huaz, CN	Improve the aqueous solubility, oral bioavailability and eliminates the influence of food on absorption of vinpocetine	CN1011 3962 (A)	[70]
Pharmaceutical composition for hyper-lipidemia treatment of self emulsify- ing phytoconstituent delivery system to increase bioabsorption and improve stability of active ingredient	Korea Research Institute of Chemical Technology,KR	Improves the absorption and stability ofdrug candidate	KR2005 0011323 (A)	[71]
Self emulsifying phytoconstituent de-livery system, wherein the fatty agentis optional	Astra Zeneca, HK	Enhance the bioavailability and aqueoussolubility	HK1050 632 (A1)	[72]

Solid self nano emulsifying controlled release drug delivery system composi- tion for enhanced delivery of water insoluble phytosterols and other hydro- phobic natural compound for body weight and cholesterol level control	Weisspapir M and Schwarz J	Composition better control the body weightand cholesterol level because of improved aqueous solubility of insoluble phytocon- stituents	US2002 103139 (A1)	[73]

Table 9: Examples of marketed products formulated as self-emulsifying systems [74]

Brand Name	Compound	Dosage Form Capsule	Company	Used as
Neoral	Cyclosporine A/I	Soft gelatin, oral solution	Novartis	Immune Suppressant
Norvir	Ritonavir	Soft gelatin, oral solution	Abbott Lab	HIV antiviral
Fortovase	Saquinavir	Soft gelatin	Hoffmann-La Roche Inc	HIV antiviral
Agenerase	Amprenavir	Soft gelatin, oral solution	Glaxo Smithkline	HIV antiviral
Convulex	Valproic Acid	Soft gelatin	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Hard gelatin	Sanofi-Aventis	Antihyperlipoproteine-Mic
Sandimmu Ne	Cyclosporine A/II	Soft gelatin, oral solution	Novartis	Immuno suppressant
Targretin	Bexarotene	Soft gelatin	Ligand	Antineoplastic
Rocaltrol	Calcitrol	Soft gelatin, oral solution	Roche	Calcium regulator
Gengraf	Cyclosporine A/III	Hard gelatin	Abbott Lab	Immuno suppressant
Solufen	Ibuprofen	Hard gelatin	Sanofi-Aventis	Analgesic, Antipyretic
Lamprene	Clofazimine	Soft gelatin	Novartis	Anti-leprosy drug
Hectorol	Doxercalciferol	Soft gelatin	Genzyme corporation	2° hyperparathyroidism
Avodart	Dutasteride	Soft gelatin	Glaxosmithkline	Benign prostatic Hyperplasia
Depakene	Valproic acid	Capsule	Abbott	Anticonvulsant
Marinol	Dronabinol	Soft gelatin	Watson	Anti-emetic

Recent Advancements in SEDDS

Self-emulsifying formulations take different forms depending upon the purpose and principle of the drug delivery system. The developments in the solid self-emulsifying technologies are discussed below:

1) **Self-emulsifying controlled-release (CR) tablet:**

This tablet (SECRET) is a newer technological improvement in the area of S-SEDDS for achieving controlled drug release profile. SECRET is a patented proprietary platform technology developed by AlphaRx Inc. (San Diego, California, United States), where liquid SE formulations are converted into tablets by adsorbing onto the surface of rate-controlling polymers such as HPC, HPMC, etc. . An eutectic based self-microemulsifying tablet of coenzyme Q10 was prepared by Nazzal and Khan [75]. They had evaluated effect of solid carrier i.e. colloidal silica and magnesium stearate and compression force on hardness and dissolution of controlled release tablet of coenzyme Q10. It was also found that the solid carriers and compression force were in optimum level. [76]. Tacrolimus was developed as gastroretentive SR tablet by using polyethylene oxide, chitosan, poly(vinyl pyrollidone) and mannitol as solid carrier. It was proved that this tablet enhance the oral bioavailability of tacrolimus .[76] The SE tablets of carvedilol containing HPMC, MCC and aeroperl as tableting excipients have been reported to result in substantial augmentation of in vitro drug uptake in HCT-116 cell lines plausibly due to the inhibition of P-gp efflux [77]. Nekkanti et al. [78] demonstrated the potential of solid SMEDDS tablets of candesartan cilexetil in significant enhancing the rate and extent of drug dissolution and consequently, the oral bioavailability [79].

2) **Self-emulsifying sustained-release (SR) pellets:**

It is a suitable dosage form for sustained release due to their smooth spherical shape and narrow size distribution. It reduces intrasubject and inter-subject variability of plasma profiles and G.I. irritation without affecting drug bioavailability [79]. A selfemulsifying controlled release pellets were prepared by Serratoni et al. [80] They had incorporated self-emulsifying excipients to prepare self-emulsifying pellets and coated the pellets with water insoluble polymer which retard the rate of drug release. They had concluded that due to presence of polymer film, the rate of drug release was controlled which was not affected by excipients. Another report on sustained release matrix pellets in which gelucire 54/02 and gelucire 70/02 were used.[81]

3) Self-emulsifying SR microspheres:

Quasi-emulsion solvent diffusion method of spherical crystallization technique is used for preparing self emulsifying sustained release microsphere. A sustained release microsphere was prepared by using zedoary turmeric oil (ZTO) as oil phase which exhibited potent pharmacological actions. The ratio of hydroxypropyl methyl cellulose acetate succinate to Aerosil 200 was used to control the release behaviour of ZTO in the formulation. Finally, it was concluded that such microspheres had shown maximum bioiavailability as compared to conventional formulation. [82]

4) **Self-emulsifying nanoparticles:**

These are prepared by solvent injection technique in which liquid formulation is injected dropwise into a stirred non-solvent. Then they are filtered and dried. An another technique to prepare nanoparticles is sonication emulsion diffusion evaporation technique in which the mixture of polylactide co-glycolide (PLGA) and O-carboxymethyl chitosan (O-CMC) were used. The nanoparticles provide controlled release profile of drug delivery and improved stability in gastric fluid, along with enhanced oral bioavailability. Such formulations produce o/w microemulsions in situ on coming in contact with GI fluids. 5-Fluorouracil and paclitaxel are Vol. 31, No. 4 (2019) csome of the examples of drugs that have recently been reported to be constituted as SE nanoparticulate systems for exploring their oral bioavailability enhancement. Holmberg and Siekmann[83] prepared the SE nanoparticles of 5-fluorouracil employing PLGA/O-carboxymethyl chitosan by solvent evaporation technique and observed significantly enhanced cellular uptake of drug through the intestinal lymphatic pathways, lower cytotoxicity, and remarkable reduction in the gliomas as evident from MTT assay, TUNNEL technique and immunohistochemical staining. The SE nanoparticles of paclitaxel by emulsion solvent evaporation using chitosan and glycerylmonooleate were observed to exhibit fourfold increase in the cellular uptake of drug and significantly lower cytotoxicity through MTT assay. [84]. An eutectic based selfnano-emulsifying formulation was prepared by Nazzal et al. [85] and studied the dug release mechanism by turbidimetric analysis and droplet size analysis. They had shown that the formulation can overcome the low solubility and irreversible precipitation formed in conventional formulation. Bakerman et al. [86] had prepared cyclosporin lipid nanoparticle by using phospholipid, span 80, Tween 80, tricaprin and cremophor RH 40. The conclusion was that nanoparticles had shown maximum oral bioavailability. In 2010, Nepal et al. [87] had prepared nanoemulsion in which the surfactants and co-surfactants was mixed at the ratio of 1:4 which provide a sufficient mechanical barrier to coalescence oil droplets. Koynova and Tihova[88] had prepared self-nanoemulsifying formulation by using nanosized SE lipid vesicles as carriers. They had suggested that it can be a good alternative for formulation which overcome the stability, sterilization problem and nonreproducibility between batches.

5) **Self emulsifying beads (non-oral):** These are prepared by incorporating very small amount of excipients into solid dosage form. Patil and Paradkar[89] had utilized solvent evaporation method for loading of self emulsifying liquid into

micro channels of porous polystyrene beads. It was found that porous polystyrene beads was considered as potential carrier for solidification. Due to its uniform bead size and pore architecture, the loading efficiency and in vitro drug release was maximum. Floating alginate self-emulsifying beads of tetrahydrocurcumin by using different propertion of sodium alginate, calcium chloride and water soluble pore former. It was concluded that gastric residence time was increased due to floating properties [90].

6) **SE suppository formulations (non-oral):** The drugs which cannot reach the maximum theraputic concentration by oral route, these drugs are formulated by incorporating selfemulsifying excipients into selfemulsifyingsuppositories[91]. Glycyrrhizin, for the treatment of chronic hepatic diseases cannot achieve maximum theraputic level orally. But when it is formulated as vaginal or rectal SE suppositories by using a mixture of a C6-C18 fatty acid glycerol ester and a C6-C18 fatth acid macrogol ester. It was found that the maximum therapeutic concentration was achieved [92].

7) **SE mucoadhesive systems:** These formulations majorly contain drug dissolved within the lipidic excipients along with mucoadhesive polymers such as acacia, tragacanth and lecithin, which undergo emulsification on contact with mucosal surface to produce fine o/w microemulsions/ nanoemulsions. The SE mucoadhesive formulations containing glycerylmonostearate and cremophor RH40, along with mucoadhesive polymers such as acacia and lecithin, have been reported for augmenting oral bioavailability of cannabnoids, ascribable to increase in GI residence time of the formulation [92].

8) **Self-emulsifying transdermal systems (non-oral):** The potential of SEDDS for transdermal delivery has not yet been fully explored. However, it has been proposed that the SE formulations can enable the transdermal delivery of hydrolyzable drugs undergoing extensive hepatic first-pass effect. These systems undergo phase inversion on when attached with excretatory fluid of the skin to produce supersaturated system This phenomenon of inversion generates the driving force, (i.e. flux) for transdermal delivery of drugs through stratum corneum to enhance its systemic availability [93]. Of late, the method of preparation of self-emulsifying matrix systems containing long-chain unsaturated fatty acids and fatty alcohols for transdermal delivery of flubiprofen has been patented for its improved therapeutic performance. In another report nearly 1.2-fold increase in the flux across rat skin for SE transdermal systems of indomethacin was observed over conventional microemulsions[94].

9) **Self-emulsifying ocular systems (non-oral)**:

Recently, the SEDDS have demonstrated their immense utility for ocular delivery system for the treatment of pathological disorders such as choroidal neovascularization, macular degeneration, edema, uveitis, diabetic retinopathy, etc. A formulation of ultrafine and stable SE oily formulations of NSAIDs containing Polyox-40 castor oil, Lumulse GRH40 and Tween 80 has been patented for opthalmic application [95]. The SE formulation of cyclosporine and rapamycin containing phosphatidylcholine, PEG 400 and Nikkol HCO-35 exhibited 10-fold more effective as compared with opthalmic preparation for the treatment of neovascularization [96].

10) **Self-double emulsifying drug delivery systems (SDEDDS):**

SEDDS is applied for the solubility and oral absorption for improvement. Self-double emulsifying drug delivery system (SDEDDS) is applied to drug having high solubility and low permeability. After dissolution, permeability is a major and important factor which affects the oral absorption of drug. So w/o/w and o/w/o are double emulsions in which drugs are encapsulated at the innermost phase to release the drug for prolonged time. Wang et al. [97] had developed topical hydrogel which is vitamin C loaded loadedself double emulsifying formulation which is used topically. Industrially, it is used limited due to its instability. But Hu et al. [98] had developed a novel SDEDDS preparation by formulating hydrophillic surfactants with w/o emulsion. They had concluded that SDEDDS of a peptidomimetic drug can be delivered. Another formulation was prepared to improve EPGCG photostability which possess sustained release behaviour. Epigallocatechin 3-gallate (EGCG) and α-lipoic acid was used for preparing SDEDDS formulation [99]. Another new formulation was investigated named as o/o/w double emulsion which is automatically formed after dilution in aqueous phase. Drugs are mainly encapsulated in the innermost oil phase. [100]

11) **Eutectic based self-emulsifying formulations:** In this kind of drug delivery system, highly lipophilic drug can be melted at body temperature by inclusion of an eutectic agent. Sometimes, the eutectic agent can be a lipid phase that does not melt at body temperature leaving the drug alone in the molten state at or below body temperature. The molten drug is then emulsified by surfactant and cosurfactant. Nazzal and Khan [74] reported improved drug stability and

superior physiochemical performance for eutectic SNEDDS of a coenzyme Q10 containing mixture of volatile oils such as menthe oil, anise oil, peppermint oil, and spearmint oil using surfactants such as Cremophor 35RH and CapmulMCM .

12) **Charged self-emulsifying formulations:**

Enhancement of bioavailability of drug through developments in self-emulsifying formulations is based on increasing drug solubility, modifying biochemical and physical barrier function and promoting lymphatic drug absorption, As GI absorptive cells carry a negative charge and charge carried by formulation may affect the absorption of drug. Positively charged self-emulsifying compositions exhibit enhanced bioavailability than negatively charged compositions. One example of positively charged SEDDS is ibuprofen SEDDS prepared from ethyl oleate as an oil, oleyl amine as a cationic lipid, and Tween 80:Span 80 (3:1) as surfactants. This system showed highest absorption than negatively charged SEDDS and pure drug in in vitro GI absorption studies .[101]

1.10 Application of SEDDS in plant and Herbal Drugs:

Recently, research has been focused on development and utilizing herbal drugs in SEDDS preparation. Herbal drugs are widely used in the east region, which can be used in allregions. SEDDS is a thermodynamically stable formulation in which herbal drugs which has hydrophobic properties and poor distribution can be incorporated. This system can spontaneously form oil in water micro or nano-emulsion which can overcome the solubility, bioavailability and instabilty problem of a poorly soluble herbal drugs[102]. In present research, by utilization of herbal drugs, Yen et al. [103] and Cui et al. [104] had developed polymeric nanoparticles, Sierant et al. [105] had developed nanocapsules, Zhou et al. [106] and Khan et al. [107] had developed liposomes, Li et al. [108] had developed solid lipid nanoparticles, Wei et al. [109] had developed nanoemulsion and enhanced solubility, bioavailability, pharmacological activity, stability, tissue macrophages distribution, sustained delivery of drugs and protection from physical and chemical degradation. Cai et al. [110] had demonstrated that by using herbal drugs self emulsifyingdrug delivery system can be more useful and effective. So for this system plant drugs are selected whose oral absorption can be enhanced by using self emulsifying excipients. Before proceeding to the formulation, preformulation studies of herbal drugs and with excipients should be done. In this review, present research emphasize on the development of SEDDS, effect of excipents and poorly water soluble phytoconstituents[111].

II. CONCLUSION

Self Emulsifying Drug Delivery Systems is a unique approach used to overcome the problem of poor oral bioavailability. In this review, a brief outline is given regarding SEDDS composition, factor affecting, various emulsification processes, studied carried out on formulation, recent advancement, bioavailability enhancement, patents, marketed preparation, recent advancements in SEDDS and application of SEDDS in plant and herbal drugs. The review focuses on newer approaches available for SEDDS with their advantages.

REFERENCES

[1]. Gursoy R.N., Benita S. Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs: Biomedicine and Pharmacotherapy, 2004; 58:173-182.

[2]. Abdalla A., Klein S., Mader K. A new Self emulsifying drug delivery system for poorly soluble drugs: European Journal of Pharmaceutical Sciences. 2008; 35:357-464.

[3]. Gershanik T., Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs: European Journal of Pharmaceutics and Biopharmaceutics. 2000; 50:179- 188.

[4]. Tang B., Cheng G., Chun J.Development of solid self emulsifying drug delivery systems, preparation techniques and dosage forms: Drug Discovery Today. 2008; 13:606-611.

[5]. Craig D.Q.M, Barker S.A., Banning D., Booth S.W. An investigation into the physicochemical properties of selfemulsifying systems using low frequency dielectric spectroscopy: International Journal of Pharmaceutics. 1993; 96:147-155.

[6]. Tang J.L., Sun J., Guihe Z. SelfEmulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drug, Current Drug Therapy. 2007;2:85-93.

[7]. Patel PA, Chaulang GM. Self Emulsifying Drug Delivery System: A Review. Research J Pharm and Tech 2008; 1(4): 313-323.

[8]. Hauss DJ, Fogal SE. (1998). Lipid-based delivery systems for improving the bioavailability and lymphatic transport of poorly water soluble LTB4 inhibitors, J Pharm Sci, 87,164-169.

[9]. Sapraa K, et al: Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs; Indo Global Journal of Pharmaceutical Sciences 2012; 2(3): 313-332.

[10]. Kumar S, Malviya R, and Sharma P K: Solid Dispersion: Pharmaceutical Technology for the Improvement of Various Physical Characteristics of Active Pharmaceutical Ingredient; African Journal of Basic and Applied Science 2011; 3(4): 116- 125.

[11]. Kumar S, Gupta S and Sharma P K: Self-Emulsifying Drug Delivery Systems (SEDDS) for oral delivery of lipid based formulations. African Journal of Basic & Applied Science 2012; 4 (1): 07-11.

[12]. Nigade P M, Patil S, Tiwari S S: Self Emulsifying drug delivery system (SEDDS): A review. International Journal of Pharmacy and Biological Sciences 2012; 2(2): 42-52.

[13]. Sharma V, et al: SMEDDS: A novel approach for lipophilic drugs. International Journal of Pharmaceutical Science and Research 2012; 3(8): 2441-2450.

[14]. Khedekar and Mittal, SELF EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW , IJPSR, 2013; Vol. 4(12): 4494-4507

[15]. BhargavaP, Bhargava S, and Daharwal S J: Self-emulsifying drug delivery System: an approach to improve the solubility of poorly water soluble drugs. Advance Research in Pharmaceuticals and Biologicals 2011; Vol 1(1): 1-9.

[16]. Christopher Porter J H, et al: Enhancing intestinal drug solubilization using lipid-based delivery systems. Advanced Drug Delivery Reviews 2008; 60: 673–691.

[17]. Kumar A, Sharma S, Kamble R: Self-emulsifying drug delivery system (SEDDS): future aspects. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(4): 7-13.

[18]. Mittal P, Seth N, Rana AC: Self-microemulsifying drug delivery system (SMEDDS): An alternative approach for hydrophobic drugs. International Journal of Natural Product Science 2012; 1: 80.

[19]. Sudheer P, et al: Approaches to development of solid- self micron emulsifying drug delivery system: formulation techniques anddosage forms – a review. Asian Journal of Pharmacy and Life Science 2012; 2(2):214-225

[20]. Patel P A, et al: Self Emulsifying Drug Delivery System: A Review. Research Journal of Pharmacy and Technology 2008; 1(4): 313-323.

[21]. Revathi S, DhanaRaju MD: Self-emulsifying drug delivery system: A review. World Journal of Pharmacy and Pharmaceutical Sciences 2013; 2(1): 89-107.

[22]. Singh G, et al: Self-emulsifying drug delivery systems (SEEDS): An approach for delivery of poorly water soluble drug. International Journal of Pharmacy & Life Sciences 2012; 3(9): 1991-1996.

[23]. Rajinikanth P S, Suyu Y, and Garg S: Development and In-Vitro Characterization of Self-nanoemulsifying Drug Delivery Systems of Valsartan. World Academy of Science, Engineering and Technology 2012; 72: 1418-1423.

[24]. Sachan R, Khatri K, Kasture S B: Self-Eumlsifying Drug Delivery System A Novel Approach for enhancement of Bioavailability. International Journal of PharmTech Research 2010; 2(3): 1738- 1745.

[25]. Patil P, Patil V, Paradkar A: Formulation of SEDDS for oral delivery of Simvastatin: In vitro and in vivo evaluation. Actapharma. 2007; 57: 111-122.

[26]. Kohli K, et al: Self-emulsifying drug delivery systems: an approach to enhance oral Bioavailability. Drug Discovery Today 2010; 15: 958-965

[27]. Jang D J, et al: Improvement of bioavailability & photo stability of amlodipine using redispersible dry emulsion. Europian Journal of Pharmaceutical Science 2006; 28: 405-411.

[28]. Kinesh V P, et al: Novel approaches for oral delivery of insulin and current status for oral insulin product. International Journal of Pharmaceutical Science and Nanotechnology 2010; 3(3): 1057- 1064.

[29]. Gupta M K, et al: Hydrogen Bonding with Adsorbent during storage governs drug dissolution from solid

dispersion granules. Pharmaceutical Research 2002; 19: 1663-1672.

[30]. Nazzal S, Khan MA: Response Surface Methodology for the Optimization of Ubiquinone Self-Nanoemulsified Drug Delivery System. American Association of Pharmcetical Sciences Pharm Sci Tech 2002; 3 (1) 240: 1-9.

[31]. Attama AA, et al: The use of solid self-emulsifying system in the delivery of diclofenac. International Journal of Pharmaceutics 2003; 262: 23-28. 27. Attama A, Nkemnele M O: In vitro evaluation of drug release from self-emulsifying drug delivery systems using a biodegradable homolipid from Capra Hircus. International Journal of Pharmaceutics 2005; 304: 4-10.

[32]. Hu Yunxia, et al: Preparation and evaluation of 5-FU/ PLGA/Gene nanoparticles. Key Engineering Materials 2005; 288- 289: 147-150. 29. Trickler WJ, Nagvekar AA, Dash AK: A novel nanoparticle formulation for sustained Paclitaxel delivery. American Association of Pharmaceutical Scientist Pharm Sci Tech. 2008; 9: 486–493.

[33]. Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. International Journal of Pharmaceutics. 2002;235(1-2):247–65.

[34]. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. European Journal of Pharmaceutical Sciences. 2000;11(2):S93–8.

[35]. Abdalla A, M¨ader K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007;66(2):220–6.

[36]. Erratoni MS, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. European Journal of Pharmaceutics and Biopharmaceutics. 2007;65(1):94–8.

[37]. Patil P, Paradkar A. Porous polystyrene beads as carriers for self-emulsifying system containing loratadine. AAPS Pharm SciTech. 2006;7(1):E199–E205.

[38]. Sriraksa S, Sermkaew N, Setthacheewakul S. Floating alginate beads as carriers for self-emulsifying system containing tetrahydrocurcumin. Advanced Materials Research. 2012;506:517–20.

[39]. You J, Cui FD, Han X, et al. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the Selfemulsification and bioavailability of the oil. Colloids and Surfaces B. 2006;48(1):35–41.

[40]. Attama AA, Nkemnele MO. In vitro evaluation of drug release from self microemulsifying drug delivery systems using a biodegradable homolipid from Capra hircus. International Journal of Pharmaceutics. 2005;304(1-2):4–10.

[41]. Patel D, Sawanth KK. Oral bioavailabilty enhancement of acyclovir by self micro emulsifying drug delivery System (SMEDDS). Drug DevInd Pharm. 2007;33(12):1318-26.

[42]. Jing Q, Shen Y, Ren F, Chen J, Jiang Z, Peng B, et al. HPLC determination of anetholetrithione and its application to pharmacokinetics in rabbits, J Pharm Biomed Anal. 2006;42(5):613-7.

[43]. Shen HR, Li ZD, Zhong MK. Preparation and evaluation of self microemulsifying drug delivery system containing atorvastatin. Yao XueBao. 2005;40(11):982-7.

[44]. Singh AK, Chaurasiya A, Jain JK, Awasthi A, Asati D, Mishra G, et al. HPLC method for the pharmacokinetic study of bicalutamide SMEDDS and suspension formulations after oral administration to rats. Talanta. 2009;78(4-5):1310-4.

[45]. Wei L, Sun P, Nie S, Pan W. Preparation and evaluation of sedds and smedds containing carvedilol. Drug DevInd Pharm. 2005;31(8):785-94.

[46]. Wei L, Li J, Guo L, Nie S, Pan W, Sun P, et al. Investigations of novel self emulsifying osmotic pump tablet containing carvedilol. Drug DevInd Pharm. 2007;33(9):990-8.

[47]. A Singh, AChaurasiya, M Singh, SC Upadhyay, R Mukherjee, RK Khar. AAPS PharmSciTech.2008;9(2): 628-34.

[48]. R Chouksey, AK Jain, H Pandey ,AMaithil. International journal of pharmacy & life

sciences.2011;2(8):982-988.
[49]. AK Gupta, DK Mishra, SC Mahajan. Int. J. of Pharm. & Life Sci. 2011;2(3):633-639.
[50]. S Sharma, PK Suresh. International Journal of Innovative Pharmaceutical Research. 2010;1(4):66-73.
[51]. B Sharif, M Zadeh, S Dahanzadeh, F Rahim. International Journal of Advances in Pharmaceutical Sciences.2010; 1:239-248.
[52]. VK Pal, A khan. Asian Journal of Pharmaceutical and Clinical Research.2012;5(1):76-78.
[53]. JB Shukla, SJ Patel. International journal of pharmacy and pharmaceutical sciences.2010;2(4):143-146.
[54]. Y Jing, L Yun, PZ Jian. J Pharm Pharmaceut Sci.2008;11 (3): 22-29.
[55]. X Jia, C Qi, CK Chan, YM Zhao, NW Geng, BS Jia, TW Yi, HYT Henry,Z Ying Zheng.AAPS PharmSciTech.2009;10(1):172-182.
[56]. L Linjie, P Xiujuan, Z Wei, W Siling. Asian Journal of Pharmaceutical Sciences. 2007; 2 (4):150-160.
[57]. MK Kale, PB Suruse, SP Warke. American Journal of PharmTech Research. 2012;2(1):338-348.
[58]. YM Lin, CC Ying, DS Yu, TK Wen, OH Hsiu, TS Ming. International Journal of Nanomed.2011;6:2445–2457.
[59]. H Thakkar, J Nangesh, M Parmar, D Patel.Journal of pharmacy and bioallied sciences.2011;3 (3): 442-448.
[60]. IT Ehab. Scientiapharmaceutica. Sci Pharm. 2009;77: 443–451.
[61]. Z Yi, W Changguang, HL Albert, Chowb, R Ke, G Tao, Z Zhirong, Z Ying. International Journal of Pharmaceutics.2010;383:170–177.
[62]. Tang, J.; Sun, J.; Cui, F.; He, Z. Preparation of self emulsifying drug delivery systems of Ginkgo biloba extracts and in vitro disso- lution studies. Asian J. Traditional Med., 2006, 1(3-4) 1-4.
[63]. Bongkyu, Y.; Hee, Y.J.; Srinivasan,S. Oral pharmaceutical compo- sition containing lutein using self microemulsion system. KR Pat- ent 20110019327(A), February 25, 2011.
[64]. Kohli, K.; Chopra,S. Self-emulsifying drug delivery system for a curcuminoid based composition. U.S. Patent 2011294900(A1), December 1, 2011.
[65]. Guo, H.M.T. Rhizoma corydalis totals alkaloids self-emulsifying drug delivery system and preparation method and application thereof. CN Patent 101912447(A), December 15, 2010.
[66]. Guo, J.W.M. Apogossypolone self-emulsifying drug delivery sys- tem and preparation method thereof. CN Patent 102247321(A), November 23, 2011.
[67]. Yin, X.X. Novel curcuminself emulsifying drug delivery system and preparation thereof. CN Patent 101627969(A), January 20, 2010.
[68]. Murty, R.B.; Lexington, K.Y.; Murty, S.B. Delivery of tetrahydrocannabinol: A self emulsifying drug delivery system to improve dissolution, stability, and bioavailability of drug compounds of dronabinol or other cannabinoids. EP Patent 1903866(A1), April 2, 2008.
[69]. Cai, Q.; Liang, L. Hemlock parsley oil self emulsifying oral medi- cine delivery system and preparing method thereof. CN Patent 101229205(A), July 30, 2008.
[70]. Nakhat, P.; Mandaogade,P. Self- emulsifying pharmaceutical com- positions of Rhein or Diacerein. U.S. Patent 2010303902(A1), De- cember 2, 2010.
[71]. Li, G.; Chen, Y. Vinpocetine oral self-micro emulsification medi- cine releasing system and preparation method thereof. CN Patent 10113962(A), January 16, 2008.
[72]. Hang, C.S.; Young, J.S. Pharmaceutical composition for hyperlipi- demia treatment of self emulsifyingphytoconstituent delivery sys- tem to increase bioabsorption and improve stability of active ingre- dient. KR Patent 20050011323(A), January 29, 2005.
[73]. Christina, H.; Britta, S. Self- emulsifying phytoconstituent delivery system, wherein the fatty agent is optional. HK Patent 1050632 (A1), March 18, 2005.
[74]. S. Revathi et al SELF EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW wjpps volume 2, Issue 1, 89-107.
[75]. S. Nazzal and M.A. Khan, Int. J. Pharm., 315, 110 (2006)
[76]. Y.P. Wang, Y. Gan and X.X. Zhang, ActaPharmacol. Sin., 32, 1294 (2011)
[77]. E.A. Mahmoud, E.R. Bendas and M.I. Mohamed, AAPS PharmSciTech, 10, 183 (2009)

[78]. V. Nekkanti, P. Karatgi, R. Prabhu and R. Pillai, AAPS PharmSciTech, 11, 9 (2010);
[79]. R. Gandhi, C.L. Kaul and R. Panchangnula, Pharm. Sci. Technol. Today, 4, 160 (1999);
[80]. M. Serratoni, M. Newton, S. Booth and A. Clarke, Eur. J. Pharm. Biopharm., 65, 94 (2007);
[81]. J. Hamdani, A.J. Moës and K. Amighi, Int. J. Pharm., 260, 47 (2003)
[82]. J. You, F.D. Cui, X. Han, Y.S. Wang, L. Yang, Y.W. Yu and Q.P. Li, Colloids Surf. B Biointerfaces, 48, 35 (2006
[83]. 83. C. Holmberg and B. Siekmann, Self-Emulsifying Drug Delivery System, US Patent US 7736666B2 (2010).
[84]. G. Shlieout, B. Boedecker, S. Schaefer, B. Thumbeck and P. Gregory, Pharmaceutical Compositions of Lipase-Containing Products, In Particular of Pancreation, US Patent 2005/0250817 (2005).
[85]. S. Nazzal, I.I. Smalyukh, O.D. Lavrentovich and M.A. Khan, Int. J. Pharm., 235, 247 (2002)
[86]. T. Bekerman, J. Golenser and A. Domb, J. Pharm. Sci., 93, 1264 (2004)
[87]. P.R. Nepal, H.K. Han and H.K. Choi, Eur. J. Pharm. Sci., 39, 224 (2010);
[88]. R. Koynova and M. Tihova, Biochim. Biophys. Acta, 1798, 646 (2010);
[89]. P. Patil and A. Paradkar, AAPS PharmSciTech., 7, E199 (2006);
[90]. A. Sookkasem, S. Chatpun, S. Yuenyongsawad and R. Wiwattanapatapee, J. Drug Deliv. Sci. Technol., 29, 159 (2015)
[91]. J.Y. Kim and Y.S. Ku, Int. J. Pharm., 194, 81 (2000);
[92]. K. Takada and M. Murakami. Glycyrrhizin Preparations for Transmucosal Absorption, US Patent 6890547 (2005).
[93]. B. Whittle and G. Guy, GW Pharma Ltd., Mucoadhesive Pharmaceutical Formulations. World Patent WO 02/064109A2 (2002).
[94]. G.M. El Maghraby, Colloids Surf. B Biointerfaces, 75, 595 (2010)
[95]. Z. Yu and S. Huth, Stable Ophthalmic Oil-in-Water Emulsions with Sodium Hyaluronate for Alleviating Dry Eye, United States Patent US 2007/0036829 (2007).
[96]. P.J. Dor, S. Mudumba, T. Nivaggioli and D.A. Weber, Formulations for Ocular Treatment, United States Patent US 2006/0182771 (2006).
[97]. Q. Wang, H. Zhang, J. Huang, N. Xia, T. Li and Q. Xia, J. Microencapsul., 35, 90 (2018);
[98]. C. Hu, G. Zhao, Q. Xia and R. Sun, J. Mater. Sci., 50, 6567 (2015);
[99]. Q. Wang, C. Hu, H. Zhang, Y. Zhang, T. Liu, A. Qian and Q. Xia, J. Microencapsul., 33, 785 (2016);
[100]. S. Tantarawongsa and T. Phaechamud, Thai Pharm. Health Sci. J., 6, 66 (2011).
[101]. K.P. Parthasarathi, D. Mudit, R. Prudhvi, D. Lavanya and L.N.V. Krishna, Int. Res. J. Pharm., 2, 82 (2011).
[102]. L. Zhang, L. Zhang, M. Zhang, Y. Pang, Z. Li, A. Zhao and J. Feng, Drug Deliv., 22, 475 (2015);
[103]. F.L. Yen, T.H. Wu, L.T. Lin, T.M. Cham and C.C. Lin, Pharm. Res., 26, 893 (2009);
[104]. J. Cui, B. Yu, Y. Zhao, W. Zhu, H. Li, H. Lou and G. Zhai, Int. J. Pharm., 371, 148 (2009);
[105]. M. Sierant, P. Paluch, M. Florczak, A. Rozanski and B. Miksa, Colloids Surf. B Biointerfaces, 111, 571 (2013)
[106]. Zhou, X. Zhu, G. Hung, N. Zhang and B. Zhang, Sheng Wu Yi Xue Gong Cheng XueZaZhi, 24, 918 (2007)
[107]. . J. Khan, A. Alexander, S. Ajazuddin, Saraf and S. Saraf, J. Control. Rel., 168, 50 (2013)
[108]. S. Li, Z. Ji, M. Zou, X. Nie, Y. Shi and G. Cheng, AAPS PharmSciTech, 12, 1011 (2011);
[109]. L. Wei, G. Li, Y.D. Yan, R. Pradhan, J.O. Kim and Q. Quan, Arch. Pharm. Res., 35, 1037 (2012);
[110]. Q. Cai, L. Liang, Y.P. Huang and S.X. Hou, ZhongguoZhongyaoZazhi, 32, 2003 (2007).
[111]. N. Chouhan, V. Mittal, D. Kaushik, A. Khatkar and M. Raina, Curr. Drug Deliv., 12, 244 (2015)