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Review Article

# A REVIEW ON SELF EMULSIFIED DRUG DELIVERY SYSTEM: A PROMISING APPROACH FOR DRUG DELIVERY OF BCS CLASS II AND IV DRUGS

Neha Tiwari*, Himansu Chopra, Manoj Sagar and Ashok Kumar Sharma
Department of Pharmacy, Gyani Inder Singh Institute of Professional Studies, Dehradun

## ABSTRACT

Purpose: The oral delivery of drugs having poor aqueous solubility presents a major challenge. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can improve the oral absorption of highly lipophilic drug compounds. The current review summarizes the latest research in the field of SEDDS and we emphasize basically the type of excipients used by current researcher.

Approaches: SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil- in- water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids.

Findings: Lipophilic drug compounds exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible plasma drug profiles.

Conclusion: Almost 40% of the new drug compounds are hydrophobic in nature which draws attention towards SEDDS to improve the oral bioavailability of such drugs.

Keyword : *Lipophilic drugs, Oral bioavailability, lipid formulations*

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## Introduction

Oral route is one of the most widely used routes for the chronic and newly diagnoseddiseases due to ease of administration and patient complience.[1,2] Current literature suggest that 40% of new chemical entities discovered in recent years have poor water solubility, which leads to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality[3]. Drugs with poor water solubility and high permeability belongs to BCS Class II drugs represent the technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption[4]. Self Emulsifying Drug Delivery system (SEDDS) is a new approach to improve the solubility of poorly soluble drugs. It can be ideally called as an isotropic mixture. Drugs which are lipophilic in nature can be formulated in this lipid based drug delivery system. SEDDS improves solubility thereby increases dissolution rate and bioavailability of drugs. Drug, oil, surfactant, solvent and co-solvent are the components of SEDDS. Self emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co surfactant and drug substance that rapidly form a fine oil-in-water micro (SMEDDS) and nano (SNEDDS) emulsions, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the GIT.[5,6]

*Corresponding Author:*
Neha Tiwari
Department of Pharmacy,
Gyani Inder Singh Institute
of Professional Studies, Dehradun
E. mail : tiwari.neha1994@gmail.com
Phone : 9758775654

## Types of SEDDS

**Table1: Types and comparative features of all self emulsifying formulations [7, 8]**

Isotropic mixture of the drug compound, surfactant, co-surfactant and lipid phase which emulsify under conditions of gentle agitation, when come in contact with gastro-intestinal fluid.

| Type of SEDDS | Comparative features | | |
|---|---|---|---|
| | Oil droplet size | Appearance | HLB value of Surfactants |
| Self-emulsifying formulations (SEFs) | 200 nm to 5 µm | Turbid | < 12 |
| Self micro emulsifying formulations (SMEFs) | Less than 200 nm | Optically clear to | |

## Advantages of self emulsifying drug delivery system [9, 10]

1. Enhanced bioavailability from oral route enabling reduction in dose.
2. More consistent and uniform profiles of drug absorption.
3. Helps in selective targeting of drug which have absorption window
4. Protect the drug from the unfavorable environment in gut.
5. Control of drug delivery profiles.
6. Reduced variability including food effects.
7. Protective for sensitive drug substances.
8. High drug payloads.
9. Liquid or solid dosage forms.

## Disadvantage of self emulsifying drug delivery system [11, 12]

1. Due to presence of high surfactant concentrationsthere may be chances of instabilities of drugs.
2. Also the high content of surfactant in selfemulsifying formulations irritates the gastrointestinal tract. This problem may be avoided by utilizing optimum less amount of surfactants.
3. Sometime co-solvents remain in the formulation and cause degradation of drugs.
4. It may allow less drug loading.

A new class of supersaturable SEDDS formulations can be used to reduce the surfactant side-effects and to achieve rapid absorption of poorly water-soluble drugs. The supersaturable SEDDS formulations contain less amount of surfactant and a polymeric precipitation inhibitor to stabilize a drug in a temporarily supersaturated state.

## Composition of SEDDS:

The SEDDs is commonly composed of the following:

Drug : The self emulsified drug delivery system can be used for all four categories of biopharmaceutical classification system (BCS) class drugs but the BCS class-II and class-IV categories of drugs are more needful as well suitable for the SEDDS formulations. Figure 1 showing drug candidates eligible for SEDDS delivery

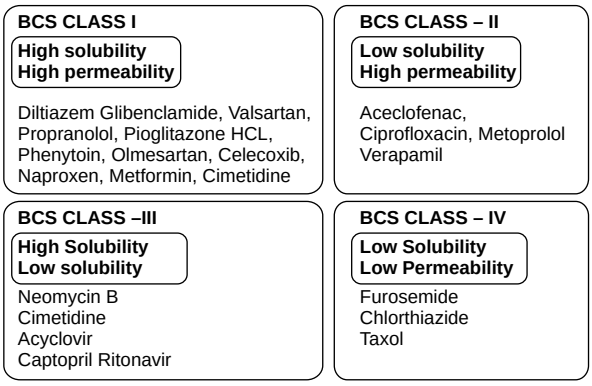


Fig. 1: Drug candidates suitable for SEDDS delivery

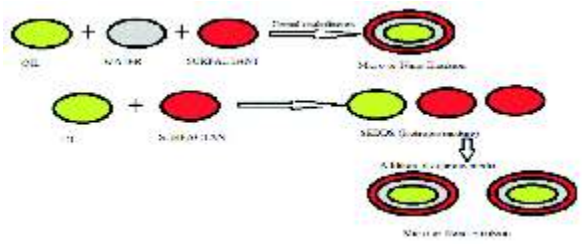

Fig. 2: Self-emulsification mechanism [13]

Self emulsifying drug delivery system form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution byan aqueous phase. A clear dispersion is formed rapidly from SEDDS and it should remain stable on dilution. The difference between normal emulsion and the emulsion formed from SEDDS after appropriate dilution is shown in Figure 2.

**Table 2: Marketed self emulsified dosage forms**

| Drug name | compound | Dosage form | Company |
|---|---|---|---|
| Neoral | Cyclosporin | Soft gelatin capsules | Novartis |
| Norvir | Ritonavir | Soft gelatin capsules | Abott laboratories |
| Fortavase | Saquinavir | Soft gelatin capsule | Hoffmann-LaRoche Inc. |
| Agenerase | Amprenavir | Soft gelatin capsule | Glaxosmithkline |
| Solufen | Ibuprofen | Hard gelatin capsule | Sanofi-Aventis |
| Lipirex | Fenofibrate | Hard gelatin capsule | Sanofi-Aventis |
| Sandimmune | Cyclosporine A/I | Soft gelatin capsule | Novartis |
| Targretin | Bexarotene | Soft gelatin capsule | Ligand |

## Surfactant

The choice of surfactants is limited as very few surfactants are orally acceptable. Generally co-surfactant of HLB value (10-14) is used in formulation of SMEDDS including Capmul MCM, Tween 20, Tween 80, Captex 200, PEG 35, Cremophore RH, Cremophore EL [14]. The role of surfactant is to enhance absorption of drug, because of induction of permeation changes in biological membrane. Numerous compounds exhibiting surfactant properties might be working for the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. It is reported that a cationic emulsion show greater absorption than an anionic emulsion. To form stable SEDDs, 30-60% concentration of surfactant is used [15].Different type of surfactants used with drugs in SEDDs and different type of surfactants used in marketed sedds are given in table 3 and table 4.

**Table 3: Type of surfactants used with drugs in SEDDs [16,17,18,19,20]**

| Surfactant | Drug |
|---|---|
| Tween 80 | Ibuprofen |
| PEG-35 | Cyclosporine-A |
| Cremophore EL | Furosemide |
| Cremophore RH 40 | Glibenclamide |
| Tween 80,Tween 20 | Diclofenac sodium |

**Table 4: Type of surfactants used in marketed SEDDs**

| Surfactant | Marketed Product | Drug |
|---|---|---|
| Cremophor RH 40 | Neoral soft gelatin capsule | Cyclosporine A |
| Span 20 | Kaletra tablet, soft gelatine capsule | Lopinavir |
| Gelucire 44/14 | Lipofen hard gelatine capsule | Fenofibrate |
| Polysorbate 80 | Targretin soft gelatin capsule | Bexarotene |

## Oils

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract[21,22].Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self emulsification markedly reduces their use in SEDDs. Long-chaintriglyceride and medium chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolysed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.[23]. Different types of oil used with drug in SEDDs and with marketed preparation are given in table 5 and table 6

**Table 5: Type of oil used with drug in SEDDs**

| Oil | Drug |
|---|---|
| Palm kernel oil | Ibuprofen |
| Castor oil | Cyclosporin-A |
| Captex 500 | Furosemide |
| Capmul MCM C8 | Glibenclamide |
| Lemon oil | Diclofenac Sodium |

**Table 6: Type of oil used in marketed preparation**

| Oil | Marketed Product | Drug |
|---|---|---|
| Corn oil | Sandimmune soft gelatin capsule | Cyclosporine A |
| Peppermint oil | Kaletra oral solutions | Lopinavir |
| Sesame oil | Marinol soft gelatin capsule | Dronabinol |
| Peanut oil | Prometrium soft gelatin capsule | Progesterone |

## Cosolvent

Usually an effective self emulsifying formulation requires a high concentration of surfactant. Cosolvents like diehylene glycol, monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydro-furfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co surfactant in the microemulsion systems. On the other hand, alcohol and other volatile co-solvents have the drawback of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of the drug.[24]

## Viscocity enhancer

The viscosity of the emulsions canbe altered by the use of additional material such as acetylalcohol, tragacanth, beeswax and stearic acids etc.

## Polymer

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

**Table 7: Some Patented formulation of SEDDS and SMEDDS [25]**

| U.S. PATENT No. | DATE | ACTIVE | INFORMATION |
|---|---|---|---|
| 7,749,540 | July 6,2010 | Modafinil | Particle-forming composition of modafinil compound and aqueouscomposition of particles comprise a modafinil compound are disclosed along with method of their prepration, uses and treatment of diseases. |
| 7,736,666 | June 15,2010 | Naproxan | The present invention claims a composition suitable for oral administration, in form of emulsionp re-concentrate, comprising a formula with one or more surfactant. |
| 6,652,865 | November 25,2003 | Simvastatin | A pharmaceutical composition of oral use is disclosed. The carrier include: therapeutically effective amount of active principle; a lipophilic phase. A method of decreasing the effect of intestinal metabolism on a drug using the composition is also disclosed. |
| 6,555,558 | April 29, 2003 | Pyranone protease inhibitors | A micro emulsion of pyranone protease inhibitors compound that issubstantially free of alcohol and propylene glycol comprising a pyranoneprotease inhibitors, one or more pharmaceutically acceptable surfactant, polyethylene glycol, di-glycerieds and optionally basic amine. |

## Evaluation of SEDDS[41, 42, 43]

1. Thermodynamic Stability Studies
   The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

1. Heating cooling cycle: Six cycles between refrigerator temperature 40ºC and 450ºC with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

2. Centrifugation: Passed formulations are centrifuged thaw cycles between 21$^0$C and 25 $^0$C with storage ateach temperature for not less than48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

2. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

3. Turbidimetric Evaluation : Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium(0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

4. Dispersibility test. The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 ml of water at 37 ± 0.5$^C$. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A Rapidly forming (within 1 min) nano-emulsion, having a clear or bluish appearance.

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

Grade C Fines milky emulsion that formed within 2 min.

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

Grade E Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

Table 8: current research in the field of SEDDS

| S.No | Research investigator | Year of publication | Drug | Surfactant/ cosurfactatnt | Conclusion |
|---|---|---|---|---|---|
| 1. | Wongsakorn Suchaoin | 2016 | 1,2-dipalmitoyl-sn-glycero-3-phosphatidic acid sodium (PA) | 30% Cremophor EL, 30% Capmul MCM, 30% Captex 355,10% propylene glycol (w/w) | Author reveled that negatively charged self emulsified drug delivery system is diffuse faster in a mucus layer as high extend of incorporated lumogen was present.[26] |
| 2. | Vrunda Suthar | 2016 | Lercanidipine hydrochloride (LCH) | Tween 80, propionic acid | The dose absorbed to improve the fraction is derived from plasma concentration time profile suggest that more than 90% drug is absorbed from S-SEN. Hence S-SEN can be proposed as useful dissolution enhancement strategy for LCH[27] |
| 3. | Caibiao Hu | 2016 | Resveratrol | Hydrophilic surfactants | The author reveled that resveratrol from SEDDS will be higher than the drug permeation from the same dose of the free form aqueoussolution.[28] |
| 4. | Apurva R. Patel | 2016 | 3,3 Diindolylmethane-14 (DIM-14) | Labrafil, tween 80 | The author revaled that the potential application of SEDDS enhances oral absorption of DIM-14 and increased anti-tumor activity against lung tumor models.[29] |
| 5. | Ozbej Zupancic | 2016 | Daptomycin | 35% Dermofeel MCT, 30% Capmul MCM and 35% Cremophor Rh40 | The oral self emulsified drug delivery system of daptomycin is exhibit the mucus permeating properties as well as protective effect toward drug degradation by α-chymotrypsin. According to this SEDDS containing 8% DAP/DOA complex may be considered as a new potential oral delivery system for daptomycin.[30] |
| 6. | Katla Venu Madhav | 2016 | losartan (LOS) | Capmul MCM 24%; Cremophor EL 37.5%; Transcutol P 37.5%;1% stearyl amine | The author reveled that self micro emulsifying drug delivery system of losartan in wistar rats was 2.82 times more than a drug suspension and stable for 3 months at room temperature.[31] |
| 7. | Vijaykumar Nekkanti | 2016 | Nisoldipine | Capmul MCM, Labrasol, Cremophor EL, Tween 80 | The author reveled that nisoldipine permeability across parallel artificial membrane permeation assay (PAMPA) and everted rat intestinal perfusion models was significantly higher with proliposomes and SEDDS. The Single oral administration of proliposomes and SEDDS, a relative bioavailability of 301.11% and 239.87% respectively, was achieved compared to pure nisoldipine suspension.[32] |
| 8. | Sunil K. Yadava | 2015 | Lovastatin | Capmul MCM , Tween 80 | The author revealed that the hydrogel system would be a potentially valuable tool for improving the oral bioavailability of lovastatin .33[] |
| 9. | Krishna Mohan Chinnala | 2015 | Furosemide | Tween 20, Cremophore RH 40 | The author reveled that If the viscosity of the oil and co-surfactant used is high or the content of Tween20 is very high will lead to a low emulsification rate and the emulsification time will be greater.[34] |
| 10. | Rajesh B. Nawale | 2015 | Ketoprofen | Polyoxyethelene 20, Sorbitan Monooleate (Tween 80) | Solid SEDDS of Ketoprofen had been designed by using silicon dioxide as adsorbent. Author revealed that by increasing the concentration of silicon dioxide increase in average droplet size was observed.[35] |
| 11. | C. Aparma | 2015 | Lornoxicam | Capryol 90, Tween 20, Tween 80, Transcutol P | They concluded that, the in vitro drug release of Lornoxicam SEDDS was sustained (87.12% for 24 hours) when compared to marketed formulation Lornoxi (tablet) (100% at 90 mins). Pharmacodynamic studies performed by inhibition in paw edema (75%) for the test formulation after 4hours as compared to the standard formulation (56 %.).[36] |
| 12. | Obitte Nicholas | 2015 | Ibuprofen | Labrasol, lauroglycol 90 | They conclude that the self emulsified drug delivery system of Ibuprofen improved the aqueous solubility of Ibuprofen and its anti-inflammatory activity.[37] |
| 13. | Ahmed A. Hussein | 2014 | Mebendazole | Oleic acid, Tween-80 | The author revealed that the In-vitro drug release and in-vivo plasma drug concentration of microemulsion and SMEDDS of mebendazole was much higher than that of marketed preparation.[38] |
| 14. | Hyma. P | 2014 | Glimepiride | Tween 80, Transcutol | They concluded that the SEDDS improving the solubility and bioavailability of the poorly water soluble BCS Class II drug glimepiride as indicated in results.[39] |
| 15. | A. S. Chudasama | 2014 | Nevirapine | oleic acid, caprylic acid,soluphor P | The author revealed that the bioavailability of nevirapine from self-emulsifying drug delivery system, after oral administration, was 2.69 times higher than that of the marketed suspension.[40] |

5. Viscosity Determination: The SEDDS system is generally administered in soft gelatin or hard gelatine capsules. So, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosity then it is w/o type of the system.

6. Droplet Size Analysis Particle Size Measurements
   The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nano-metric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.

7. Refractive Index and Percent Trans-mittance
   Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water(1.333) and formulation have percent transmittance > 99 percent, then the formulation have transparent nature.

8. Electro conductivity Study
   The SEDD system contains ionic or nonionic surfactant, oil, and water. So, this test is used to measure the electroconductive nature of system. The electro conductivity of resultant system is measured by electroconductometer.

9. In Vitro Diffusion Study
   In vitro diffusion study is performed to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique.

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

## CONCLUSION:

Self-emulsifying drug delivery system is a promising tool for the formulation development of drugs compounds having poor aqueous solubility. Development of this technology SEDDS will continue to enable novel applications in drug delivery system. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and traditional preparation of SEDDS involves in enhancement of dissolution of drugs in oils and their blending with suitable solubilizing agents.

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