Review Article
CODEN (USA): IJPLCP

[Singh et al., 3(9): Sep., 2012]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Self emulsifying drug delivery systems (SEEDS): An approach for delivery of poorly water soluble drug

Gajendra Singh*, M.P.Khinchi, M.K.Gupta, Dilip Agrawal, Adil Hussain and Natasha Sharma
Department of Pharmaceutics, Kota College of Pharmacy, Kota, (RJ) - India

Abstract

Oral route is the easiest and most convenient route for drug administration. The major problem in oral drug formulation is low erratic bioavailability. This may lead to high inter and intra variability lack of dose proportionality and therapeutic failure Self-emulsifying drug delivery systems (SEDDS) have gain exposure to improve the bioavailability of hydrophobic drugs. SEDDSs are belongs to lipid formulations, and size range is from100nm (SEDDs) to less than 50nm (SMEDDs) and contains an isotropic mixtures of oils, surfactants, and co-surfactants, which are emulsified in aqueous media under conditions of gentle stirring. SEDDS can be orally administered in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution.

Key-Words: Improvement of bioavailability, self-emulsifying drug delivery, Oral route

Introduction

The oral route is the most popular route among all the route of administration. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.[1]To overcome these problems, a variety of strategies have been developed including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions, and self emulsifying drug delivery system, etc. self-emulsifying drug delivery systems to improve the oral bioavailability of lipophilic drugs.[2] Self-emulsifying drug delivery systems SEDDSs has gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants, sometimes containing cosolvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds.[3]

*** Corresponding Author**
E.mail: jaduangajendra@gmail.com
Mob.: +91-7737567731

Why SEDDS are needed [4]

SEDDS are promising approach for oral delivery of poorly water soluble compounds. It can be achieved by pre-dissolving the compounds in suitable solvents and fill the formulations into capsules. Pre-dissolving the compounds overcome the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract.

Advantages of SEDDS [5]

- Improvement and reduction in the variability of GI absorption of poorly water soluble, lipophilic drugs.
- Possible reduction in, or elimination of, a number of development and processing steps (e.g., salt selection or identification of a stable crystalline form of the drug, coating, taste masking, and reduced need for containment and clean-up requirements during manufacture of highly-potent or cytotoxic drug products).
- Food does not interfere with the absorption of drug by use of such systems.
- Relative ease of manufacture using readily available equipment.
- The dose ranging from less than 25 mg to greater than 2000 mg can be administered by using these systems.
- These systems enhance oral bioavailability due to by pass of hepatic metabolism and delivers drug directly into systemic circulation.

- Inhibition of p- glycoprotein mediated drug efflux and pre absorptive metabolism by gut membrane bound cytochrome enzyme.
- Protection of sensitive drug substances
- High drug payloads.
- Liquid or solid dosage forms.
- Reduced energy requirement for emulsion formation.
- Control of Delivery Profile
- Promotion of lymphatic drug transport.
- They enhance absorption of lipophilic drugs by stimulating pancreatic and biliary secretions and by prolongation of gastric residence time.

Disadvantages of SEDDS [1,6]

- Lack of good predicative in vitro models for assessment of the formulations.
- Traditional dissolution methods do not work, because formulations dependent on digestion prior to release of the drug.
- In vitro model needs further development and validation.
- Different prototype lipid based formulations needs to be developed and tested in vivo.
- Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) may irritate GIT.
- Volatile co solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- Formulations containing several components become more challenging to validation.

Mechanism of Self Emulsification [4,7]

According to "Reiss" self emulsification occurs when the entropy changes that favor dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phase and can be described by the equation-

$$DG = SNPr2s$$

Where, DG is the free energy associated with the process (ignoring the free energy of mixing),

N is the number of droplets of radius r and s represents the interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents,which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then,the emulsification process occurs spontaneously).

Examples of oils, surfactant and co-surfactant.

Composition of SEDDS[3,7,8]

The self-emulsifying process is depends on:

- The nature of the oil–surfactant pair
- The surfactant concentration
- The temperature at which selfemulsification occurs.

Surfactant

Surfactants are formed by two parts with different affinities for the solvents. One of them has affinity toward the water (polar solvents) and the other has for oil phase (non-polar solvents). A little amount of surfactant molecules are rest upon the water-air interface and decrease the water surface tension value (the force per unit area needed to make available surface).

The surfactants used in self emulsifying formulations are known to improving the bioavailability by various mechanisms including: increased intestinal epithelial permeability, improved dissolution increased tight junction permeability to GIT.

Cosolvents

Co-surfactant/Co-solvents like Spans, capyrol 90, Capmul, lauroglycol, diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl 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 cosurfactants in the microemulsion systems.

Oil

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate selfemulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages.

Table1. Examples of oils, surfactants, cosurfactant and cosolvents used in Self Emulsifying [7]

Oils	Surfactants	Cosurfactants/ Cosolvent
Cotton seed oil Soybean oil Corn oil Sunflower oil Sesame oil Peanut oi Labrafac Labrafil Castor oil	Polysorbate 20 (Tween 20) Polysorbate 80 (Tween 80) Labrasol Polyoxy-40-hydrogenated castor oil(Cremophor RH40) D-alpha Tocopheryl polyethylene glycol 1000 succinate	Span 20 Span 80 Capryol 90 Capmul Ethanol Polypylene glycol Polyethylene glycol

Dosage Forms from Self-Emulsifying System [5,2,9,7]

Dry Emulsions

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be further prepared as tablets and capsules. Dry emulsion formulations are typically prepared from oil/water (o/w) emulsions containing a solid carrier (lactose, maltodextrin etc) in the aqueous phase by rotary evaporation, freeze-drying or spray drying.

Self emulsifying suppositories

Some investigators proved that solid-SEDDs could not only increase the GI absorption but also increase the rectal/vaginal adsorption. Glycyrrhizin, hardly achieves therapeutic plasma concentrations by oral route, but can achieve acceptable therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6– C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.

Self-emulsifying solid dispersions

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling SE excipients like Gelucire1 44/14, Gelucire1 50/ 02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field.

Self emulsifying beads

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

Self Emulsifying Sustained/ Controlled Release Tablets

These controlled/ sustained release tablets can be prepared by using a combination of polymers.The newest advancement in the research field of self emulsifying tablet is the self emulsifying osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of self emulsifying system (SES). This system has outstanding features such as stable plasma concentrations and controllable drug release rate.

Evaluation [3,4,9,10,11,12]

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.

- Heating cooling cycle: Six cycles between refrigerator emperature (40C) and 450C 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.
- Centrifugation: Passed formulations are centrifuged thaw cycles between 21 0C and +25 0C with storage at each temperature for

not less than 48 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.

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

Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size.

Electro Conductivity Study

The SEDD system contains ionic or non-ionic surfactant, oil, and water.This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

Viscosity Determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. so, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of microemulsion are evaluated by Brook Field viscometer it is o/w types and if a high viscosity it is w/o types.

Dispersibility test

The efficiency of self emulsification of oral nano or microemulsion is assessed using a standard USP apparatus.

The in vitro performance of the formulations is visually assessed using the following:

- Grade A: rapidly forming(within 1 min) nanoemulsion, Having a clear white appearance.
- Grade B: rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- Grade C: fine milky emulsion that formed within 2 min.
- Grade D: dull, grayish white emulsion that formed longer than 2 min.
- Grade E: poor and minimal emulsification.

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.

Solidification techniques for transforming liquid/semisolid SEDDS to S-SEDDS [9,13,14,15]

Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

Adsorption to solid carriers

Free flowing powders may be obtained from liquid SE formulations (LSEF) by adsorption to solid carriers. The adsorption process is simple and involves only addition of the liquid formulation to carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels up to 70% w/w onto suitable carriers . Solid carriers can be microporous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents. For example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crosspovidone.

Melt Extrusion/Extrusion Spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%) as well as content uniformity. The extrusion–spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The steps involved in extrusion–spheronization process: dry mixing of the active ingredients and excipients to achieve a momogenious powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating.

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a one-step operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the

subsequent drying phase are omitted. A wide range of solid and semisolid lipids can be applied as meltable binders. The melt granulation process was usually used for adsorbing self emulsifying system (lipids, surfactants and drugs) onto solid neutral carriers mainly silica and magnesium aluminometa silicate.

Capsule filling with liquid and semisolid self emulsifying formulation –

It is the simple technology for the encapsulation of liquid or semisolid formulation .it is the four step process –

- Heating Of Semisolid Excipient To At Least 20c Above Its Melting Point.
- Incorporation of Active Substances with Continous Stirring.
- Capusle Filling with the Molten Mixture.
- Cool At Room Temp.

For Liquid Formulation It Involve A Two Step –

- Filling Of Formulation In To
- Sealing of the Body and Cap of the Capsule either by Banding or by Micro spray Sealing.

Examples of some marketed products in which it has been used.[2]

- Vesanoid soft gelatin capsule
- Gengraf hard gelatin capsule
- Ritonavir soft gelatin capsule
- Ritonavir oral solution
- Sandimmune soft gelatin capsules
- Sandimmune oral solution
- Agenerage Soft gelatin capsule
- Agenarage oral solution
- Nerol soft gelatin Capsule
- Nerol Oral Solutio

Conclusions

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. Solid- SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration and GI irritation is avoidable and controlled and sustained release of drug of drug release is achievable.

References

1. Sharma Vijay , Saxena, Pratiush Lalit Singh, Singh Pooja , Self Emulsifying Drug Delivery System, Journal of Pharmacy Research, 2011, pp.500-504
2. Sunitha R., Satya Sireesha D and Aparna M.V. L. Novel Self-Emulsifying Drug Delivery System- an Approach To Enhance Bioavailability of Poorly Water Soluble Drugs Ijrpc ,1, 2011, pp.828-838
3. V Khasia Hetal 1 and D Khasia Vasant, A Review on Self Emulsifying Drug Delivery 1, 2012, pp.353-359
4. Khinchi M. P., Gupta Akanksha, Gupta, M. K., Agrawal D., Sharma N., Malav A.,Singh A, Self Emulsifying Drug Delivery System, Asian Journal of Biochemical and Pharmaceutical Research.,1, 2011, pp.359
5. Sharma S., Sharma A.D , Chauhan B., Sanwal R ,Self Emulsifying Drug Delivery Systems: A Modern Approach for Delivery of Lipophilic Drug,Ordonear research library, 2011, pp.121
6. Shukla Jill B., Koli Akshay R., Ranch Ketan M. and Parikh Rajesh K, Self Micro Emulsifying Drug Delivery System, Pharma Science Monitor an International Journal of Pharmaceutical Sciences, 2010, pp.13-33
7. Kumar Ajay, Sharma Surabhi Kamble, Ravindra, Self Emulsifying Drug Delivery System (Sedds), International Journal of Pharmacy and Pharmaceutical Sciences ,4, 2010.
8. Solanki Trupti B , Thakar Divyesh M., Drbharadia. P. D., M.Pandya V. M and Modi. D.A, Self-Emulsifying Drug Delivery System: an Alternative Approach for Poorly Water Soluble Drugs, Ijpi journals, 15, 2011, pp.98-109
9. Pawar Sagar D, Waghmare Amol S, Pawar Ravi G, Gadhave Manoj, Self-Emulsifying Drug Delivery System, Ijupls, 2012, pp.223
10. Patel Pa , Chaulang Gm, A Akolkotkar, Mutha Ss, Hardikar Sr ,Bhosale Av, Self Emulsifying Drug Delivery System, Rjpt. 2008, pp.313-323
11. Sanket Shah P. Mansi Shah D., Yadvendr Agrawal, Self- Micro Emulsifying Drug Delivery System: A Novel Approach For Enhancement of oral Bioavailability of Poorly Soluable Drugs, Ajptr, 2012, pp.445
12. R1 Sachan , K Khatri, S. Kasture B., Self-Eumlsifying Drug Delivery System A Novel Approach For Enhancement of Bioavalibility, International Journal of Pharmtech Research Coden (Usa): Ijprif ,2010, pp.1738-1745
13. Katteboinaa Suman, Chandrasekhar VSR, Pb,Balaji, Solid Self-Emulsifying Drug Delivery Systems/Asian Journal Of Pharmaceutical Sciences 4 , 2009, pp.240-253

14. V.Mallikarjuna,and V.Rajesh Babu,,Self-Emulsifying Therapeutic System; Ijprbs, 2, 2011, pp.18-22
15. Solanki Nitesh, Prajapati Snehal, Self Emulsifying Drug Delivery System ,Ijprbs,1, 2012, pp.20-29.
16. Wadhwa Jyoti , Nair Anroop, Kumria Rachna, Self-Emulsifying Therapeutic System: A Potential Approach For Delivery of Lipophilic Drugs, Brazilian Journal of Pharmaceutical Sciences, 47, 2011, pp.448

Different categories of drugs, formulations and excipients used in self-emulsifying therapeutic range [16]

Category	Drug (s)	Formulation type	Excipients (oil, surfactant(s), co-surfactant/ cosolvent)	Comments	References
Antimalarial agents	Halofantrine	SEF (Powder)	Soybean oil: Maisine Cremophor EL Absolute ethanol	selfemulsifying formulations of Halofantrine improved oral bioavailability significantly (~6-8fold) relative to previous data of the solid Halofantrine HCl tablet formulation	Khoo *et al.* (1999)
Calcium channel blocker	Nitrendipine (NTD)	SEF (pellets)	Miglyol 812 Cremophor® RH40 andTween80 (2:1) Transcutol P	AUC of NTD of SE pellets was 1.6-fold greater than the conventional tablets and were comparable with the liquid SEFs.	Wang *et al.* (2010)
Benzoquinone derivative	Coenzyme Q10 (CoQ10)	SNEFs	Lemon oil Cremophor EL Capmul MCM-C8	Cumulative percent of CoQ10 released within 8 h ranged from 40.6% to 90%.	Nazzal, Khan (2006)
NSAIDS	Nimesulide	SEF (Pellets)	Mono and diglycerides Polysorbate 80	Bioavailability: Pellets>Emulsions.	Francesc hinis *et al.* (2005)
Immuno-suppressants	Cyclosporina	SNEFs	Phospholipids Chremophor RH 40, Tween80, Span 80	Higher AUC and Cmax with lipospheres of small diameter.	Bekerma n *et al.* (2004)
Diuretics	Furosemide	SMEF	Mygliol 812® Caprylocaproyl macrogol glycerides, Labrasol® polyglyceryl-6 dioleate PlurolOleique	Self-microemulsifying cores with completely solubilized drug (SMEFs with 1 and 5% furosemide) exhibited the fastest release profiles with pronounced initial release.	Zvonar *et al.* (2010)
Barbiturate derivative	Diazepam	SEF (pellets)	C18 mono and di-glycerides Solutol HS15	Significant improvement in the *in vitro* dissolution of diazepam compared to the release from the non-emulsifying formulation.	Abdalla, Mader (2007)