INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Review Article

RECENT TRENDS IN DEVELOPMENT OF SOLID-SELF EMULSIFYING DRUG DELIVERY (S-SEDDS) SYSTEMS: AN OVERVIEW

V. Mallikarjun*[1], V. Rajesh Babu[2]
[1]Department of Pharmacy, SR College of Pharmacy, Kakatiya University, Warangal, A.P, India
[2]Department of Pharmacy, MESCO College of Pharmacy, Hyderabad, A.P, India

Article Received on: 13/04/2011 Revised on: 20/05/2011 Approved for publication: 09/06/2011

*V.Mallikarjun, Department of Pharmaceutics, SR College Of Pharmacy, Ananthasagar, Hanamkonda Warangal-506371 India Email; mallikarjunvasam@gmail.com

ABSTRACT
According to an FDA survey conducted between 1995 and 2002, only 9% of the new drug entities belonged to BCS class-I category, majority of new drug candidates (approximately more than 40%) have poor aqueous solubility because of their low bioavailability. Self emulsifying drug delivery systems (SEDDS) are a class of lipid based delivery systems consisting of oil, one or more surfactants and optionally a co-surfactant that spontaneously emulsifies to form oil-in-water micro and nano-emulsions under gentle mixing conditions in the gastrointestinal environment. These systems have shown great promise for enhancing bioavailability of low solubility compounds. Conventional SEDDS are normally prepared in a liquid dosage form that can be administered in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. Accordingly, Solid-self emulsifying drug delivery systems (S-SEDDS), prepared by solidification of liquid/semi-solid self emulsifying ingredients into powders in order to create solid dosage forms. This article focuses on the recent trends in the development of S-SEDDS, especially the related solidification techniques.
KEY WORDS: Self emulsifying drug delivery systems, Bioavailability, Oils and Surfactants.

INTRODUCTION

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 (O/W) emulsion/lipid droplets, ranging in size from approximately 100 nm, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the GIT. Recently, SEDDS have been formulated using medium chain triglyceride oils and non-ionic surfactants, the latter being less toxic. A potential advantages of these systems include enhance oral bioavailability enabling dose reduction, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GIT, and drug protection from the hostile environment in the gut, control delivery profiles, reduced variability including food effects, protective of sensitive drug substances, high drug pay loads[1-5].

SEDDS are generally encapsulated in either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell, to avoid this limitation, liquid lipid formulations could be transformed into free flowing powder by loading the formulation on a suitable solid carrier combines the features of a lipid based drug delivery systems and solid dosage forms. Thus, S-SEDDS combine the advantage of SEDDS, i.e., enhanced solubility and bioavailability, with those of solid dosage forms, for example, low production cost, convenience of process control, high stability and reproducibility, better patient compliance. SEDDS loaded powder however should have acceptable flow properties to facilitate capsule or tablet manufacturing in order to pass compendial limit for content uniformity and weight variation .

S-SEDDS have been extensively exploited in recent years, as they frequently represent more effective alternative to conventional liquid SEDDS. From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanopaticles by different solidification techniques (e.g. adsorption to solid carriers, spray drying, melt extrusion, nano-particle technology). Such powders / nano particles, which refer to SE nanoparticles/dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsule into

which liquid/semisolid SEDDS are directly filled without any solidifying excipient[4].Few examples of self-emulsifying systems are showed in table 1.

In the 1990s, solid-self emulsifying drug delivery systems (S-SEDDS) were usually in the form of self emulsifying capsules, self emulsifying solid dispersions and dry emulsions, but other solid self emulsifying dosage forms have emerged in recent years, such as self emulsifying pellets/tablets, self emulsifying microspheres/nanoparticles and self emulsifying suppositories/implants[5].

ADVANTAGES OF SEDDS OVER EMULSION

- ✓ SEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting over a long time. SEDDS can be easily stored since it belongs to a thermodynamics-stable system.
- ✓ SEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.
- ✓ Emulsion can not be autoclaved as they have phase inversion temperature, while SEDDS can be autoclaved.
- ✓ Microemulsions formed by the SEDDS exhibit good thermodynamics stability and optional transparency. The major difference between the above microemulsions and common emulsions lies in the particle size of droplets[4,6,8].

COMPOSITION OF SEDDS

The self-emulsifying process depends on:

- ❖ The nature of the oil-surfactant pair
- ❖ The surfactant concentration
- ❖ The temperature at which self-emulsification occurs.

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 . Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS 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 [6].

Surfactant: Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules (Table 2).

Cosolvents: Cosolvents like 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 co surfactant in the microemulsion systems [7-8].

FORMULATION OF SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble co solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SEDDS [9-10]

- The solubility of the drug in different oil, surfactants and cosolvents.
- The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.
- The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and cosolvent.

The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent.

SOLIDIFICATON TECHNIQUES FOR CONVERTING LIQUID/SEMISOLID SEDDS TO S-SEDDS

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 [10].

Adsorption to solid carriers

The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resultant powder may then be filled directly into capsule or alternatively, mixed with suitable excipients before compression into tablets. The major advantage of using this technique is good content uniformity. SEDDS can be adsorbed at higher levels (up to 70% w/w) onto suitable carriers. Solid carrier can be microporous substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbent, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone[11].

Extrusion spheronization

The extrusion spheronization process is commonly used in the pharmaceutical industry to make uniformly sized pellets. This process requires the following steps:

Mix dry active ingredients and excipients to form a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids uniform size; drying; sifting to achieve the desired size distribution. Applying this technique, self emulsifying pellets of diazepam and progesterone has been prepared to provide a good *in vitro* drug release (100% with in 30 min, $T_{50\%}$ at 13 min) and bi-layered cohesive self emulsifying pellets have also been prepared [12].

Melt extrusion

Melt extrusion is a solvent-free process that allows high drug loading approximately 60%. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing through a die under controlled temperature, product flow, and pressure conditions. The size of the extrude aperture will determine the approximate size of the resulting spheroids (Pellets) [13].

Spray drying

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 evaporates, and forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules [14-15].

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid self emulsifying formulations for the oral route. For semisolid formulations, it is a four-step process: i) heating of the semisolid excipient to at least 20^{o}C above its melting point ii) incorporation of the active substance with continuous stirring iii) capsule filling with the molten mixture and iv) cool at room temperature. For liquid formulations it involves a two-step process: i) filling of the formulation into the capsules ii) sealing of the body and cap of the capsule, either by banding or by microspray sealing [16].

EVALUATION STUDIES

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 capsule shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug [17, 23].

- Heating cooling cycle: six cycles between refrigerator temperature (4^{0}C) and 45^{0}C with storage at each temperature of not less than 48 hrs is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
- Centrifugation: Passed formulations are centrifuged thaw cycles between 21^{0}C and +25^{0}C with storage at each temperature for not less than 48 hrs 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 test: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

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 drug [24].

***In Vitro* Diffusion study**

In vitro diffusion studies are performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.

Electro conductivity study

The SEDD system contains ionic or non-ionic surfactant, oil and water. So this test is used to measure the electro conductive nature of system. The electro conductivity of resultant system is measured by electroconductometer [25].

Refractive index and Percent transmittance

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. 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 and formulation have percent transmittance >99 percent. Then formulations have transparent nature.

Turbid metric 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 (0.1 N HCL) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using turbid meter. 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).

CONCLUSION

Solid-self emulsifying drug delivery systems (S-SEDDS) are very flexible to develop various dosage forms for oral and parenteral administration, and superior in reducing cost, simplifying industrial manufacture and improving stability as well as patient compliance. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable.

REFERENCES

1. Jing ling Tang, Jin Sun Zhong Gui He, Self emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs, Current drug therapy 2007; 2: 85-93.
2. Obitte NC, Ezeiruaku H, Preliminary studies on two vegetables oil based self emulsifying drug delivery system for the delivery of metronidazole: A poorly water soluble drug, Journal of applied sciences 2008; 8(10): 1950-1955.
3. Jingling Tang, Jin Sun, preparation of self emulsifying drug delivery system of Ginkgo biloba extracs and *in vitro* dissolution studies, Asian journal of traditional medicines 2006; 1(3):1-4.
4. Jayvadan Patel and Anand Shah, self emulsifying delivery systems for poorly absorbed drugs, Int. J. Phrrm.sci. And Nanotechnology 2008; 1(2): 123-127.
5. Gursoy RN, Benita S, self emulsifying drug delivery systems for improved oral delivery of lipophilic drugs, Biomed Pharmacother 2004; 58(3):173-82.
6. Vikas Agarwal and Akhtar siddiqui. Dissolution and powder flow characterization of solid self emulsified drug delivery systems. Int J Pharm, 2005; 12(2):1-9.
7. Bo Tang, Gang Cheng, Development of solid self emulsifying drug delivery systems: preparation techniques and dosage forms, Drug discovery 2008; 13(13/14): 606-612.
8. Cannon JB. Oral solid dosage forms of lipid-based systems.; Am.Pharmaceut Rev, 2005; 8(1): 108-115.
9. Craig DQM and Lievens HSR. An investigation into the physico chemical properties of self emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements particle size analysis. Int. J Parma,1996; 147-155.
10. Newton JM, The rheological properties of self emulsifying systems, water and microcrystalline cellulose, Eur J Pharm Sci 2005; 26: 176-183.
11. Lijuan Wang, Jinfeng Dong, Design and Optimization of a new self nano emulsifying drug delivery system, Journal of colloid and interface science 2008; 1-6.
12. Fulden Buyukozturk and Hong Long. Self emulsifying drug delivery system release kinetics. Dependence on physical and chemical emulsion formulation properties. Nanosystems for drug delivery. 2007;18(2):25-27.
13. Tao Yi., Jiangling Wan. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. Eur. J.Pharm. and Biopharm. 2008; 70:439-444.
14. Wei Wu., Yung wang Li Que. Enhanced bioavailability of silymarin by self-microemulsifying drug delivery system. Eur.J.Pharm and Biopharm. 2006; 63:288-294.
15. Madhav Vasanthavada., Abu T M Serajuddin. Lipid based self-emulsifying solid dispersions. Drugs and the Pharmaceutical sciences.2006; 170: 149-182.
16. Shafiq. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur. J. Pharm. Biopharm 2007; 66:227-243.
17. Patil, Vandana, Paradkar. Formulation of SEDDS for oral delivery of simvastatin: in vitro and in vivo evaluation. Acta Pharma 2007; 112-122.
18. Patil, Joshji, Paradkar. Effect of formulation variables on preparation and evaluation of gelled SEDDS of ketoprofen. AAPS Pharm Sci Tech 2004; 5(3): 34-42
19. Robert G Strickley. Currently marketed oral lipid based dosage forms: drug products andexcipients. Drugs and the Pharmaceutical sciences. Vol 170:1-31.
20. Lowell Gibson. Lipid based excipients for oral drug delivery, Drugs and the Pharmaceutical sciences. Vol 170:33-61.
21. Lijuan wang and Jinfeng Dong. Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid Interface Sci. 2008;16(1):24-27.
22. Pouton CW. Formulation of self-emulsifying drug delivery systems. Adv Drug Delivery Rev. 1997; 25:47-58.
23. Pradeep Patil., Prasad Joshi. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery (SEDDS) of ketoprofen. AAPS PharmSciTech 2004; 5(3): 1-5.
24. Wasan KM. Formulation and physiological and biopharmaceutical issues in the development of oral lipid based drug delivery systems. Drug Dev. Ind. Parm.2001; 27(4): 26-28.
25. Ping Gao. and Walter morozowich. Design and development of supersaturable SEDDS for enhancing the gastrointestinal absorption of poorly soluble drugs. Drugs and the pharmaceutical science.2008;14(1): 30-32 .

Table: 1 Examples of Pharmaceutical Products formulated as self-emulsifying systems

Drug Name	Compound	Dosage form	Company	Indication
Juvela®	Tocopherol nicotinate	Soft gelatin capsule	Eisai Co.	Hypertension, Hyperlipidemia
Selbex®	Teprenone	Hard gelatin capsule	Eisai Co.	Acute gastritis
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno suppressant
Restandol®	Testosterone undecanote	Soft gelatin capsule	Organon Labs.	Hormone replacement therapy
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Lipirex®	Fenofibrate	Hard gelatin capsule	Genus	Antihyper-lipoproteinemic
Infree®	Indometacin farnesil	Hard gelatin capsule	Eisai Co.	Anti-inflammatory and analgesic
Epadel®	Ethyl icosapentate	Soft gelatin capsule	Mochida Pharmaceuticals.	Hyperlipidemia
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporin A/III	Hard gelatin capsule	Abbott Laboratories	Immuno suppressant
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Glakay®	Menatetrenone	Soft gelatin capsule	Eisai Co.	Osteoporosis
Fenogal®	Fenofibrate	Hard gelatin capsule	Genus	HIV antiviral
MXL®	Morphine sulfate	Hard gelatin capsule	Napp Pharmaceuticals.	Analgesic

Table: 2 Solubilizing excipients used in commercially available Lipid based oral formulations

Water-insoluble excipients	**Triglycerides**	**Surfactants**
Bees wax	Corn oil	Glyceryl mono-oleate
Oleic acid	Peanut oil	polyoxyl 35 castor oil
Soy fatty acids	Hydrogenated soyabean oil	Polyoxyl 40 hydrogenated castor oil
medium chain(C_8/C_{10}) mono and diglycerides	Hydrogenated vegetable oil	Polysorbate 20 (tween 20)
propylene glycol esters of fatty acids	Caprylic/capric triglycerides	Polysorbate 80 (tween 80)