Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 4, Issue 2, 2012

Review Article

SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH

NAISARG D. PUJARA*[1]

[1] Department of Pharmaceutics, S. J. Thakkar Pharmacy College, Rajkot – 360005, India. Email: naisargpujara2007@gmail.com

Received: 21 March 2012, Revised and Accepted: 31 March 2012

ABSTRACT

Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost-effective and leads the worldwide drug delivery market. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. It is estimated that 40% of active substances are poorly water soluble (water insoluble in nature). For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Various technological strategies are reported in the literature including solid dispersions, cyclodextrines complex formation, or micronization, and different technologies of drug delivery systems. Including these approaches self-emulsifying drug delivery system (SEDDS) has gained more attention for enhancement of oral bio-availability with reduction in dose. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or micro-emulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

Keywords: Self emulsifying drug delivery system (SEDDS), Oil, Co-surfactant, Surfactant, Self-micro-emulsifying drug delivery systems (SMEDDS).

INTRODUCTION

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. To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions [1,2]. Recently, much attention has been paid to lipid based formulations with particular emphasis on self-emulsifying drug delivery systems (SEEDS) to improve the oral bioavailability of lipophilic drugs. SEEDS or self-emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively one or more hydrophilic solvents and co-solvents/ surfactants. Upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsions [3,4,5]. 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 encountered during extended contact between bulk drug substances and the gut wall. An additional 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. Table 1 shows Examples of some pharmaceutical product formulated as self emulsifying system [6]. SEEDS formulations have also attracted interest because they can improve the bioavailability of compounds that fall into Class II of the biopharmaceutical classification system (BCS). Class II compounds are poorly water soluble and highly permeable .The difference between SEDD and SMEDDS in Table-2.

ADVANTAGES [7]

1. Protection of sensitive drug substances
2. More consistent drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT
4. Protection of drug(s) from the gut environment.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Enhanced oral bioavailability enabling reduction in dose
8. High drug loading efficiency
9. For both liquid and solid dosage forms

LIMITATIONS

One of the obstacles for the development of self emulsifying drug delivery systems (SEEDS) and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations [4,8]. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an *in vitro* model simulating the digestive processes of the duodenum has been developed. 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. Future studies will address the development of the *in vitro* model [6,9].

COMPOSITION

The self-emulsifying process depends on [10]

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

Oil

Both long and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. 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 [11,12]. Medium chain triglycerides were preferred in the earlier self-emulsifying formulations because of higher fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium chain derivatives which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation.

Surfactants

Non-ionic surfactants with a relatively high hydrophilic ± lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylated polyglycolyzed glycerides and Tween 80 are the most frequently used excipients. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability. The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation [13]. A large quantity of surfactant may irritate the GI tract. Thus, the safety aspect of the surfactant vehicle should be carefully considered in each case. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self emulsifying performance. The surface-active agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of the hydrophobic drug. The latter is of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption.

Co-solvents

Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid phases and it can be used to solubilize a hydrophobic drug [14].

Consistency builder

Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax [15].

Polymers

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc [16].

Co-surfactant

In SEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion [14,17].

Various examples of surfactant, co-solvents and oil are given in Table 3.

FORMULATION

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 [14].

The following should be considered in the formulation of a SEDDS

- The solubility of the drug in different oil, surfactants and co solvents.
- The selection of oil, surfactant and co solvent 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 mixture of oil, surfactant and co-solvent [18].

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 [19].

MECHANISM OF SELF – EMULSIFICATION

The process by which self-emulsification takes place is not yet well understood. However, according to Reiss [20], self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a 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 equation [20]

$$\Delta G = \sum_{i} N_i \pi r_i^2 \sigma$$

Where, G 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. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. 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. 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). Emulsification requiring 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 [21]. In earlier work, it was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various LC or gel phases formed on the surface of the droplet [22,23,24].

According to Wakerly et al. [22], the addition of a binary mixture (oil/nonionic surfactant) to water results in 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. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will be LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The involvement of the LC phase in the emulsion formation process was extensively studied by Pouton et al. [22,24,25,26]. Later, Craig et al. used the combination of particle size analysis and low frequency dielectric spectroscopy (LFDS) to examine the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic acids)/Tween 80 systems [27,28,29]. The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the relationship was clearly complex [29]. The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase [28]. However, the correlation between the spontaneous emulsification and LC formation is still not definitely established [28,30].

CHARACTERIZATION

Visual assessment

This may provide important information about the self-emulsifying and microemulsifying property of the mixture and about the resulting dispersion [31].

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 temperature (4°C) and 45°C 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°C and +25°C 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 [32].

Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 ml of water at 37 ± 0.5^0C. 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) nanoemulsion, having a clear or bluish appearance.

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

Grade C: Fine milky emulsion that formed within 2 minutes

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 [32].

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) [33,34].

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 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 viscosities then it is w/o type of the system [33,34].

Droplet size analysis and 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 nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water [33,34].

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

Refractive index and Percentage 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 (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 formulation have transparent nature.

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 electro conductometer.

In Vitro Diffusion study

In vitro diffusion studies were performed for all the formulations developed, using a dialysis technique. The dialyzing medium was phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread, and then 1 ml of self-emulsifying formulation was placed in it along with 0.5 ml of dialyzing medium. The other end of the tubing was also secured with thread and was allowed to rotate freely in 200 ml of dialyzing medium and stirred continuously at 100 rpm with magnetic bead on magnetic plate at 37°C. Aliquots of 1 ml were removed at different time intervals and diluted further. Volume of aliquots was replaced with fresh dialyzing medium each time. These samples were analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer.

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.

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed [35,36]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including

Alterations (reduction) in gastric transit

Thereby slowing delivery to the absorption site and Increasing the time available for dissolution.

Increases in effective luminal drug solubility

The presence of lipids in the GI tract stimulates

An increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilisation capacity [37].

Stimulation of intestinal lymphatic transport

For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism [38,39,40].

Changes in the biochemical barrier function of the GI tract

It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [41,42,43].

Changes in the physical barrier function of the GI tract

Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs [44,45].

FACTORS AFFECTING SEDDS [46]

Polarity of the Lipophillic Phase

The polarity of the lipid phase is one of the main factors that govern the drug release from the micro-emulsions. 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 the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

Nature and Dose of the Drug

Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the components of SEDDS, preferably lipophillic phase. The drugs which have limited or less solubility in water and lipids 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. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract.

APPLICATIONS

Supersaturable SEDDS (S-SEDDS)

The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier [47].

Solid SEDDS

SEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules).

Improvement in Solubility and Bioavailability

If drug is formulated in SEDDS, then it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability). In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and C_{max} is observed with many drugs when presented in SEDDS [7].

Protection against Biodegradation

The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, hydrolytic degradation, or enzymatic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug [7].

Table 1: Examples of pharmaceutical product formulated as Self-emulsifying systems

Drug name	Compound	Dosageform	Company
Neoral	Cyclosporine-A	Soft gelatin capsule	Norvatis
Norvir	Ritonavir	Soft gelatin capsule	Abbott Laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.
Agenerase	Amprenavir	Soft gelatin capsule	Glaxo Smith Kline
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi-Aventis
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi-Aventis

Table 2: Difference between SEEDS and SMEDDS

SEEDS	SMEDDS
Can be a simple binary formulation with the drug and lipidic excipients able to self emulsify in contact with Gastrointestinal fluids(GIF) Or A system comprising Drug, surfactant, oil (also referred to as lipid phase).	Are composed of the Drug compound, Surfactant, Cosurfactant, and Oil(or lipid phase)
Lipid droplets size in the dispersion ranges from 200nm-5µm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplets size in the dispersion is< 200nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEEDS systems are not Thermodynamically stable in water or physiologic conditions.	SEEDS systems are Thermodynamically stable in water or physiologic conditions.

Table 3: Example of surfactants, co-surfactant and co-solvent used in commercial formulations [7]

Excipient Name (commercial name)
Surfactants/co-surfactants
Polysorbate 20 (Tween 20)
Polysorbate 80 (Tween 80)
Sorbitan monooleate (Span 80)
Polyoxy-40- hydrogenated castor oil (Cremophor RH40)
Polyoxyethylated glycerides (Labrafil M 2125 Cs)
Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)
Co-solvents
Ethanol
Glycerin
Polypylene glycol
Polyethylene glycol
Lipid ingredients
Corn oil mono,di,,tri-glycerides
DL-alpha-Tocopherol
Fractionated triglyceride of palm seed oil (medium-chain triglyceride)
Medium chain mono-and di-glycerides
Corn oil
Olive oil
Oleic acid
Sesame oil
Soyabean oil
Peanut oil
Beeswax
Hydrogenated soyabean oil
Hydrogenated vegetable oils

CONCLUSION

SEEDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water soluble drugs. As improvement or alternatives of conventional liquid SEEDS is superior in reducing production cost, simplifying industrial manufacture, and improving patient compliance and stability. GI irritation is avoidable and controlled/sustained release of drug is achievable. SEEDS 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 SEEDS, which have been shown to improve oral bioavailability substantially. The efficiency of the SEEDS formulation is cases-specific in most instances; thus, composition of the SEEDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SEEDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self emulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency.

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. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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 Bio-pharmaceutics. 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 self-emulsifying systems using low frequency dielectric spectroscopy: International Journal of Pharmaceutics. 1993; 96:147-155.
6. Tang J.L, Sun J. Guihe Z. Self- Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drug, Current Drug Therapy. 2007;2:85-93.
7. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Handicap SR and Bhosale AV. "Self Emulsifying Drug Delivery System: A Review" Research J. Pharm. And Tech. 2008; 1(4): 313-323.
8. Zhang P, Liu Y. Xu J. Preparation and Evaluation of SEEDS: International Journal of Pharmaceutics. 2008; 355:269-276.
9. Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: *In vitro* and *in vivo* evaluation: Acta Pharm. 2007; 57:111-122.
10. Gursoy R.N, Benita S. "Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs," Biomedicine and Pharmacotherapy. 2004;58: 173-182.
11. 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.
12. Aungst B.J, Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism: Journal of. Pharmaceutical Sciences. 1993;82:979- 986.
13. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism: J. Pharm. Sci. 1993; 82:979-986.
14. Crison JR, Amidon GL. Methods and formulation for increasing the bioavailability of poorly water soluble drugs. US Patent 5993858; 1999.
15. Arthur Osol. Editor. Remington's pharmaceutical sciences: Emulsifying and suspending agents. Pennsylvania: Mack Publishing. 1975;15:1246.
16. Barthelemy H. Composition with sustained release of active principle capable of forming microemulsion, US Patent 6309665; 2001.
17. Bose S, Kulkarni PK. Self emulsifying drug delivery systems: A review. Ind J Phar Edu 2002;36(4):184-190.
18. Farah N, Laforet JP, Denis J. Self Micro Emulsifying Drug Delivery Systems for Improving Dissolution of Drugs: *In vitro* Evaluations: presented by Gattefosse Patented Technology at the AAPS Annual Meeting in San Diego; 1994.
19. Nazzal S, Khan MA. Controlled Release of Self-Emulsifying Formulation from Tablet Dosage Form: Stability Assessment and Optimization of Some Processing Parameters, International Journal of Pharmaceutics. 2006; 315: 110-121.
20. H. Reiss. Entropy-induced dispersion of bulk liquids, J.Colloids Interface Sci. 1975; 53:61-70.
21. T. Dabros, et al. Emulsification through area contraction, J.Colloids Interface Sci.1999; 210 :222-230.
22. Wakerly MG, Pouton CW, Meakin BJ, Morton FS. Self-emulsification of vegetable oil-non-ionic surfactant mixtures. ACS Symp. Ser. 1986; 311: 242-255.
23. Groves MJ, Mustafa RMA, Carless JE. Phase studies of mixed phosphated surfactants n-hexane and water, J. Pharm. Pharmacol. 1974; 26: 616-623.
24. Rang MJ, Miller CA. Spontaneous emulsification of oils containing hydrocarbon, non-ionic surfactant, and oleyl alcohol, J. Colloids Interface Sci. 1999; 209: 179-192.
25. Wakerly MG, Pouton CW, Meakin BJ. Evaluation of the self-emulsifying performance of a non-ionic surfactant vegetable oil mixture, J. Pharm. Pharmacol. 1987; 39: 6.
26. Pouton CW, Wakerly MG, Meakin BJ. Self-emulsifying systems for oral delivery of drugs, Proc. Int. Symp. Control. Release Bioact. Mater. 1987; 14: 113-114.
27. Craig DQM, et al. An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int. J. Pharm. 1993; 96: 147- 155.

28. Craig DQM, et al. The use of self-emulsifying systems as ameans of improving drug delivery, B.T. Gattefosse 1993;86; 21-31.
29. Craig DQM, et al. An investigation into the mechanismsof self-emulsification using particle size analysis and low frequency dielectric spectroscopy, Int. J. Pharm. 1995; 114:103-110.
30. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification, Int. J. Pharm. 1985; 27: 335-348.
31. Shah NH, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self emulsifying drug delivery systems (SEDDS) with polyglycolized glycerides for improving *in vitro* dissolution and oral absorption of lipophilic drugs. Int J Pharm. 1994; 106: 15-23.
32. Shafiq S, et al. Development and bioavailability assessment of ramipril nanoemulsion formulation Eur. J. Pharm. Biopharm. 2007; 66: 227–243.
33. Patil P, Joshij, Paradkar P. Effect of formulatiuon variables on preparation and evaluation of gelled self-emulsifying drug delivery system(SEDDS)of ketoprofen.AAPS Pharm Sci Tech.2004;5(3):34-42.
34. Patil P, Vandana P, Paradkar P. formulation of selfemulsifying drug delivery system for oral delivery of simvastatin:In vitro and in vivo evaluation. Acta pharma. 2007; 57: 111-122.
35. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Adv Drug Del Rev. 1997; 25: 103-28.
36. Charman WN, Porter CJ, Mithani S, Dressman JB. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci. 1997; 86: 269-82.
37. Porter CJ, Charman WN. In vitro assessment of oral lipid based formulations. Adv Drug Deliv Rev. 2001; 50(1): 127-47.
38. Porter CJH, Charman WN. Uptake of drugs into the intestinal lymphatics after oral administration. Adv Drug Deliv Rev. 1997; 25:71-89.
39. Porter CJH, Charman WN. Intestinal lymphatic transport: an update. Adv Drug Deliv Rev 2001;50:61-80.
40. Muranishi S. Drug targeting towards the lymphatics. Adv Drug Res. 1991;21:1-38.
41. Benet L. The drug efflux-metabolism alliance: biochemical aspects. Adv Drug Deliv Rev. 2001;50:3-11.
42. Dintaman JM, Silverman JA. Inhibition of P-glycoprotein by Dalpha- tocopheryl polyethylene glycol 1000 succinate (TPGS). Pharm Res. 1999;16:1550-1556.
43. Nerurkar MM, Burton PS, Borchardt RT. The use of surfactants to enhance the permeability of peptides through Caco-2 cells by inhibition of an apically polarized efflux system. Pharm Res. 1996; 13:528-34.
44. Aungst BJ. Intestinal permeation enhancers. J Pharm Sci. 2000;89:429-42.
45. Muranishi S. Absorption enhancers. Crit Rev Ther Drug Carrier Syst. 1990;7:1-33.
46. Kyatanwar AU, Jadhav KR, Kadam VJ. Self micro-emulsifying drug delivery system (SMEDDS): Review Journal of Pharmacy Research. 2010, 3(1),75-83.
47. Gao P, Rush BD, Pfund WP. Journal of Pharmaceutical Sciences. 2003; 92:2386-2398.