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SELF EMULSIFYING DRUG DELIVERY SYSTEM: HITHERTO AND RECENT ADVANCES

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ABSTRACT

Oral delivery of poorly water-soluble drugs creates critical problem for their formulation as 35- 40% of new active pharmaceutical ingredients have poor water solubility and frequently associated with low bioavailability. Recently much attention has been given to lipid-based formulation with particular emphasis on self emulsifying drug delivery system (SEDDS) to improve the oral bioavailability. These can exist in either liquid or solid states. Self-emulsifying system formulation mainly depends on the nature of oil/lipid excipients, surfactants, their concentration and temperature at which emulsification occurs. As advancement or substitute of conventional liquid SEDDS, Solid SEDDS are better in minimizing manufacturing cost, makes simpler industrial manufacture, enhancing stability, patient compliance and most prominently these are very flexible to develop different solid dosage forms for oral and parentral administration. In addition, such formulation prevents GI irritation and able to control drug release. Recently self emulsifying drug delivery system is used as an efficient approach for the formulation of drugs that are beneficial in the diseases such as hypertension and congestive heart failure, HIV infections, cancer etc. The main difficulty in the development of SEDDS and other lipid-based formulations is the lack of high-quality *in vitro* models for their evaluation. Finally, the existing problems and the possible future research directions in this field are pointed out.

Key words: Self-emulsifying system, Oral Bioavailability, Solubilization, Lipophillic drugs, Solid Carriers.

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INTRODUCTION

The oral drug delivery system has been traditionally preferred for prolonged use. However, oral delivery of poorly water-soluble drugs creates critical problems during their formulation. Approximately 35-40% of new active pharmaceutical ingredients have poor water solubility, frequently associated with low bioavailability, variable pharmacokinetic profile and dose proportionality. Several recent techniques have been used for their solubilization including micronization, complexation, solid dispersion and co-precipitation etc. However, their success ratio and utility have been challenged by several disadvantages.[1-3] Recently, much attention has focused on lipid-based formulations to improve the bioavailability of poor water soluble drugs. Among many such delivery options, like incorporation of drugs in oils, surfactant dispersion, emulsions and liposomes,[4-7] one of the most popular approach is the self-emulsifying drug delivery system (SEDDS).

Self-Emulsifying Drug Delivery System (SEDDS)

Self-emulsifying drug delivery system (SEDDS) is the mixture of oil and surfactants, ideally isotropic containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under gentle agitation. It is the dosage form with unique property to get self emulsify rapidly into fine o/w emulsion in the gastrointestinal tract (GIT) fluid, under gentle agitation provided by gastrointestinal peristalsis. These fine emulsions disperse readily in GIT providing large surface area for the drug absorption with minimum GIT irritation. SEDDS can be easily formulated with little energy input and are more stable than conventional emulsions. Thus, self-emulsifying system offers excellent vehicle for the formulation of

poorly water-soluble drugs with dissolution rate-limited absorption.[8]

Mechanism of Self-Emulsification

Self-emulsification process is related to the free energy. According to Reiss (1975), self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formation is a direct function of the energy required to create a new interface between the two phases is given by [9]

$$\Delta G = \sum N\pi r^2\sigma$$

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

N is the number of droplets

r is radius of droplets

σ is the interfacial energy

From equation it is known that the spontaneous formation of interface between oil and water phase is energetically not favorable. With time, the two phases of the emulsion tend to get separate, in order to reduce the interfacial area, and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents that form monolayer around the emulsion droplets, and hence reduce the interfacial energy, as well as provide a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is very low, positive or negative (than, 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.[10]

FORMULATION ASPECTS OF SEDDS

Formulation of SEDDS mainly depends on the nature of oil/lipid excipients, surfactants, their concentration and temperature at which emulsification occurs. In addition; factors affecting oral absorption of the drug compound from SEDDS include surfactant concentration, oil/surfactant ratio and polarity of the emulsion.[11]

I. Oils

Oils are the most essential excipients of SEDDS. Oils solubilize the lipophilic drug in a definite quantity, assist self-emulsification and enhance its absorption from the gastrointestinal tract. A number of natural oils, resulting primarily from plant sources, processed to remove impurities or to separate various fractions of the original product, are available and suitable for use in encapsulated oral formulation. Naturally occurring oils and fats are mixture of triglycerides, which contains fatty acids of varying chain lengths and degrees of unsaturation. The melting point of particular oil is directly proportional to degree of unsaturation, which also increases the relative susceptibility to oxidation. These might be hydrogenated synthetically to decrease the degree of unsaturation and conferring resistance to oxidative degradation. Both long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used for the formulation of SEDDS. Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages.[12]

Several semi synthetic liquid and thermo softening (semisolid) excipients, usually prepared by chemically combining medium chain saturated fatty acids or glycerides from natural oils are also used in oral formulations. These excipients are used as a drug solubilizing vehicles, surfactants and wetting agents in SEDDS. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.[12]

II. Surfactants

Various nonionic surfactants such as tween, labrasol, labrafac CM 10, cremophore etc with high HLB values, can be used in combination with oils to facilitate self-emulsification. Emulsifiers from natural origin are preferred because of their safety profile compared to synthetic emulsifiers. Nonionic surfactants are known to be less toxic than ionic surfactants but may exhibits moderate reversible changes in intestinal wall permeability. The general surfactant concentration in SEDDS formulation ranges between 30-60% w/w. Surfactants with high HLB values assist the immediate formation of O/W droplet and rapid spreading of the formation in aqueous media. Surfactants being amphiphilic in nature are capable of dissolving relatively high quantity of lipophilic drug compound. This prevents precipitations of the drug in GI lumen and facilitates greater absorption. Surfactant provides enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum. A cationic emulsion has greater bioavailability than an anionic emulsion. The self emulsifying lipid formulations are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the

drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood.[13]

III. Co-Solvents

Usually more than 30% w/w surfactant concentration is required for efficient self emulsification system. Organic solvents may help to dissolve large amount of hydrophilic surfactant or the lipophilic drug in the lipid base. These solvents like diethylene glycol monoethyl ether, propylene glycol, polyethylene glycol(PEG), polyoxyethlene, propylene carbonate, tetrahydro furfuryl alcohol polyehthylene glycol ether, etc, may act as Co-solvent/co-surfactants in the micro emulsion systems.[14] The physical state of these excipients at ambient room temperature is determined by their molecular weight. PEG ranging from 200 to 600 in molecular weight is liquid where as those possessing molecular weight of 1000 or greater are thermo softening semi solid at room temperature. Polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water soluble drugs. These excipients can be used alone or in mixture with other lipid excipients to improve solubilizing power of formulation. Among the polymeric glycol based excipients, PEGs are versatile, well characterized and widely applied class of solubilizers which are available as both liquid and thermo softening semisolid.[15]

Generally from formulation point of view SEDDS can be categorized into following types:

A. Liquid SEDDS

- Self emulsifying drug delivery system
- Self micro emulsifying drug delivery system
- Super saturable self emulsifying drug delivery system

SEDDS has been used for administration of poorly water-soluble drugs due to its excellent thermodynamic stability, high drug solubilization capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis. However, its poor palatability due to the lipid content leading to poor patient compliance. More over due to liquid in nature, it shows stability and handling difficulties. Therefore it is required to convert SEDDS into alternative formulation like solid self emulsifying drug delivery system.[16]

B. Solid SEDDS

Solid SEDDS offer the potential advantages including: enhanced solubility and bioavailability with that of solid dosage forms e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance.

TECHNIQUES OF SOLID SEDDS

Mainly Solid SEDDS are developed by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc.

i] Solid carriers

Solid carriers (powders) adsorb liquid/semisolid self emulsifying formulations (SEF). In formulation process, the desired mixture is uniformly blended for proper adsorption. The resulting powder is then incorporated into capsule or compressed into tablets using suitable excipients.[17] The most important benefit of this method include good content uniformity. Moreover up to 70% w/w SEDDS can be adsorbed on to suitable solid carriers. Solid carriers can be micro porous inorganic substances, colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticles adsorbents such as silica, silicates, magnesium trisilicates, crosspovidone, cross-linked sodium carboxy methyl cellulose, cross-linked polynethyl methacrylate, carbon nanotubes, carbon nanaohorns etc. A cross-linked polymer helps to sustain drug dissolution and minimizes drug precipitation.[18]

ii] Spray Drying

Spray drying constitutes spraying of the solubilized liquid formulation containing oil, surfactant, drug, solid carrier into a drying chamber via nozzle. Initially, droplets are formed and the vehicle (e.g. water) evaporates leaving small solid particles behind. These particles then filled into capsules or compacted into tablets.

iii] Spray cooling

Spray cooling also known as spray congealing, is a process whereby the molten formula is sprayed into a cooling chamber and upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder further can be converted into solid dosage forms such as tablets or capsules.[19] Most of the recent research carried out on spray cooling with lipid-based excipients; facilitating the production of solid particles that exhibit appreciably enhanced drug release profiles for poorly soluble drug such as diclofenac or praziquantel.[20]

iii] Melt extrusion

This formulation technique is solvent free process that facilitates high drug loading (60%) and content uniformity. It depends on the property of the plastic mass which can be easily extruded and spheronised with pressure. Addition of liquid excipients is generally not required but a constant temperature and pressure need to be maintained.[21]

iv] Capsule filling with liquid/ semisolid SEDDS

It is one of the simplest methods for encapsulation of liquid or semisolid SEF for oral delivery of drug. Semisolid formulations involves heating of excipients to at least 20° C above its melting point and simultaneous addition of active ingredients with stirring, followed by capsule filling with molten mass cooling at room temperature. Liquid formulations are filled into capsules followed by sealing. Compatibility of the excipients with the capsule shell is major consideration in capsule filling technology. Generally liquid and semisolid lipophillic vehicles are compatible with hard gelatin capsules.[17]

EVALUATION OF SEDDS

- **Thermodynamic Stability Studies**

The physical stability of a lipid –based formulation is also important for its performance, as there may be precipitation of the drug in the excipient matrix. In addition, the poor physical stability of the formulation can lead to phase separation of the excipient, which affects not only formulation performance, as well as visual appearance of formulation. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug. For thermodynamic stability studies following are the main steps

1. Heating cooling cycle: Six cycles between refrigerator temperature (4°C) and (45°C) with storage at each temperature for not less than 48 h. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
2. 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. Formulations that does not show any phase separation further taken for the freeze thaw test.
3. Freeze thaw cycle: Three freeze for the formulations. Formulations which passed this test usually show good stability with no phase separation, creaming, or cracking.[22]

- **Dispersibility Test**

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by standard USP XXII dissolution apparatus. One ml of each formulation dissolves in 500 ml of water at 37 ± 1°C. A standard stainless steel dissolution paddle is used with rotating speed of 50 rpm to provide gentle agitation. The in vitro performance of the formulations is visually assessed by 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: Fine 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 nano emulsion when dispersed in GIT, whereas formulation falling in Grade C could be recommended for SEDDS formulation.[22]

- **Turbidimetric Evaluation**

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self emulsifying system is combining with fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring [50 rpm] on magnetic hot plate at appropriate temperature, and the increase in turbidity is measured, by 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).[23]

- **Viscosity Determination**

SEDDS system is generally administered in soft gelatin or hard gelatin capsules. Thus, it should be easily pourable into capsules, and should not be too thick. 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 the system has low viscosity then it is o/w type of the system and if a high viscosity then it is w/o type of the system.[22]

- **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 zeta sizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at 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.[23]

- **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 putting a drop of solution on slide and comparing it with water (1.333). The percent transmittance of the system is measured at

particular wavelength by UV spectrophotometer using 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.[24]

- **Electro Conductivity Study**

The SEDD system contains ionic or non-ionic surfactant, oil, and water. This test is performed for measurement of electroconductive nature of system. The electro conductivity is measured by electro conductometer. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.[25]

- ***In vitro* Diffusion Study**

In vitro diffusion studies are carried out to study the drug release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.[23]

- **Drug Content**

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method against the standard solvent solution of drug.[24]

RECENT ADVANCEMENTS

Recently, solid self-emulsifying drug delivery system focus on the conversion of liquid/semisolid self emulsifying ingredients into powders by different solidification techniques. Such powders, called as dry emulsions/solid dispersions, are usually further processed into other solid dosage self emulsifying forms, or alternatively, filled into capsules. SE capsules also include liquid/semisolid self emulsifying formulations directly filled into capsules without any solidifying excipients. In addition, several new solid self emulsifying dosage form have emerge in recent years including SE pellets, tablets, microspheres, nanoparticles, suppositories and implants.

Self emulsifying drug delivery system is now used as an efficient approach for the formulation of drugs used to treat hypertension, congestive heart failure, HIV infections and cancer.

An antioxidant coenzyme Q_{10} (CoQ_{10}), used in the treatment of angina pectoris, hypertension and congestive heart failure. The drug is lipid soluble and poorly absorbed from the GI tract perhaps due to its high molecular weight and water insolubility. T. R. Kommuru *et al.* (2001) prepared SEDDS of CoQ10 in solid form containing sodium lauryl sulphate as the wetting agent and lactose as the bulking agent which provides improved oral bioavailability.[26]

Curry R *et al.* (2001) developed new SEDDS formulation of potent anti-HIV drug tipranavir (TPV), belongs to new class of nonpeptidic protease inhibitors. Compared to hard filled capsule, the new SEDDS formulation in a soft gelatin capsule, provide two-fold greater bioavailability.[27]

Docetaxel (DTX) anti- mitotic mainly use for the treatment of breast, ovarian, and non-small cell lung cancer. Ying Chen *et al.* (2011) prepared a solid supersaturatable SEDDS of DTX by spray drying, using lactose as the solid carrier and hydroxyl propyl methylcellulose [HPMC] as the supersaturation promoter. The bioavailability of the DTX-S-sSEDDS compared with other formulations of DTX showed sustained release with reduced precipitation of drug as present in supersaturated state.[28]

Balakrishnan P *et al.* (2009) prepared a solid form of lipid-based self-emulsifying drug delivery system by spray drying liquid SEDDS with an inert solid carrier Aerosil 200 to improve the oral bioavailability of poorly water-soluble drug dexibuprofen. In vivo results suggested that solid SEDDS could be used as an effective oral solid dosage form to improve the bioavailability about two-fold higher of dexibuprofen.[29]

Setthacheewakul S *et al.* (2011) developed novel self-emulsifying floating pellets with improved solubility, dissolution, and controlled release of the poorly water-soluble tetrahydrocurcumin. The liquid SEDDS was mixed with adsorbent silicon dioxide, glyceryl behenate, pregelatinized starch, sodium starch glycolate, and microcrystalline cellulose and transformed into pellets by the extrusion/spheronization technique.[30]

Solid Dosage forms from self emulsifying system

- **Dry emulsions**

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules.

- **Self emulsifying capsule**

It is a capsule filled with liquid or semisolid form of self emulsifying system. After administration, the capsules get disperse readily in the GIT to SES uniformly in the fluid to micron size, enhancing bioavailability. However, if irreversible phase separation of the emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation. With the similar purpose, the super saturatable SEDDS was designed, using a small quantity of hydroxyl propyl methyl cellulose (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects. Second type of self emulsifying capsule is solid SES filled into capsule that increases stability, portability and patient compliance.[31]

- **Self emulsifying tablets**

Combinations of oils and surfactants have offered great prospective of preparing self-emulsifying tablets that have been widely researched. It is consist of solidified liquid SES either compressed or moulded into tablets. These preparation offers advantages like tablets melt at body temperature without agitation and in GIT, agitation as peristaltic movement lowers the melting time, resulting in faster emulsification with increased plasma concentration. The resultant SE tablets consistently maintain a higher drug concentration in blood plasma over the same time frame compared with a non emulsifying tablet. Self- nanoemulsified tablet dosage form of Ubiquinone was developed by S. Nazzal *et al.* (2002). SES was absorbed by granular materials and then compressed into tablets.[32]

- **Self emulsifying pellets**

Pellets as multiple units' solid dosage form more advantageous over conventional solid dosage such as flexibility of manufacture, reduction of intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Pellets are able to produce significantly smaller droplets with respect to corresponding emulsions. These are prepared by extrusion–spheronization method. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs. Formulation of SE controlled-release pellets by incorporating drugs into SES that improves their rate of release, whereas coating pellets with a water-insoluble polymer reduces the rate of drug release and simultaneously controls drug release.[33]

- **Self emulsifying beads**

Self emulsifying beads can be formulated as a solid dosage form by using less excipient. Patil and Paradkar (2006) reported deposition of SES into microporous polystyrene beads by solvent evaporation method. Porous polystyrene beads (PPB) with complex internal void structures were typically produced by co - polymerizing styrene and divinyl benzene. It was inert and stable over a wide range of pH, temperature and humidity. Bead size and pore architecture of PPB, decides the loading efficiency and in vitro drug release from SES-loaded PPB.[34]

- **Self emulsifying microsphere**

Solid SE sustained-release microspheres are prepared by the quasi emulsion solvent diffusion method for the spherical crystallization technique. You J [2006] reported that Zedoary turmeric oil release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres into rabbits, with a bioavailability of 135.6% compared to the conventional liquid SEDDS.[35]

- **Self emulsifying nanoparticles**

Nanoparticles technology is used in the formulation of self emulsifying nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%. Second technique is sonication emulsion diffusion evaporation; by this method co-load 5-flurouracil and antisense epidermal growth factor receptor (EGFR) plasmids into biodegradable poly-lactide-coglycolide and O-carboxymethyl-chitosan (PLGA/O-CMC) nanoparticles. The mixture of PLGA /O-CMC had a SE effect, with no additional surfactant required. Trickler (2008) developed a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/ GMO nanoparticles was prepared by multiple emulsion (o/w/o) solvent evaporation methods.[36, 37]

- **Self-emulsifying suppositories**

S-SEDDS could augment not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin, by the oral route, hardly reaches therapeutic plasma concentrations, can attain acceptable therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation integrated glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.[38]

- **Self-emulsifying implants**

SE implants have improved the utility and application of S-SEDDS. As an example, 1, 3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its efficacy was limited due to its short half-life. In order to enhance its stability compared with that released from poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil (polyglycolyzed glyceride).Then the formulation of BCNU was made into wafers with flat and smooth surface by compression molding. Ultimately, in vitro half-life of self emulsifying BCNU increased to 130 min compared with 45 min of intact BCNU. Similarly, in vitro release of BCNU from SE PLGA wafers were extended up to 7 days. Such wafers have high in vitro

antitumor activity and are less prone to hydrolysis than those devoid of SES.[39]

Potential Advantages

The potential advantages of self emulsifying drug delivery system can be summarized as follows:

1. Enhanced oral bioavailability (enabling dose reduction)
2. SEDDS protect drugs against enzymatic hydrolysis in GI tract and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism.
3. More consistent temporal profiles of drug absorption
4. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut.
5. S-SEDDS are very flexible to develop various solid dosage forms for oral and parentral administration.
6. Sustained release of drug is achievable by SEDDS.

LIMITATIONS OF SEDDS

Although SEDDS offer several advantages over conventional dosage form it is frequently associated with chemical instabilities of drugs due to high surfactant concentrations. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

The major hurdles in the development of self emulsifying drug delivery systems (SEDDS) and other lipid-based formulations is the lack of high-quality *in vitro* models for evaluation of SEDDS formulations. The conventional dissolution methods do not work, because these are suitable for formulations that are reliant 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.

APPLICATIONS

Many drugs get degraded in physiological system, may be because of acidic pH in stomach, hydrolytic degradation, or enzymatic degradation etc. Such drugs when presented in self emulsifying formulations are well protected against these degradation processes as liquid crystalline phase in SEDDS act as barrier between degradation environment and the drug. Self emulsifying drug delivery system reduces degradation as well as improves absorption essentially for drugs which have both low solubility and degradation in the GI tract contributes to a low oral bioavailability.

In addition conversion of conventional SEDDS to solid form is better in controlling or sustaining drug release and provides flexibility to develop different solid dosage form for oral administration. It also provides improved stability and patient compliance.

CONCLUSION

In conclusion, it is widely accepted that solid SEDDS significantly enhanced solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. As advancement or substitute of conventional liquid SEDDS, S-SEDDS are better in minimizing manufacturing cost, make simpler industrial manufacture and enhancing stability over and above patient compliance. Most prominently, S-SEDDS are very flexible to develop different solid dosage forms for oral and parentral administration. In addition, such formulation prevents GI irritation and able to control/sustain drug release. There is still a long way to go, however, before more solid SE dosage forms (except for SE capsules) appear on the market. Because there exist some fields of S-SEDDS to be further exploited, such as studies about human bioavailability and correlation of in vitro/in vivo. It is also worth pointing out some issues to which much attention should be paid, for example physical aging phenomenon associated with glycerides, oxidation of vegetable oil, and interaction between drugs and excipients. Selection of suitable excipients is the major obstacle of developing S-SEDDS. Thus, these characteristic should signify the main working guidelines for S-SEDDS.

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Table1. Examples of various solid self emulsifying systems

Self emulsifying capsules

Drug/Compound	Solidifying additive	References
Candesartan cilexetil	Microcrystalline cellulose and Colloidal silicon dioxide.	Nekkanti *et al.* 2010 [40]
Cyclosporine	Porous Magnesium Aluminometasilicate Tablets	Sander and Holm 2009 [41]
Gentamicin	Microporous calcium silicate, magnesium alminometa silicate and silicon dioxide	Ito *et al.* 2005[17]

Self emulsifying tablets

Coenzyme Q_{10}	Colloidal silicates	Nazzal , Khan 2006[32]
Griseofulvin	Silica and silicates, magnesium aluminum silicate, calcium silicate and silicon dioxide	Agarwal *et al.* 2009[42]
Diclofenac	Goat fat and Tween 65	Attama *et al.* 2003[43]
Carvedilol	Gelucire 44/14, Lutrol F68, Transcutol P, silicon dioxide, mannitol, citric acid, and sodium hydrogen carbonate	Wei L *et al.* 2007[44]

Self emulsifying pellets

Nimesulide	Microcrystalline cellulose and lactose	Franceschinis *et al.* 2005[33]
Diazepam	MCC	Abdalla and Mader 2007[45]
Progesterone	Microcrystalline cellulose, Solutol HS 15	Abdalla 2008[46]
Nitrendipine	Silicon dioxide and crospovidone	Wang *et al.* 2010[47]
Vinpocetine	MCC, Lactose,croscarmellose sodium	Iosio *et al.* 2008[48]
Aceclofenac	Lactose, polyvinyl pyrrolidone (PVP K30) and microcrystalline cellulose.	Rathnanand *et al.* 2011[49]

Self emulsifying beads

Loratadine	Microporous polystyrene beads	Patil and Paradkar 2006[34]

Self emulsifying microsphere

Zedoary turmeric oil	Hydroxypropyl methylcellulose acetate succinate, Aerosil 200	You 2006[35]
Piroxicam	Homolipid Capra Hircus and tween 65	Attama, Mpamaugo 2006[50]

Self emulsifying nanoparticle

5-flurouracil and antisense EGFR [epidermal growth factor receptor] plasmids	Sonication emulsion –diffusion –evaporation	Hu 2005[37]
Paclitaxel [PTX].	Multiple emulsion o/w/o solvent evaporation	Trickler 2008[36]

Self-emulsifying implants

1,3-bis[2-chloroethyl]-1-nitrosourea carmustine, BCNU	poly [d,l-lactide-co-glycolide] [PLGA] wafer	Chae 2005[39]