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SMEDDS: A Dominant Dosage Form Which Improve Bioavailability

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ABSTRACT

Self Micro-emulsifying drug delivery systems (SMEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Approximately 60-70% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. SMEDDS is isotropic (one phase system) mixture of oil or modified oils, surfactants and co-surfactants, which form the fine oil-in-water microemulsion when introduced into aqueous phase under condition of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self-microemulsion *in-vivo*. Triglyceride is the one of the component of SMEDDS, which helps in the absorption of drugs from the GI tract. SMEDDS enhance the bioavailability enabling reduction in dose of the drug. SMEDDS is evaluated by various methods like visual assessment, droplet polarity and droplet size, size of emulsion droplet, dissolution test, charge of oil droplets, viscosity determination, *in-vitro* diffusion study. This article gives an overview of improvement in the rate and extent of oral absorption of drugs by SMEDDS approach. The characterization of SMEDDS and application of SMEDDS is also introduced, with particular emphasis being placed on the developments of Solid self micro-emulsifying delivery system and dosage form of SMEDDS.

Keywords: SMEDDS, Solubility, Microemulsion.

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INTRODUCTION

Approximately 60-70% of new drug candidates have poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter-subject and intra-subject variability and lack of dose proportionality.[1, 2] as a drug must invariably be in solution within the gastrointestinal tract before it crosses the GI mucosa, and poor water solubility may lead to incomplete and erratic absorption. Ongoing efforts are being made to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles such as oils, surfactant dispersions, self emulsifying formulations, emulsions and liposomes.[3] Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs.[4] Micro emulsions has got advantage like excellent thermodynamic stability, high drug solubilization capacity, improvement in oral bioavailabity and protection against enzymatic hydrolysis. The only problem with micro emulsion is poor palatability due to the lipid content leading to poor patient compliance, more over due to their water content, micro emulsions cannot be encapsulated into soft gelatin or hard gelatin capsule. There is a need for converting it into an alternative formulation like anhydrous self microemulsifying drug delivery system (SMEDDS) etc., because of its loading dose.[5] Self microemulsifying drug delivery systems (SMEDDS) consist of isotropic mixture of natural or synthetic oil and solid or liquid surfactants or alternatively one or more hydrophilic solvents and co-solvents. They can improve the oral bioavailability of drugs, which are poorly soluble in water.[6,7,8,9] Formulation of drugs in this manner represents a possible alternative to traditional tablets and capsules as the system is expected to self emulsify in the aqueous contents of the stomach. The digestive mobility of the stomach and intestine provides the agitation necessary for self emulsification. Consequently the drug may be rapidly emptied from the stomach and distributed in fine droplet form throughout the GIT. This would theoretically confer the advantage of a large surface area from which dissolution may occur as well as a reduction in the irritation caused by the prolonged direct contact between drugs in conventional dosage forms and the gut wall.[7] Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.

Advantages[10]

Potential advantages of SMEDDS include:

- Enhanced oral bioavailability enabling reduction in dose.
- More consistent temporal profiles of drug absorption.
- Selective targetting of drugs toward specific absorption window in GIT.
- Protection of drugs from the hostile environment in gut.
- Control of delivery profiles.
- Reduction variability including food effects.
- Protection of sensitive drug substances.
- High drug payloads.

Composition of SMEDDS

Various components of SMEDDS are:

- Oils
- Co-solvents
- Surfactants
- Co-surfactants
- Consistency builder
- Polymer

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.[12] Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SMEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SMEDDS 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.[13]

Cosolvents like diehylene 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 micro emulsion systems.[14]

Nonionic **Surfactants** with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SMEDDS (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

SMEDDS. 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.[15]

Generally **Co-surfactant** of HLB value 10-14 is used with surfactant together to decrease the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as "spontaneous emulsification" forms the microemulsion. However, for many non-ionic surfactants it is not compulsory/mandatory to use co-surfactant in microemulsion. The selection of co-surfactant and surfactant is crucial not only to form the formation of microemulsion, but also to solubilization in microemulsions. Other variables such as the chemical nature of oil, salinity and temperature are also expected to influence the curvature of the interfacial film.[15] Organic solvents like ethanol, propylene glycol, polyethylene glycol suitable for oral administration may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as cosurfactant in the microemulsion systems. Literature has been described alcohol and propylene glycol free self emulsifying microemulsions. Such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. But the drugs in the alcohol free formulations may exhibit limited solubility. Hence, proper choice has to be made during selection of components.[16] 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 micoemulsion.[17]

Table 1.1 Excipients used in SMEDDS

Oils	Co-solvents	Surfactants/ Co-surfactants	Consistency builder	Polymers
Cotton seed oil, Corn oil, Soyabean oil, Castor oil,	Ethanol, Glycerine, Polyethylene glycol, Polypropylene glycol	Span 20, Span 80, Tween 20, Tween 80,	Tragacanth, Cetyl alcohol, Stearic acid, Bees wax	Hydroxy propyl methyl cellulose, Ethyl cellulose

Consistency builder like tragacanth, cetyl alcohol, stearic acid or beeswax can be added to alter the consistency of the emulsion.[18]

Polymers in inert polymer matrix representing from 5-40% 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.[19]

Mechanism of Action

Self emulsification occurs, when the entropy change occurs**,** dispersion is greater than the energy required to increase the energy required to increase the surface area of the dispersion.[20] The free energy of 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 the equation.

$$\Delta G=\sum Ni \prod r_i^{\,2} \sigma$$

Where,

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

N is the number of droplets

r is the radius of droplet,

σ is 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 system. 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.[21] In case of self emulsifying system, the free energy required to form the emulsion is either very low and positive or negative then, the emulsion process occurs spontaneously.[22]

Emulsification require 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.[23] In earlier work it was suggested that the case of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or phases get formed on the surface of the droplet.[24] The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the 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, which occurs until the solubilization limit is reached close to the interface.[25] Further aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceed, eventually all materials close to the interface will be liquid crystal, 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 solubility of these self emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets. A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine self emulsifying properties of a series of Imwitor 742 (a mixture of mono-and diglycerides of Caprylic acids/Tween 80) systems, which provided evidence that the formation of the emulsion may be associated with liquid crystal formation, although the relationship was clearly complex. The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase.[25]

FACTORS AFFECTING SMEDDS

Nature and dose of the drug

Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) are most difficult to deliver by SMEDDS. The ability of SMEDDS 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 solubilization then there could be a risk of precipitation, as dilution of SMEDDS 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, crystallization could be slow in the solubilising and colloidal stabilizing environment of the gut.[26]

Polarity of the lipophilic phase

The polarity of the lipid phase is one of the factors that govern the drug release from the microemulsions. 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 micronized for their propensity to inhibit crystallization and generate and maintain the supersaturated state for prolonged time periods. A supersaturable self microemulsifying drug delivery system (S-SMEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. *In vitro* dilution of the S-SMEDDS formulation resulted in formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicated that the system was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS

formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (Cmax) and a 5-fold higher oral bioavailability (F ~ 9.5%) compared with that of the orally administered Taxol formulation (F ~ 2.0%) and the SMEDDS formulation without HPMC (F ~ 1%).[26]

APPROACHES OF DELIVERY SYSTEMS

Self microemulsifying drug delivery systems (SMEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including co solvents, which emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastro-intestinal tract. Hydrophobic drugs can often be dissolved in SMEDDS allowing them to be encapsulated as unit dosage forms for per oral administration. Generally, self emulsifying formulations form a fine emulsion when exposed to aqueous media under conditions of gentle agitation. The resulting oil-in-water emulsions are thermodynamically stable due to the relatively small volume of the dispersed oil phase, the narrow range of droplet size distribution and the polarity of the oil droplets.[27] Oral administration of SMEDDS, which can be conveniently encapsulated in soft gelatin capsules, the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification.[28] Improvement in the extent and rate of absorption of lipophilic compounds from self emulsifying formulations is more as compared to traditional oral formulations.[29,30,31] The potential of lipoids self microemulsifying drug delivery systems (SMEDDS) and self microemulsifying drug delivery systems (SMEDDS) for improving the extent and reproducibility of the oral absorption of Halofantrine was investigated as such and formulations have been reported to improve the rate and extent of absorption of lipophilic drugs.[32,33]

In recent study, the self emulsifying properties of Glyceryl Monooleate (GMO) formed a hydrophobic core, presumably micellar, to enhance the solubility of Paclitaxel (PTX) and provide a foundation for chitosan aggregation. The near 100% loading and entrapment efficiencies of PTX in this formulation are attributed to the self emulsifying properties of GMO-mono glycerides (like GMO), a polar lipids with poor water solubility that exhibit properties resembling non-ionic surfactants have been comprehensively described.[34]

Solidification Techniques for Transforming Liquid/Semisolid SMEDDS to SOLID-SMEDDS

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 SE formulations for the oral route. For semisolid formulations, it is a four-step process: (i) heating of the semisolid excipient to at least 20˚C above its melting point; (ii) incorporation of the active substances (with stirring); (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing. The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading potential (up to 50% w/w).[35]

Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.[35]

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. Moreover, it is also a good alternative to the use of solvent.[35]

Adsorption to solid carriers

Free flowing powders may be obtained from liquid SE formulations by 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 resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS/SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers.[36]

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a

product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. [37]

EVALUATION OF SMEDDS

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 ^{0}C) and 45^{0}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 ^{0}C and +25 ^{0}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.[38]

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 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.[38]

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. 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).[39, 40,41]

Droplet Size

This is a crucial factor in self emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used further determination of the emulsion droplet size. The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.[42]

Equilibrium phase diagram

Although self emulsification is a dynamic nonequilibrium process involving interfacial phenomena, information can be obtained about self emulsification using equilibrium phase behavior. There seems to be a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water. An equilibrium phase diagram enables comparison of different of different surfactants and their synergy with cosolvent or cosurfactant. The boundaries of one phase region can easily be assessed visually. The phase behavior of a three-component system can be represented by a ternary phase diagram.[43]

Viscosity Measurement

This SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it should 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.[44]

Zeta potential measurement

The emulsion stability is directly related to the magnitude of the surface charge. In conventional SMEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.[45] the zeta potential of the diluted SMEDDS formulation was measured using a zeta meter system.

The SMEDDS were diluted with a ratio 1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting microemulsion was determined using the Zetasizer (Malvern instrument, Australia).[46]

***In vitro* release**

The quantitative *in vitro* release test is performed in 900 ml purified distilled water, which is based on USP XXIV dissolution method. SMEDDS is placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution is withdrawn at predetermined time intervals, filtered through a 0.45µ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium is replaced immediately after withdrawl of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert's equation.[47]

APPLICATIONS

Improvement in Solubility and bioavailability

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Vergote et al. (2001) reported complete drug release from sustained release formulations containing ketoprofen in nanocrystalline form.[48] Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen,[48] sustained release ketoprofen microparticles[49] and formulations[49], floating oral ketoprofen systems[50], and transdermal systems of ketoprofen.[51] Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavilability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen. 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.

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, enzymatic degradation or hydrolytic 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 degradation environment and the drug. Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. When the drug was formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) and compare with a commercial formulation, it showed the good plasma profile as compare to reference formulation. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles™ Oral Lipid Matrix System formulation compared to the reference formulation. This suggests that the SEDDS formulation has a capacity to protect drugs from degradation in the GI tract.[52]

Proteins have been encapsulated for local activity in the gastrointestinal tract. LCNP carriers can be combined with controlled-release and targeting functionalities. The particles are designed to form *in situ* at a controlled rate, which enables an effective in vivo distribution of the drug. LCNP carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for drugs that have narrow regional absorption windows. SMEDDS composition that showed a good chemical stability and a higher bioavailabibty with respect to a conventional formulation.[53]

DOSAGE FORM DEVELOPMENT OF SMEDDS

Various dosage forms of S-SMEDDS are as listed below; [54]

- Dry emulsions
- Self-emulsifying capsules
- Self-emulsifying sustained/controlled-release tablets
- Self-emulsifying sustained/controlled-release pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained-release microspheres
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories

- Self-emulsifying implants

RECENT ADVANCEMENTS IN SEDDS

Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing self-emulsifying tablets that have been widely researched. After evaluation the effect of some processing parameters (colloidal silicates X1, magnesium stearate mixing time X2, and compression force X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design.[55] In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipeints and aiding in slowing down of the drug release.[56]

Self-emulsifying capsules

After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation.[57] 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.[58,59] The SEDDS formulations, empty soft gelatin capsules were filled with the formulation using a syringe and sealed with hot gelatin. The optimized self-emulsifying formulation contained 30% (w/w) Tagat TO, 67.1°/,) (w/w) Miglyol 812 and 2.9% (w/w) cyclosporin, and each capsule was filled to contain 25 mg of cyclosporine. The limited drug loading capacity and incomplete emulsification characteristics of the EG formulation were improved by developing a surfactant enhanced system (SEEG). Although the drug loading capacity of these systems is still relatively low, for potent, lipophilic compounds, solid SEEG formulations may provide advantages in administration and chemical stability over traditional formulation alternatives such as emulsions and liquid fill soft gels.[60]

Self-emulsifying suppositories

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption .[61] Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.[62]

Microemulsion Drug Delivery

Dioctyl sodium sulfosuccinate (aerosol OT) has proved to increase the intestinal absorption of many drugs.[63,64] While the number of publications on the possible application of aerosol OT microemulsions for topical drug delivery is already extensive, aerosol OT applicability for oral micro emulsion drug delivery still needs to be studied.[65] Recently, a patent cooperation treaty (PCT) provided a stable, self-emulsifying water/oil microemulsion in which the surfactant with high Hydrophilic Lipophilic Balance (HLB) comprises a medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt dissolved in a polyhydric alcohol to improve the delivery characteristics of a therapeutic peptide drug.[66]

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE 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 were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%.[67] More recently, a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like PTX.[68]

Self-emulsifying sustained/controlled-release pellets

To formulate and prepare SEDDS, there were some basic guidelines needed to conform: safety, compatibility, drug solubility, efficient self-emulsification efficiency and droplet size, etc. Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reduction of intra subject and inter subject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of SEDDS by SE pellets.

Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique.

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