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A REVIEW ON SELF EMUSIFYING DRUG DELIVERY SYSTEM: NOVEL APPROACH

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ABSTRACT

Keywords:

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The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil in water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulations related parameters, such as surfactant concentration, oil/surfactant ratio, and polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as SEDDS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. At present, there are four drug products, Sandimmune® and Sandimmun Neoral® (cyclosporine A), Norvir® (ritonavir), and Fortovase® (saquinavir) on the pharmaceutical market, the active compounds of which have been formulated into specific SEDDS. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

INTRODUCTION

Self emulsifying lipid formulations have improved the bioavailability of poorly water soluble & highly permeable compound. This bioavailability enhancing property has been associated with a number of in vivo properties of lipid formulation including:

- The formation of fine dispersions and micellar suspensions to prevent precipitation and re-crystallization of the drug compound.
- The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favor improved drug absorption.
- The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
- Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.^[5]

Within these oral dosage forms, lipids are simple emulsions, self emulsifying and self-micro-emulsifying formulations. SELF systems comprise a defined mixture of lipid excipients, including simple oils, nonionic surfactants and co-surfactants. SELF-systems act as carriers for drugs by forming fine emulsions, or micro-emulsions, under gentle stirring when diluted in water or physiological media with physiological motion. Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption. SELF-system exists: self emulsifying drug delivery systems (SED DS) micro-emulsifying drug delivery systems (SMED DSs). Both SED DSs and SMED DSs have distinct features associated with improved drug delivery properties.^[7]

SED DS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. SED DS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 µm and the dispersion has a turbid appearance. SMED DSs, however, have a smaller lipid droplet size (<200 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs. The choice of whether a SED DS or a

SMEDDS is the preferred formulation option often depends on the interplay between the intrinsic properties of the drug compound and its solubility and dissolution profile during in vitro screening with a number of excipients. ^[16]

NEED OF SEDDS

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in another lipid droplet. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option. ^[1, 12]

ADVANTAGES

- Enhanced oral bioavailability enabling reduction in dose.
- More consistent temporal profiles of drug absorption.
- Selective targeting of drug toward specific absorption window in GIT.
- Protection of drug from the environment in gut.
- Control of delivery profiles.
- Protective of sensitive drug substances.
- Liquid or solid dosage forms.
- Improve the dissolution.

- Increases the surface area on dispersion.
- Stable preparation.

DISADVANTAGES

- Chemical instabilities.
- GIT irritation.
- Precipitation of lipophilic drug.
- Physical and chemical changes in crystalline solid in cryogenic grinding.

COMPOSITION OF SEDDS ^[2]

Self-emulsification has been shown to be specific to:

1. The nature of the oil/surfactant pair;
2. The surfactant concentration and oil/surfactant ratio;
3. The temperature at which self- emulsification occurs

OILS:

Oils are the most important excipient because oil can solubilise the lipophilic drug in a specific amount can terminate facilitate self- emulsification and increase the fraction of lipophilic drug transported via intestinal lymphatic system, thereby increasing absorption from the GI tract. Both long chain triglyceride and medium chain triglyceride oils with different degrees of saturation have been used for the formulation of SEDDSs. Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of SEDDSs 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.

SURFACTANT:

Various non-ionic surfactants such as the polysorbates and polyoxyls, which cover the HLB range from 2 to 18, may be used in combination with lipid excipients to promote self-emulsification or micro-emulsification. Due to their relatively low toxicity, the acceptable quantities for use of these surfactants are limited primarily by their tendency, at high concentration, to cause brittleness of hard and soft gelatin capsules due to their dehydrating effects on capsule gelatin. Surfactant have a high HLB & hydrophilic which assist the immediate formation of O/W droplet & rapid spreading of the formation in

aqueous media. Surfactants are amphiphilic nature & they can dissolve or soluble relatively high amount of hydrophobic drug compound. This can prevent precipitations of the drug within the GI lumen & for prolong existence of drug molecules. Due to their relatively low toxicity, the acceptability quality for use of these surfactant are limited primarily by their tendency, at high concentration, to cause brittleness of hard & soft gelatin capsule due to their dehydrating effect on capsule gelatin.

CO-SOLVENTS

Co-solvent like diethylene glycol monoethyle ether, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydro furfuryl alcohol polyethylene glycol ether, etc, may help to dissolve large amount of hydrophilic surfactant or the hydrophobic drug in the lipid base. 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 at ambient room temperature where those possessing molecular weight of 1000 or greater exit as thermo softening semi solid. 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 combination with other lipid excipients to improve the overall solubilizing power of the formulation. However, their pronounced water miscibility can compromise formulation performance due to uncontrolled precipitation of the drug substance following dilution in the aqueous contents of the GIT this typically results in dose-dependent bioavailability enhancement.

A few examples of the most commonly applied excipients in this class and their application follows. Among the polymeric glycol based excipients finding pharmaceutical application, the polyethylene glycols (PEGs) are a versatile, well-characterized and widely applied class of solubilizers which are available as both liquids and thermo softening semi-solid. The physical state of these excipients at ambient room temperature is determined by this molecular weight. In comparison to natural product oils, PEGs have the following disadvantages: They tend to be more chemically reactive; they can be more irritating to the GI mucosa than oils. PEGs are also known to contain varying levels of peroxide impurities and secondary products formed by

auto-oxidation, which can contribute to chemical instability of the incorporated drug substance 8. These excipients are widely used in soft gelatin capsule formulations but find limited use in conjunction with hard gelatin capsules due their hygroscopic and resultant effects on gelatin moisture content, which can compromise capsule physical integrity. Propylene glycol, a pharmaceutically-acceptable, monomer solvent possessing humectants and plasticizing properties, finds application for soft gelatin capsule formulations of poorly water-soluble drugs. The Poloxamers, which are co-polymers of polyoxyethylene and polyoxypropylene, possess both solvent and surfactant properties and thus find application in the oral delivery of poorly water-soluble drugs. As with the PEGs, they are available in a range of molecular weights which control the physical state of the excipient at room temperature. In addition to improving the bioavailability of poorly water-soluble drugs, they have found application in modified release formulations.

EXCIPIENT USED IN SEDDS

Table 1: Physicochemical Properties and Main Fatty Acid Composition of Labrifil Oils (Compiled from Gattefossé Specification Sheets) ^[2]

Oil(MW)	Main fatty acid(%)	PEG group	HLB	Water solubility at 20	Viscosity at 20(m.Pa.s)
Labrasol(430)	Caprylic (C8) 50-80% Capric (C10) 20-50%	PEG 400	14	Soluble	80-110
Labrafac CM 10 (440)	Caprylic (C8) 50% Capric (C10) 50%	PEG 200	10	Dispersible	0-90
Labrafil WL 2609 BS (850)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 400	6	Dispersible	120
Labrafil M 1944 CS (530)	Oleic (C18:1) 58-68% Linoleic (C18:2) 22-32%	PEG 8	4	Dispersible	75-95
Labrafil M 2125 CS (682)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 6	4	Dispersible	70-90
Labrafac Lipophile WL 1349 (504)	Caprylic (C8) 50-80% Capric (C10) 20-50%	—	1	Insoluble	25-35

FORMULATION OF SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard

or soft gelatin or mixtures which disperse to give fine colloidal emulsions . The following should be considered in the formulation of a SEDDS:

- 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 mix of oil, surfactant and co solvent.

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.^[14,15]

TYPE OF SEDDS ^[11]

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 stood even although several studies have been carried out to investigate this(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. Supersaturation 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.^[13] The S-SEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are well recognized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods

A supersaturable self-emulsifying drug delivery system (S-SEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SEDDS

formulation. *In vitro* dilution of the S-SEDDS formulation results in formation of a micro emulsion, followed by slow crystallization of paclitaxel on standing. This result indicates that the system is supersaturated with respect to crystalline paclitaxel, and the supersaturated state is prolonged by HPMC in the formulation. In the absence of HPMC, the SEDDS formulation undergoes rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SEDDS formulation produces approximately a 10-fold higher maximum concentration (C_{max}) and a 5-fold higher oral bioavailability (F 9.5%) compared with that of the orally administered Taxol formulation (F 2.0%) and the SEDDS formulation without HPMC (F 1%)^[13]

A poorly soluble drug, PNU-91325, was formulated as a supersaturable SEDDS. The comparative *in vitro* studies indicated that the presence of a small amount HPMC in the formulation was critical to achieve a stabilized supersaturated state of PNU-91325 upon mixing with water. A S- SEDDS formulation composed of 30% w/w Cremophor (surfactant), 9% PEG 400, 5% DMA, 18% Pluronic L44, 20% HPMC, and other minor components had an oral bioavailability of ~ 76%, comparable with that of a neat Tween formulation (bioavailability: ~ 68%). Note that the weight ratio of drug to cremophor EL is 1:7.5 in the S-SEDDS formulation while the weight ratio of drug to Tween is 1:39 in the neat Tween formulation. Applying the supersaturable SEDDS approach, a reduced amount of surfactant is deliberately used with HPMC in order to produce a temporarily supersaturated state with reduced solubilisation. This is to obtain a high free drug concentration through generating and maintaining a supersaturated state *in vivo* and to increase the driving force for absorption

It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations. However, the underlying mechanism of the inhibited crystal growth and stabilized super saturation by means of these polymers is poorly under-

Solid SEDDS

SEDDS are normally prepared as liquid dosage forms that can be administrated in

soft gelatin 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). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 min, T50% at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C_{max} and T_{max} values. A method of producing self-emulsifying pellets by wet granulation of a powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, polysorbate 80 and water has been investigated. The pellets produced with oil to surfactant ratio of 1:4 (w/w) showed improved performance in permeation experiments. At-tama *et al.* used goat fat and Tween 65 admixtures to formulate self-emulsifying tablets containing diclofenac by pour-moulding using a plastic mould. The tablets showed good release profiles, as well as acceptable tablet properties. Under mild agitation, such as occurs under gastrointestinal conditions, the release rates are comparable with those of conventional tablets. Encapsulating the emulsion lipid droplets in HPMC by spray-drying has been demonstrated to produce an improved bioavailability following release of the lipid droplets from the powder *in vivo*. Tue *et al.* [70] have investigated the oral bioavailability of a directly compressible dry emulsion as a tablet and compared it with an HPMC dry emulsion powder and a simple lipid solution. Four female Beagle dogs received a single dose of each formulation containing the same amount of MCT and model drug, Lu 28-179. Cyclodextrin solutions administered orally and intravenously were used as references. The absolute bioavailability decreased in the order: cyclodextrin solution (0.14) > HPMC dry emulsion (0.11) > technically improved dry emulsion (0.10) > MCT solution (0.06). The directly compressible dry emulsion tablets were concluded to be comparable with the HPMC dry emulsion powder in terms of bioavailability.

MECHANISM OF SELF-EMULSIFICATION

According to Reiss, 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 the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

$$DG = S N_i p r_i 2s$$

Where, DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and s represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence. ^[12]

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/ SEMISOLID SEDDS TO S-SEDDS ^[11]

- **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 seal, either by banding or by micro spray sealing. In parallel with the advances in capsule technology proceeding, liquid-Ores technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation

through an orifice in the hard or soft capsule. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. ^[1]

The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w)) potential.

- **Spray drying:**

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

- **Adsorption to solid carriers:**

Free flowing powders may be obtained from liquid SE formulations 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 can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be micro porous inorganic substances, high surface- area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate. Cross linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo Charcoal. ^[3]

- **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. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Thereinto, Gelucire®, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SE property. ^[5]

Other lipid-based excipients evaluated for melt granulation to create solid SES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) on to solid neutral carriers (mainly silica and magnesium aluminometa silicate). ^[6]

- **Self-emulsifying capsules:**

After administration of capsules containing conventional liquid SE formulations, microemulsion 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. With the similar purpose, the supersaturatable SEDDS was designed, using a small quantity of HPMC (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. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self-micro emulsification upon mixing

with water. Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thromboembolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: microporous calcium silicate (Florite™ RE); magnesium aluminum silicate (Neusilin™ US2) and silicon dioxide (Sylysia™ 320). Eventually these solids were filled into hard capsules ^[11]

- **Self-emulsifying solid dispersions:**

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling SE excipients like Gelucire1 44/14, Gelucire1 50/ 02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field. For example, Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method. Seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide-containing drug (phenacetin) and a drug with no proton-donating groups (progesterone) were chosen. Gelucire1 50/13 was used as the dispersion carrier, Whereas Neusilin US2 was used as the surface adsorbent. ^[11]

DOSAGE FORM DEVELOPMENT OF SELF EMULSIFYING DRUG DELIVERY SYSTEM:

- ▶ Self emulsifying dry emulsion
- ▶ Self emulsifying solid dispersion
- ▶ Self emulsifying capsule
- ▶ Self emulsifying sustain release/controlled release tablets

- ▶ Self emulsifying sustain release/controlled release pellets
- ▶ Self-emulsifying sustained-release microspheres
- ▶ Self emulsifying beads
- ▶ Self emulsifying nanoparticles.
- ▶ Self emulsifying suppositories
- ▶ Self emulsifying implants

CHARACTERISATION OF SEDDS ^[16]

The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution. The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

1. Visual assessment:

This may provide important information about the self-emulsifying and micro-emulsifying property of the mixture and about the resulting dispersion

2. Turbidity Measurement:

This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. Nepheloturbidimetric evaluation is done to monitor the growth of emulsification.

3. Thermodynamic stability studies.

- Heating cooling cycle: There are six cycles between the temperatures 40°C and 45°C. In between these temperatures the formulation to be stored and storage at each temperature is not less than 48 hr is studied. The formulations, which are stable here, are then subjected to centrifugation test.
- Centrifugation: Those formulations are stable above are centrifuged thaw cycles between 21°C and +25°C. And the storage time at each temperature is not less than 48 h, and is carryout at 3500rpm for 30min. If formulations that are stable here, that means they does not show any phase separation, then they are transferred 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.

4. Dispersibility *test*.

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

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

- ▶ Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear 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.

5. 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 are mainly used for the 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

6. Precipitation method.

7. Viscosity Determination.

The SEDD 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 are w/o type of the system.

8. Refractive Index and Percent Transmittance.

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refract meter by placing drop of solution on slide and it compare with water. The percent transmittance of the system is measured at particular wavelength using UV- spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance >99 percent, then formulation have transparent nature.

9. In Vitro Diffusion Study.

10. Drug content

11. 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.

APPLICATION

- Improvement in solubility
- Improvement in bioavailability
- Achieve sustained release drug delivery system
- Achieve transdermal drug delivery system
- Protection against biodegradation
- Targeting drug delivery system
- Achieve controlled released drug delivery system

RECENT APPORECHES IN SEDDS

- SEDDS of coenzyme Q10 was prepared and this resulted in enhanced bioavailability and reduced toxicity.
- Lipophilic compound WIN 54954 was formulated as SEDDS in triglyceride oil/non-ionic surfactant mixtures and resulted in improved reproducibility of the plasma profile in terms of C_{max} and T_{max}. (18)
- Self micro emulsifying drug delivery system (SMEDDS) of simavastin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds. (5)

- A novel SEDDS of PTX (used for the treatment of solid tumors) was prepared and it was found that SEDDS was chemically stable for at least 1 year when kept as two part formulation and also the drug loading was increased by approximately fivefold. Compared to marketed i.v. formulation, the excipient presented a significantly reduced cytotoxicity and led to a stable micro emulsion. (11)
- An antimalarial drug, Halofantrine, was prepared as SEDDS and SMEDDS and resulted in an eightfold improvement in absolute oral bioavailability relative to previous data of the solid. (2)
- Enhanced bioavailability upto 1.88 of silymarin was achieved by SMEDDS.(2)
- Using SEDDS, self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone was prepared and the study revealed that SNEDDS overcame the drawbacks of the traditional emulsified system, such as low solubility and irreversible precipitation of the active drug in the vehicle with time.(1)
- The two novel SMEDDSs containing Labrasol with different dilutions on tight junction were studied and found that Labrasol at a concentration of 0.1 and 1% was shown to increase the permeability of mannitol by 4.6-fold and 33.8-fold, respectively.^[7]
- The solid self-emulsifying system (SES) was used in the delivery of diclofenac and results indicated that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 65 admixtures.
- SEDDS containing ketoprofen was formulated as sustained release dosage form and it was found that drug release was increased.^[16]

CONCLUSION

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.

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