A REVIEW ON: SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Self-microemulsifying drug delivery systems (SMEDDS) possess unparalleled potential in improving oral bioavailability of poorly water-soluble drugs. Following their oral administration, these systems rapidly disperse in gastrointestinal fluids, yielding micro- or nano-emulsions containing the solubilized drug. Owing to its miniscule globule size, the micro/nano-emulsified drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect. Solid-SMEDDS represent more effective alternatives to conventional liquid SMEDDS. Purpose of this study is to understand the fact of Solid-SMEDDS(S-SMEDDS) which provide characteristics of both SMEDDS as well as solid dosage form (e.g. excipients selection, specificity, characterization). S-SMEDDS is formulated by incorporating liquid/semisolid Self emulsifying ingredients into powders/ nano-particles form by different solidification techniques.

KEYWORDS: Solid SMEDDS, hepatic first-pass effect, lymphatic pathway, liquid SMEDDS.

1. INTRODUCTION

Most of the new drug candidates used for formulation development today are sparingly soluble and have poor bioavailability. Various formulation strategies have been developed to solve these problems; these include the use of surfactants, cyclodextrins, drug nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers. Majority of these
formulation approaches have resulted in limited success because of the need for specialized equipments, complicated manufacturing process, longer processing time, and regulatory complexity. In recent years, an area that is gaining popularity with formulation scientists is using lipid-based careers to develop self-emulsifying drug delivery systems (SEDDS) to improve oral bioavailability of many lipophilic drugs. Lipid-based vehicles mainly decrease the intrinsic limitations of slow and incomplete dissolution of poorly aqueous soluble drugs by facilitating the formation of solubilised phases from which absorption takes place. A mixture of oil and non-ionic surfactant forms a clear and transparent isotropic solution known as self-emulsifying systems, if the mixture forms an emulsion when mixed with water. Such formulations form a fine oil-in-water emulsion with gentle agitation, which may be provided by gastrointestinal motility. Self micro-emulsifying drug delivery system (SMEDDS) are mostly prepared in liquid dosage forms in soft and hard gelatine capsules, which have some manufacturing and leakage problems. The solid self-microemulsifying drug delivery systems (S-SMEDDS) are a new approach to overcome the above mentioned problems. In this formulation the liquid self-emulsifying agents are incorporated into powder to make solid dosage form such as tablets, capsules using various techniques like extrusion, spheronation etc.

2. S-SMEDDS overcoming the need of liquid SMEDDS
   - S-SMEDDS form is more preferred than liquid SMEDDS form.
   - S-SMEDDS (solid micro-emulsion pre-concentrate) readily forms microemulsion when comes in contact with water.
   - Need for outsourcing of soft gelatine capsule manufacturing at early stage of drug product development may be avoided.
   - S-SMEDDS remain solid at room temperature, yet maintains all the advantage of liquid SMEDDS.
   - S-SMEDDS can be filled into hard gelatine capsules.
   - S-SMEDDS are highly stable and reproducible than liquid SMEDDS.
   - S-SMEDDS can also be incorporated in other solid dosage forms (e.g. fast dissolving tablets, films etc.)

3. Components of S-SMEDDS
   Lipid is an essential component of the SMEDDS formulations. Not only the lipid can solublize marked amounts of lipophilic drug or facilitate self-emulsiﬁcation, but has the
propensity to augment the fraction of drug transported via intestinal lymphatic system too, thereby increasing its absorption from the GI tract. Natural edible oils, comprising of medium chain triglycerides, in this regard, are not frequently preferred owing to their poor ability to dissolve large amounts of lipophilic drugs. Modified long and medium chain triglyceride oils, with varying degrees of saturation or hydrolysis, have widely been used for the design and development of SMEDDS formulations. These oils offer distinct formulative and physiological advantages, as their degradation products resemble that of the natural end products of intestinal digestion. Most of the mono-, di- and tri-glycerides and their mixtures in varying proportions, with or without the fatty acid esters of propylene glycol, are available commercially in the purified form. Both unsaturated and saturated fatty acids have been widely employed in the formulation of lipidic systems. However, the SMEDDS, in particular, comprise of saturated fatty acids like, caproic, caprylic, capric, lauric and myristic acid. One can make appropriate choice amongst these looking into their composition, potential utilities, physical state and hydrophilic-lipophilic balance (HLB). Also omega-3 fatty acid containing oil for e.g fish oil can also be used as a lipid carrier in S-SMEDDS.\(^4\)

**Surfactant**

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) . Safety is a major determining factor in choosing a surfactant. The four main groups of surfactants are defined as following- A) Anionic surfactants B) Cationic surfactants C) Ampholytic surfactants D) Non-ionic surfactants.

A) **Anionic Surfactants:** where the hydrophilic group carries a negative charge such as carboxyl (RCOO\(^-\)), sulphonate (RSO\(_3\) -) or sulphate (ROSO\(_3\) -).

**Examples:** Potassium laurate, sodium lauryl sulphate.

B) **Cationic surfactants:** - where the hydrophilic group carries a positive charge.

**Example:** quaternary ammonium hallide

C) **Ampholytic surfactants:** - (also called zwitter ionic surfactants) contain both a negative and a positive charge.

**Example:** sulfobetaines.
D) **Nonionic surfactants:** - where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene.

**Examples:** Sorbitan esters (Spans), poly-sorbates (Tweens).

**Surfactants can also be classified as**
- **Water soluble:** E: Labrafil M 1944CS, Caprol PGE 860
- **Water in-soluble:** E: Span 80, Span 20[^5]
- **Solid state surfactants:** These surfactants can be used to produce solid SMEDDS since they have dual nature of surfactant as well as solidifying agent. E: Gelucire 44/14 and 50/13, Poloxamer L-188 and L-407.[^6]

**Co-solvent / Co-surfactant**
Co-solvents like diethyl-glycol-monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate etc, may help to dissolve large amount of hydrophilic surfactants or hydrophobic drug in the lipid base. These solvents sometimes play role of co-surfactant in microemulsion systems.[^5]

**Adsorbents / solidifying agents**
Conversion of liquid SMEDDS to S-SMEDDS generally involve adsorption of liquid SMEDDS to some solid carrier or various techniques for solidification are used like spray drying, spheronization etc. E: of some adsorbents used are neusilin US2, fujicalin, cellulose etc.

### 4. Solidification techniques

#### a. Spray drying
In this technique, formulation preparation involves by mixing lipids, surfactants, drug, solid carriers, and solublization of mixtures before spray drying. The solublized liquid formulation is then atomized into a spray of droplets. The volatile phase (e: the water contained in an emulsion) evaporates as the droplets introduced in a drying chamber, forming dry particles under controlled temperature and airflow conditions. A variety of solid carriers have been used for preparation of S-SMEDDS e: Dextran 40 (water soluble solid carrier, Aerosil® 200 (non-porous and hydrophilic solid carrier).

**Critical parameters of spray drying system includes**
- Inlet temperature of air
Advantages

- Able to operate in applications that ranges from aseptic pharmaceutical processing to ceramic powder production.
- Process is very rapid
- Available in wide designs to meet various product specifications
- It can be used with both heat-resistant and heat-sensitive products
- Offers high precision control over particle size, bulk density, degree of crystallinity, organic volatile impurities, and residual solvents.

Disadvantage

- The equipment is very bulky and with the ancillary equipments it is costly.
- The overall thermal efficiency is low, as large volumes of heated air pass through the chamber without contacting a single particle, thus not contributing directly to drying.\(^7\)

b. Adsorption to solid carriers

Free flowing powders may be obtained from liquid self micro-emulsifying formulation by adsorption to solid carriers. The process involves addition of liquid formulations onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or may be formulated as a tablet. Solid carriers that can be used are e.g Neusilin US2, Avicel PH 101, Spray dried lactose.

Advantage

- The most important advantage of using this technique is good content uniformity.\(^8\)

c. Capsule filling with liquid and semisolid self-emulsifying formulation

Capsule filling is the most economical and common technique for encapsulation of liquid or semisolid self-emulsifying formulations for oral route. For semisolid preparations it is a four
step process that involves: 1) Heating semisolid excipients to 20°C above its melting point
2) Incorporation of active substances 3) Capsule filling with molten temperature and 4) Cooling to room temperature. For liquid formulations process involves, filling of liquid formulation into capsules followed by sealing of body and cap of the capsule, either by banding or by microspray sealing.

Advantage
- Simplicity of the process.
- Suitable for low-dose and highly potent drugs.
- High drug loading potential.\textsuperscript{[1]}

d. Melt extrusion/extrusion spheronization
Melt extrusion is a solvent free process. Extrusion is a process 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.\textsuperscript{[9]} The size of extruder aperture will determine the approximate size of resulting spheros.

The extrusion spheronization process involves the following steps
a) Dry mixing of active ingredient and excipients to form a homogenous powder and then forming a wet mass with help of a binder.
b) Extrusion into a spaghetti-like extrudate
c) Spheronization from the extrudate into spheros of uniform size
d) Dry sifting to achieve the desired size distribution and coating.

Advantage
- High drug loading (60%).
- Good content uniformity.
- Short processing time and simple equipment.\textsuperscript{[10]}

e. Dry emulsions
Dry emulsions are powders from which emulsions spontaneously occurs \textit{in vivo} or when exposed to an aqueous solution. These dry emulsions can be further used for preparation of tablets or capsules. Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextrin etc) in the aqueous phase by rotary evaporation, freeze-drying or spray drying.\textsuperscript{[11]}
f. Supercritical fluid based technique
Lipids can be used in supercritical fluid based methods either to coat the drug particle or produce a solid dispersion. For environmental reasons, generally the supercritical fluid of choice is supercritical carbon dioxide.\[^{[3]}\]

g. Solid lipid nanoparticles and nanostructured lipid carriers
Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have submicron particle size of about 50-1000nm, they are composed of physiologically tolerated lipid components. SLN are produced by high pressure homogenization of solid matrix and drug with an aqueous solution of glyceryl dibehenate as solid lipid matrix and poloxamers 188 and polysorbates 80 as surfactant. They have generally been employed in controlled-release applications in oral, intravenous and topical routes.\[^{[3]}\]

h. Cryogenic grinding
This method is mostly used for formulations containing Gelucire\(^®\) 44/14 as a self emulsifying excipient. Gelucire has low melting point, hence it has to be melted first and then mixed with drug as a result only semi-solid dosage forms could be produced. Hence cryogenic grinding process can be employed to form solid dosage forms like tablets, pellets etc. Cryogenic grinding is a process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues) and for unstable compounds (vitamins, volatile substances).\[^{[12]}\]

i. Self solidification by surfactant
This method is mostly used for formulations containing Gelucire\(^®\) 44/14 as surfactant. As gelucire has low melting point, hence on preparing a mixture of oil, surfactant and co-surfactant and keeping it in room temperature or freezing it causes the solidification of the mixture. This is possible since Gelucire has dual nature of a surfactant as well as a solidifying agent.\[^{[6]}\]

5. Characterization of S-SMEDDS formulations
a. Flow property (Micromeritics)
The prepared S-SMEDDS can be evaluated for micromeritics properties such as angle of repose, bulk and tapped density, compressibility index, hausner ratio.\[^{[13,14,15]}\]
b. Reconstitution properties of S-SMEDDS
In order to study this property, the solid SMEDDS are dispersed with water and incubated at 37°C for specified time. The samples were then withdrawn and investigated by transmission electron microscope.[1,13]

c. Drug-excipient compatibility studies
This study is important in case of solid self micro-emulsifying drug delivery systems, since in these formulations the drug is mixed with excipients like oils, surfactants, co-surfactants etc, it is essential to know that on addition of these excipients the drug properties are unaltered. The study is usually carried out by taking FTIR spectra of pure drug, physical mixture of drug and oily excipients and solid SMEDDS using FTIR spectrophotometer with diffuse reflectance principle. The resultant spectra is then scanned for any spectral changes.

As seen in a study carried out by Smita S. Pimple for formulation and evaluation of self micro-emulsifying formulation of Risperidone, the FTIR spectra showed prominent peaks of pure risperidone in thermograms of, physical mixture as well as in selected solid SMEDDS, revealed the compatibility between drug, excipients and the carrier.[16]

d. Morphological evaluation
Scanning electron microscopy
The surface morphology of solid SMEDDS can be determined using analytical electron microscope. In this method sample was sprinkled on a double adhesive tape stuck on aluminium stubs. The stubs were then coated with platinum to thickness of above 10 Å under an argon atmosphere, under high pressure vaccum and then the sample coated stubs were placed in scanning electron microscope chamber.

As seen in study carried out by Mrs Maria Saifee in formulation and evaluation of solid self-emulsifying drug delivery system of Glibenclamide, the SEM images of solid SEDDS showed, well separated particles with no agglomeration.[17]

e. Effect of solidification on globule size
Zeta potential
Droplet size of S-SMEDDS can be determined by Zetasizer Nano ZS (Malvern instruments UK) with dynamic light scattering particle size analyzer. All studied are to be repeated three times and values of Z- average diameter are to be used. The Z-average diameter also referred
to as harmonic intensity-weighted average hydrodynamic diameter, of emulsions can be derived from cumulated analysis by Automeasure software.\textsuperscript{[18]}

**Droplet size measurement**

The mean droplet size of emulsion globules can be determined using photon correlation spectroscopy which analyses the light scattering due to Brownian motion of the particles.\textsuperscript{[18]}

**Transmission electron microscopy (TEM)**

Examining the surface of polymeric drug delivery system can provide vital information on porosity and microstructure of the system. So the most common technique to study the surface properties of system is TEM. By comparing TEM results of pure drug and drug encapsulated as S-SMEDDS, we can confirm that there has been no changes in properties of drug on conversion to S-SMEDDS.\textsuperscript{[18]}

![Fig 1. TEM image of Telmisartan solid self micro-emulsifying formulation\textsuperscript{[19]}](image)

**f. Solid-state characterization of Solid SMEDD**

**Differential scanning calorimetry (DSC) & X-ray diffraction studies (XRD)**

DSC & XRD are carried out to confirm that the drug presented in formulation is in amorphous state. This helps us to confirm that the molecular structure of the drug is intact in the formulation.\textsuperscript{[20]}

**g. Dissolution studies**

*In-vitro* drug release studies of S-SMEDDS can be carried out by dialysis method, dissolution appartus II and diffusion cell.

Now, as given by Pathak Chirag Vilas in a review on self micro-emulsifying drug delivery system, *in-vitro* release studies was carried out using modified diffusion cell in a 200 ml buffer solution of 6.8 Ph.
1 gm SMEDDS formulation was placed in boiling tube, both side of boiling tube was opened and one side of tube with cellophane membrane and dipped in a buffer solution kept in a beaker below. Upper side of cylinder was clamped to hold. The beaker was continuously stirred by magnetic stirrer and sample was withdrawn at specific time intervals and analysed using UV- spectrophotometer.\[21\]

Linje liu in Formulation design and in-vitro evaluation of sliymarin-loaded SMEDDS have performed in-vitro drug release studies using bulk-equilibrium reverse dialysis bag technique (BERDBT) in 900ml distilled water, 0.1 mol/l hydrochloric acid with/without sodium dodecyl sulphate and pH 6.8 phosphate buffer at 37±0.5ºC based on ChP (2005) release test method II.\[22\]

**h. Stability studies**

**For thermodynamic stability studies three main steps can be performed**

a) **Heating cooling cycle**
Six cycles between refrigerates temperature and 45ºC with storage at each temperature of not less than 48 hr studied, those formulations which are stable at these temperatures are subjected to centrifugation tests.

b) **Centrifugation**
Passed formulations are centrifuged between 21ºC and 25ºC with storage at each temperature not less than 48hr is done at 3500 rpm for 30 mins.

c) **Freeze thaw cycle**
Those formulations which passed this test showed good stability.\[23\]

**6 Various dosage forms of S-SMEDDS**

a. **Self-emulsifying capsule:** It is a capsule containing liquid or semisolid form of self-emulsifying system. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing bioavailability. Second type of self-emulsifying capsule is solid SES filled into capsule.\[24\]

**Example:** CyclosporinA “Neoral®” soft gelatin capsules from Novartis.

b. **Self-emulsifying tablets:** In this system the prepared self-micro or nanoemulsion system are adsorbed by granular materials and finally compressed to form tablets. In GIT, the tablets undergo disintegration and dissolution to release the active constituent from self-emulsifying
formulation. Example: Self-emulsifying tablet of ubiquinone was prepared by adsorbing the liquid formulation on granulating materials and the compressed into tablets.\[^{25}\]

c. Self-emulsifying pellets: In this method a binder solution containing an oil, surfactant and model drug in specified proportion is developed. The oil-surfactant mixture is then stirred and water is added to form the self-emulsifying system. This binder solution is then sprayed onto the granules of microcrystalline cellulose and lactose present in the granulator to form the pellets. These pellets are able to generate significantly smaller droplets with respect to corresponding emulsions.\[^{26}\]

d. Self-emulsifying beads: In this method the self-emulsifying system can be formulated as a solid dosage form by using less excipient where the SES are deposited into microporous polystyrene beads by solvent evaporation.\[^{27}\]

e. Self-emulsifying microspheres: Solid self emulsifying sustained release microspheres can be formulated using the quasi-emulsion solvent diffusion method. The plasma concentration time profiles achieved after oral administration of such microspheres into rabbits showed a bioavailability of 135.6% with respect to the conventional liquid SEDDS. Example: Solid self emulsifying sustained release microspheres were prepared using Zedoary Turmeric oil (ZTO), a traditional Chinese Medicine (TCM), as oily phase \[^{28}\]

f. Self-emulsifying nano-particle: Self-emulsifying nano-particles can be developed with the help of Nano-particle technology. This technique involves preparation of injection of molten lipid mass containing lipid, surfactant and drug. The lipid molten mass is then injected drop wise into a non-solvent system. This is filtered and dried to get nano-particles. By this method 100nm size particle with 70-75% drug loading efficiency was obtained. Second technique is sonication emulsion diffusion-evaporation. Example: a novel nano-particle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX) is developed where the SE property of GMO enhances the solubility of PTX and provides foundation for chitosan aggregation thereby causing 100% drug loading and entrapment efficiency of PTX.\[^{29}\]

7) Future aspects
Supersaturable SMEDDS
Conventional SMEDDS are widely used for enhancing oral absorption of poorly water soluble drugs. But when conventional SMEDDS formulation are introduced in GI area, drug
precipitation may occur and lead to failure of improvement of intestinal absorption. On other hand high surfactant concentration in SMEDDS can cause GI irritation. Hence to irradiate such unwanted effects, supersaturable SMEDDS have been developed which represents a new thermodynamically stable formulation approach. Supersaturable SMEDDS is designed to contain reduced amount of surfactant and a water soluble polymer which acts as precipitation inhibitor or supersaturated promoter. Zhang Nan had prepared Carbamazepine supersaturable self-microemulsifying formulation.\textsuperscript{30}

8. Recent approaches in self-emulsifying drug delivery systems

- 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 Cmax and Tmax.
- Self-microemulsifying drug delivery system (SMEDDS) of simvastatin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds.
- 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 microemulsion.
- 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.
- Enhanced bioavailability upto 1.88 of silymarin was achieved by SMEDDS.
- 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.
- 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.
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.

9. CONCLUSION

SMEDDS formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. Self-microemulsifying drug delivery system can be use for the formulations of drugs compounds with poor aqueous stability. Development of this technology SMEDDS will continue to enable novel applications in drug delivery system. SMEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SMEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents.

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