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# A Review on Solid-Selfmicroemulsifying Drug Delivery System: Formulation Strategies to Improve the Bioavailability of Poorly Soluble Drugs

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**ABSTRACT:**

Poorly water soluble drug candidates are becoming more prevalent and it has been estimated that 40-50% of drug molecules are poorly soluble in aqueous media or have a low permeability which does not allow for their adequate absorption from gastrointestinal tract following by oral administration. Formulation scientists have to adopt different strategies to enhance their absorption. Lipidic formulations are seen to be a promising approach to combat the challenges and especially self-microemulsifying drug delivery(SMEDDS) system approach are used to increase the absorption of poorly absorbed drug which ultimately increased there bioavailability. The attempts of various scientist to convert the liquid SMEDDS to solid-SMEDDS by adsorption, spray drying, lyophilisation, melt granulation and extrusion techniques. Formulation of SMEDDS is a potential strategy to deliver poorly soluble drug and low absorption drug with enhanced dissolution rate and bioavailability.

**KEYWORDS:** Self-microemulsifying, adsorption technique, surfactant, poorly water soluble drug, bioavailability, absorption, ternary phase diagram

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## Introduction

The advancement in combinatorial chemistry and screening resulted in development of new chemical entities. As increased in used of these technologies, the screening of new chemical entities shift the identification of lead compounds of higher molecular weight and high lipophilicity which ultimately leads to poor aqueous solubility.[1] The solubility behaviour is one of the key determinants for oral Bioavailability. In recent years number of poorly solubility drugs has increased significantly [2]. For researchers and scientist it is most important challenge for formulation of poorly soluble drugs. The most widely oral route is preferred compared to others route due to better patience compliance and economical cheap. The drug should be dissolved in gastric fluid to be absorbed from systemic circulation.[3]The dissolution step acts as the rate-controlling step for hydrophobic drugs which ultimately determine the rate and extent of absorption. The drugs to absorb through gastrointestinal tract, the molecules should present minimum solubility in physiological media and should present in dissolved state at site of absorption.[4]

The development in new chemical entities, severe limiting factors must be overcome like poor solubility in GI fluid, stability and reasonable intestinal

permeability.[5] More than 40% of new chemical entities are of poor water soluble or insoluble drugs also up to 50% of orally administered drugs substance suffers from formulation problem of low solubility and high lipophilicity.[6]The few studies have been made for micronization of medication by diminishing the molecular size but problem occur in physical and chemical stability of drugs and thus faced difficulties in formulation design and development. There are certain drugs molecule whoseBioavailability and absorption is solubility dependent. In order to design a better delivery system which provides required bioavability, the poor water solubility of drugs should be improve.[7]

**Lipid formulation classification system**[8,9]

The number of possible combination in liquid formulation especially self-emulsifying system, the Lipid formulation classification system (LFCS) was introduced by Poultan in 2000 and updated in 2006. Based on the composition, effect of dilution and digestion ability to prevent drug precipitation, the LFCS classified lipid-base formulation into four major parts.

**Type I** system comprise of formulation in which drug is solubilised in triglycerides and/or mixed glycerides or in oil water emulsion stabilized by low amount of emulsifiers as 1% w/v polysorbate 60 and 1.2% w/v lecithin. Moreover this system exhibit poor initial aqueous dispersion and need digestion by pancreatic lipase/co-lipase in GIT for more amphiphilic lipid digestion products and the transfer of drug into colloidal aqueous phase is promoted.

**Type II** lipid formulation system also known as non-water soluble component system in which self-emulsification is obtained at surfactant content above 25% w/w, but higher surfactant content of 50-60% w/w cause formation of viscous liquid crystalline gels at oil/water interface. The slow dissolution step in solid oral dosage form can be overcome by type II lipid based formulation.

**Type III** lipid based formulation known as self-microemulsifying drug delivery system are made by inclusion of hydrophilic surfactant having HLB>12 and co-solvent like ethanol, propylene glycol and PEG. These systems are further differentiating into type IIIA and type IIIB formulation in order to known specific hydrophilic system.

**Type IV** system is recently added system to LFCS which exclude natural lipid from the formulation and represent hydrophilic formulation. Due to maximum solubility of drug in surfactant and co-solvent, the drug payload is increased in these formulations. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These system produce very fine dispersion in aqueous media compared to simple glycerides containing formulation.

**Self-microemulsifying drug delivery system**

Self-microemulsifying are defined as a physically stable isotropic mixtures of oils, surfactants, co-surfactant and dissolve drug substance which upon contact with aqueous phase with gentle agitation, spontaneously emulsify to form fine oil in water emulsion. Therefore upon admistration to GI tract it readily dispersed due to agitation provided by the motility of stomach and small intestine.[10] Depending on screening and selection of oil, surfactant and co-surfactant and there relative composition, aqueous dilution will result in spontaneously generation of globule size of SEDDS produce emulsion and SMEDS produce clear transparent micro emulsion.[11]The optimum concentrations of oil, surfactant and co-surfactant which are responsible to promote self-emulsification are obtained by constructing Pseudo-ternary phase diagram. The affection of drug loading of micro emulsification is also assessed.[12]In SMEDS the globule size is less than 50 nm produce a large surface area which facilitates drug release and drug absorption.[13] The drugs are present in dissolve state in oil phase in liquid SMEDS which avoid slow and rate-limitating dissolution process for hydrophobic drugs. The liquid SMEDS are encapsulating in soft and hard gelatine capsules which is admistered as oral dosage form. The ability to form fine oil-in-water microemulsion upon gentle agitation is a principle behind SMEDS.[14] The poorly soluble drugs formulated as Self-microemulsifying drug delivery system increased the drug absorption through enhancement in dissolution rate of drugs, promote intestinal lymphatic transport of drugs, prevents from enzymatic degradation and inhibitory effect of P-glycoprotein (Pgp).[15]The conventional emulsions prepared are not stable as they are sensitive and metastable dispersed forms and require high shear of agitation to form emulsion. While in SMEDS simple mixing is required and does not required a high agitation to form microemulsion, also they are physically stable, manufacturing is easy and simple and are convenient for oral delivery in soft and hard gelatine capsules. But in formulation of liquid SMEDDS in soft and hard gelatine capsules, the incompatibility problem arises with the

shells of soft gelatine capsules. Therefore a solid SMEDS was introduced which shows a good patients acceptability. Some of the problems which can be overcome by SMEDDS.[16, 17]

**Advantage of self microemulsifying drug delivery system[18]**

- Increased the bioavailability of the drugs.
- Globule size of less than 50 nm is achieved.
- May enhanced the oral bioavailability which enables of active ingredients.
- Dose of active ingredients is reduced.
- More consistent temporal profiles of drug absorption is achieved.
- Provide 100% drug entrapment efficiency capacity.
- Drug targeting of drug can be achieved to site specific absorption site.
- Provide a protection of drugs from hostile environment in gut.
- Decreased the variability of food effects.
- Thermodynamically stable system can be achieved for long time without creaming and phase separation
- Manufacturing process and scale-up is easy and simple as it does not demand high force of agitation compared to normal emulsion to for micro emulsion.
- No specific condition of storage is required.
- Can preserve protein and peptides in microemulsion form.
- No dissolution step is required after oral administration because drug is in solubilise form and thus it ultimately increased rate of absorption rate.

**Disadvantage of self-microemulsifying drug delivery system[19]**

- Require comparatively high amount of surfactants which may be toxic in certain cases.
- For unit dosage preparation in gelatin capsules, it may produce softening or hardening effect on capsule shell, so for long term storage it is undesirable.
- In microemulsion there is presence of oil with its own odour or taste so for oral delivery it may produce patient noncompliance.
- Drug precipitation after long term storage may be a problem with certain component system.
- It may form bulky dosage form compare to solid oral dosage, so storage & transportation may be a problem.

**Mechanism of self-microemulsion [20]**

The mechanism involves in formation of self-microemulsion is not very well clarified and understood. From the surface free energy of emulsion formation, It can be understood that the change in the Gibbs free energy of the system (ΔG), produced by dispersing procedure at constant composition and pressure, can be expressed by following equation:

**$\Delta G = \Delta H - T\,\Delta S$**…….. Equation 1

Where ΔG = change in free energy
ΔH= change in enthalpy
ΔS= change in entropy
T = absolute temperature

The change in entropy (ΔS) is defined as a measure of the extent of disorder in the physical system and thus measures the extent of size reduction of the oil phase (or increase in droplet number). As the increased in disorder in system during the formation of an emulsion means a positive ΔS value which contribute the stability of prepared microemulsion.The ΔH means the change in enthalpy of the system and can be considered as the binding energy of the oil phase or the energy input required to achievea optimum average globule size (surface area). Thus it has been suggested that self-emulsification process takes place when the entropy change favoring dispersion (ΔS) is greater than the energy required to increase the surface area of the dispersion (ΔH).On the other hand, emulsification occurs spontaneously with SEDDS because the free Energy which is necessary to form the emulsion is either low and positive or negative. According to Reiss equation, the spontaneous formation of microemulsion can be achieved if free energy change (ΔG) of system must become negative in order to fulfill the thermodynamic requirement of SMEDS.

$$\Delta G = \Sigma\, Ni\, \pi\, ri^2 \sigma$$

Where N = number of droplets of radius r σ= represents the interfacial energy.

Thus it has been suggested that self-emulsification process takes place when the entropy change favoring dispersion (ΔS) is greater than the energy required to increase the surface area of the dispersion (ΔH).The free energy required in conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. Thus two phases of the emulsion tend to separate with time to reduce the interfacial tension and free energy of systems. In conventional emulsion, emulsifying agents stabilize emulsions resulting from aqueous dilution by forming a monolayer around the emulsion droplets, decreasing the interfacial energy and forming a barrier to provide from coalescence of droplets.On the other hand, emulsification occurs spontaneously with SEDDS because the free Energy which is necessary to form the emulsion is either low and positive or negative. According to Reiss equation, the spontaneous formation of microemulsion can be achieved if free energy change (ΔG) of system must become negative in order to fulfill the thermodynamic requirement of SMEDS,

$$\Delta G = \Sigma N_i \pi r_i^2 \sigma$$ …… Equation 2

Where N = number of droplets of radius r

σ= represents the interfacial energy.

**Excipients used in smedds**

The preliminary studies and screening are performed for selection of oil, surfactant and co-surfactant which is an important and critical component for formulation of SMEDDS. SMEDDS comprise of oil, surfactant and co-surfactant. The Solubility of drug is carried in various oils and surfactants. The Pharmaceutical acceptability for excipients and the toxicity issues of components used makes the selection of excipients more critical. There is a great restriction as which excipients should be used so it does goes out to its toxic level.[21]

**Oils**

The oil is an important component as it facilate the self-micro emulsion formation. The lipophilic drug can be solubilise in oils and increase the drug transport across intestinal lymphatic system and increased the drug absorption rate. Hydrogenated vegetable oils have many advantages as the foundation of lipid-based delivery systems. They are frequently ingested with food as they are fully digested and absorbed without any safety issues.[22] Vegetable oils are glyceride product of glycerolysis esters of mixed containing unsaturated long-chain fatty acids which is commonly known as long-chain triglycerides (LCT). The Oils from different vegetable sources have different proportions of each fatty acid. The Coconut oil is carry over distillation to produce the 'medium-chain triglycerides' (MCT) (also known as glyceryl tricaprylate/caprate) which is available from several suppliers and commonly comprises glyceryl esters containing saturated C8 (50–80%) and C10 (20–45%) fatty acid [23]. Castor oil is common source of Glyceryl ricinoleate, which uniquely has a hydroxyl group coupled to the alkyl chain.[24]

**Surfactants**

The choice of surfactant and its concentration range are very important for formation of microemulsion. The surfactant lowers the interfacial tension and upon the mild agitation produce by the digestive motility of stomach and small intestine is sufficient to achieve microemulsion.[25, 26] Many compounds exhibit surfactant properties as they are employed for the design of self-microemulsifying systems, but the selection of surfactant is limited as only very few surfactants are orally. The choices of surfactant are mainly control by two parameter: (a) hydrophilic-lipophilic balance, (b) safety

Usually surfactant should have high HLB value. Non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) are most widely acceptable for microemulsion formation [27]. The most widely used emulsifiers/surfactant are various solid or liquid ethoxylated-polyglycolized glycerides and polyoxyethylene20oleate (Tween 80). The safety of the surfactant is very important factor while choosing and selection of surfactant. Generally the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.[28]

**Co-surfactant**

In order to prepare optimum SMEDDS, it requires relatively high concentrations (generally more than 30% w/w) of surfactants but at high concentration it may irritate to GI tract and cause toxicity. Thus the concentration of surfactant can be minimize by incorporation of co- surfactant in the formulation. The selection of surfactant and co-surfactant is crucial step

not only for formation of SMEDDS, but also for solubilisation of drug in the SMEDDS. [29, 30]

**Solid self-microemulsifying drug delivery system**

Self-microemulsifying drug delivery system generally exist in either liquid or solid states, but SMEDDS offers a disadvantage to liquid dosage forms because many excipients used in SMEDDS are not solids at room temperature. Recent innovation for conversion of liquid SMEDS to solid-SMEDS have been extensively exploited they are frequently more effective alternatives to conventional liquid SMEDDS. In the 1990s, S-SMEDDS were normally in the form of SE (self- emulsifying) capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have developed in recent years, such as SE pellets/tablets, SE beads, microspheres, nanoparticles and SE suppositories/implants.[31]

**Method of s-smedds[32]**

**Adsorption**

Generally the liquid SMEDS are converted to free flowing powders by adsorption on to solid carriers. The adsorption of liquid SMEDS on the carries is simple process and just only involves addition of the liquid (SMEDS) formulation onto carriers by mixing in a blender. The resulting form powder is filled directly into capsules or, it can be mixed with suitable excipients and then compress 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)) ontosuitable carriers.Solid carriers might be micro porous inorganic substances, high surface-area colloidalinorganic adsorbent substances, cross-linked polymers or nanoparticles adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum,crospovidone, cross-linked sodium carboxy methyl cellulose and cross linked polymethyl methacrylate.

**Spray drying**

The spray drying technique usually involve the mixing of lipids, surfactants, drug, and solid carriers in order to form o/w emulsion. Then the mixture of o/w emulsion atomized into spray of droplet by spray drying. The droplets formed is 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. The particles can be further transferred into tablets or capsules dosage form.

**Freeze-drying**

Freeze drying also called as lyophilization technique which concerned with transfer of heat and mass to and from the product. Freeze drying involve the mixing of drug and carrier which is dissolved in a common solvent, then frozen and then last sublimated to form lyophilized dispersion.

**Melt granulation**

Melt granulation is a technique in which powder agglomeration is obtained through the addition of a binder that melts or softens relatively at low temperatures. As a 'one step' operation, melt granulation offers several advantages compared with conventional wet granulation technique, because the liquid addition and the subsequent drying phase are usually omitted.

**Melt extrusion/extrusion spheronization**

Extrusion is a process in which raw material with plastic properties is converted into a product of uniform shape and density, by passing through a die under controlled temperature in a extruder with optimum pressure condition. Melt extrusion is a solvent-free technique that allows maximum amount of drug loading (60%).The extrusion–spheronization process is most widely used in the pharmaceutical industry in order to prepare a uniformly sized spheroids (pellets).The extrusion–spheronization process is achieved by following steps:

- **(a)** dry mixing of the active ingredients and other excipients to form homogeneous powder mixture
- **(b)** addition of binder solution( wet massing)
- **(c)** powder mass is passed through extrudate at optimum speed
- **(d)** the formed extruder is spheronize to form spheroids in spheronizer
- **(e)** Drying; sifting to achieve the desired size distribution and coating.

**Evaluation parameter of self-microemulsifying drug delivery sysetm**[33,34]

**Macroscopic evaluation**

Macroscopic evaluation is checked by colour transparency or phase separation observed during normal storage condition (37±2$^{O}$C) in micro emulsion formulation.

**Robustness to dilution**

Robustness to dilution is important in SMEDDS to check the microemulsion formed have similar properties at different dilution to achieve uniform drug release profile and to ensure that the drug will not get precipitated at higher dilution *in-vivo*which retard the significant absorption of the drug from the formulation. The SMEDDS formulation is diluted in various dilution with various diluents to know the effect of dilution on liquid SMEDDS and their effect on the properties of formed emulsion. The diluted SMEDDS were store at room temperature and observed for any phase separation or precipitation occur or not.

**Self-emulsification test**

The self-emulsification of SMEDDS is performed by using a standard USP type II(Paddle) apparatus. The liquid SMEDDS upon dilution with water at 37 ± 0.5$^{O}$C at 50rpm; the time required to obtain clear homogenous mixture are recorded as emulsification time.

Grade A: Micro emulsion formed rapidly within 1 min having clear appearance.

Grade B: Micro emulsion formed are less clear rapidly formed having white appearance in less than 2 min.

Grade C: Micro emulsion with white fine milky appearance within 2 min.

**Cloud point measurement**

The cloud point measurement is important factor in SMEDDS as it gives information about the stability of micro-emulsion formed at body temperature.The formulation is diluted in water and kept on water bath and temperature is increase gradually. The point at which cloudiness observed is noted as cloud point.

**Droplet size and zeta potential**

The globule size of formed emulsion is important as it determine the rate and extent of drug release as well as absorption. The globule size of reconstituted formulation is measured after diluting the liquid SMEDDS in distilled water by using Zetasizer.The Zeta potential are carried out to identify charge on the surface of droplet. The liquid SMEDDS containing drug is diluted in distilled water in a flask and were mixed gently by inverting the flask. The particle size occurred are determine by dynamic light scattering spectroscopy by using instrument Zetasizer

**% Transmittance**

The primary means of self-microemulsion is visual assessment. To avoid any subjective variations, %transmittance of the resulting microemulsion obtained on dilution of self-emulsifying is measured using UV-visible spectrophotometer.

***In-vitro* drug release**

The development of dissolution methods for SMEDDS is performed in USP type-II Paddle apparatus using suitable dissolution medium at 37$^{0}$C±2$^{O}$C and is compared with standard formulation.

**Conclusions**

Advancement of the technologies and design and development of new chemical moieties having targeting potential is leading to emergence of new drug molecules having therapeutics effect but unfavourable there drug absorption in the body. This emerges the greatest challenge to the researcher to efficiently deliver such drug molecules which exhibit poor aqueous solubility.Lipid formulations are promising approach for various categories of drug molecules having poor aqueous solubility. Among the various lipid formulation, the self-microemulsifying drug delivery systems offers additionally advantages of increased bioavailability, higher stability, high drug loading capacity, potential for oral drug delivery(solid-SMEDDS), ease of manufacture etc. SMEDDS are mostly investigated for BCS class II drugs having low aqueous solubility for their bioavailability enhancement.

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