Review article

Self-micro emulsifying drug delivery systems: State-of-art a technology to enhance the solubility of poorly water-soluble drug

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ABSTRACT

As new technologies are invented, research in the discovery of new active pharmaceutical moieties is reverberating now a day. Drug solubility is an extensive challenge for formulation scientists as approximately 35-40% of newly discovered drugs show lipophilicity. Low solubility is a rate limiting step for drug dissolution and extends of drug absorption to the systemic circulation. Poor dissolution results in low bioavailability, leading to difficulty to achieve desired therapeutic effect. Drug solubility can be increased by different methods like micronization, solid dispersion, salt formation, complexation etc. Self-micro emulsifying Drug Delivery System (SMEDDS) is in fame for enhancing solubility of poorly aqueous soluble drugs. Self-emulsifying drug delivery system, Self-micro emulsifying drug delivery system (SMEDDS) are isotropic mixers of oil, surfactant, drug and co-solvent which spontaneously form transparent micro-emulsions. When SMEDDS formulation administered orally, the solution disperses in GI fluid and instantly forms a fine emulsion by which drug gets a larger surface area which leads to quick dissolution of the drug. Objective of the present review is to update about advancements associated with SMEDDS preparation. It elaborates the evaluation tests required to analyse self-micro emulsifying drug delivery systems. This review article also highlights on recent patents on SEDDS, SMEDDS and SNEDDS formulations.

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid/liquid surfactants, otherwise one or more hydrophilic solvents and co-solvents/surfactants. Fine O/W (oil−in−water) emulsions or micro-emulsions (SMEDDS) can be formed when these formulations are mixed with gastric fluid after being administered orally [1]. Prompt dispersion of self-emulsifying dosage forms occurred in the aqueous media e.g. gastric juice. Necessary agitation required for formation of emulsion is supported by mobility of gastrointestinal tract. As a broad term, SEDDS indicates emulsion having droplet size ranging from a few nanometres (nm) to several micrometres (μm). These formulations are characterized by formation of in vitro lipid droplets of 200 nm to 5 mm size. It appears turbid after formulation of emulsion. However, SMEDDS forms smaller lipid globules, i.e. < 200 nm. The dispersion formed by SMEDDS is optically clear to translucent in appearance.

Primary objective of manufacturing of both systems is formation of dispersion which provides a larger surface area that creates a favourable environment to improve absorption of poorly water-soluble drugs [2]. Self-nano emulsifying drug delivery system (SNEDDS) is a newer technology that consists of oil, surfactants and co-surfactant/co-solvent, spontaneously formulate oil in water nano-emulsion when exposed to GI fluid. SEDDS are easy to manufacture and physically stable while compared with conventional emulsions.

Self-micro emulsifying drug delivery system desirably keep the hydrophobic drug in dissolved state in lipid-base and the micelles formed provide a larger surface area for the drug absorption. Thus, formulation of SMEDDS may ascertain improvement in absorption of drugs which show poor water solubility and perform dissolution rate limited absorption, thereby therapeutic effect of drug can be improved.

Advantages associated with SMEDDS

SMEDDS offer adequate number of benefits over formulation of

emulsion [3, 4]. They are:

- Drugs can be protected from the GI environment.
- Sensitive drugs can be protected.
- Selective drug targeting to specific absorption window in gastrointestinal tract.
- Consistent drug absorption profile can be achieved.
- Oral bioavailability can be enhanced.
- Drug delivery profiles can be improved.
- Variety of dosage form can be manufactured as solid or liquid dosage forms.
- Reduced variability including food effects helps predictable therapy.
- Payloads on drugs are high.

Disadvantages associated with SMEDDS

Self-micro emulsifying drug delivery systems are also having many disadvantages [3, 5]. They are:

- SMEDDS are potentially dependent of digestion prior to release of the drug so, conventional dissolution methods do not exhibit any effect.
- Further development and validation are required before its strength can be evaluated.
- Many prototype formulation batches of lipid-based delivery system required to be prepared and evaluated in vivo in an appropriate animal model to correlate *in vitro-in vivo* models.
- High quantity of surfactant used in the formulations (approx. 30-60%) and chemical instabilities of drugs are the primary drawbacks of this delivery system.

Figure 1: Types of Lipid-based formulations
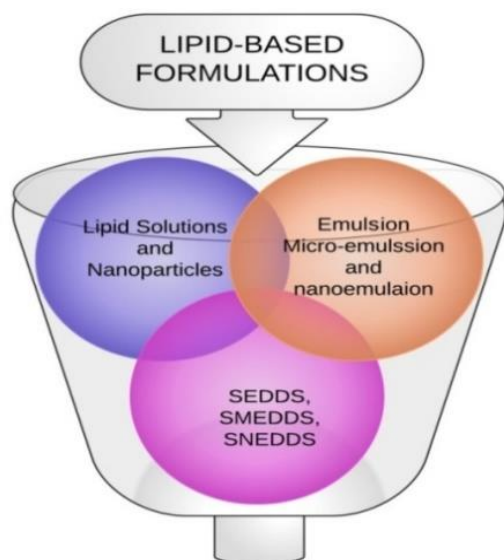
Examples of many circumstances where formulation of Self emulsifying drug delivery system can be proved beneficial [6] shown in table 1.

Table 1: Benefits of SEDDS with respect to BCS classification of drugs

BCS Classification	Aqueous solubility	Membrane permeability	Hurdles overcome by SEDDS
I	High	High	Gut wall efflux, enzymatic degradation
II	Low	High	Solubilization, Bioavailability
III	High	Low	Gut wall efflux, enzymatic degradation
IV	Low	Low	Enzymatic degradation, solubilization

Mechanism of self-emulsification

Self-emulsification is associated with a change in entropy. While, the entropy change favouring dispersion is greater than the energy required to increase the surface area of the dispersion then self-emulsification occurs. The free energy of the conventional emulsion can be stated as the equation below:

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

Where,

ΔG= Free energy, N= Number of droplets, r= Radius of droplets, σ = Interfacial energy

The free energy of the emulsion is directly proportional to the energy required to form a new interface between the oil and water phase. It is presumed from the above stated equation that higher energy level is discouraging for spontaneous creation of an interface between oil and water phase [7-9].

As conventional emulsion possesses high free energy it leads to instability of emulsion and results in the separation of two phases. As free energy needed for self-emulsification process may be very low or positive or negative in some cases so the emulsification process takes place spontaneously. Microemulsions are thermodynamically stable. Equilibrium of the system is maintained, whereas an exchange of matter between two phases occurs continuously.

Factors affecting SMEDDS

Following are the factors which affects self-micro emulsification drug delivery system [10, 11]:

Dose of the drug

Drugs, which can exert desired therapeutic effect in low doses, are suitable candidates for SMEDDS preparation. The drugs required to be formulated as SMEDDS should possess good solubility at least in any one component of the formulation.

Drug solubility

Solubility of a drug in lipid phase is desirable because this may affect its bioavailability. Formulators must consider risk of precipitation of the drug from the system, while addition of surfactants and co-surfactants in high concentrations.

Polarity of lipid phase

Polarity says about affinity of the drug towards lipid and aqueous phase. Drug release depends on polarity of the lipid phase.

Oils having high polarity value enhance the drug release from the system.

Droplet size and charge

When droplet size is reduced it increases surface area. A larger surface area will increase the drug absorption. The stability of the microemulsion also depends upon droplet size.

Figure 2: Factors that affect the bioavailability of drugs formulated as SEDDS, SMEDDS or SNEDDS
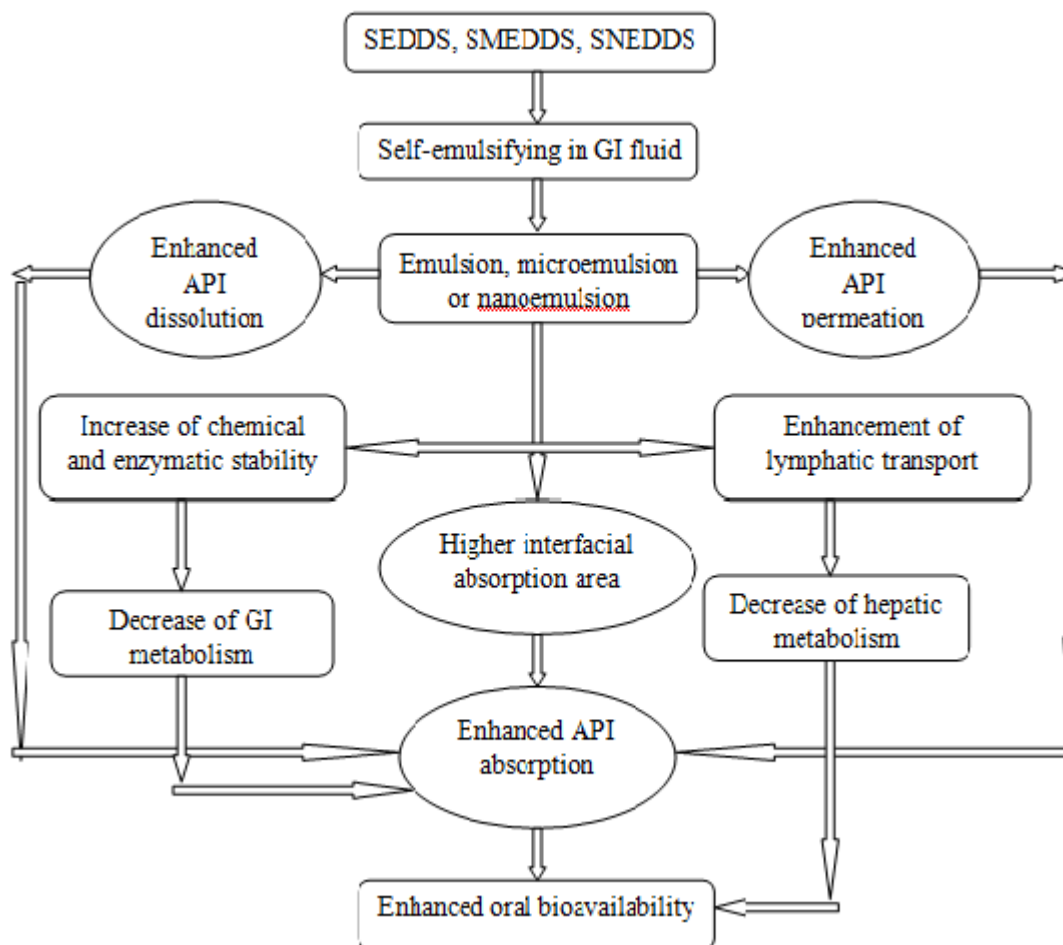
Formulation of SMEDDS

The following criteria should be considered during preparation of SMEDDS [12, 13]:

- Determination of drug solubility in various oils, surfactants, and co-surfactants.
- The oil, surfactants, and co-surfactants can be selected based on the drug property like solubility.
- In the next step, pseudo ternary phase diagram may be constructed by water titration method.
- SMEDDS formulations may be prepared by dissolving the drug in oil, surfactants, and co-solvents/co-surfactants mixture.

Components of SMEDDS formulation

Following are the components used in SMEDDS preparations:

Active Pharmaceutical Ingredient

Drug moieties that have some therapeutic effects are the most essential formulation component of self-micro emulsifying drug delivery system.

Oils

These are the significant constituents of self-micro emulsifying

drug delivery system as it has the property to solubilize the hydrophobic drug in it. It also eases the process of self-emulsification. Oils also improves absorption of the drug from the gastro-intestinal tract by increasing fraction of hydrophobic drug transported through the intestinal lymphatic system [14].

Surfactants

Surfactants gain attention for its bipolar nature. As it has both polar and non-polar parts, it can reduce surface tension at water-air interface. This facilitates increase in bioavailability. Few mechanisms that help to improve bioavailability are increased permeability through intestinal epithelial layer, enhanced dissolution and improved tight junction permeability [14]. Non-ionic surfactants which exhibit relatively high HLB values are recommended for oral formulations. Generally, 30-60 % w/w of surfactant concentration required to form stable SMEDDS. Surfactants should be used in small concentration as it may cause gastric irritation.

Co-surfactants

Co-surfactants or co-solvents may help to improve solubility by helping in two ways: first one by dissolving large

quantities of hydrophilic surfactants or secondly by dissolving the poorly water soluble drug in the lipid-base. Ethanol, polyethylene glycol, propylene glycol etc. are suitable for preparation of oral delivery systems [15].

Table 2: Examples of oils, surfactants, co-surfactants/ co-solvents used in SMEDDS

Components of self-micro emulsifying drug delivery systems			
Oils	Triglycerides	LCT (Fixed oils)	Corn oil, peanut oil, soyabean oil, castor oil, arachis oil, sunflower oil, triolein, palm oil, cottonseed oil, sesame oil, olive oil
		MCT and related esters	Labrafac CC, miglyol 812, captex 300, captex 355, triacetin
	Vegetable oils derivatives	Hydrogenated vegetable oil	Hydrogenated cotton seed oil
		Mixed partial glycerides	Capmul MCM
		Polyoxyglycerides/macrogol glycerides	Gelucire 44/14, labrasol, labrafil M 2125 CS, labrafil 1944 CS
		Ethoxylated glycerides	Cremophor RH 40, cremophor EL, cremophor RH 60
		Polyalcohol esters of fatty acids	Capryol, plurol oleique CC 497
	Fatty acids		Oleic acid, myristic acid, caprylic acid, capric acid
	Ethanol esters		Ethyl oleate
Surfactants			Polyoxyethelene sorbitan monolaurate, Polyoxyethelene- sorbitan-20 mono-oleate, sorbitan monolaurate, sorbitan mono-oleate
Co-surfactants/ co-solvents			Propylene glycol ethanol, Peg 400, Water Lauroglycol

Pseudo-ternary phase diagrams

Pseudo-ternary phase diagram is a useful tool to determine the micro-emulsification region. The phase diagram can be fabricated by the water titration technique. Oil, surfactant/co-surfactant, and water are used to construct the phase diagram. In this technique, water is added drop wise to the pre-concentrate with gentle stirring to achieve equilibrium [15]. Then the system is visually examined for transparency. The point at which transparent to turbid and turbid to transparent transitions occurred is ascribed as emulsion and microemulsion respectively. From the phase diagram boundaries, the formation of microemulsion can be determined. Thereby, values of oils, S/CoS mix ratio at which emulsification possibilities lie can determine.

Method of preparation of SMEDDS

Drug solubility in different oils, surfactants, and co-solvents/co-surfactants can be determined from solubility studies. Micro-emulsification region can be determined from pseudo-ternary phase diagrams. From this data oil, surfactant and co-solvents to be used in the preparation can be selected. Then components are mixed by a vortex mixer to get self- microemulsions [16, 17].

Evaluation of Self-micro emulsifying drug delivery system

Thermodynamic stability

The effect of temperature on SMEDDS formulation may be analyzed to verify the thermodynamic stability of the preparation [18]. Due to temperature variation precipitation may occur which interferes with drug performance.

Heating cooling cycle

In this method samples should be subjected to six cycles of refrigerator temperatures 4°C and 45°C. Samples should be stored for not less than 48h for each temperature condition. Formulations, which passed this test, are subjected to a centrifugation test [16].

Centrifugation

In this technique, samples are centrifuged for 30 min at 3500 rpm. Samples that do not exhibit phase separation can be analyzed further for freeze thaw stress test.

Freeze thaw cycle

In this method, samples should be subjected to three freeze thaw cycles (temperature of - 21°C and +25°C). Samples should be stored for not less than 48h for each temperature condition. Samples that are thermodynamically stable are selected for further evaluations [17].

Droplet size measurement

It is essential to determine droplet size of SMEDDS. The rate as well as extent of drug release are directly related to globule size. Stability of the self-micro emulsion also depends on droplet size [19]. Zetasizer is used to analyze the globule size of SMEDDS. SMEDDS that is isotropic and clear O/W dispersion which is stable, can be achieved with reduction of droplet size to optimum range.

Zeta (ζ) potential analysis

It is essential to determine charge of the SMEDDS droplets. Oil carries a negative charge due to the existence of free fatty acids [20]. That's why SMEDDS also shows negative potential when analyzed under Zetasizer.

Viscosity determination

To verify whether the system is of O/W or W/O, determination of viscosity is required. O/W type shows low viscosity of the system whereas high viscosity indicates W/O type of microemulsion [21]. Brookfield viscometer is used to evaluate rheological properties of the microemulsion.

Percentage transmittance

The transparency of prepared formulation may be determined in terms of percentage transmittance. The percentage transmittance of the system is measured at λ_max of the drug by UV-Visible spectrophotometer. 1 mL of SMEDDS formulation can be diluted suitably and analyzed for percentage transmittance [22].

Dispersibility test

Self emulsification efficiency of SMEDDS may be estimated visually with the help of dissolution apparatus 2 (USP XXII). 1 mL of the formulation may be subjected to test for clarity, emulsification speed, and stability of the emulsion and further categorized as per grading system[23] as mentioned in table 3:

Table 3: Grading system for SMEDDS

Dispersibility and appearance of SMEDDS Grade	Dispersibility and Appearance
I	Clear or slightly bluish in appearance
II	Bluish white appearance
III	Bright white emulsion (similar to milk)
IV	Dull, greyish white emulsion with slightly oily appearance
V	Turbid appearance

Table 4: Examples of patents on SEDDS, SMEDDS, SNEDDS collected from google

Patent no/ Year	Title	Inventor/Company	Drug used	Composition	Link
US8592490B2 (2013)	Self-microemulsifying drug delivery systems	Igor Legen, Janez Kerc, Polona Jurkovic Lek Pharmaceuticals D.D., Ljubljana (SI)	Candesartan cilexetil	Miglyol 812, polysorbate 80, Imwitor 308	patents.google.com/patent/US8592490B2/ja
EP1961412A1 (2006)	Self-microemulsifying drug delivery systems	Igor Legen, Janez Kerc, Polona Jurkovic Lek Pharmaceuticals d.d., 1526 Ljubljana (SI)	Candesartan cilexetil	Miglyol 812, polysorbate 80, imwitor 308	patents.google.com/patent/EP1961412A1/en
KR100449818 B1 (2001)	Soft capsule and injection of ibuprofen using smedds solubilization technique	Choi Young-wook, Kim Hyung-soo, Nam-gu, Baek Gwang-seok, Incheon Lee Sang-kil Baek Gwang-seok, Korea University Industry-Academic Cooperation	Ibuprofen	Lauroglycol FCC, cremophore EL or cremophor ELP, labrasol, PVP, ethanol or transcutol	patents.google.com/patent/KR100449818B1/en
KR101151711B1 (2009)	Self-emulsifying drug delivery system composition containing olmesartan medoxomil under the title of the invention and method for preparing the same	Choi Young-wook Kim Hyung-soo Lee Sang-gil Min Won-min Kang Myung-joo Yoon Bae-choi Korea University Industry-Academic Cooperation	Imesartan medoxomil	Capryol 90, labrasol, transcutol	patents.google.com/patent/KR101151711B1/en
US2009124670 (2006)	Method for designing formulation of self-emulsifying preparation	Sakai Kenichi Chugai Pharmaceutical Co Ltd	Nilvadipine	Sefsol-218, polysorbate 20, polysorbate 40, polysorbate 80, labrasol, HCO-40, HCO-60, BL-9, labrafil 944, capryol 90, CO-10, SO-10, CO-3, DGMO-C, CO-10	patents.google.com/patent/US20090124670A1/en
WO2009040776 (2008)	Self emulsifying pharmaceutical composition of rhein or diacerein	Nakhat Premchand and Managade Prashant Wockhart research centre	Rhein or diacerein	Labrafil, labrasol, tween 80	ptentscope.wipo.int/search/en/detail.jsf?docId=WO2009040776
WO2008128960 (A1) (2008)	Process for dosing self-emulsifying drug delivery systems	Schwarz, Franz, Xaver Sandoz, Switzerland	Azithromycin dihydrate, Amoxycillin trihydrate	Miglyol 810, strawberry 501094A, saccharose, glycerine, labrafil M 1944, plurol oleique, tween 80, ethyl oleate	patents.google.com/patent/WO2008128960A1/en
US20070104741 (2007)	Delivery of tetra hydrocannabinol: A self-emulsifying drug delivery to improve dissolution, stability, and bio availability of drug compound of dronabinol or other cannabinoids	Ram B. Murty, K. Y. Lexington and Santos B. Murty Murty Pharmaceuticals Inc., US	Dronabinol or other Cannabinoids	Oleic acid, cremophor RH 40, labrasol, ascorbyl palmitate	patents.google.com/patent/US20070104741A1/en
US8790723B2 (2012)	Eutectic-based self-nanoemulsified drug delivery system	Mansoor A Khan, Sami Nazzal Jarrow Formulas, Inc., Los Angeles, CA (US)	Ubiquinone	Lemon oil, cremophor, capmul	patents.google.com/patent/US8790723B2/en

Conductivity measurement

An electro conductometer may be used to analyse the conductivity of SMEDDS. There is a possibility of a transition from oil microemulsion system to water microemulsion system [24]. That's why it is crucial to measure conductivity to know the type of microemulsion, whether O/W or W/O.

Turbidity measurement

Efficiency of self-emulsification is analysed by determining the turbidity of the emulsion. If the dispersion occurs immediately and in a reproducible time, then the SMEDDS preparation is of good

quality [25]. Turbidity meter is used for this evaluation process.

In vitro dissolution studies

Drug release pattern of the SMEDDS can be studied by performing dissolution test [26]. Media, RPM can be maintained as per the requirements. Temperature should be maintained at $37\pm0.5°C$ to simulate human body temperature. Mechanism of drug release may be studied by various kinetic models such as zero order, first order, Higuchi's, Korsmeyer equation, etc.

Stability studies

Shelf life of any prepared dosage form is related to time and storage temperature. SMEDDS formulations can be diluted with purified water and evaluated visually for any physical changes. Temperature stability of samples may be evaluated by keeping them in three different temperature ranges [2-8°C (refrigerator), room temperature, etc.] After a predefined time interval, samples can be analyszed for physical stability, particle size accelerated centrifugation cycle, drug content, and zeta potential [27].

Animal study

The optimized formulations are tested in vivo by using suitable animal models to evaluate whether the drug has the desired therapeutic effect [28].

CONCLUSION

Although an increase in the dissolution is a priority in the manufacture of many dosage forms, but it always hovers a challenge to enhance solubility. Currently, a considerable number of choices are available with researchers to get the desired therapeutic effect of a drug by improving the aqueous solubility of the hydrophobic drug. Formulation of self-micro emulsifying drug delivery systems is an emanating technique for enhancing the solubility of lipophilic drugs. Drug absorption at blood stream can be improved by formulating this delivery system. Effectiveness of the SMEDDS depends on the excipients used and proportion of those components. This review article gave attention to understand mechanism of self-emulsification, the role of each component used in formulation of SMEDDS and evaluation tests required to determine the efficiency of the formulation. From this review it is clear that with further attention towards development of the technology, SMEDDS will be a potential drug delivery system, which continue to have many novel applications and can solve problems associated with the delivery of hydrophobic drugs. *In vitro-in vivo* correlation studies should be prioritized in further study. Human bioavailability studies can be carried out as advanced research work.

Acknowledgments

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