JOURNAL OF DRUG DELIVERY RESEARCH

eISSN 2319-1074

REVIEW ARTICLE

SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

In modern drug discovery techniques, there has been a consistent increase in the number of poor water soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Self-emulsifying drug delivery (SEDDS) is the one of the method for the improvement of oral bioavailability. SEDDS are the isotropic mixtures of oils, surfactants, solvents and co-solvents. Self-emulsifying drug delivery systems (SEDDS) 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 nanoemulsions containing the solubilized drug. Owing to its miniscule globule size, the micro/nanoemulsifed drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect. We present an exhaustive and updated account of numerous literature reports and patents on diverse types of self-emulsifying drug formulations, with emphasis on their formulation, characterization, and systematic optimization strategies. This review article tries to describe the formulation of SEDDS and also talks about the construction of the phase diagram for SEDDS. It describes the mechanism involved in self-emulsification and the bio-pharmaceutical aspects involved. The advantages of SMEDDS over conventional emulsions are listed. Some of the marketed preparations of SEDDS are listed.
Key words: Nanoemulsified drugs, Self-emulsifying drug delivery, SEDDS, SMEDDS

INTRODUCTION

Oral formulations find the widest acceptance among patients and manufacturers for treating diverse pathological ailments. Consequently, the majority of the drug delivery systems available in the health-care market today are the oral ones. Development of such oral drug delivery products poses major challenges to the pharmaceutical development scientist, since more than half of new molecular entities (NMEs) are hydrophobic (BCS class 2), exhibit poor and inconsistent bioavailability[1]. Various ostensible causes for these variable bioavailability issues encompass poor aqueous solubility, an extensive hepatic first-pass effect, acid liability in gastric fluid, restricted intestinal permeability, gut wall metabolism by the cytochrome P450 (CYP450) family of isozymes, and high P-glycoprotein (P-gp) efflux[2].

SMEDDSs are isotropic and thermodynamically stable solutions consisting of oil, surfactant, cosurfactant (CoS; or solubilizer), and drug mixtures that spontaneously form oil-in-water (o/w) micro-emulsions when mixed with water under gentle stirring. The motility of stomach and intestine provides the agitation required for self-emulsification in vivo. SEDDS spreads readily

eISSN 2319-1074

in the GI tract, and the digestive motility of the stomach and the intestine provides the agitation necessary for self-emulsification. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. The lipid composition of SEDDS may be related to facilitate the extent of lymphatic drug transport by stimulating lipoprotein formation and intestinal lymphatic liquid flux [3, 4].

Self-emulsifying lipid formulations have improved the bioavailability of poorly water soluble and 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 flavor 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 [4, 5].

Advantages of SEDDS:

- The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
- Initiation of changes in the GI fluid in favour of improved drug absorption due to the ability of certain lipid compounds and their metabolites.
- Ability to deliver peptides that are prone to enzymatic hydrolysis in gastrointestinal tract.
- Ease of manufacture and scale-up.
- Reduction of first-pass drug metabolism in the liver due to association of certain lipidic excipients with selective drug uptake into the lymphatic transport system.
- Formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
- Reduction in drug dose.
- Quick onset of action.
- Reduced inter-subject and intra-subject variability and food effects.
- No-influence of lipid digestion process.

eISSN 2319-1074

Types of SEDDS

Table1: Types and comparative features of all self emulsifying formulations[5]

Mechanism of selfemulsification

The thermodynamic relationship for the net free energy change is described by Equation:

$$\Delta G = \sum N_i 4\pi r_i^2 \sigma$$

Where, ΔG is the free energy associated with the process, r_i is the radius of droplet, Ni is the number of droplets, σ is the interfacial energy. Self-emulsification occurs when the energy involvement in the dispersion is greater than the energy required for the formation of droplets. The free energy of conventional emulsion is very high as high energy is required to form new surface between two immiscible phases like oil and water. Due to high free energy, the emulsion may not be stable and the two phases tend to separate. But in case of SMEDDS, emulsion formation occurs instantaneously because the free energy of the system is very low and sometimes negative due to the presence of flexible interface. On mixing oil and surfactant/cosurfactant mixture with water, up on mild agitation, an interface is formed between two phases. Then, aqueous phase penetrates through interface and gets solubilized within the oil phase up to the solubilization limit [6].

Marketed preparations of SEDDS

Table 2: Marketed preparations of SEDDS[7]

COMPOSITION OF SEDDS

1. Oils
2. Surfactants/ Cosurfactants
3. Solvents/ cosolvents

1. **Oils:** Oils are the important component of SMEDDS, as solubilization and access of the drug to the lymphatic circulation of poor water soluble drugs depend on the type and concentration of oil used for formulation. The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/triglycerides. Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SEDDS. E.g. cotton seed oil, soybean oil, corn oil, sunflower oil, sesame oil, peanut oil, castor oil, Labrafil, Labrafac, Captex 200, Captex 300, Captex 350, Captex 500, ethyl oleate, etc.[6,8].

2. Surfactants / Co-surfactants

A surfactant is needed to adopt self-emulsification property by SMEDDS which is prime process to form microemulsion and it is also helpful to solubilize the hydrophobic drug; in turn the

eISSN 2319-1074

dissolution rate can be improved. Permeability barrier that is intestinal cell membrane comprised of lipids can be disrupted by surfactant partition; thereby permeability will be enhanced. The inhibitory effect of surfactants on p-glycoprotein helps in the improvement of overall bioavailability of many drugs that are substrates to p-glycoprotein transporter.

Although natural surfactants are less toxic, the efficiency of self-emulsification is limited. For spontaneous emulsification, the surfactants are required to be selected with attention to attain ultralow interfacial tension. The selection of surfactant is based on HLB value. The surfactants with high HLB facilitate the formation of O/W microemulsion. Surfactants with hydrophilic nature, that is, HLB value of greater than 12, along with water soluble cosolvents, are used for drugs with relatively low octanol: water partition coefficient to increase the solvent capacity of the formulation and these systems produce very fine droplets of size less than 100 nm with high surfactant concentration. The less toxicity offered by nonionic surfactants like oleates, polysorbates, polyoxyls, and so forth compared to ionic surfactants allows them to be used more commonly in the formulation of SMEDDS. With commonly used lipids in the formulation of SMEDDS like medium and long chain triglycerides, the nonionic surfactants like oleates of HLB 11 having unsaturated acyl side chains are more suitable excipients for efficient self-emulsification. E.g**.** Polysorbate-20 (Tween-20), Polysorbate-80 (Tween-80), D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS), Polyoxy-35-castor oil(Cremophor RH40), Polyoxy-40- hydrogenated castor oil(Cremophor RH40), Labrasol, etc[8,9].

3. Solvents / Co-solvents

Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile cosolvents comprised in the conventional self- emulsifying formulations are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Drug release from the formulation increases with increasing amount of cosurfactant. Following are the some examples of the oils, surfactants, cosurfctants, and some csosolvents[6,8,9].

FORMULATION DESIGN OF SMEDDS

Formulation of SMEDDS involves the following steps:

1. Screening of excipients.
2. Construction of pseudoternary phase diagram.
3. Preparation of SMEDDS.
4. Characterization of SMEDDS.

eISSN 2319-1074

1. SCREENING OF EXCIPIENTS

Solubility Studies: These are mainly useful for the selection of the most suitable excipients that can be used in the preparation of SMEDDS and helps in the prediction of drug precipitation in vivo. Solubility of the drug in various oils, surfactants, and cosurfactants should be tested. These studies are generally performed by shake flask method in which the drug is usually added to the excipient in excess amount and then shaken for 48 hours in water bath shaker or in air oscillator at room temperature. Then, the samples should be subjected to centrifugation followed by filtration through 0.45µm filters and drug content should be determined. These solubility studies are generally performed with the objective of choosing oil that shows maximum solubility for the drug and surfactant/cosurfactant which have maximum capacity to solubilize the drug. The other objective is achievement of optimum drug loading with minimized total volume of the formulation. Drug precipitation may occur from diluted SMEDDS which is dependent on octanol: water partition coefficient of the drug and also on the level of involvement of surfactant in the solubilization of the drug [6, 10].

Screening of Surfactants and Cosurfactants for their Self-Emulsification Ability

The emulsification ability of surfactants can be known by mixing the equal proportions of selected oil and surfactant which is followed by homogenization. When this mixture is added to the double distilled water, the number of flask inversions required to form homogenous emulsion is noted and this gives indication about ease of emulsification. Then, the resultant microemulsion should be tested for clarity, turbidity, and percentage transmittance. The surfactants that show highest emulsification efficiency, that is, that show high percentage transmittance and that require low flask inversions, should be selected. Similarly, the cosurfactants should be screened with the same procedure by mixing selected surfactant and oil phase with cosurfactant [10, 11].

2. CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM

These are the diagrams which represent change in phase behavior of the system according to the change in composition. Ternary phase diagram is used to study the phase behavior of three components. In SEDDS, this represents the system with three components like oil, water, and surfactant. But in case of SMEDDS, the additional component like cosurfactant/cosolvent addition is most common. Ternary diagram contains three corners that correspond to the 100% of the particular component. In case of addition of fourth component, the ternary diagram can be called pseudoternary phase diagram as one of the corners corresponds to the mixture of two components like surfactant and cosurfactant.

For construction of pseudoternary phase diagram, mixtures containing different compositions of microemulsion components should be evaluated for emulsification efficiency. At different compositions, different structures may be formed like emulsions, microemulsions, micelles, inverted micellar forms, and so forth and the extent of formation of these structures can be known with the construction of phase diagram. This phase diagram helps in the determination of dilutability of formulation and in getting information about the different compositions that form monophasic clear solutions. Pseudoternary diagrams are constructed by keeping the ratio of any two of the four components as constant and this ratio along with the remaining two components generally forms three corners of the phase diagram. This fixed (mixture) ratio is generally

eISSN 2319-1074

formed by the combination of surfactant and cosurfactant and sometimes it may be the mixture of oil and surfactant. This is mixed with the required volume of the third phase like oil or cosurfactant ; then the other component which is usually water is added in incremental amounts and for every addition of fourth component, the solution should be tested for the clarity, flowability, time for self-emulsification, and dispersibility. The total percent concentration of all components in each mixture should be 100%.

Then pseudoternary diagram should be plotted with the help of suitable software. The samples which formed clear solution should be denoted by suitable symbols in the phase diagram. The area that is formed when these points are joined indicates the monophasic microemulsion existing area and wide area indicates the good emulsification efficiency [10, 11].

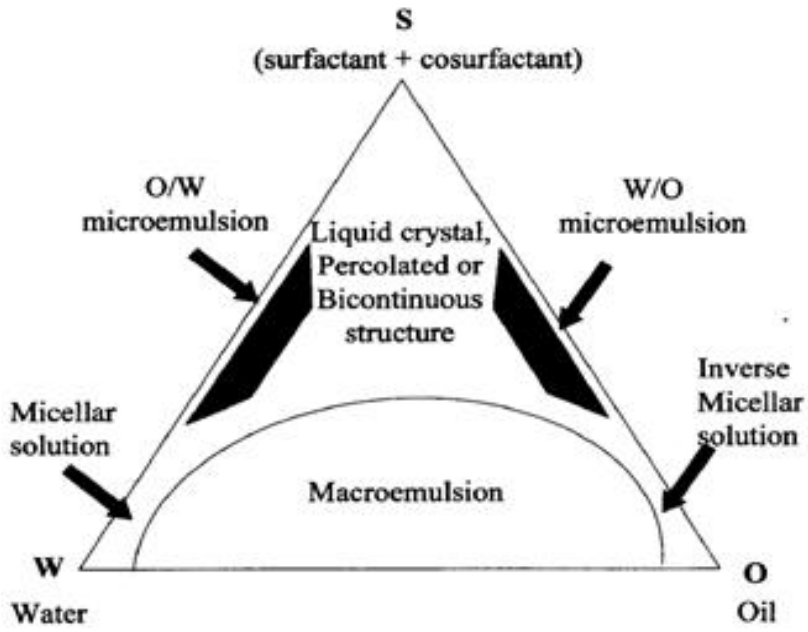

Figure 1: Pseudoternary phase diagram

3. PREPARATION OF SMEDDS

The preparation involves the addition of drug to the mixture of oil, surfactant, and cosurfactant and then it should be subjected to vortexing. In some cases, drug is dissolved in any one of the excipients and the remaining excipients are added to the drug solution. Then, the solution should be properly mixed and tested for the signs of turbidity. After equilibration at ambient temperature for 48 hours, the solution should be heated for the formation of clear solution, if required. Depending on the final volume, the formulation should be stored in capsules of suitable size [10].

eISSN 2319-1074

Table 1:

Isotropic mixture of the drug compound, surfactant, co-surfactant and lipid phase which emulsify under conditions of gentle agitation, when come in contact with gastro-intestinal fluid.			
Types of SEDDS	**Comparative Features**		
	Oil droplet size	**Appearance**	**HLB value of surfactant**
Self-emulsifying formulations (SEFs)	200 nm to 5 µm	Turbid	<12
Self-micro emulsifying formulations(SMEFs)	Less than 200 nm	Optically clear to translucent	>12
Self-nanoemulsifying formulations (SNEFs)	Less than 100 nm	Optically clear	>12

Table 2:

S. No.	Trade Name (Company)	Drug Molecule	Type of formulation	Excipients
1.	Sandimmune® (Novartis)	Cyclosporin A	Oral solution (100 mg/ml)	Olive oil, polyoxyethylated oleic glycerides (Labrafil M 1944 CS)
2.	Gengraf® (Abbott)	Cyclosporin A	Soft gelatin capsule (25, 100 mg)	Polyoxyl 35 castor oil (Cremophor EL), polysorbate 80
3.	Kaletra® (Abbott)	Lopinavir & Ritonavir	Oral solution lopinavir (80 mg/ml) & ritonavir (20 mg/ml)	Polyoxyl hydrogenated castor oil (Cremophor RH 40), peppermint oil
4.	Norvir® (Abbott)	Ritonavir	Soft gelatin capsule (100 mg)	Oleic acid, polyoxyl 35 castor oil (Cremophor EL)
5.	Fenogal® (Genus)	Fenofibrate	Hard gelatin capsule (200 mg)	Lauryl macrogol-glycerides (Gelucire 44/14)

eISSN 2319-1074

4. CHARACTERIZATION OF SMEDDS

Visual Evaluation

The assessment of self-emulsification is possible by visual evaluation. After dilution of SMEDDS with water, the opaque and milky white appearance indicates the formation of macroemulsion whereas the clear, isotropic, transparent solution indicates the formation of microemulsion. Assessment of precipitation of drug in diluted SMEDDS is also possible by visual evaluation. The formulations can be considered as stable when drug precipitation is not evident. Precipitation is common if the formulation contains water-soluble cosolvents and can be avoided by increasing the concentration of surfactant [12].

Thermodynamic Stability Studies

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug [21].

1. Heating cooling cycle
   Six cycles between refrigerator temperature (40°C) and 45°C with storage at each temperature of not less than 48h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
2. Centrifugation
   Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
3. Freeze -thaw cycle
   Three formulations for the freeze-thaw cycle chosen. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking [13, 14].

Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A- Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B- Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

eISSN 2319-1074

Grade C- Fines 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. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation [13, 15].

Time for Emulsification

The time needed for self- emulsification for different formulations can be assessed generally using dissolution apparatus USP type II in which the formulation is added drop wise to the basket containing water and observing the formation of clear solution under agitation provided by paddle at 50rpm. Assessment of self-emulsification helps to determine the efficiency of self-emulsification of the formulation. Rate of emulsification is found to be dependent on nature of oil phase and oil/surfactant ratio. Rapid rate of emulsification is observed with higher surfactant concentration because of rapid ejection of oil droplets by penetration of water into interface. The emulsification time can also be determined by visual evaluation after placing the formulation in 0.1N HCl under stirring at body temperature by which the GI conditions can be simulated [13].

Viscosity Determination

The SEDDS 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 viscosity then it is w/o type of the system.

Droplet Size Analysis Particle Size Measurement

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water [13,14].

Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333)**.** 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 [14, 15].

eISSN 2319-1074

Electro Conductivity Study

The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electoconductive nature of system. The electro conductivity of resultant system is measured by electoconductometer.

In Vitro Diffusion Study

In vitro diffusion study is performed to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique.

Drug content

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug[16].

Stability Assessment

Stability studies are performed as per the ICH guidelines on the formulation which is filled in gelatin capsules. At regular intervals the samples should be collected and tested for appearance, color, drug content, pH of diluted formulation, and dissolution profile. If there is no change in all these properties during storage conditions, formulation can be concluded as stable formulation[2, 15].

CONCLUSION

From the above review we can conclude that Self-emulsifying drug delivery systems are 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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