Review Article

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SELF EMULSIFIED DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Oral route is the easiest and most convenient route for drug administration. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. The dissolution is the rate limiting step in their absorption and oral bioavailability. Self-emulsifying drug delivery systems (SEDDS) possess unparalleled potential in improving oral bioavailability of poorly water-soluble or lipophilic drugs. Following their oral administration, these systems rapidly disperse in gastrointestinal fluids, yielding micro- or nanoemulsions containing the solubilized drug. In particular SEDDS is isotropic mixture of lipids, surfactant and cosurfactant that can disperse spontaneously in aqueous media and form fine emulsion. This review includes the current research and development in the field of SEDDS with emphasis of excipients, formulation aspects and characterization.

Keywords: SEDDS, lipids, surfactants and co surfactants.

Introduction

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability. Various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions[1,2]. Self emulsifying drug delivery system (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants; sometimes it contains co-solvents and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds[3]. On dilution by an aqueous phase they form fine stable oil-in-water (o/w) emulsions or fine lipid droplets which is the characteristic feature of these systems. When such a formulation is released into the lumen of the GIT, it disperses to form a fine emulsion generally o/w emulsion, so that the hydrophobic drug get remain in solution in the GIT which avoids the dissolution step. Dissolution step is the rate limiting step in the absorption of poorly water-soluble drugs[4]. The size of droplets ranges approximately less than 100 nm. SEDDS are prepared in two forms liquid and solid. SEDDS can be prepared by solidification of liquid self-emulsifying components into powder. This powder is then used to produce various solid

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dosage forms, for example self-emulsifying pellets, self-emulsifying tablets etc[5-8]. In many studies it have been reported that SEDDS are used for delivering and targeting hydrophobic drugs such as coenzyme Q10, halofantrine, vitamin E and cyclosporine-A[9-12]. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and nonionic surfactants, the latter being less toxic. The process of self-emulsification proceeds through formation of liquid crystals (LC) and gel phases. Release of drug from SEDDS is highly dependent on LC(liquid crystal) formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media[13]. Due to its small globule size, the micro/nanoemulsifed drug can easily be absorbed through lymphatic pathways, thereby bypassing the hepatic first-pass effect[14]. Factors affecting the in vivo performance of SEDDS include their ability to form small droplets of oil (<5mm) and the polarity of the oil droplets to promote faster drug release into aqueous phase[15]. The smaller oil droplets provide a large inter- facial area for pancreatic lipase to hydrolyze triglycerides and thereby promote the rapid release of the drug and/or formation of mixed micelles of the bile salts containing the drug[16].

Criteria of Drug Selection

BCS (Bio-pharmaceutical classification system) classifies the drug based on solubility and 'permeability of a drug (Table 1: Biopharmaceutical Classification of Drugs). Mainly Class 2 (Low Solubility, High Permeability) is used for SEDDS. A primary candidate may be selected by assessing the drug lipophilicity (lop P) value and its solubility in pharmaceutical manufacturing grade lipid excipients which dissolve entire amount of dose of drug to be administered. Log P is the primary criteria and high log P value greater than 4 is desirous for lipidic systems. Another parameters that play important role are melting point and dose. Low melting point and low dose are required for development of lipidic systems[17].

Table No. 01: Biopharmaceutical Classification of Drugs

Class	Solubility	Permeability	Absorption pattern	Rate-Limiting Step in Absorption
1	High	High	Well absorbed	Gastric emptying
2	Low	High	Variable	Dissolution
3	High	Low	Variable	Permeability
4	Low	Low	Poorly absorbed	Case by case

Composition of SEDDS

The self emulsifying process depends on[18]

- The nature of the oil–surfactant pair.
- The surfactant concentration.
- The temperature at which self-emulsification occurs.

1. **Oils**

   Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride (Table 2: Excipients for SEDDS).

2. **Surfactant**

   Nonionic surfactants with high hydrophiliclipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature they can dissolve or solubilise relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug

within the GI lumen and for prolonged existence of drug molecules.

3. **Co-surfactants/Co-solvents**
   Formulation of effective SEDDSs requires high concentration of surfactants, co-surfactant /Cosolvents like span, capyrol 90, capmul, lauroglycol, diethylene glycol.

Table No. 02: Excipients for SEDDS

Oil	Surfactants	Co- surfactants/ Co-solvents
Cotton seed oil	Polysorbate 20(tween20)	Span 20
Soybean oil	Polysorbate 80(tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Capryol 90
Sunflower oil	Polyoxy-35- castor oil (cremophor RH40)	Lauroglycol
Caster oil	Polyoxy-40-hydrogenated castor oil (cremophor RH40)	Transcutol
Sesame oil	Labrasol	Isopropyl alcohol
Peanut oil		Ethanol
Labrafac		Polyethylene glycol

Formulation development

Solubility Screening

The first and foremost step in designing a lipid formulation is to assess the solubility of the lead compound in various lipid excipients, cosolvents, and surfactants. Since the clinical dose is usually unknown in early discovery, a general rule of thumb is that solubility in a range of 25−50 mg/mL in lipid excipients is needed to support future studies. The solvent capacity of lipids can be increased by addition of cosolvents and surfactants. The incorporation of cosolvents and surfactants can also help to reduce the interfacial tension and the oil−water partition coefficient and therefore can facilitate emulsification and effective absorption[19].

Designing of formulation[19]

Lipid formulation classification system proposed by Pouton and Porter.[18, 27] On the basis of this system in which lipid formulations are classified into three categories, one can start with simple lipid solutions without surfactants (type I). If the whole dose cannot be solubilized in the lipid solution in a typical unit dosage form (e.g., 0.5-1.0 mL), then the option could be either type II formulations containing oils and water insoluble surfactants or type III formulations which are mixtures of oils, surfactants, and cosolvents.

The properties of lipid excipients such as the fatty acid chain length have been shown to affect lipid digestion and drug solubilization. In general, the medium-chain glycerides tend to work well with less lipophilic compounds that can be readily transferred to the highly solubilizing aqueous environment after lipid digestion. The long chain glycerides, on the other hand, prefer highly lipophilic compounds that would either remain in the undigested oil phase or partition into mixed micelles after digestion.

Mechanism of self emulsification

The exact mechanism behind the self-emulsification is not clearly known. According to 'Reiss', self-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases. It can be represented by following equation:

$$\Delta G = \Sigma N \pi r2\sigma$$

Where,

G- is the free energy,

N -is the number of droplets of radius

r and σ indicates the interfacial energy[20-22].

According to "Wakerly et al", the addition of a binary mixture to water, results in interface formation between the oil and aqueous continuous phases, followed by the solubilisation of water within the oil phase owing to aqueous penetration through the interface. This process will occur until the solubilisation limit is reached close to the interface[23, 24].

Characterization of SEDDS

1) In vitro Dispersion Test

The in vitro dispersion test offers a quick assessment of lipid emulsification and drug solubilization in the stomach. It can be used as the first-tier assay for screening lipid formulations at early stages of drug discovery when resources and compound supply are limited. It is conducted by diluting the lipid formulation in water or simulated gastric fluid at different dilution ratios. At predetermined time points, the dispersion is examined visually for the formation of an emulsion or microemulsion and the particle size of the oil droplets can be measured by laser light diffraction or photon correlation spectroscopy. The drug solubilization can be quantified by HPLC analysis of drug concentration in the aqueous phase[25].

2) In vitro Lipid Digestion Test

The in vitro digestion test is a useful tool for assessing solubilization and absorption potential of a lipid formulation in the small intestine. It helps formulation scientists to better understand the efficiency of drug transfer from oil phase to aqueous phase, the amount of drug available in aqueous phase for absorption, and the precipitation potential of the compound in the GI tract. To conduct the test, the lipid formulation is first dispersed in a digestion buffer containing bile salts and phospholipids, followed by addition of pancreatic lipase and co-lipase to initiate the digestion. At a predetermined time, samples are collected and ultracentrifuged into a poorly dispersed oil phase (containing undigested TG and DG), a highly dispersed aqueous phase (containing solubilized drug as well as bile salts, MG, and FA) and a precipitated pellet phase (containing precipitated drug and undissolved bile salts). The drug concentration in each phase can then be quantified by HPLC analysis[26].

3) Ternary Phase Diagram

Pseudo-ternary phase diagrams are studied for development of SEDDS. It helps in accessing the optimum concentration of different excipients necessary to obtain homogenous self emulsification ability and drug loading. Once the appropriate microemulsion components have been selected, ternary pseudo phase diagram was constructed to define the extent and nature of the microemulsion regions[27].

4) Droplet Size

Droplet size is critical factor in self emulsification performance because it determines the rate and extent of drug release as well as absorption. It is measured by dynamic light intensity to measure the velocity of the Brownian diffusion and consequently the dispersed droplets. Photon correlation spectroscopy, microscopic techniques or a coulter Nanosizer are mainly employed for the determination of the emulsion droplet size. Particle size distribution can be further verified by cryogenic transmission electron microscopy (cryo-TEM). For cryo-TEM studies, samples are prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at -180 UC and transferred to liquid nitrogen at -196 UC. Cryo-TEM offers the advantage of visualizing the size as well as shape. Small-angle neutron scattering and small-angle X-ray scattering can also be used to obtain information on the size and shape of the droplets.

5) Zeta Potential

This is used to identify the charge on droplets. The charge on the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1-3% will yield cationic SMEDDS. Zeta potential helps to predict the stability and flocculation effect in emulsion system. If the zeta potential falls below a certain level, colloid will aggregate due to attractive forces. Conversely, a high zeta potential maintains a stable system.

6) Conductivity test

Conductivity measurements are able to determine the point of aqueous phase addition where the system changes from oil continuous to a water continuous phase. It also helps in monitoring phase inversion phenomena.

7) Turbidity measurement

This identifies efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. The measurements are carried out on turbidity meters.

List of drugs currently incorporated in SEDDS

A lot of drugs recently found to be incorporated in SEDDS as per the available literature. We summarized recent research in Table 3: Drugs recently incorporated in SEDDS. The bioavailability improvement, enhanced solubility and dissolution were the major advantages achieved by the researchers.

Table No. 03: Drugs recently incorporated in SEDDS

S.no	Drug	Author	Type of formulation	Inference
1.	Amphotericin B[28]	Bhattacharyya A (2012)	SEDDS	Increased the solubility and dissolution of Amphotericin B
2.	Atorvastatin[29]	Fariba KHAN (2012)	SEDDS	Dissolution of ATV can successfully be enhanced
3.	Ciprofloxacin[30]	BAKSHI MADHURA,(2013)	SMEDDS (self micro emulsifying drug delivery system)	Significant improvement in drug solubility, absorption rate of ciprofloxacin
4.	Efavirenz[31]	V. KIRAN KUMAR (2013)	Solid SEDDS	Enhance solubility and dissolution of sparingly soluble compounds like Efavirenz
5.	Gliclazide[32]	Vikrant Wankhade (2012)	SNEDDS (Self nano- emulsified drug delivery system)	Concentration of oil present in the formulation having greater impact on surfactant and co-surfactant which reduces the particles size in the effective ranges. They obtain an optimum formulation with particle size 145.8 nm
6.	Ibuprofen[33]	Sadika Akhter (2012)	SEDDS	Increased dissolution for poorly water soluble drug Ibuprofen
7.	Indomethacin[34]	Nicholas C. Obitte (2013)	Solid SEDDS	Improving the in vitro and corresponding anti-inflammatory properties of indomethacin.
8.	Irbesarten[35]	Jaydeep Patel (2011)	Self nano-emulsifying drug delivery system	IRB showed a significant increase in the dissolution rate and oral absorption
9.	Nimodipin[36]	Amit A. Kale (2008)	SEDDS	Improve in vitro and in vivo performance of nimodipine,
10.	Tacrolimus[37]	Pranav V Patel (2013)	Solid SMEDDS	Improved emulsification properties and good thermodynamic stability
11.	Valsartan[38]	Gupta A.K. (2011)	SEDDS	Increased dissolution rate

Marketed Formulations of SEDDS

The current scope of SEDDS is shown by the available marketed commercial products. We summarized a list of marketed formulation available worldwide in Table 4: Marketed Formulations of SEDDS[39-43].

Table No. 04: Marketed Formulations of SEDDS

Brand name	Drug used	Dosage form	Company
Neoral	Cyclosporine	SGC (soft gelatin capsule)	Novartis
Norvir	Ritonavir	SGC	Abott laboraties
Fortovase	Saquinavir	SGC	Hoffmann roche
Agenerase	Amprenavir	SGC	GSK
Convulex	Volporic acid	SGC	Pharmacia

Conclusion

An increasing number of drug candidates discovered in recent years are highly lipophilic compounds with poor aqueous solubility. Self emulsifying drug delivery system is a promising approach in bioavailability enhancement of poorly water soluble drugs. The increasing interest and availability of literature now make it possible to produce clinically effective commercial formulations using such approach. Selection of excipients with utmost care and understanding of biopharmaceutical aspects are helpful in designing of stable formulation. The efficiency of system is case specific, thus proper characterization should be performed. The preclinical evaluation and clinical evaluation can be connected early in the process, which significantly reduce the formulation development time and increases the overall success potential of a clinically viable formulation.

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