SELF EMULSIFYING FORMULATION, PLATFORM FOR SOLUBILITY ENHANCEMENT: A REVIEW

Panner Selvam R[1], Kulkarni P.K[1], Mudit Dixit[1]

[1]J.S.S college of pharmacy, Mysore, Karnataka, India

E-mail of corresponding author: selva.r9@gmail.com

ABSTRACT

Poor drug solubility remains a significant and frequently encountered problem for pharmaceutical scientists. Lipid formulations are one of the approach to enhance rate and extent of oral absorption for poor drug soluble drugs, because along with drug solubility it enhances drug permeability. Self emulsifying drug delivery system (SEDDS) composed of oils, surfactants and cosolvents which emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastro-intestinal tract. But the solubility of the drugs in these medium and the proportion of ingredients taken are the most important criteria to have a proper, stable SEDDS. Thus, only very specific pharmaceutical excipients combinations will lead to efficient self-emulsifying systems. This review provides a comprehensive summary of the mechanism, development, characterization of SEDDS. SEDDS appears to be a unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophillic drugs.

Key words: Self emulsifying drug delivery system, surfactants, bioavailability.

INTRODUCTION

Although oral delivery is the most preferred method of drug administration, this is not possible for roughly 50% of currently marketed drug compounds due to their low solubility in water and low oral bioavailability[1,2]. In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality[3,4]. Thus, for such compounds, the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution[5].There are various techniques available to improve the solubility of poorly soluble drugs[6,7]. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-

in-water emulsions when introduced into aqueous phase under gentle agitation[8,9]. Therefore, an SEDDS can be an efficient vehicle for class II to IV molecules of the Biopharmaceutical Classification System (BCS) drugs[10]. Currently the market value of the lipid formulation comprises an estimated 2–4% of the commercially available drug products surveyed in three markets (UK- 2%, US- 3%, and Japan- 4%) worldwide[11, 12]. The concept of using these systems for pharmaceutical purpose was initially developed by group of Groves. Therefore aspect of formulation of the SEDDS is to improve the bioavailability of the pharmaceutical product[13]. In this article SEDDS is a general name that includes all self-emulsifying formulations regardless of size.

LIPID FORMULATION CLASSIFICATION SYSTEM (LFCS) [14, 15]

LFCS was established by Pouton in 2000 and recently updated in 2006 to help stratify formulations into those with similar component parts. The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation and they are shown in Table I. Type I are Non-dispersing systems, Type II lipid formulations, referred as a self-emulsifying drug delivery systems, Type III lipid-based formulations, commonly referred to as self-microemulsifying drug delivery systems. Type IV is dispersion systems: non-oil micellar Systems.

Table I: Lipid formulation classification system

Increasing Hydrophilic	Content →				
Typical composition (%)	Type I	Type II	Type IIIA	Type IIIB	Type IV
Triglycerides or mixed glycerides	100	40–80	40–80	< 20	—
Water-insoluble surfactants (HLB < 12)	—	20–60	—	—	0–20
Water-soluble surfactants (HLB > 12)	—	—	20–40	20–50	30–80
Hydrophilic cosolvents	—	—	0–40	20–50	0–50
Particle size of dispersion 100–250 (nm)	Coarse	100–250	100–250	50– 100	< 50

ADVANTAGES [16-20]

1. Fine oil droplets formed will pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby reduces the irritation.
2. Bioavailability enhancement results from the increased surface area by finely dispersed state of the drug containing lipid globules which leads to increased dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The surfactants in the formulations enhance absorption by membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. A cationic emulsion has greater bioavailability than an anionic emulsion. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum.
3. Enhanced oral bioavailability enabling reduction in dose.
4. More consistent temporal profiles of drug absorption.
5. Selective targeting of drug(s) toward specific absorption window in GIT.
6. Protection of drug(s) from the hostile environment in gut.
7. Control of delivery profiles.
8. Protective of sensitive drug substances.
9. High drug payloads.
10. Solid, semisolid or liquid dosage forms.
11. Thermodynamically stable when compared to the simple emulsions.

DISADVANTAGES

The main drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs [21]. One of the another obstacles for the development of SEDDS is the lack of good predicative *in vitro* models for assessment of the formulations [22-25].

MECHANISM OF SELF EMULSIFICATION

There are many mechanisms proposed in emulsion formation, are as follows

Self emulsifying process are related to the free energy, ΔG given by

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

Here, N is the number of droplets with radius r and σ the interfacial energy [26]. It is clear from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. Mustafa and Groves developed a method using phosphated nonylphenoloxylate (PNE) and phosphated fatty alcohol ethoxylate

(PFE) in n-hexane. The results suggested that the emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at the interface, thereby resulting in greater ease of emulsification[27]. Consequently, the authors were able to relate the phase behavior to the spontaneity of emulsification, with liquid crystals formation, tending to form emulsion more readily, as indicated by the lower equilibration times[28].

Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behaviour of the system[29]. For example, if one increases the temperature of the oil in the water system stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion[30]. Pouton has suggested that the specificity of surfactant combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, there by increasing the ease of emulsification[29]

FORMULATION ASPECTS
Ideal properties of drug:
The poorly soluble drugs having high/low permeability, in association with low melting point, critical stability, and low dose (highly potent) are suitable candidates[31, 32].
Composition of SEDDS:
1. Oil: Both long and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of SEDDS. 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[33, 34]. MCT were preferred in the earlier SEDDS because of its higher fluidity, better solubility properties and self emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium chain derivatives which can be defined rather asamphiphilic compounds exhibiting surfactant properties. Polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths giving them a varied hydrophile-lipophile balance (HLB) value, in combination with vegetable oils have been used to solubilise poorly water-soluble drugs and improve their bioavailability[35].

2. Surfactants: Non-ionic surfactants with a relatively high hydrophilic± lipophilic balance (HLB) were advocated for the design of self dispersing systems, where the various liquid or solid ethoxylated polyglycolyzed glycerides and Tween 80 are the most frequently used excipients. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability. The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation[36].

3. Co-solvents: Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol etc. may help to dissolve large amounts of either the

hydrophilic surfactant or the drug in the lipid base[37].

Example: Co-solvents like diethylene glycol monoethyl ether(transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (glycofurol) etc[38].

4. Consistency builder: Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax.

5. Polymers: Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc[39].

SOLIDIFICATION TECHNIQUES[40, 41]
Spray cooling, Spray drying, Adsorption to solid carriers, Melt granulation, Melt extrusion/extrusion spheronization, Supercritical fluid based methods, Solid lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC)

DOSAGE FORM DEVELOPMENT OF S-SEDDS[42]
Dry emulsions, Self-emulsifying capsules, Self-emulsifying sustained/controlled-release pellets
Self-emulsifying sustained/controlled-release tablets, Self-emulsifying solid dispersions
Self-emulsifying beads, Self-emulsifying sustained-release microspheres, Self-emulsifying nanoparticles, Self-emulsifying suppositories, Self-emulsifying implants

TERNARY DIAGRAM [43, 44]
This technique was mainly used to map the micro emulsion areas (composition ranges). Ternary phase diagram is used to map the optimal composition range for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity.

CONSTRUCTION OF PHASE DIAGRAM [43, 44]
A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is
prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3,6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w /w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25∘c for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution. Coarse emulsion is the region of cloudy dispersion.

EVALUATION PARAMETERS
Turbid metric evaluation: Nepheloturbidimetric evaluation was done to monitor the growth of emulsification. Self-emulsifying system was added to 0.1N hydrochloric acids under continuous stirring on magnetic plate at ambient temperature,

and the increase in turbidity was measured using a turbid meter[45, 46].

Viscosity determination: Viscosities of the systems as such and after dilution with 5% v/v water were determined using Brookfield rheometer at ambient temperature. Under varying shear rate, viscosities were measured and the data obtained were further analyzed by regression treatments[47].

Droplet size analysis or particle size measurements: The droplet size of the emulsions is determined by microscopic techniques or Coulter Nanosizer or photon correlation spectroscopy [48]. 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[49].

Droplet polarity: Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophillic drug[50].

Electrical Conductivity Measurement: Electrical conductivity of the samples was measured using a conductivity meter. Electrical conductivity of the formulations was determined to check the stability and assert the nature of the formulation[51].

Refractive index and percent transmission: Refractive index and percent transmittance proves the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it is compared with water. If refractive index of system is similar to the refractive index of water and formulation has percent transmittance > 99 percent then formulation has transparent nature [52].

Centrifugation: Microemulsion systems were subjected to centrifugation at 3000 rpm for 30 minutes and then examined for any phase separation This technique helps to determine behaviour of small particles in gravitational field[53].

Differential scanning calorimetry (DSC): Physical state of the drug in lipid carrier was analyze by DSC studies. Thermal analysis of drug, the physical mixture of drug and Lipid carrier were carried out using differential scanning calorimetry method[54].

X-ray diffraction studies: X-ray diffraction studies analyze the crystalline nature of the drug in the mixture. X-ray diffraction was performed using a diffractometer, with a monochromatics radiation having suitable voltage and current at an angle of 2θ over a range of 5º 40º. Diffraction patterns of pure drug and Lipid carrier were prepared at the suitable drug-to-lipid ratio for the determination[55].

In vitro diffusion study: _In vitro_ diffusion studies were performed using dialysis technique/Dissolution apparatus[56]

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.

In vivo Characterization includes Nonclinical Evaluation, Choice of non-human Test Species, Lymphatic Transport[57].

APPLICATIONS

Table II: Applications of self emulsifying drug delivery system

Drugs	Self emulsifying excipients	Observation	References
Halofantrine	Captex 355 , Capmul MCM, soybean oil BP Maisine 35-1 Cremophor EL	The lipid-based formulations of Hf base afforded a six- to eight-fold improvement in absolute oral bioavailability	10
Simvastatin	Capryol 90 of 37%, Cabitol of 28%, and Cremophor EL	Bioavailability of SMEDDS to the conventional tablet (Zocor®, simvastatin 20 mg) was 159 and 143%, respectively	23
Indomethacin	castor oil, Macrogol-glycerol hydroxystearate, Glyceryl monocaprylate	Drug release after 30 minutes (93%).	54
Furosemide	Captex 500, Cremophore el	SMEDDS formulation showed complete drug release >60 min	56

CONCLUSION

Approximately 40% of new chemical drug moieties have poor aqueous solubility and it is a major challenge to modern drug delivery system. Self emulsifying drug delivery system are suited for BCS class 2 and class 4 drugs. The proper selection of the oil and surfactants are most important for successful development of SEDDS. Solidification techniques enhances the stability and easy handling. By exploiting studies about human bioavailability and *in vitro* methods for predicting the dynamic changes involving the drug in the gut in order to monitor the solubilisation state of the drug *in vivo,* open the gateway for the many drugs to enter market as SEDDS.

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