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Solubility enhancement for Aqua phobic drug through Self micro emulsifying Drug Delivery System: A recent access

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ABSTRACT: Self-microemulsifying drug delivery system (SMEDDS) tactics to improve solubility and bioavailability of hydrophobic drugs. SMEDDS formulations include *in vivo* drug precipitation, SMEDDS helps to overcome liquid handling and stability problems. About 40% drugs exhibit poor aqueous solubility and low bioavailability. The bioavailability of poor water soluble drugs may be enhanced when co-administered with meals rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. SMEDDS are surfactant, isotropic mixtures of oil, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. This is a very decent method for the stability point of view of hydrophobic drugs mightily increases solubility also improves the bioavailability and is easy to manufacture. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption.

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Keywords: SMEDDS, Dissolution rate, lipid-based drug delivery system, Co-solvent.

INTRODUCTION:

Combinatorial screening of the hydrophobic drug and therapeutic activity. According to the BCS class about 40 % new chemical entities confirm poor aqueous solubility and nowadays it is a most important task to the drug delivery system. For the absorption of these drugs and its rate-limiting step for their solubilization in the gastrointestinal tract [1]. These drugs are categorized class II drugs according to (BCS), Biopharmaceutical classification system with high permeability and poor aqueous solubility. Formulation and development department apply various techniques like Micronization, Solid dispersion, and Complexation, but there is a problem with chemical stability, that is the drugs may

lose bioactivity. Complexation method is not suitable for aqueous and organic solvents [2]. To overcome these problems SMEDDS is a most promising tool. In SMEDD, the emulsions with having a 100 to 300 nm droplet size, are transparent micro emulsions. The emulsion with a droplet size of < 50 nm also achieved with the concentration of oil in SMEDDS is < 20 % as compared to 40 to 80 % [3].This is a very reliable method for the stability point of view of hydrophobic drugs drastically increases solubility and the bioavailability, easy to manufacture. The strategy of formulating SMEDDS and lipid based systems shown in Fig 1 and 2. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles[4].

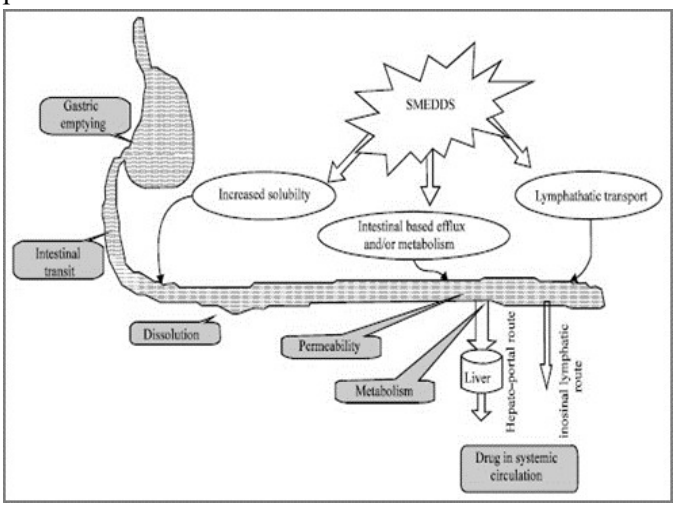

Fig 1. The general strategy of formulating SMEDDS and their subsequent conversion to micro-emulsion.

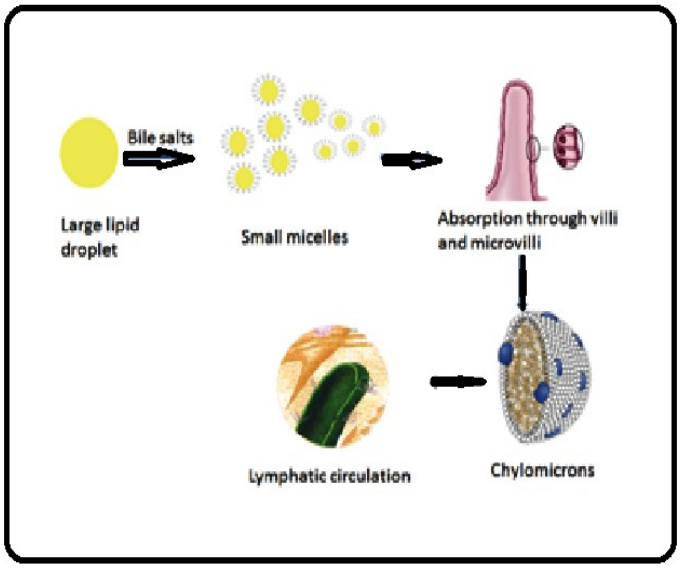

Fig 2. Absorption mechanism of lipid-based systems.

Classification System of Lipid Formulation:

The lipid formulations are classified into different systems that are as the lipid emulsion, micro-emulsion, lipid solution, and dry emulsions systems [8].

***Type I*:**

In this type I systems consist of formulations encompass drug in solution triglycerides and/or mixed glycosides or oil-in water emulsion stabilize by fewer concentrations of emulsifiers like as 1 % (w/v), 1.2 % (w/v) lecithin and polysorbate 60 [9].

***Type II*:**

Type II system self-emulsification is usually obtained surfactant contents above 25 % (w/w) [10].

***Type III*:**

In type II system formulations can be further lonely into both the Type III A and Type III B formulations in order to recognize more hydrophilic systems (Type III B) [11].

***Type IV*:**

In type II system formulations do not contain any natural lipids and represent the most hydrophilic formulations [12].

IMPORTANCE OF SMEDDS [13-16]:

- SMEDDS formulation removes the surmount irritation between drug and wall of the GIT.
- SMEDDS improves the stability as it possess low energy consumption formulation.
- SMEDDS offers stable plasma-time profile for the hydrophobic drugs and it improved the dissolution rate.
- SMEDDS formulation can also be protects the susceptibility to degraded by the chemical and enzymatic means in GIT.

ADVANTAGES OF SMEDDS [17,18]:

- For efficient drug transport, SMEDDS increases solubility and oral bioavailability.
- For the comparison of other lipid dosage forms, formulation of SMEDDS is easy and scale- up.
- SMEDDS reduces the inter- and intra-subject variability and food effects.
- SMEDDS having the ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.

COMPOSITION OF SMEDDS:

In regards to basic components for composition of SMEDD, the constituents are oils, surfactant, co-solvents and co-surfactant.

Table 1. LFCS showing typical compositions and properties of lipid-based drug delivery system [5].

Type	Composition	Aqueous Solubility	Membrane Permeability	Characteristics
Type I	Oils without surfactants	High	High	Poor solvent capacity except for highly lipophilic drugs, requires digestion to release drug [6]
Type II	Oils and water-insoluble surfactants	Low	High	SMEDDS, turbid o/w dispersion (particle size 0.25 to 2 µm),
Type III	Oils, water-soluble surfactants and co-solvent	High	Low	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvents solvent capacity on digestion
Type IV	Water-soluble surfactants and co-solvent (oil free)	Low	Low	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion unlikely to be digested [7]

Oil Phase:

For the nontoxic and safe components like oil to obtain naturally and their derivatives like: fatty acid methyl esters and triglycerides are easily degraded by microorganism and considered to be risk-free to the environment [19]. The formation of discontinuous micro emulsions with mineral oils has been intensively investigated in model experiments and for application in industrial products [20]. An acceptable lipophilic phase for pharmaceutical uses would be vegetable oils. The expansion of a micro emulsion region generally depends on the nature of oil. This is due to differences in oil penetration into the surfactant layer [21]. Examples of oils are Olive oil, Seseam oil, Castor oil, Sunflower oil, Hydrogenated specialty oils.

Surfactant:

A surfactant molecule is also known as surface active agent; it is formed by two parts with dissimilar affinities for the solvents [22]. One of them has an affinity towards polar solvents and the other has for non-polar solvents. A little quantity of surfactant molecules rests upon the water-air interface and decreases the water surface tension value. Surfactant is also further classified as Anionic surfactants, Cationic surfactants, Ampholytic surfactants and Nonionic surfactants [23].

Anionic Surfactants, are those in which the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphate (ROSO3-), sulphonate (RSO3-). Examples are sodium lauryl sulphate.

Cationic surfactants, are those in which the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

Ampholytic surfactants are also known as zwitterion surfactants as they contain both the negative and positive charge. Example - Sulfobetaines.

Nonionic surfactants, are those in which the hydrophilic group carries no charge but derives its water solubility from highly polar groups like hydroxyl or polyoxyethylene [24]. Examples: Sorbitan esters (Spans), polysorbates (Tweens).

According to the high hydrophilic lipophilic balance (HLB) values are used in formulation of SMEDDS. Surfactant strength ranges between 30 to 60 % w/w of the formulation in order to form a stable SMEDDS. Surfactants having a high HLB and hydrophilicity assist the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media [25].

Cosolvents:

Organic solvents such as ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are suitable for oral delivery and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. Solvents can even act as co surfactants in microemulsion systems [26]. Alternately alcohols and other volatile cosolvents have the disadvantage of evaporating into the shells of the soft gelatin or hard sealed gelatin capsules in conventional SMEDDS leading to drug precipitation [27].

Co-surfactant:

For the optimum SMEDDS, we required high concentration of surfactant is needed in order to diminish interfacial tension adequately, which can be damaging, for that co-surfactants are used to reduce the concentration of surfactants, because co-surfactants provide flexibility to interfacial film to form micro-emulsion over a wide range of composition [28].

Table 2. Example of oil phase, surfactant and co-surfactant.

Oil Phase	Surfactant	Co-surfactant
Isopropyl Myristate	Tween 80	Propylene glycol
Olive oil	Span 40	Ethylene glycol
Oleic acid	Tween 40	Ethanol
Mineral oil	Labrafil M1944CS	PEG 600
Soyabean oil	Brij 58	1-butanol
Captex 355	CremophorEL	PEG 400
Sunflower oil	Lecithin	Glycerol

FACTORS AFFECTING SMEDDS:

Polarity of the lipophillic phase:

SMEDDS is dependent upon the polarity of the oil phase used. The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions [29].

Nature and dose of the drug:

SMEDDS maintain the drug solubility in the oil phase if surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation.

APPLICATIONS OF SMEDDS [30,31]:

- SMEDDS increases the solubility and bioavailability of hydrophobic drugs.
- SMEDDS reduces the gastric irritation of hydrophobic drugs in the GIT.
- SMEDDS formulation also reduces the toxic and GIT side effects.
- SMEDDS prevents the degradation of drugs and protects from biodegradation changes in barrier properties of Caco-2 cell monolayer's, including Trans epithelial electrical resistance and permeability to the paracellular marker (Mannitol).

EVALUTATION PARAMETERS OF SMEDDS:

To identify the well suitable ratio in SMEDDS Pseudo-Ternary Phase Diagrams different weight ratios range from 1:9 to 9:1. According to the optimized results of oils, surfactants and co-surfactants, the range of the amount of each ingredient was further studied by means of a pseudo-ternary phase diagram. Pseudo-ternary phase diagrams provided information on the phase behavior of various compositions in SMEDDS [32]. Therefore, the pseudo-ternary phase diagrams were important for evaluating the self-microemulsifying ability of SMEDDS formulations and determining the range of prescription composition. The pseudo-ternary phase diagrams of PEG-400 and Transcutol HP are shown in Fig 3.

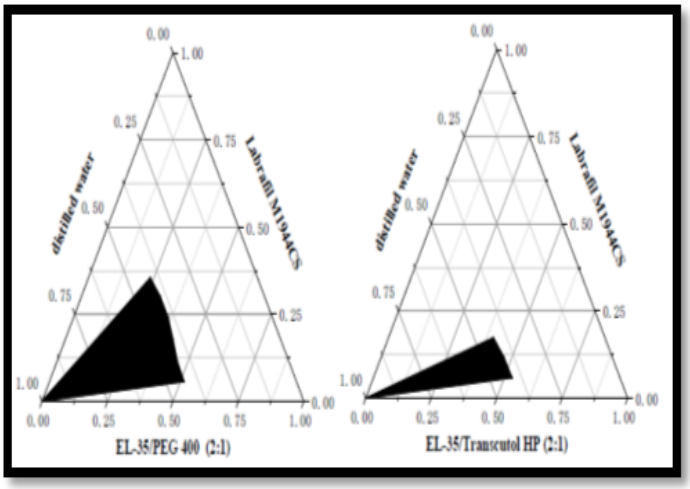

Fig 3. Absorption mechanism of lipid-based systems.

EVALUATION TESTS FOR SMEDD:

The SMEDD can be evaluated for the Thermodynamic Stability Studies, Dispersibility test, Turbidimetric evaluation, Viscosity determination, Droplet size analysis and Particle size, Measurements, Refractive Index and Percent Transmittance, Electro Conductivity study, *In vitro* Diffusion study, Drug content and *In vivo* permeability studies [33-42].

Thermodynamic stability studies:

Heating cooling cycle:

Six cycles between refrigerator temperature 4 and 45 ºC with storage at each temperature of not less than 48 h. Those formulations, which are stable at these temperatures, are subjected to centrifugation tests.

Centrifugation:

Passed formulations are centrifuged at room temperature at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

Freeze thaw cycle:

Freeze was employed to evaluate the stability of formulation. Thermodynamic stability was evaluated at

different temperature. To check the effect of temp. The formulation was subjected to a freeze thaw cycle (-20 ºC) for 2 to 3 days. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test:

The efficiency of self-emulsification of oral nano or micro emulsion is evaluated by using a standard USP XXII dissolution apparatus for dispersibility test. For the dispersibility test, the parameters are the solution volume to be tested is 1 ml, medium volume is 500 ml, temperature is 37 ± 1 °C and Paddle speed is 50 rpm. As per the value of dispersibility, the formulations are graded as given in Table 3.

Table 3. Various grades of SMEDD as per their Dispersibility values [43,44].

Sl. No.	Grades	Descriptions
1	A	Rapidly forming (within 1 min) nano-emulsion, having a clear or bluish appearance
2	B	Rapidly forming slightly less clear emulsion having a bluish white appearance
3	C	Fine milky emulsion that formed within 2 min
4	D	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min)
5	E	Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface
6	A and B	Formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be for SMEDDS formulation

Turbidimetric evaluation:

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self-emulsifying system is added to a fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on a magnetic hot plate at appropriate temperature, and the increase in turbidity is measured by using a turbidimeter.

Viscosity determination:

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. The viscosity determination conforms to whether the system is w/o or o/w.

Droplet size analysis:

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, which is able to measure sizes between 10 and 5000 nm.

Refractive index and percent transmittance:

Refractive index and percent transmittance prove the transparency of formulation. The refractive index of the system is measured by Refractometer by putting a drop of solution on slide and comparing it with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV spectrophotometer by using distilled water as blank. If the refractive index of the system is similar to the refractive index of water (1.333) and formulation have > 99 % transmittance, then formulation has transparent nature.

Electro conductivity study:

The SMEDD system contains ionic or non-ionic surfactant, oil, and water. This test is performed for measurement of the electro-conductive nature of the system. The electro conductivity of the resultant system is measured by an electro conductometer. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids. The viscosity determination conforms to whether the system is w/o or o/w.

Table 4. Self-emulsifying drug delivery systems and their marketed products [40,45]

Drug Name	Comp-ound	Dosage form	Company	Indi-cation
Convulex	Valproic acid	SGC	Pharmacia	Anti-epileptic
Neoral	Cyclos porine A/I	SGC	Novartis	Immune supper-ssant
Fortovase	Saqui-navir	SGC	Hoffmann -La Roche Inc.	HIV antiviral
Targretin	Bexa-rotene	SGC	Ligand	Anti-neoplastic
Gengraf	Cyclo sporine A/III	HGC	Abbott Laboratories	Immuno suppr
Lipirex	Feno-fibrate	HGC	Genus	ALP

SGC and HGC are Soft gelatin capsule and hard gelatin capsule. ALP – Antihyperlipoproteinemic.

CONCLUSION:

For the improvement of bioavailability of hydrophobic drug lipid-based drug delivery systems, is a promising tool and its comes under the SMEDDS formulation is prefer because drug may be degrade in the GIT, increase bile solution that are believed to facilitate drug absorption, stimulation of gastric lymphatic transport and increased intestinal permeability. The effect of lipids on the bioavailability of orally administered drugs is highly complex due to numerous mechanisms by which the lipids can alter the biopharmaceutical characteristics of the drug. Better understanding of the role of individual lipids, surfactants and co-surfactants in the formation of SMEDDS, with regard to the dispersion process, the structure of the formed emulsion particle and drug solubilisation is very important in successful designing of these formulations. Therefore this review focused on the physic-chemical and biopharmaceutical aspects of the SMEDDS which may be helpful for the advancement of this technology to obtain safer, more stable and efficacious SMEDDS formulations.

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