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SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR POORLY SOLUBLE DRUGS: A REVIEW

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Abstract:

As oral drug delivery system is problematic for the drugs which are deprived of solubility in aqueous solutions. Delivery of poorly soluble drug is slowed down where dissolution is the rate limiting step. It gives exposure to a novel drug delivery system to improve the poor solubility as well as low bioavailability. The various strategies have been come out into literature such as solid dispersions, eutectic mixtures, complexation, permeation enhancers, use of surfactants and self emulsifying drug delivery system (SEDDS). Self emulsifying drug delivery systems have been reported to increase the oral absorption of lipophilic drugs. This review focuses on excipients required for the preparation of SEDDS, formulations studied as well as advantages and disadvantages of SEDDS.

Key words: SEDDS, GRAS, lipophilic

Introduction:

Approximately one-third of the active pharmaceuticals have poor aqueous solubility which challenge us to develop formulations of these drugs. Drug has to be dissolved in the GI tract before it gets absorbed. Thus, their rate and extent largely depends on the rate of dissolution, therefore, poorly soluble drugs by using conventional approaches face this challenge in which dissolution is the rate limiting step. As per Biopharmaceutical Classification System (BCS), BCS-I drugs have high solubility and high permeability; BCS-II have low solubility and high permeability; BCS-III have high solubility and low permeability whereas BCS-IV have low solubility and low permeability. Class IV drugs are nearly impossible to prepare unless dose is very small. BCS-II formulation preparation is challenging because it requires improved dissolution characteristics. SEDDS improves the bioavailability of of lipophilic substances where dissolution is the rate limited.

SEDDS are the isotropic mixture of oil, hydrophilic surfactants/cosurfactant and a solubilised drug. These formulations readily form fine oil-in-water emulsions when come in the contact with gastric fluid and dispersed readily with the gentle agitation provided by motility of the stomach and intestine for the necessary emulsification. Upon aqueous dilution, the drug remains in the oil droplets or as a micellar solution since the surfactant concentration is very high in such formulations.[1]

Mechanism of Self Emulsification:

Emulsion is formed when two immiscible phases get miscible with each other in the presence of emulsifying agent i.e. surfactant. Addition of the surfactant expands the surface area between the two phases. In case of conventional emulsions, excess of free energy is formed depending upon the size of oil droplets as well as interfacial tension.

The mechanism, by virtue of which self-emulsification is most likely to occur has not yet been comprehensively revealed. Nonetheless, self-emulsification takes place by change in entropy which favors dispersion that is better as that of energy required to increase the surface area of the dispersion. In case of SEDDS free energy formation is low. It is represented as an equation:

$$DG=SN_i pr_i 2S$$

Here, DG represents the free energy

N is the number of droplets

S is the interfacial energy

R is the radius of the droplet

Emulsifying agents form the monolayer of emulsion droplets to make it stable and also provides a barrier to prevent coalescence.

Excipients of SEDDS Formulations:

Excipients are the inert substances that would be used in the manufacturing of final drug products. They mainly act as diluents, lubricants, binding agents, solvents or any coating materials. There is a wide range of pharmaceutical excipients, but all have their own characteristics. Knowledge of their physicochemical characters is very essential prior to use.

In the United States, the Food and Drug Administration (FDA) has published listing in the code of Federal Regulations for Generally Recommended as Safe (GRAS) substances that are safe to use. Over the years, FDA also entitled 'Inactive Ingredient Guide' that has been approved to use or somewhere incorporated into the marketed products (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)[2] with the maximum dosage level or their route of administration. Once an inactive ingredient has been approved for a product through a particular route of administration, it can be used in any new drug formulation and does not require extensive review.

a) **Oils:** Long (>12 carbon) and medium (6-12 carbons) chain triglyceride oils with varying degree of saturation or hydrolysis are opted for the design of SEDDS formulation. Edible oils have lesser capacity to dissolve large amount of lipophilic drug, and their self emulsification efficiency is also poor which limits its use in SEDDS. Therefore, modified vegetable oils are preferred. Vegetable oils comprise of mixture of triglycerides, free fatty acid, non-saponifiable products as well as vitamins like tocopherols which act as antioxidant.

b) **Surfactants**: Also known as 'Surface active agents'. It reduces the interfacial tension between the liquid-liquid or liquid-solid. Surfactants are amphiphilic in nature and have the capacity to dissolve comparatively higher amount of hydrophobic compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules[3]. Selection of surfactant is based on the hydrophilic-lipophilic balance (HLB) value and their approval as safe. Surfactants with high HLB value >10(hydrophilic) are chosen for instant oil droplets formation. Higher concentration of surfactant in the formulation may cause gastric irritation, concentration range of surfactants lies between 30-68% for the SEDDS formulation. Types of surfactants include anionic, cationic and non-ionic surfactants. Nonionic surfactants are most preferred due to their less toxic effect.

c) **Cosurfactants**: Cosurfactants are added to dissolve the large quantities of surfactants (hydrophilic or lipid base). Concentration range of co-surfactant lie within 7-25% of the formulation. Mainly propylene glycol, polyethylene glycol, ethanol are used but alcohol has the limitation of evaporation from the shells of hard and soft gelatin capsules which may lead to the precipitation of the drug.

Table : List of Excipients used in SEDDS:

Oils	Surfactants	Cosurfactants
Olive	Polysorbate 80	Propylene glycol
Soyabean	Cremophore RH40	Polyethylene glycol
Oleic acid	Span 80	Isopropyl alcohol
Castor	Span 20	Transcutol
Coconut	Phosphotidylcholine	Ethanol
Isopropyl myristate	Vitamin E TPGS	Glycerol
Corn	Polysorbate 20	
Sesame	Labrafil M 1944 CS	

SEDDS possess various advantages such as:

1) Drug doesn't come in direct contact with stomach so, it protects the drug molecule from the hostile environment of the gastrointestinal tract.

2) SEDDS formulations are helpful in the taste masking of the drug to make it more palatable.

3) SEDDS are used to dissolve poorly soluble drugs hence improves the oral bioavailability of drug by facilitating dissolution.

4) It helps in selective targeting of the drug at specific site of gastrointestinal tract

5) SEDDS can be prepared in different forms such as liquid as well as solid. Liquid can be filled into soft gelatin capsules.

6) It acts as substitute for the traditional oral formulations of lipophilic/hydrophobic drugs.[1]

7) It gives better consistent profile of drug absorption by secreting bilary and pancreatic secretions or by increasing gastric residence time.[4]

8) No interference of the food with the drug absorption by using SEDDS delivery system

9) These systems possess high payload drug efficiency

10) SEDDS also improves bioavailability due to bypass of the hepatic metabolism and drug directly goes into the systemic circulation.[4]

Disadvantages of SEDDS[5]

1) No good experimental *in vitro* models are available for assessment of the formulations.

2) Traditional dissolution methods do not work, because formulations depend on digestion prior to release of the drug.

3) Different prototype lipid based formulations needs to be developed and tested *in vivo.*

4) Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) may irritate GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.

5) Volatile co solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

6) The precipitation tendency of the drug dilution may be higher due to the dilution effect of the hydrophilic solvent.

7) Formulations containing several components become more challenging to validation.

Table : SEDDS based formulations studied

S.No.	Drug	Objective of the study	Excipients used	Reference
1	Amphotericin B	Enhanced oral bioavailability and stability of the drug	Glyceryl monooleate Tween 80 PEG 400 PG	6
2	Celecoxib	Improved dissolution by preparing super-saturable SEDDS	Capryol 90 Tween 20 Tetraglycol	7
3	Coenzyme Q10	Two fold increase in the bioavailability	Myvacet-9 45 Lauroglycol	8

		compared to the powder formulation	Labrasol	
4	Baicalein	200.7% enhancement in bioavailbility as compared to Baicalein susension	Caprylic capric triglyceride, Cremophor RH 40 Lauroglycol	9
5	Flutamide	Enhanced dissolution rate	Sesame oil, Tween 20 PEG 400	10
6	Griseofulvin	Solubility enhancement due to the presence of Hydrochoric acid and absorption behavior	Peanut oil Tween 80	11
7	Lercanidipine hydrochloride	Improved solubility	Capmul MCM L8 Tween 80 PEG 400	12
8	Nimodipine	*In vitro* and *invivo* performance was improved	Labrasol Transcutol Plurol oleque CC 497	13
9	Paclitaxel	Enhanced oral absorption	Cremophor EL Lauroglycol Labrasol	14

10	Simvastatin	Improvement in hypolipidemic and pharmacodynamic performance	Polyoxy castor oil Di and tri glycerides	15
11	Tacrolimus	Enhanced absorption	Lauroglycol Cremophor RH PEG 400	16
12	Tamoxifen citrate	Improved oral efficacy	Capryol 90 Propylene glycol Cremophor RH 40	17

Conclusion: Oral liquids are the most preferred route due to difficulty in swallowing of solid dosage form as well this route follows non invasive administration. The conventional approaches of oral route suffers from certain limitations such as low bioavailability, high inter and intra subject variability. The current strategies of novel oral drug delivery systems i.e. self emulsifying drug delivery system have significant improvement over conventional approaches (syrups, emulsions, elixirs and suspensions) with enhanced dissolution and improved bioavailability resulting in improved patient compliance.

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