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A REVIEW ON SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

The oral route is the most preferred route for the drug administration. But the major problem in oral drug formulations is low bioavailability which leads to poor water solubility. Some approaches are being studied for the improvement of solubility and bioavailability of poorly aqueous soluble drugs such as BCS class II and class IV drugs. One of the novel approache is Self-emulsifying drug delivery system. SEDDS are isotropic mixtures of oil, surfactant, solvents, and cosolvents/surfactants. These forms fine emulsion in the GI-tract upon mild agitation produced by gastric mobility. Present review describes about composition, Mechanism of self-emulsification, Advantages and Disadvantages, and evaluation of Self emulsifying drug delivery system.

KEYWORDS: Self emulsifying drug delivery system, SMEDDS, SNEDDS, Isotropic mixture, Pseudo ternary phase diagrams.

INTRODUCTION

Self-emulsifying drug delivery system are novel drug delivery systems used to improve oral bioavailability of poorly water-soluble drugs. As most of the new chemical moieties are insoluble in aqueous media, SEDDS plays an important role in to improve bioavailability of poorly aqueous soluble drugs. After oral administration, SEDDS forms fine emulsion in gastrointestinal tract, due to agitation produced by stomach and small intestine.[1,2,3,4,5] Enhancement of bioavailability of less water-soluble drugs occurs by increasing their solubility by various methods such as salt formation, coprecipitation, solvent deposition, size reduction, H-bond formation.[1] SEDDS are mainly formulated to improve the solubility, dissolution rate of BCS class II (Nifedipine) and class IV (Taxol) which have low solubility, high permeability and low solubility, low permeability respectively.[6] These are administered in soft/hard gelatin capsules.[2] Lipinski's rule of five is a qualitative method used for assessment of absorption of poorly absorbed compounds. It predicts that poor absorption or permeation occurs when there are more than 5 H-bond donors, 10 H-bond acceptors, molecular weight 500 Daltons and log P-5.[7,8]

Self Emulsification Drug Delivery System

These are isotropic mixtures of natural or synthetic oils, surfactants, solvents, cosolvents/surfactants form fine emulsion in GI-tract upon mild agitation produced by gastric mobility. These are formulated by using medium chain triglycerides and non-ionic surfactants due to their less toxic in nature. Droplet size ranges from 100-300nm and dispersion appears as turbid.[9,10]

Self Micro Emulsifying Drug Delivery System

SMEDDS are also isotropic mixtures of oil, surfactant, solvent, co-solvent/surfactant forms thermodynamically stable micro emulsion. They appear as transparent liquids and their size range is about less than 50nm.[11]

Self Nano Emulsifying Drug Delivery System

SNEDDS is an isotropic mixtures of oil, surfactant, solvent, co-solvent/surfactant which have unique ability to form O/W Nano emulsion under mild agitation.[12] It is also called as mini emulsion or ultra- fine emulsion. Droplet size range is about less than 100nm.[13] These are thermodynamically and kinetically stable.

TYPES OF SNEDDS

1. Water in Oil (W/O) type of Nano emulsion[13]
2. Oil in Water (O/W) type of Nano emulsion[13]
3. Bicontinuous Nano emulsion

Bicontinuous Nano emulsion in which surfactant was soluble in both oil and water phase, and droplets was dispersed both in oil and water phase.[14]

Advantages[15,16]

- Quick onset of action
- Increased oral bioavailability
- No hepatic first pass metabolism
- Reduced drug dose frequency
- Ease of manufacture and scale-up

- Reduction in inter and intra subject variability

DISADVANTAGES[16,17]

- Traditional dissolution methods do not work because SEDDS potentially are dependent on digestion prior to release of the drug.
- Development based on *Invitro-Invivo* Correlation (IVIVC) therefore different proto type lipid based formulations needs to be developed and tested *Invivo* in suitable animal model.
- Drawbacks of this system includes chemical instability of drug and high surfactant concentration in formulations which irritate GI tract.
- High production cost.
- Low drug incompatibility.
- Drug leakage, so it may allow less drug loading.

Composition of Self Emulsifying Drug Delivery System

I. Active pharmaceutical ingredient (API)
II. Excipients

- Oil
- Surfactants
- Solvents
- Co-solvents/surfactants

Active Pharmaceutical Ingredient (Api)

These formulations are prepared mainly to improve the bioavailability of less water soluble drugs which are BCS class II and class IV drugs are used as active ingredient.[18,19]

Examples: Nifedipine, Carbamazepine, Naproxen, Ketoconazole, Simvastatin, Taxol

EXCIPIENTS

Selection of excipients plays a crucial role in formulation of SEDDS, SMEDDS and SNEDDS as they should undergo self-emulsification process in the GI-tract upon mild agitation produced by stomach and small intestine mobility. Parameters like surfactant concentration, nature of oil, oil surfactant ratio, and surfactant- cosurfactant ratio are the factors considered during selection of excipients.[1]

Oil: The oil is the most important excipient in the formulation of SEDDS as it can solubilize the required dose of lipophilic drug or facilitate self-emulsification and it increase fraction of lipophilic drug transport via intestinal lymphatic system, thereby increasing absorption from the GI-tract.[1] Oil occurs as natural and synthetic oils. The mixture of oil and fats are triglycerides contain in long chain fatty acids. Triglycerides are classified as short chain triglycerides (< 5 carbon atoms), medium chain triglycerides (6-12 carbon atoms), and long chain triglycerides (>12 carbon atoms). Long chain triglycerides (LCT) and medium chain triglycerides (MCT) are used for the formulation of self-micro emulsifying drug delivery system. MCT's are mostly used because it has higher solvent capacity and prevent oxidation when compared to LCT. MCT's are replaced with novel semi-synthetic MCT's. It is important to influence water solubility of poorly soluble drugs and oil phases are modified by vegetable oils, digestible or non-digestible oils.[3]

Table 1: List of Different Oils Used to Solubilize Different Drugs.[1]

S.no	Type of oil	Drug	Marketed product
1.	Corn oil	Valproic acid	Depakane capsules
2.	Sesame oil	Dronabinol	Marinol soft gelatin capsules
3.	Soybean oil	Isotretinoin	Accutane soft gelatin capsules
4.	Peanut oil	Progesterone	Prometrium soft gelatin capsules

Surfactants: Surfactants are the compounds that lowers the interfacial tension and provide interfacial area at the interface.[20] Most of the compounds exhibit surfactant property but limited surfactants are orally acceptable.[2,3] Mostly non-ionic surfactants are used (fig 1, 2). They are thermodynamically stable, non-toxic and having high hydrophilic lipophilic balance (HLB). The higher concentration of surfactant, co-surfactant and oil ratio leads to the formation of SMEDDS and SNEDDS.[3] Higher concentration of surfactant increasing the droplet size.[3]

Examples: Sorbitan esters (Spans), Polysorbates (Tweens)[2]

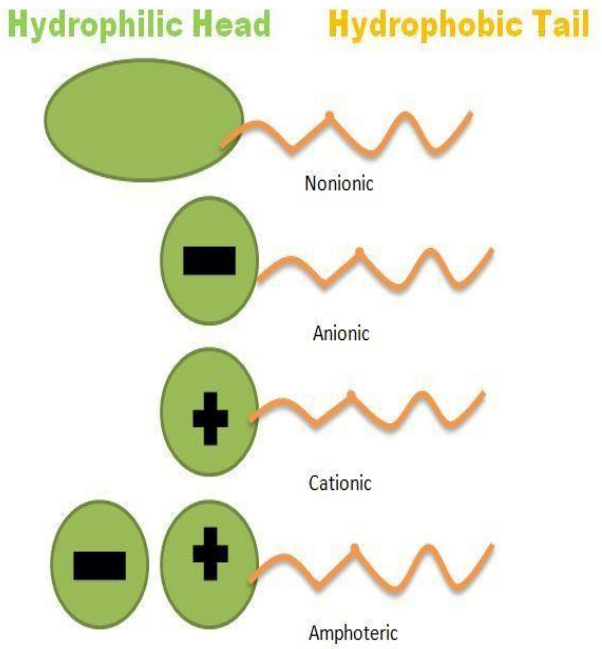

Figure 1: Types of surfactants.

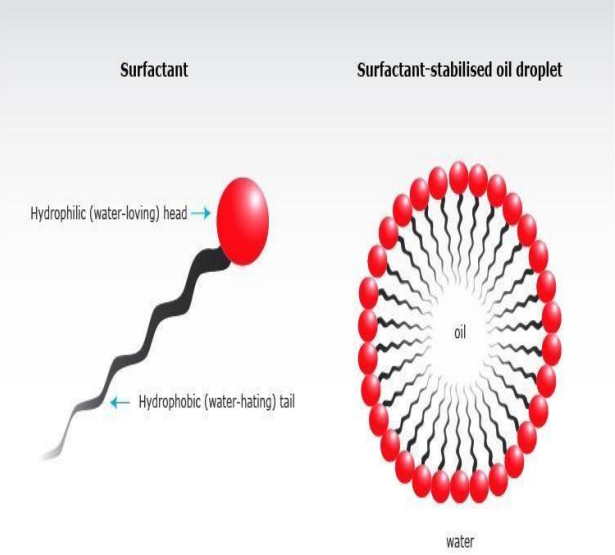

Figure 2: Structure of Surfactant.

Co-surfactants: These are used along with surfactants which are able to increase the ability of surfactants to improve water solubility of poorly water soluble drugs. These are single chain surfactants, able to prevent interfacial fluidity.[21]

Co-solvents: These are used to prevent interfacial tension and provide large surface area, which increases oral bioavailability of poorly water soluble drugs.[22]

Examples: Ethanol, Methanol, Glycol, Propylene glycol[3]

Mechanism of Self Emulsification Process

When changes in entropy (energy) occurs self-emulsification takes place. The free energy of traditional emulsion formation is a direct function of energy required to create a new surface between the two phases and can be given by an equation.[1]

$$\Delta G = \Sigma N \Pi r^2 \sigma$$

Where, ΔG = free energy associated with the process
N = number of droplets
r = radius
σ = interfacial energy with time

Two phases of the emulsion will tend to separate, in order to reduce interfacial area and the free energy of the system. The emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a monolayer around the emulsion droplets and reduce the interfacial energy and also provides a barrier to coalescence.[23] In order to get self-emulsifying system, the free energy requires to form the emulsion is either very low or positive or negative, the emulsion process occurs spontaneously.[2,4]

Construction of Ternary Phase Diagram

It is used for the determination of self-emulsifying drug delivery system. It is the first step before starting the formulation. As SEDDS are isotropic mixture of oil, surfactant, co-surfactant, it identifies the best region of emulsification. Each apex represents the 100% concentration of each phase contents (fig 3). Software's used for the construction of ternary diagram: Chemix school software, Triplot, Delta plot ware.

The methods used to plot ternary phase diagram are:

1. Dilution method
2. Water titration method/pseudo ternary phase diagram

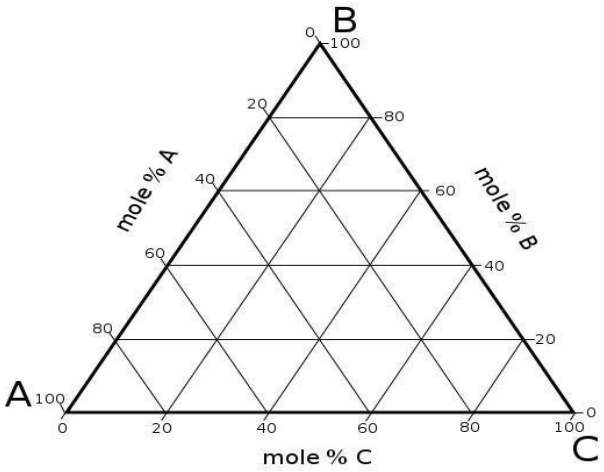

Figure 3: Ternary phase diagram.

Dilution method

With varying composition of surfactant, co-surfactant and oils gives the ternary mixture. The percentage of oil, surfactant, co-surfactant is depend on the type of formulation based on their requirements. The composition are evaluated for Nano emulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersion was determined by using spectroscopy.[1]

Water titration method

The pseudo ternary phase diagram are also constructed by titration of homogenous mixture of oil, surfactant, and co-surfactant. The oily mixtures of oil, surfactant, co-surfactant were prepared varied from 9:1 to 1:9 and vortexed for the formation of isotropic mixture which are titrated with aliquot of distilled water. And the mixtures visually observed, if the turbidity seem then its coarse emulsion, if it is clear, transparent then it is Nanoemulsion.[1]

Evaluation of Self Emulsifying Drug Delivery System

1. **Drug Content:** Drug from pre-weighed SEDDS is extracted by dissolving in a suitable solvent.
   Drug content in the solvent extract is analyzed by suitable analytical techniques.[26]
2. **Rheological Property:** Viscosity is determined by using Brookfield viscometer.[1]
3. **Droplet Size:** It is determined by photon correlation spectroscopy that analyses the fluctuations in light scattering due to Brownian motion of the particle using Zetasizer. Dynamic light scattering (DLS),

Laser diffraction technique are also used.[1]

4. **Freeze thaw cycle:** In this test storing the emulsion between -21º and 25° and observed for any phase separation, cracking, or creaming. Formulation pass this test represents the good emulsion.[1]
5. **Centrifugation studies:** Formulations are centrifuged at 5000 rpm for 30 mins, and observed for any phase separation occurs. If no phase separation occurs then it said to be stable formulation.[1]
6. **Dispersibility test:** The dispersibility test of SEDDS is carried out to assess its capability to dispense into emulsion and categorize the size of resulting globules. It is carried by using standard USP dissolution apparatus II. One ml of each formulation is added to 500ml of water at 37±0.5° and rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture which is of different types depending upon which the *Invitro* performance of formulation can be assessed using grading system.[27]

GRADE A: Rapidly forming(less than 1min), having a clear or bluish appearance.

GRADE B: Rapidly forming, slightly less clear emulsion having bluish white appearance.

GRADE C: Fine milky emulsion that formed within 2mins.

GRADE D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2mins).

GRADE E: Formulations exhibiting poor or minimal emulsification with large oil globules present on the surface.

7. **pH measurement:** It is measured by using pH meter or potentiometer.[28]
8. **Percent transmittance:** Using UV-visible double beam/single beam spectrophotometer using distilled water as blank at 560 nm.[29]

APPLICATIONS

- Improvement in solubility and bioavailability of poorly water soluble drugs.[2,3]
- Used in drug delivery systems such as in cosmetics, transdermal drug delivery system, cancer therapy, vaccine delivery, cell culture technology, ocular drug delivery, parenteral drug delivery, intranasal and pulmonary drug delivery system.[30]
- Protection against biodegradation and enzymatic degradation.[2,3]
- Controlling the release of drug.[2]
- SEDDS have ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors by protecting them from enzymatic hydrolysis.[30]

Table 2: Sedds Marketed Formulations.[2]

Brand Name	Drug	Company
Neoral	Cyclosporine	Novartis
Norvir	Ritonavir	Abbott Laboratories
Agenerase	Amprenavir	GSK
Convulex	Valproic acid	Pharmacia

CONCLUSION

Self-emulsifying drug delivery system can be used for the formulations of poorly water soluble drugs. Development of this technology will continue to enable novel applications in drug delivery system. When the dosage form reaches the GI-tract produce fine emulsion on mild agitation produced in stomach and intestine. The finer droplets have higher surface area thereby increase the absorption. It also avoid GI irritation, controlled and sustained drug release is achievable.

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