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REVIEW ARTICLE

SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM- A NOVALAPPROACH FOR IMPROVING BIOAVAILABILITY

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ABSTRACT

The primary object of self-nanoemulsifying drug delivery system (SNEDDS) is to enhance the oral bioavailability of poorly water soluble drugs. The major problem in oral formulations is low and erratic bioavailability, which mainly results due to poor aqueous solubility of active constituents. Among various approach SNEDDS has gained more attention due to enhanced oral bio-availability enabling reduction in dose. The primary mechanism of action which leads to improved bioavailability is usually avoidance, or partial avoidance, of the slow dissolution process which limits the bioavailability of hydrophobic drugs from solid dosage forms. Nano-emulsions can be easily fabricated by low-energy emulsification methods, such as the phase inversion, temperature method and phase inversion composition method. SNEDDS are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug and co-emulsifier or solubilizer, which spontaneously form oil-in-water nanoemulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring.

Keywords: Self emulsifying drug delivery system, surfactant, co-surfactant etc.

1 INTRODUCTION

The drugs are most often administered by oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is difficult because of Their low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.[1] To overcome these problems, various strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins,

nanoparticles and solid dispersions .BCS Class II drugs suffer from poor water solubility and high lipophilicity resulting in a highly variable oral bioavailability of formulations. They contain potential pharmacodynamic activity they fail to reach in the market. Bioavailability of Class II drugs is rate limited by its dissolution profile . So a increase in its dissolution rate results in a large increase in bioavailability. The solubility of the drug could be increased in three ways: changing the chemical structure in the lead optimization phase; prodrug approach and the formulation approach. Formulation strategies such as micronization, co-solubulization, solid dispersion, inclusion complex, nanosuspension, lipid based formulations etc., may be employed to enhance their dissolution, thereby their bioavailability.[2-6]

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, Enzymatic degradation, gut wall efflux and bioavailability

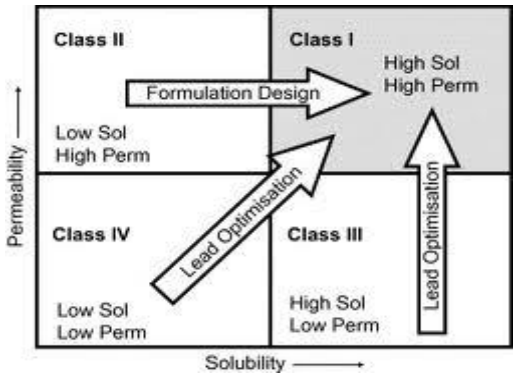


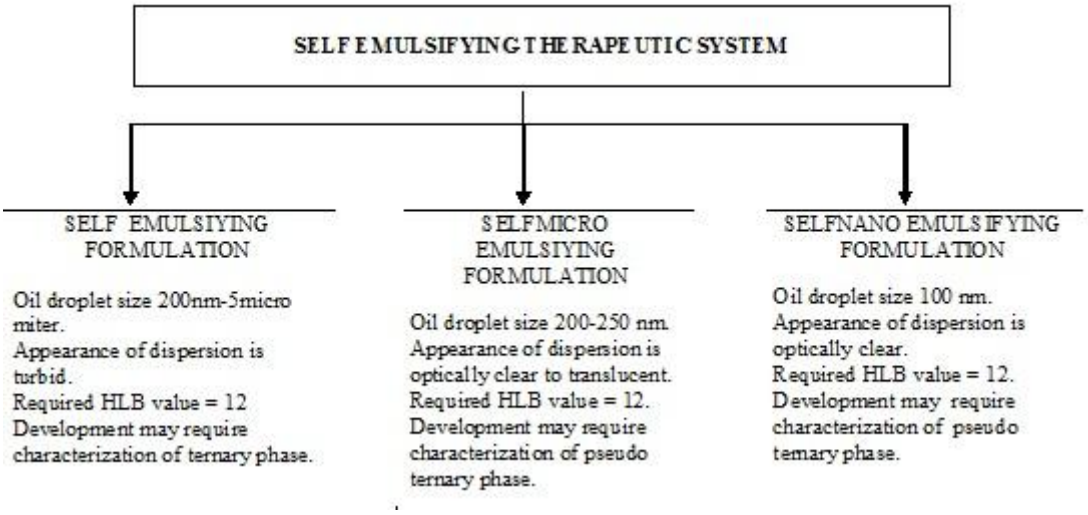
Figure 1: Biopharmaceutics classification system

Figure 1 indicating that absorption of a class II drug can be markedly improved by attention to the formulation. Formulation may improve the bioavailability of class IV drugs but they are likely to be compromised by their poor membrane permeability. If a class II drug can be maintained in a solubilized state in the lumen of the gut one can achieve an absorption profile more like that of a class I drug. Formulation strategies can do little to improve the absorption of classes I and III drugs which are limited by poor membranepermeability.[7]

Self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation which is mixture of oils and surfactants, ideally isotropic, and sometimes containing co-solvants, which emulsify spontaneously to produce fine oil in water emulsion when introduced into aqueous phase under gentle agitation. Self nanoemulsifying (SNEDDS), self microemulsifying (SMEDDS) and self-emulsifying drug

delivery systems (SEDDS) to improve the oral bioavailability of poorly water- soluble drugs .Self nano-emulsifying drug delivery systems. These systems have a unique property, they are able to self-emulsify rapidly in gastro-intestinal fluids and under the gentle agitation provided by the motion of the gastro- intestinal tract and they form fine O/W emulsions.[8] These fine O/W emulsions produce small droplets of oil dispersed in the gastro -intestinal fluids that provide large interfacial area increasing the activity of pancreatic lipase to hydrolyze triglycerides and, thereby, promote a faster release of the drug and/or formation of mixed micelles of the bile salts containing the drug. Furthermore, in most cases the surfactant used for such formulations increases the bioavailability of the drug by activation of different mechanisms, maintaining the drug in solution and, thus, avoiding the dissolution step from the crystalline state and enhancing intestinal epithelial permeability at the same time. Moreover, the oil droplets lead to a faster and more uniform distribution of the drug in the gastrointestinal tract, minimizing the irritation due to contact between the drug and the gut wall. In addition, lipids affect the oral bioavailability of drugs by exerting their effect through several mechanisms, including protection of the drug from enzymatic or chemical degradation in the oil droplets and activation of lipoproteins promoting the lymphatic transport of lipophilic drugs.[9] These systems may then be incorporated into capsules directly, or transformed into granules, pellets, and powders for dry filled capsules as well as tablet preparations. Various formulation techniques have been developed to improve the bioavailability of poorly water-soluble drugs, such as solid dispersion, cyclodextrins, emulsions, liposomes, and nanoparticles.[10] Among these methods, much attention has recently been focused on self-nanoemulsifying drug delivery systems (SNEDDSs) to improve the oral bioavailability of poorly soluble drugs.[11–15] For SNEDDSs, isotropic mixtures of oils and surfactants are used to form fine oil-in-water nanoemulsions when exposed to aqueous media, such as

gastrointestinal fluids under mild agitation with droplet size less than 200 nm.The latter option is possible by innovative adaptations of conventional equipment with relative ease and process simplicity, using methods like melt granulation, adsorption on a solid support, spray drying, spray cooling, melt-extrusion/spheronization, and supercritical fluid based methods.[16]



1.2 Potential advantages of these systems include[17-19]

- Enhanced oral bioavailability enabling reduction in dose.
- More consistent temporal profiles of drug absorption.
- Selective targeting of drug(s) toward specific absorption window in GIT
- Protection of drug(s) from the hostile environment in gut.
- Control of delivery profiles.
- Reduced variability including food effects.
- Protection of sensitive drug substances.
- High drug payloads.
- Quick onset of action.
- Ease of manufacture and scale up.

1.3 Factors affecting SNEDDS[20]

- Drugs which are administered at very high dose are not suitable for SNEDDS
- The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SNEDDS.
- The ability of SNEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase.
- If the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, thenthere could be a risk of precipitation.

1.4 Composition of SEDDs: [21-23]

The SEDDs is mainly composed of the following:

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Drugs:

Generally, SEDDs are prepared for drugs possessing poor water-solubility. BCS class II drugs are usually employed in preparation of SEDDs. Examples include itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefanimicacid, carbamazepine, glibenclamide, cyclosporine-A, ritonavir etc.(Table 1)

Table 1: Type of drugs used with surfactants in SEDDs

Surfactant	Drug
PEG-35	Ibuprofen
Tween 80	Cyclosporine-A
Cremophore RH 40	Furosemide
Cremophore EL	Glibenclamide

Surfactant:

Numerous compounds exhibiting surfactant properties might to the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively highhydrophilic lipophilic balance (HLB). To form stable SEDDs, 30-60% concentration of surfactant is used .[24] Table (2)

The four main groups of surfactants are -

1)Anionic surfactants: Potassium laurate, sodium lauryl sulphate**.**

2) Cationic surfactant : Quaternary ammonium halide.

3) Ampholytic surfactants: Sulfobetaines**.**

4) Nonionic surfactants: Sorbitan esters (Spans), poly – sorbates(Tweens).

Table 2: Type of surfactants used in marketed SEDDs:

Surfactant	Marketed drug product	Drug
Cremophor RH 40	Neural soft gelatin capsule	Cyclosporine A
Span 20	Kaletra tablet, soft gelatin capsule	Lopinavir
Polysorbate 80	Lipofen hard gelatin capsule	Fenofibrate
Gelucire 44	Targretin soft gelatin capsule	Bexarotene

Oils:

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in 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 markedly reduces their use in SEDDs. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE. other suitable oil phases are and fats which are used normally such as olive oil, corn oil, soya bean oil, and animal fats .[25](Table 3)

Table 3: Type of oil used with drug in SEDDs

Oil	Drug
Palm kernel oi	Ibuprofen
Castor oil	Cyclosporin-A
Captex 500	Furosemide
Capmul MCM C8	Glibenclamide
Lemon oil	Diclofenac Sodium

Co-solvents:

Usually an effective self emulsifying formulation requires a high concentration of surfactant. Accordingly, co - solvents such as ethanol, propylene glycol and polyethylene glycol are required to facilitate the dissolution of large quantities of hydrophilic surfactant. These co -solvents sometimes play the role of the co-surfactant in the micro- emulsion system. On the other hand, alcohol and other volatile co-solvents have the drawback of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of the drug.

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 - hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

2 MECHANISM OF SELF EMULSIFICATION:[26]

Self emulsification occurs when the entropy change that favors 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 phase and can be described by the equation 1.

$$DG = SNpr\ 2s \ldots\ldots (1)$$

Where

DG =free energy associated with the process .

N = number of droplets

r = radius of droplets .

s = interfacial energy.

The two phase of emulsion tend to separate with time to reduce the interfacial area and subsequently the emulsion is stabilized by emulsifying agent ,which form

a monolayer of emulsion droplets and hence reduce the interfacial energy as well as providing a barrier to prevent coalescence.

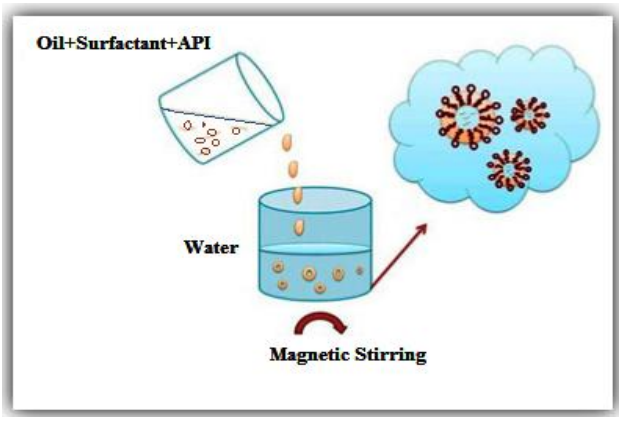

Figure 2: Formulation of SNEDDS

3. EVALUATION:

3.1 Thermodynamic stability studies[27]

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

1. Heating cooling cycle: Six cycles between refrigerator temperature (40C) and 450C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

2. Centrifugation: Passed formulations are centrifuged thaw cycles between 21 0C and +25 0C with storage at each temperature for not less than 48 h is done at 3500rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

3. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

3.2 Dispersibility test[28]

The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 0C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

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

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

3.3 Turbidimetric Evaluation[27]

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbid-meter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification)

3.4 Viscosity Determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. so, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it are w/o type of the system.

3.5 Droplet Size Analysis Particle Size Measurements[27]

The droplet size of the emulsions is determined by photoncorrelation spectroscopy (which analyses the fluctuationsin light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between10 and 5000 nm. Light scattering is monitored at 25°C ata 90° angle, after external standardization with sphericalpolystyrene beads. The nanometric size range of theparticle is retained even after 100 times dilution withwater which proves the system's compatibility withexcess water.

3.6 Refractive Index and Percent Transmittance[29]

Refractive index and percent transmittance proved thetransparency of formulation. The refractive index of thesystem is measured by refractometer by placing drop ofsolution on slide and it compare with water (1.333)**.** Thepercent transmittance of the system is measured atparticular wavelength using UV-spectrophotometerkeeping distilled water as blank.If refractive index ofsystem is similar to the refractive index of water(1.333)and formulation have percent transmittance > 99 percent,then formulation have transparent nature.

3.7 Electro conductivity Study

The SEDD system contains ionic or non-ionic surfactant,oil, and water.so, this test is used to measure

theelectoconductive nature of system. The electro-conductivity of resultant system is measured byelectoconductometer

3.8 In Vitro Diffusion Study

In vitro diffusion studies is performed to study the releasebehavior of formulation from liquid crystalline phasearound the droplet using dialysis technique.

3.9 Drug content:

Drug from pre-weighed SEDDS is extracted by dissolvingin suitable solvent. Drug content in the solvent extractwas analyzed by suitable analytical method against thestandard solvent solution of drug.

3.10 Bioavailability study:[30]

Based on the self emulsification properties, particle size data and stability of micro emulsion the formulation is selected for bioavailability studies. The *in vivo* study is performed to quantify the drug after administration of the formulation. Pharmacokinetic parameters of the maximum plasma concentration (Cmax) and the corresponding time (tmax) for the drug following oral administration are calculated. The relative Bioavailability of SEDDS formulation to the conventional tablet is calculated using the following Equation.

Relative Bioavailability.

(%) = (AUC test/AUC reference) X (Dose reference/Dose test).

CONCLUSION

The oral delivery of hydrophobic drugs can be made possible by SNEDDSs, which have been shown to substantially improve oral bioavailabilitywith future development of this technology. SEDDSs will continue to enable novelapplications in drug delivery and solve problems associated with the delivery of poorly soluble drugs .The nanosize of these formulations is responsible for facilitating enhancement of drug dissolution and absorption, owing to the large surface area. The lipidic nature of these systems allows delivery of drugs to the lymphatic system. The method employed in the investigation for screening of SNEDDS excipients helped in understanding the emulsification efficiency of various surfactants for selected oily phase.

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