SEMINAR

ON

SELF EMULSIFYING DRUG DELIVERY SYSTEM

BY

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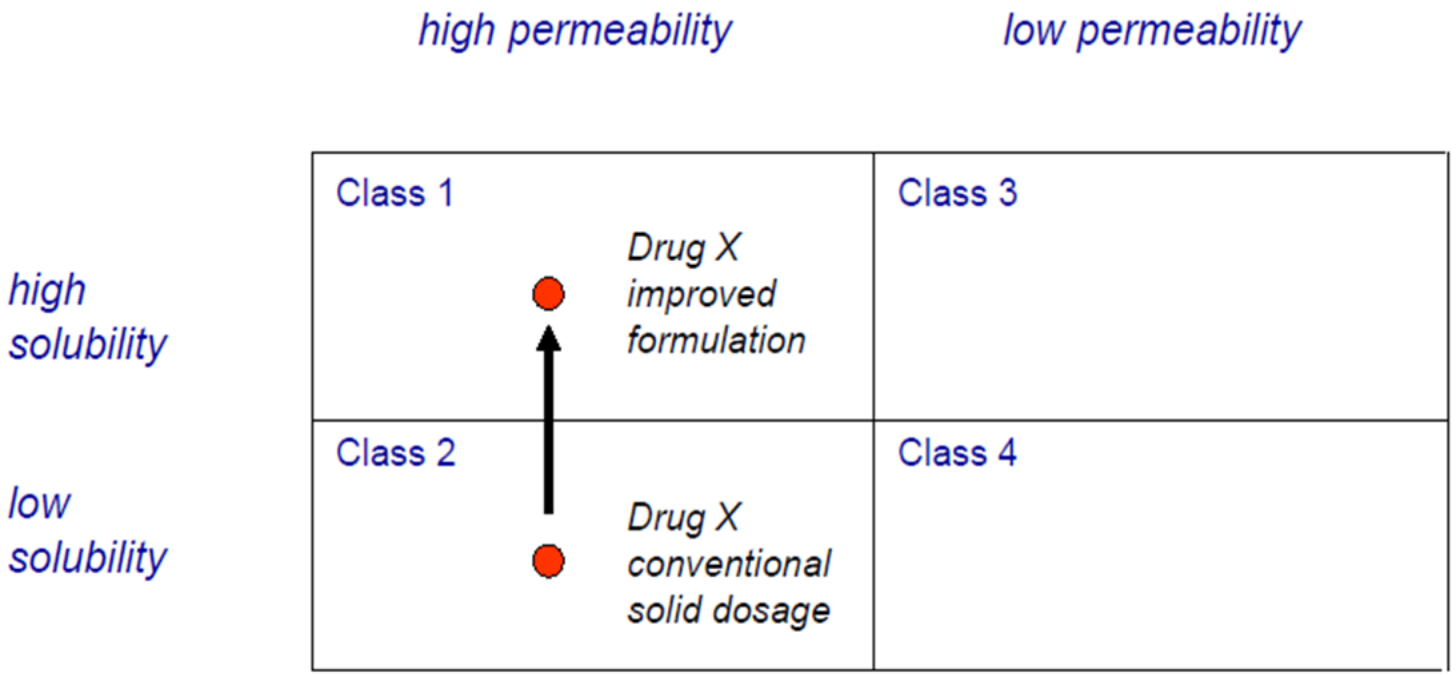
CONTENTS

INTRODUCTION

- Oral route is the easiest and most convenient route for non invasive administration.
- Approximately 40% of new chemical drug moieties have poor aqueous solubility and it is a major challenge to modern drug delivery system.

- To overcome these problems, various formulations strategies are exploited including the use of surfactant, lipid permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions.
- The concept of SEDDS for pharmaceutical purpose was initially developed by the Group of Groves (Dunkan QM et al., 2000, Fernando- Warnkulasuriya GLP et al., 1981).

BIOPHARMACEUTICAL CLASSIFICATION OF DRUGS



DEFINITION:

- SEDDS or self-emulsifying oil formulations (SEOP) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and co-solvents/surfactants.

- SEDDSs emulsify spontaneously to produce fine oil in- water emulsions when introduced into an aqueous phase under gentle agitation and spread readily in the gastro intestinal tract.

- SEDDSs typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems (SMEDDSs) form transparent micro-emulsions with a droplet size of less than 50 nm.

ADVANTAGES OF SEDDS

- Protection of sensitive drug substances
- More consistent drug absorption,
- Selective targeting of drugs toward specific absorption window in GIT
- Protection of drug(s) from the gut environment.
- Control of delivery profile
- Reduced variability including food effects
- Enhanced oral bioavailability enabling reduction in dose
- High drug loading efficiency.

- For both liquid and solid dosage forms.
- These dosage forms reduce the gastric irritation produced by drugs.
- Emulsion are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.
- As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.

DRAWBACK OF SEDDS:

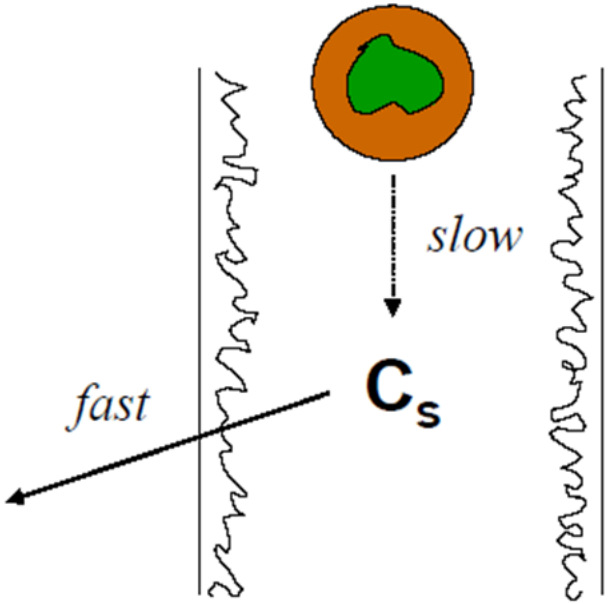
- Lack of good *in vitro* models for assessment of the formulations for SEDDS.
- The traditional dissolution methods does not work, because these formulations potentially are dependent on digestion prior to release of the drug.

CLASSIFICATION OF LIPID FORMULATION SYSTEMS

Composition	Type I oil	Type II SEDDS	Type III IIIA SEDDS	 IIIB SMEDDS	Type IV oil-free
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	< 20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	0-20%
(HLB > 12)	-	-	20-40%	20-50%	20-80%
Hydrophilic cosolvents	-	-	0-40%	20-50%	0-80%

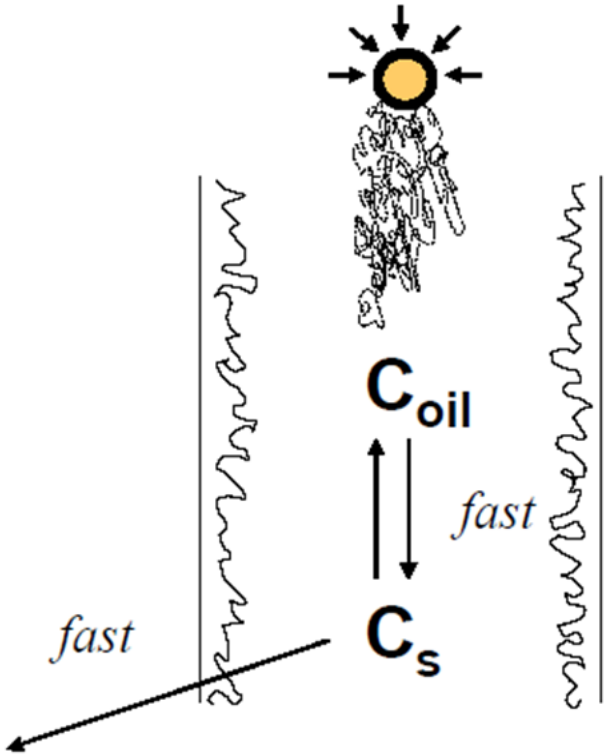
Why we need SEDDS ?

crystalline drug



may be insufficient time for this process during intestinal transit

SEDDS



dissolution step is avoided provided that the drug remains in solution

COMPOSITION OF SEDDS

- Oils
- Surfactants
- Cosolvents / cosurfactants
- polymers

OILS:

- Oils are the most important excipient because oils can solubilize the lipophilic drug in a specific amount.
- Both long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used for the formulation of SEDDSs.
- Unmodified edible oils have poor ability to dissolve large amount of hydrophilic drugs.
- Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages.

- MCTs were preferred in the earlier self-emulsifying Formulations. Because of 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.

- The absorption enhancement is greater when using unsaturated fatty acids.

- Very polar or nonpolar oils tend to form poor emulsion. Miglyol-812 and 840 with intermediate polarity have shown favorable emulsification properties with tween 85.

LIPID INGREDIENTS

- Corn oil mono,di,tri-glycerides
- DL-alpha-Tocopherol
- Fractionated triglyceride of coconut oil(medium-chain triglyceride)
- Fractionated triglyceride of palm seed oil(medium-chain triglyceride)
- Mixture of mono-and di- glycerides of caprylic/capric acid
- Medium chain mono-and di- glycerides
- Corn oil
- Olive oil
- Oleic acid
- Sesame oil
- Hydrogenated soyabean oil
- Hydrogenated vegetable oils
- Soyabean oil
- Peanut oil
- Beeswax

SURFACTANTS

- Natural surfactants have limited ability to emulsify.
- Non ionic surfactants are less toxic when compared to ionic surfactants.
- The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS.
- Non-ionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDS.
- Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds

Examples of surfactants:

- Polysorbate 20 (Tween 20)
- Polysorbate 80 (Tween 80)
- Sorbitan monooleate (Span 80)
- Polyoxy-35-castor oil(Cremophor RH40)
- Polyoxy-40- hydrogenated castor oil (Cremophor RH40)
- Polyoxyethylated glycerides (Labrafil M 2125 Cs)
- Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)
- D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)

Table 1. Physicochemical Properties and Main Fatty Acid Composition of Labrifil Oils (Compiled from Gattefossé Specification Sheets) [14]

Oil (MW)	Main fatty acid (%)	PEG group	HLB	Water solubility at 20℃	Viscosity at 20℃ (m.Pa.s)
Labrasol (430)	Caprylic (C8) 50-80% Capric (C10) 20-50%	PEG 400	14	Soluble	80-110
Labrafac CM 10 (440)	Caprylic (C8) 50% Capric (C10) 50%	PEG 200	10	Dispersible	0-90
Labrafil WL 2609 BS (850)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 400	6	Dispersible	80-120
Labrafil M 1944 CS (530)	Oleic (C18:1) 58-68% Linoleic (C18:2) 22-32%	PEG 8	4	Dispersible	75-95
Labrafil M 2125 CS (682)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 6	4	Dispersible	70-90
Labrafac Lipophile WL 1349 (504)	Caprylic (C8) 50-80% Capric (C10) 20-50%	—	1	Insoluble	25-35

COSOLVENTS/COSURFACTANTS

- Cosolvents may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base.
- These solvents sometimes play the role as co-surfactant in the microemulsion systems.
- Alcohol is not included in SEDDS/SMEDDS due to it's migration.
- Drug release is increased with increasing concentration of cosurfactant in formulation.

Examples of cosolvents:

- Ethanol
- Propylene glycol
- Polyethylene glycol
- Polyoxyethylene
- Propylene carbonate
- Tetrahydrofurfuryl alcohol polyethylene glycol ether(Glycofurol)

POLMERS:

- Polymres like hydroxy propyl methyl cellulose and ethyl cellulose are used in sustained / controlled release SEDDS.

PREPARATION OF SEDDS

- Accurately weighed amount of drug was placed in a glass vial, and oil, surfactant and cosurfactant were added.
- Then the components were mixed by gentle stirring and vortex mixing for 30 min.
- This mixture were heated at 40ºC on a magnetic stirrer, until drug was perfectly dissolved.
- The mixture was stored at room temperature until further use.

MECHANISM OF SELF EMULSIFICATION

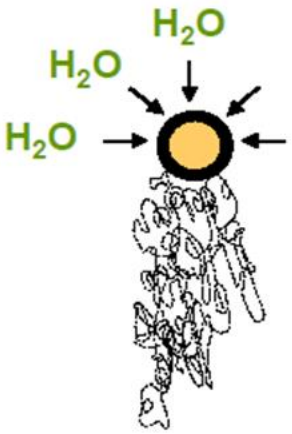
According to Reiss

- 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 a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation

$$\Delta G = \sum N_i \pi r_i^2 \sigma$$

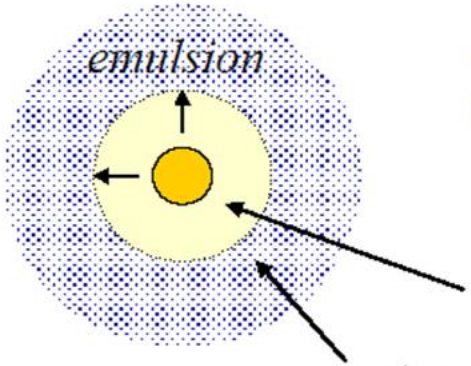
- Where, G is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and Ọ represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems.



1. Water-insoluble 'Type II' systems

- penetration of water and interfacial disruption
- usually associated with liquid crystal formation and PIT

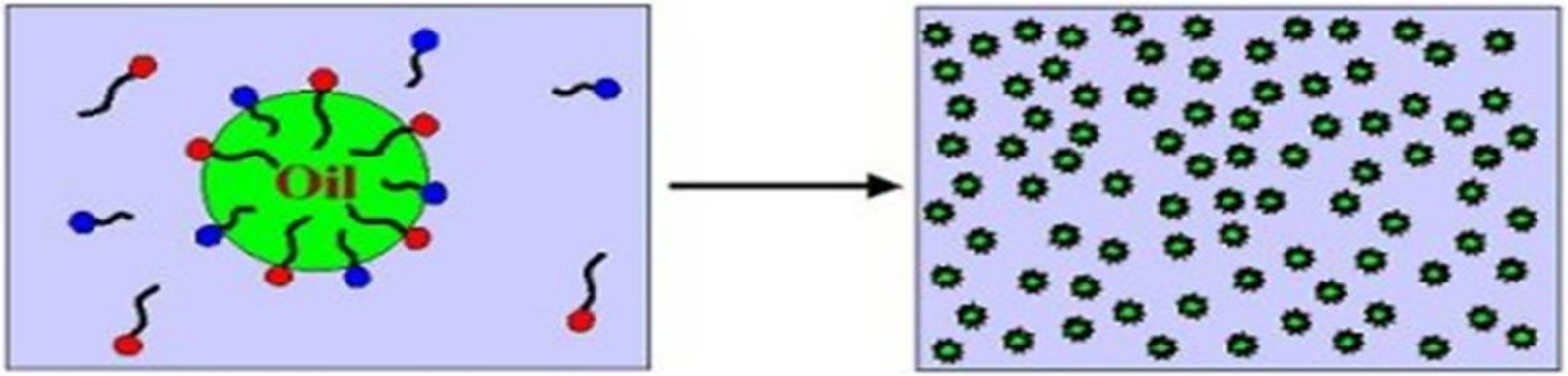
2. 'Type III' systems containing a water-soluble component



- diffusion and stranding
- may have complete mutual colloidal solubility on dilution

region of mutual solubility

o/w emulsion forms as cosolvent is diluted



FACTORS EFFECTING SEDDS

- Nature of oil and surfactant pair.
- Surfactant concentration and surfactant/ cosurfactant ratio.
- Temperature at which self emulsification occur.
- Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the components of SEDDS, preferably lipophillic phase.
- The ability of SEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase.

Polarity of the Lipid Phase:

- The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier.

- The polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase.

- The design of optimum SEDDS requires preformulation soubility and phase diagram studies.

IN VITRO EVALUATION OF SEDDS

- Droplet size analysis and zeta potential measurements
- Viscosity determination
- In vitro diffusion studies
- Thermodynamic stability studies
- Dispersibility test
- Drug content analysis
- Turbidimetric evaluation
- Refractive index and percent transmittance
- Electroconductivity studies

1. Droplet size and Zeta potential measurements:

Droplet size and zeta potential are measured by Zeta sizer 3000 HAS (malvern instruments , UK) able to measure size between 10 to 3000nm.

2.Viscosity determination:

- It is determined by brookfield vicsometer.

3.In vitro diffusion studies:

This test is carried out by dialysis technique. Drug is placed in dialysis tube which is kept in USP dissolution apparatus II containing 900ml of dialysis medium at 37^0C and stirred at 100rpm.

3.Thermodynamic stability studies:

- The poor physical stability of the formulation can lead to phase separation of the excipient, which affects not only formulation performance, as well as visual appearance of formulation.

- Incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

- For thermodynamic stability studies we have performed three main steps, they are-
  - Heating cooling cycle
  - Centrifugation
  - Freez thaw cycle

4.Dispersibility test :

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation was added in 500 mL of water at 37 ± 1 ^{0}C at 50 rpm. It passes the test

- If it is rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance. Or
- If it is rapidly forming, slightly less clear emulsion, having a bluish white appearance. Or
- If it is fine milky emulsion that formed within 2 min.

5.Drug content:

- It is measured by HPLC.

6.Refractive Index and Percent Transmittance:

- The refractive index of the system is measured by refractometer by putting a drop of solution on slide and it comparing it with water (1.333).
- The percent transmittance of the system is measured at particular wavelength using Uv spectrophotometer.

7.Electro Conductivity Study:

- The electro conductivity of resultant system is measured by electro conductometer.
- In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

8.Turbidimetric Evaluation

- Nepheloturbidimetric evaluation is done to monitor the growth of emulsification.

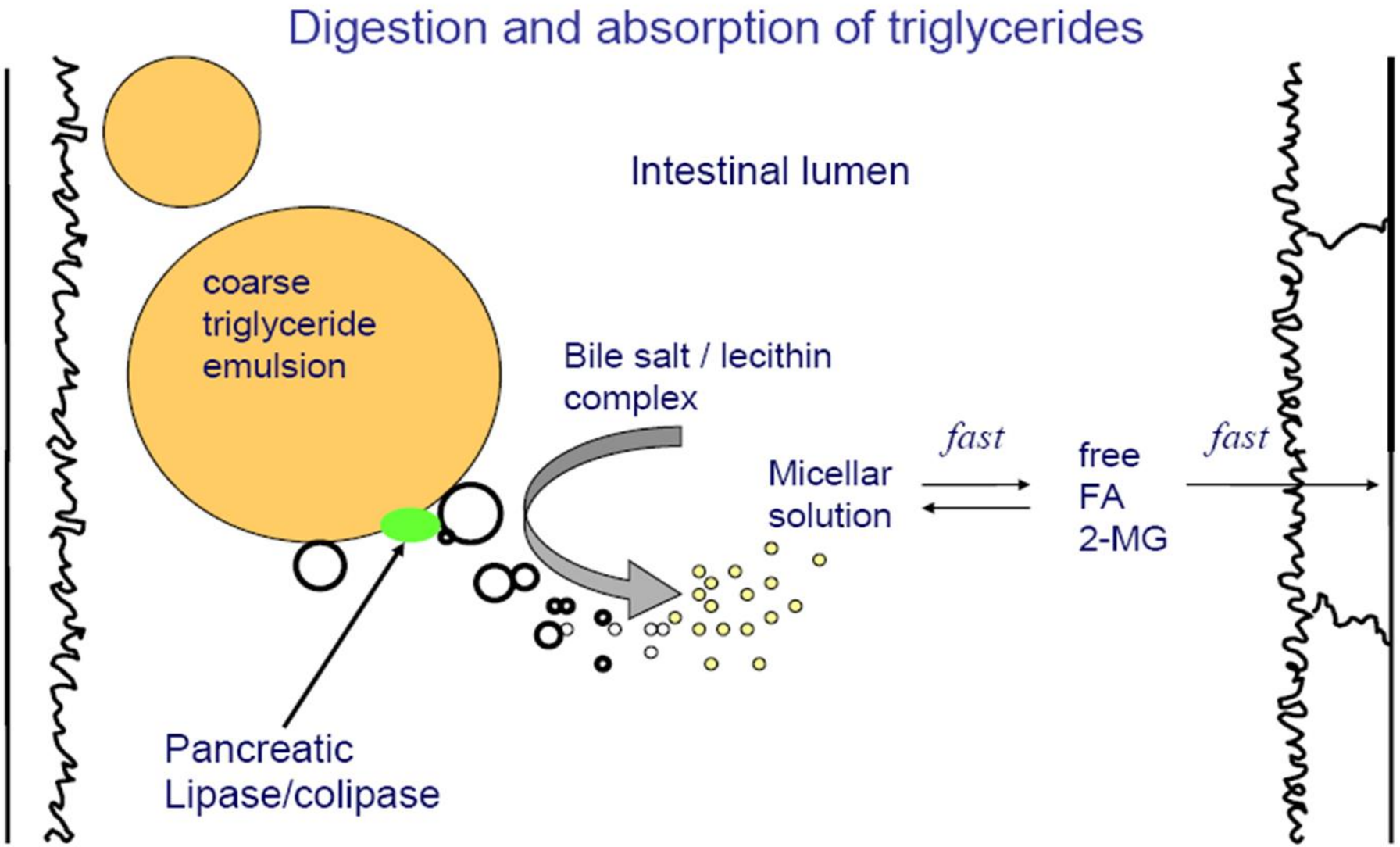
IMPROVEMENT OF ORAL ABSORPTION BY SEDDS

- Inhibition of gastric motility caused by the presence of lipid phase of emulsion might allow more time for dissolution and absorption of drug from lipid phase. Eg; griseofulvin

- Large surface area afford by emulsion may be a contributing factor to enhanced absorption of drugs.

- Mucosal permeability of drug is increased by lipids and surfactants and enhanced mesetri lymph flow may be responsible for drug absorption. Surfactants partition into the cell membrane and disrupt the structural organization of the lipid bilayer leading to permeation enhancement

ROLE OF LIPOLYSIS:



EFFECT OF P-GLYCOPROTEIN INHIBITION

- Bile salts, fatty acids, phospholipids, and surfactants were potent absorption enhancers and efflux-reducing agents.

- Also investigated the non-ionic surfactants, such as Tween 80, Pluronic P85, and Cremophor have the potential ability to reverse MDR caused by p-glycoprotein (P-gp) and multidrug resistance-associated proteins.

- TPGS (d-tocopheryl polyethylene glycol 1000 succinate) has been shown to be an effective inhibitor of P-gp mediated drug resistance and has been used to enhance the bioavailability of CsA.

- Inhibition of MDR-related pumps by various excipients has been proposed to occur due to

  - Binding competition-Tween80 with vinca alkaloid
  - ATP depletion-pluronic copolymer which sensitize MDR cells.
  - Membrane perturbation-BRIJ30 ,MYRJ52 cause structural changes to lipid domains in plasma membrane.

- Paclitaxel formulated as sedds show improve in bioavailability due to Pgp inhibition by surfactants.

SUPERSATURABLE SEDDS:

- supersaturable(S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs.

- Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier.

- The S-SEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state.

- paclitaxel S-SEDDS formulation produces approximately a 10-fold higher maximum concentration (Cmax) and a 5-fold higher oral bioavailability (F =9.5%).

POSITIVELY CHARGED SEDDS:

- A novel SEDDS, which results in positively charged dispersed oil droplets upon dilution with an aqueous phase, showed an increase in the oral bioavailability of progesterone in young female rats.

- More recently, it has been shown that the enhanced electrostatic interactions of positively charged droplets with the mucosal surface of the everted rat intestine are mainly responsible for the preferential uptake of the model drug cyclosporine A (CsA) from positively charged droplets .

APPLICATIONS OF SEDDS

1.Improvement in Solubility and Bioavailability:

- Ketoprofen,, it is a drug of choice for sustained release formulation but it has produce the gastric irritation during chronic therapy. Along with this due to its low solubility, ketoprofen shows incomplete release from sustained release formulations.

- This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.

- Tipranavir and Saquinavir sedd formulations has shown that two folder higher bioavailability.

Protection against Biodegradation:

- Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation or hydrolytic degradation etc.

- Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug.

- Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment.

- The SEDDS formulation of GBE (Ginkgo biloba) was accordingly developed to increase the dissolution rate and thus improve oral absorption and acquire the reproducible blood-time profiles of the active components of GBE.

- Silybin, the principal component of a *Carduus marianus* extract, is known to be very effective in protecting liver cells.

- The SEDDS formulation provides a greatly increased level of *in vivo bioavailability of silybin, the level being at* least 4-fold higher than that achievable by conventional formulations.

SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEMS

- SEDDS are usually limited to liquid dosage forms because many excipients used in SEDDS are not solids at room temperature.
- They are frequently more effective alternatives to conventional liquid SEDDS.
- S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques.
- Solid SEDDS has the flexibility to develop into different solid dosage form for oral and parenteral administrations.

SOLIDIFICATION TECHNIQUES:

- spray-cooling,
- spray drying,
- adsorption onto solid carriers,
- melt granulation,
- melt extrusion,
- super-critical fluid based methods and
- high pressure homogenization (to produce solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC)).

DIFFERENT DOSAGE FORMS OF S-SEDDS:

- Dry emulsions
- Self emulsifying capsules
- Self emulsifying sustained/controlled release tablets
- Self emulsifying sustained/controlled release pellets
- Self emulsifying solid dispersions
- Self emulsifying beads
- Self emulsifying sustained/controlled release microspheres
- Self emulsifying nanoparticles
- Self emulsifying implants
- Self emulsifying suppositories

RECENT APPROACHES IN SEDDS

Table: 3 Example of bioavailability enhancement of pooly soluble drug after administration of SEDDS and SMEDDS fo

Compound	Observation after Study
Win 54954	No difference in BA but improved reproducibility, increased C max
Cyclosporin	Increased BA and C max and reduced T max from SMEDDS
	Increased Cmax, AUC and dose linearity and reduced food effect ffrom SMEDDS
	Reduced intra- and inter-subject variability from SMEDDS
Halofantrine	Trend to higher BA from LCT SMEDDS
Ontazolast	BA increase of at least 10- fold from all lipid based formulations
Vitamin E	BA 3- fold higher from SEDDS
Coenzyme Q_{10}	BA 2- fold higher from SEDDS
Ro-15-0778	BA 3- fold higher from SEDDS when compared with other formulations
Simvastatin	BA 1.5 fold higher from SMEDDS
Biphenyl Dimethyl Dicarboxylate	BA 5- fold higher from SEDDS
Indomethacin	BA singnificantly increased from SEDDS
Progesterone	BA 9- fold higher from SEDDS
Tocotrienols	BA 2-3 fold higher from SEDDS
Danazol	BA from LCT solution and LC-SMEDDS 7- fold and 6- fold higher than that from MC-SMEDDS
Carvediol Solvent green 3	BA 4- fold higher from SEDDS BA 1.7-fold higher from SMEDDS
Silymarin	BA approximately 2-and 50- fold higher from SMEDDS
Atorvastatin Itraconazole Atovaquone Seocalcitol	BA significantly increased from all SMEDDS Increased BA and reduced food effect BA 3-fold higher from SMEDDS BA LC-SMEDDS=MC-SMEDDS
PNU-91325	5-6 fold enhancement in oral bioavailability for super saturable cosolvent, S-SEDDS, and Tween 80 formulations relative to cosolvent
Model Compounds inclunding disopyramide, ibuprofen, Ketoprofen, and Tolbutamide	Improved BA relative to the suspension formulations for either or both of the liquid microemulsion and SEDDS formulation in all cases

MARKETED PRODUCTS OF SEEDS

Drug Name	Compound	Dosage form	Company	Indication
Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir®	Ritonavir	Sof tgelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin capsule	Genus	Antihyper-lipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno suppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin capsule	Abbott Laboratories	Immuno suppr

CONCLUSION

- SEDDSs are a promising approach for the formulation of liphophilic drugs and to improve the oral bioavailability of drugs with poor aqueous solubility.
- As alternatives for conventional forms, liquid SEDDS, S-SEDDS are superior offering reduced production costs, simplified industrial manufacture, and improved stability as well as better patient compliance.
- Most importantly, S-SEDDS are very flexible for developing various solid dosage forms for oral and parenteral administration
- It appears that more drug products will be formulated as SEDDS in the very near future and these aspects are the major areas for future research into S-SEDDS.

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