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Review Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR IMPROVED ORAL DELIVERY OF LIPOPHILIC DRUGS

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ABSTRACT

The oral delivery of poor water soluble drug candidate is a major challenge because of the low aqueous solubility and less bioavailability. Lipid based drug delivery system such as self emulsifying drug delivery system (SEDDS) is isotropic mixtures of oils, surfactants and hydrophilic co-solvents/surfactants. These formulations are designed to improve the oral absorption of highly lipophilic drug compounds. Mostly as per biopharmaceutical classification system (BCS), class II drug and class IV are formulated as lipid based formulations. SEDDS is used to formulate formulation containing hydrophobic drug in solubilized form which enhances oral absorption and bioavailability of drug. SEDDS comprises of a mixture of oil surfactant, co-surfactant which act as a carrier for drugs by forming emulsion under gentle stirring when diluted in water or physiological media with physiological motion. A pseudo ternary phase diagram is used for identifying emulsification region. The fact 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug formulated as SEDDS will reach the pharmaceutical market in the future.

Keywords: Oral delivery, SEDDS, Hydrophobic drugs, Lymphatic absorption.

INTRODUCTION⁽¹⁻⁴⁾

The oral route has been the major route of drug delivery for chronic treatment of many diseases. Oral drug delivery system is the most cost-effective and leads the world wide drug delivery market. However, in the present scenario, oral drug delivery is continuously looking into newer avenues as 40% of new drug candidates have poor water solubility and/or absorption, high intra-and inter-subject variability, rapid metabolism, high fluctuation in the drug plasma level, variability due to food effect, and lack of dose proportionality which are playing major role in disappointing in vivo results leading to failure of conventional drug delivery system. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrin, solid dispersion (suspension), co-precipitation, micronisation, salt formation, emulsion, use of micelles, and co grinding. Recently much attention has been focused on lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more Hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. SEDDS is abroad

term, typically producing emulsions with a droplet size ranging from a few nano meters to several microns. Self-micro emulsifying Drug delivery system (SMEDDS) indicates the formulations forming transparent micro emulsions with oil droplets ranging between 100 and 250 nm. Self nano-emulsifying drug delivery system is a recent term construing the globule size range less than 100 nm.

1. Properties of SEDDS (5-6)

- They are able to self emulsify rapidly in gastro-intestinal fluids and under the influence of gentle agitation provided by Peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.
- They require lower dose of drug with respect to conventional dosage forms.

2. Need of SEDDS (7-10)

- SEDDS are promising approach for oral delivery of poorly water-soluble compounds.
- It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules.
- The oral drug delivery of hydrophobic drugs can be made possible by SEDDS.
- The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract.
- A potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol).

3. Advantages (2-3,11-13)

1. Enhanced oral bioavailability enabling reduction in dose.
2. More consistent temporal profiles of drug absorption.
3. Selective targeting of drug(s) toward specific absorption window in GIT.
4. Protection of drug(s) from the gut environment.
5. Control of delivery profiles.
6. Reduced variability including food effects.
7. Protection of sensitive drug substances.
8. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.
9. Quick onset of action.
10. Liquid as well as solid dosage forms.
11. Ease of manufacture and Scale up.
12. High drug payloads.

4. Disadvantages (8,12-13)

- Since these formulations depend on digestion prior to release of the drug, traditional in vitro dissolution methods do not work, for SEDDS.
- In vitro - in vivo correlations are responsible for further development, therefore development of different prototype lipid based formulations and there in vivo testing in a suitable animal model are necessary.
- High concentration of surfactants in formulation (approximately 30-60%) which causes irritation in GIT.

5. Mechanism of self-emulsification

When the energy required for increasing the surface area of dispersion is less than the change in entropy required for dispersion, self emulsion takes place. Moreover, the free energy of traditional emulsion formation and the energy required for increasing surface area are directly related as shown below

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

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets having radius, r and s is the interfacial energy. The above equation shows that spontaneous formation of interface between oil and aqueous phase is thermodynamically stable.

6. Mechanism of absorption of SEDDS ⁽¹⁴⁾

Lipids may enhance bioavailability via a number of potential mechanisms, including:

1. Alteration (reduction) in gastric transit.
2. Increase in effective luminal drug solubility.
3. Stimulation of intestinal lymphatic transport.

Changes in the biochemical barrier function of the GI tract.

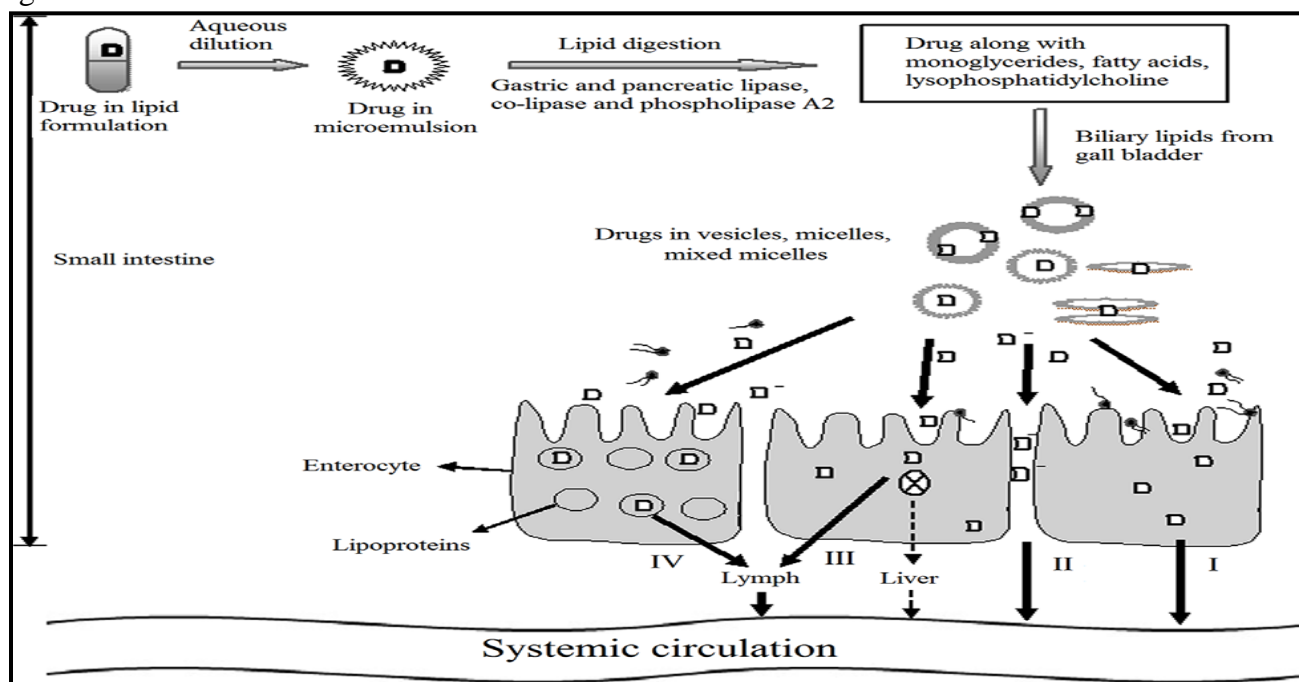


Figure 1: Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations

7. Composition of SEDDS

The process of self-emulsification depends on.

- The nature of the oil-surfactant pair.
- The surfactant concentration.
- The temperature at which self-emulsification occurs.

The components used in the formulation of SEDDS are given below.

I. Drug ⁽¹⁵⁻¹⁷⁾

According to Biopharmaceutical Classification System (BCS), drugs are classified as below,

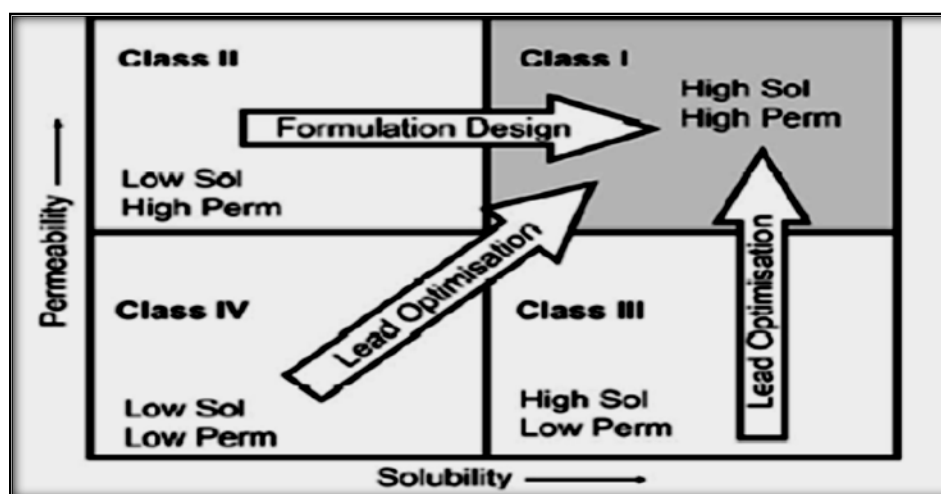


Figure 2: A typical representation of biopharmaceutical classification system

Generally, SEDDS are prepared for drugs possessing poor water-solubility. Lipid based formulations offer a potential platform for improving oral bioavailability of drugs especially those belonging to BCS class II and IV. SEDDS usually provide advantage of increased drug loading capacity when compared with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition co-efficient.

Examples. Ketoconazole, Smvastatin, Atorvastatin calcium, Amphotericin B.

II. Oils/Lipids ^(8-9,18)

Oil is an important component in the formulation of SEDDS. It is used as a carrier to dissolve the lipophilic drug. Naturally-derived oils are not frequently used as the oil fraction in SEDDS due to their poor ability to dissolve a large amount of lipophilic drug. Thus, synthetic or chemically modified oils, such as hydrolyzed vegetable oils are widely used in SEDDS. Besides having better drug solubility properties, chemically modified oils also have better ability to facilitate self-emulsification because they possess surfactant properties of their own. Medium chain triglycerides were frequently used in earlier work to formulate SEDDS because of their higher fluidity, better solubility properties and self-emulsification ability. However, they have become less attractive when novel semi-synthetic oils with amphiphilic properties were introduced, such as the polyglycolized glycerides with varying fatty acid and polyethylene glycol chain lengths. A study investigated the self-emulsification properties of six different types of polyglycolized glycerides, it was observed that C8/C10 polyglycolized glycerides (Labrasol) with the highest HLB value of 14 displayed the most satisfactory self emulsification properties.

Examples. Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Sesame oil, Peanut oil, Labrafac, Labrafil, Castor oil.

III. Surfactant ^(8-9,18)

Surfactants or surface-active agents are amphiphilic molecules and consist of both hydrophilic and lipophilic parts. They are used to facilitate the self emulsification process of the SEDDS, which in turn help to improve or increase the bioavailability of poorly absorbable drugs. The mechanisms involved are complex and were described as diffusion and stranding. Surfactants are classified according to their hydrophilic- lipophilic balance (HLB) values. This HLB value indicates the hydrophilicity of surfactants wherein surfactants which

are more hydrophilic possess higher HLB values. The o/w emulsions can be formed using surfactants which have HLB values in the range of approximately 8-18. It was reported that surfactants with high HLB values will provide rapid emulsification, with excellent spreading properties and rapid cloud formation, leading to the formation of very fine o/w droplets. Selection of the type of surfactant to be used in the formulation of SEDDS will depend on factors such as its emulsification performance, safety as well as the stability of the emulsion formed upon contact with aqueous medium. Naturally derived surfactants are safe to consume but they display limited self emulsification capacity. As for synthetic surfactants, non-ionic surfactants are widely recommended as compared to ionic surfactants because the former are less toxic. To form stable SEDDS, the concentration of surfactants to be used was suggested to be within the range of 30% to 60% (w/w). The amount of surfactants to be used is critical as too large an amount may cause irritation of the gastrointestinal tract while insufficient amount of surfactants used may compromise the self emulsification ability of SEDDS. Surfactants commonly used in SEDDS are emulsifiers which include solid or liquid ethoxylated polyglycolized glycerides and polyoxy ethylene 20 oleate (polysorbate 80). The most efficient SEDDS could be formulated using surfactants with predominantly unsaturated acyl chains. Amongst these, the most efficient were oleates with HLB value of approximately 11.

Examples. Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Labrasol Polyoxy 40- hydrogenated castor oil (Cremophor RH40), D-alpha Tocopheryl polyethylene glycol 1000 succinate.

IV. Co-Surfactant/ Co-Solvents (8-9,18)

Co-solvents, like ethanol, propylene glycol and PEG are also commonly required to enable the dissolution of large quantity of hydrophilic surfactant(s) in SEDDS. The lipid mixtures with higher surfactant/oil and/or co-surfactant/oil ratios lead invariably to the formation of SMEDDS. Mostly however, the co-solvents have a serious limitation of getting evaporated from the shells of sealed gelatin capsules, leading eventually to the precipitation of drug inside the shell. Newer co-solvents like Transcutol™ and Glycofurol™ have several stellar advantages over the traditional ones, including better stability and less volatility.

Various SEDDS formulations in commercial circulation along with their excipient composition, drug solubility, final dosage form (s) and storage recommendations. Drugs of choice in such marketed delivery systems have been the poorly soluble drugs including antiretrovirals like lopinavir, saquinavir, ritonavir, tipranavir and amprenavir, immunosuppressants like cyclosporine A, NSAIDs like ibuprofen and indomethacin, hypolipidemic agents like fenofibrate, and flavonoids like isotretinoin.

Examples. Span 20, Span 80, Capryol 90, Capmul, Ethanol, Polyethylene glycol, Polyethylene Glycol.

8. Construction of ternary phase diagram (19-20)

The methods are used to plot Ternary phase diagrams are namely Dilution method and Water Titration method

1. Dilution Method

Ternary mixtures with varying compositions of surfactant, co-surfactant and oil will be equipped. The surfactant concentration will diverge from 30 to 75% (w/w), oil concentration will diverge from 25 to 75% and co-surfactant concentration will diverge from 0 to 30% (w/w). For any mixture, the total of surfactant, co-surfactant and oil concentrations always added to 100%. For example, in the experiment, first mixture consisted of 75% of surfactant, 25% of the oily phase and 0% of co-surfactant. Further, the co-surfactant was increased by 5% for each composition, oily phase concentration will keep constant and the surfactant concentration will adjust to make a total of 100%. The percentage of surfactant, co-surfactant and oil used herein will decide on the basis of the requirements.

2. Water Titration Method

The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. In this work, phase diagrams are referred to as

“pseudo-ternary” phase diagrams as the surfactant phase was a mixture of surfactant and co-surfactant. Oil phase, Surfactant and the co-surfactant (surfactant: co-surfactant ratio) will be prepared in different ratios and weighed in the same screw-cap glass tubes and were vortexed. The mixture was titrated with water and visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the microemulsion region. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SMEDDS.

9. Solidification techniques ⁽²¹⁻²³⁾

a. Spray drying

In this technique, formulation preparation involves by mixing lipids, surfactants, drug, solid carriers and solubilization of mixtures before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The volatile phase (eg. The water contained in an emulsion) evaporates as the droplets introduced in adrying chamber, forming dry particles under controlled temperature and airflow conditions. A variety of solid carriers have been used for preparation of S-SMEDDS eg. Dextran 40 (water soluble solid carrier, Aerosil 200 as nonporous and hydrophilic solid carrier.)

Critical parameters of spray drying system includes

- Inlet temperature of air
- Outlet temperature of air
- Viscosity
- Solid content
- Surface tension
- Feed temperature
- Volatility of solvent
- Nozzle material

Advantages

- Able to operate in applications that ranges from aseptic pharmaceutical processing to ceramic powder production
- Process is very rapid
- Available in wide designs to meet various product specifications
- It can be used with both heat-resistant and heat sensitive products
- Offers high precision control over particle size, bulk density, degree of crystallinity, organic volatile impurities, and residual solvents

Disadvantages

- The equipment is very bulky and with the ancillary equipment it is costly

- The overall thermal efficiency is low, as large volumes of heated air through the chamber without containing a single particle, thus not contributing directly to drying.

a. Adsorption to solid carriers

Free flowing powders may be obtained from liquid self micro-emulsifying formulation by adsorption to solid carriers. The process involves addition of liquid formulations onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or may be formulated as tablet. Solid carriers that can be used are eg. Neusilin US2, Avicel PH 101, Spray dried lactose.

Advantage

- The most important advantage of using this technique is good content uniformity.

b. Capsule filling with liquid and semisolid self-emulsifying formulation

Capsule filling is the most economical and common technique for encapsulation of liquid or semisolid self-emulsifying formulations for oral route. For semisolid preparations it is a four steps process involves

1. Heating semisolid excipients to 20° C above its melting point
2. Incorporation of active substances
3. Capsule filling with molten temperature
4. Cooling to room temperature. For liquid formulations process involves, filling of liquid formulation into capsules followed by sealing of body and cap of the capsule, either by microscopy sealing.

Advantage

- Simplicity of the process
- Suitable for low-dose and highly potent drugs
- High drug loading potential

c. Melt extrusion/extrusion spheronization

Melt extrusion is a solvent free process. Extrusion is process of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow and pressure conditions. The size of extruder aperture will determine the approximate size of resulting spheroids.

The extrusion spheronization process involves the following steps:

1. Dry mixing of active ingredient and excipients to form a homogeneous powder and then forming a wet mass with help of a binder.
2. Extrusion into a spaghetti-like extrudate.
3. Spheronization from the extrudate into spheroids of uniform size.
4. Dry sifting to achieve the desired size distribution and coating

Advantage

- High drug loading (60%)
- Good content uniformity.
- Short processing time and simple equipment

d. Dry emulsions

Dry emulsions are powders from which emulsions spontaneously occurs in vivo or when exposed to an aqueous solution. These dry emulsions can be further used for preparation of tablets or capsules. Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextran etc) in the aqueous phase by rotary evaporation, freeze-drying or spray drying.

e. Supercritical fluid based technique

Lipids can be used in supercritical fluid based methods either to coat the drug particle or produce a solid dispersion. For environmental reasons, generally the supercritical fluid of choice is supercritical carbon dioxide.

f. Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have submicron particle size of about 50-1000nm, they are composed of physiologically tolerated lipid components. SLN are produced by high pressure homogenization of solid matrix and drug with an aqueous solution of glyceryldibehenate as solid lipid matrix and poloxamers 188 and polysorbates 80 as surfactant. They have generally been employed in controlled- release applications in oral, intravenous and topical routes.

g. Cryogenic grinding

This method is mostly used for formulations containing Gelucire 44/14 as a self emulsifying excipient. Gelcire has low melting point, hence it has to be melted first and then mixed with drug as a result only semi-solid dosage forms could be produced. Hence cryogenic grinding process can be employed to form solid dosage forms like tablets, pellets etc. Cryogenic grinding is process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues) and for unstable compounds (vitamins, volatile substances).

10. Evaluation

a. Flow property (Micromeritics)

The prepared SEDDS can be evaluated for micromeritics properties such as angle of repose, bulk density, tapped density, compressibility index, hausner ratio etc.

b. Drug excipient compatibility studies

This study is important in case of solid self emulsifying drug delivery systems, since in these formulations the drug is mixed with excipients like oils, surfactants, co-surfactants etc, It is essential to know that on addition of these excipients the drug properties are unaltered. The study is usually carried out by taking FTIR spectra of pure drug, physical mixture of drug and oily excipients and solid SEDDS using FTIR spectrophotometer with diffuse reflectance principle. The resultant spectra are then scanned for any spectral changes.

c. Morphological evaluation

Scanning electron microscopy (SEM)

The surface morphology of solid SEDDS can be determined using analytical electron microscope. In this method sample was sprinkled on a double adhesive tape stuck on aluminium stubs. The stubs were then coated with platinum to thickness of above 10° A under an argon atmosphere, under high pressure vacuum and then sample coated stubs were placed in scanning electron microscope chamber.

d. Effect of solidification on globule size

1. Zeta potential

Droplet size of SEDDS can be determined by Zetasizer Nano ZS (Malvern instruments UK) with dynamic light scattering particle size analyzer. All studied are to be repeated three times and values of Z-average diameter are to be used. The Z-average diameter also referred to as harmonic intensity- weighed hydrodynamic diameter, of emulsions can be derived from cumulated analysis by Automatic software.

2. Droplet size measurement

The mean droplet size of emulsion globules can be determined using photon correlation spectroscopy which analyses the light scattering due to Brownian motion of the particles.

3. Transmission electron microscopy (TEM)

Examining the surface of polymeric drug delivery system can provide vital information on porosity and microstructure of the system. So the most common technique to study the surface properties of system is TEM. By comparing TEM results of pure drug and drug encapsulated as SEDDS, We can confirm that there has been no changes in properties of drug on conversion to SEDDS.

e. Solid-state characterization of Solid SEDDS

Differential Scanning Colorimetry (DSC) and X-ray diffraction studies (XRD)

DSC and XRD are carried out to confirm that the drug presented in formulation is in amorphous state. This helps us to confirm that the molecular structure of the drug is intact in formulation.

f. Dissolution studies

In-vitro drug release studies of SEDDS can be carried out by dialysis method, dissolution apparatus II and diffusion cell.

g. Stability studies

For thermodynamic stability studies three main steps can be performed

1. Heating cooling cycle

Six cycles between refrigerates temperature and 45°C with storage at each temperature of not less than 48 hr studied, those formulations which are stable at these temperatures are subjected to centrifugation tests.

2. Centrifugation

Passed formulations are centrifuged between 21°C and 25°C with storage at each temperature not less than 48 hr is done at 3500 rpm for 30 minutes

3. Freeze thaw cycle

Those formulations which passed this test showed good stability.

11. Applications ⁽²⁴⁻²⁷⁾

1. Improvement in Solubility and Bioavailability

If drug is formulated in SEDDS, SMEDDS then it increases the solubility because it circumvents the dissolution step in case of Class II and class IV drug owing to their frequently high content oil, as well as of surfactant, SMEDDS are usually efficient solubilizers of substances of a wide range of lipophilicity.

2. Protection against Biodegradation

The ability of self-emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, hydrolytic degradation, or enzymatic degradation etc.

12. Examples of marketed SEDDS formulations ⁽⁴⁾

Sr. No	Drug Name	Compound	Dosage form	Company	Indication
1.	Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune Suppressant
2.	Norvir®	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
3.	Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
4.	Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
5.	Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
6.	Lipirex®	Fenofibrate	Hard gelatin Capsule	Genus	Antihyperlipoproteinemic
7.	Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immune suppressant
8.	Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
9.	Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium Regulator
10.	Gengraf®	Cyclosporine A/III	Hard gelatin Capsule	Abbott Laboratories	Immune suppressant

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