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A SELF-MICROEMULSIFYING DRUG DILIVERY SYSTEM (SMEDDS)

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Self-micro emulsifying drug delivery systems (SMEDDSs), Lipophillic compound, Droplet Size, Oral Bioavailability

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ABSTRACT

The oral delivery of drugs is considered by decision-makers in the pharmaceutical industry to be the most appealing route of administration. 'Lipid' formulations for oral administration of drugs generally consist of a drug dissolved in a blend of two or more excipients, which may be triglyceride oils, partial glycerides, surfactants or co-surfactants. 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. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion. This objective can be achieved by formulation of the drug in a self-micro emulsifying system or alternatively by taking advantage of the natural process of triglyceride digestion. SMEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SMEDDS depends on many formulation−related parameters, such as surfactant concentracon, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case.

INTRODUCTION

The oral delivery of drugs is considered by decision-makers in the pharmaceutical industry to be the most appealing route of administration. This belief has led to the identification of many very successful drugs, but also to the downfall of some promising therapeutics that failed to meet criteria required for sufficient oral bioavailability. In modern drug discovery techniques, there has been a consistent increase in the number of poor water soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophillic and exhibit poor water solubility. A self-micro emulsifying drug delivery system (SMEDDS) is a drug delivery system that uses a microemulsion achieved by chemical rather than mechanical means. That is, by an intrinsic property of the drug formulation, rather than by special mixing and handling. Actual applications of Self-microemulsifying drug delivery system' (SMEDDS) remain rare. The first drug marketed as a SMEDDS was cyclosporine, and it had significantly improved bioavailability compared with the conventional solution various techniques are use for improve the bioavailability of those drugs like salt formation, pH change, β-cyclodextrin complex, micro emulsion etc. Self-micro emulsifying drug delivery (SMEDDS) is the one of the method for the improvement of oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant (sometimes with added co surfactant) that form emulsion on mixing with water with little or no energy input. SMEDDS (or self-emulsifying oil formulations) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsions. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm. SMEDDS are physically stable formulations that are easy to manufacture and improve the dissolution of the drug due to increased surface area on dispersion. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles SMEDDS generally contain relatively high concentrations of surfactant (typically 40-60% w/w), and regularly contain hydrophilic co solvents (e.g. propylene glycol, polyethylene glycols) Therefore, they are not dependent on bile secretion for absorption SMEDDS can be

formulated with little energy input and shelf life is longer than conventional emulsion, therefore SMEDDS can be efficient vehicle for class II to IV molecules of the bio pharmaceutical classification system (BCS) drugs. The lipophilic (poorly water soluble) drugs such as Nifedipine, Griseofulvin, Cyclosporin, Digoxin, Itraconazole Carbamazepine, Piroxicam, Fluconazole, Indomethacin, Steroids, Ibuprofen, Diazepam, Finasteroids, Difunisal, etc. are formulated in SMEDDS to improve efficacy and safety. Enhanced oral bioavailability enabling reduction in dose.

Advantages of these systems include

1. Enhanced oral bioavailability enabling reduction in dose e.g. Ketoprofen
2. More consistent temporal profiles of drug absorption e.g. Ontazolast
3. Selective targeting of drug(s) toward specific absorption window in GIT
4. Protection of drug(s) from the hostile environment in gut e.g. Acetylsalicylic acid
5. Control of delivery profiles e.g. Paclitaxel
6. Reduced variability including food effects e.g.Cyclosporine
7. Protective of sensitive drug substances
8. High drug payloads
9. Liquid or solid dosage forms e.g. Progesterone
10. Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved

Disadvantages of these systems include

1. Lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.

Physicochemical properties for the selection of drug

Poorly water soluble drugs are a broad class of drugs that differ significantly in physicochemical properties, so it would be useful if there were practical guidelines to help identify the most appropriate formulation for specific drugs. Lipophilic drugs, such as cinnarizine with log P values greater than 5, are good candidate for SMEDDS.

Mechanism of self-emulsification

The mechanism by which self-emulsification occurs is not yet well understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion.

The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus the free energy of the system. The conventional emulsifying agent stabilizes emulsion resulting from aqueous dilution by forming a monolayer around the emulsion droplets, reducing the interfacial energy and forming a barrier to coalescence. On the other hand, emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion is either low and positive or negative. It is necessary for the interfacial structure to show no resistance against surface shearing in order for emulsification to take place. The ease of emulsification was suggested to be related to the ease of water penetration into the various LC or gel phases formed on the surface of the droplets. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture. This is followed by the solubilization of water within the oil phases as a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interphase.Further aqueous penetration will loaded to the formation of the dispersed LC phase In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruptions and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, SEDDS become very stable coalescence. Moreover, the presence of the drug compound may alter the emulsion characteristics, probably by interacting with the LC phase.

Improvement of oral absorption by SMEDDS

The release of the drug compound from SMEDDS takes place upon its partitioning into the intestinal fluids during droplet transport and disintegration along the GI tract. It was proposed that two main factors, small particle size and polarity of the resulting oil droplets determine the efficient release of the drug compound from SMEDDS. In o/w micro emulsions, however, the impact of the polarity of the oil droplets is not very significant because the drug compound reaches the capillaries incorporated within the oil droplets. The oral bioavailability of hydrophobic drugs formulated in o/w emulsions indicated better absorption profiles but, the use of these systems is limited due to their poor physical stability and the large volumes needed. Thus, SMEDDS may be a promising alternative to orally administered emulsions because of their relatively high physical stability and ability to be delivered in standard soft

gelatin capsules. Greater AUC values in addition to higher Cmax and Cmin values were reported for patients given the SMEDDS as compared to the ones given the elixir. If dug is formulated in SMEDDS, then it increases the solubility because it circumvents the dissolution step in case of class ii drug (low solubility/high permeability).in SMEDDS, the lipids matrix interacts readily with water, forming a fine particulate oil-in-water emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption, therefore increase in AUC I.e. bioavailability and Cmax is observed with many drugs when presented in SMEDDS

Incorporation of Drug into SMEDDS

The efficiency of drug incorporation into a SMEDDS is generally specific to each case depending on the physicochemical compatibility of the drug/system. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The addition of solvents including ethanol, PG and PEG, may also contribute to the improvement of drug solubility in the lipid vehicle. In most cases, there is an interference of the drug with the self emulsification process up to a certain extent leading to a change in the optimal oil/surfactant ratio. The efficiency of a SMEDDS can be altered either by halting charge movement through the system by direct complexation of the drug compound with some of the components in the mixture through its interaction with the LC phase, or by penetration into the surfactant interfacial monolayer. The interference of the drug compound with the self-emulsification process may result in a change in droplet size distribution that can vary as a function of drug concentration. It should be pointed out that emulsions with smaller oil droplets in more complex formulations are more prone to changes caused by addition of the drug compound.

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, enzymatic degradation or hydrolytic degradation etc. For water-soluble peptides typical bioavailability enhancements range from twenty to more than one hundred times. In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract

Construction of phase-diagram

The relationship between the phase behavior of a mixture and its composition can be explained with the aid of a phase diagram. Compositional variables can also be studied as a function of temperature and, pressure, although with the exception of micro emulsions prepared using supercritical or near critical solvents. The phase behavior of simple microemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component. The Co-surfactant is also amphiphilic with an affinity for both the oil and aqueous phases and partitions to an appreciable extent into the surfactant interfacial monolayerpresent at the oil-water interface. In the case where four or more components are investigated, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / Co-surfactant, water /drug or oil / drug. The number of different phases present for a particular mixture can be visually assessed. A highly schematic (pseudo) ternary phase diagram illustrating these features is presented in figure It should be noted that not every combination of components produce micro emulsions over the whole range of possible compositions, in some instances the extent of microemulsion formation may be very limited. Constructing phase diagrams is time consuming, particularly when the aim is to accurately delineate a phase boundary, as the time taken for the system to equilibrate can be greatly increased as the phase boundary is approached. Heat and sonication are often used, particularly with systems containing nonionic surfactants, to speed up the process.

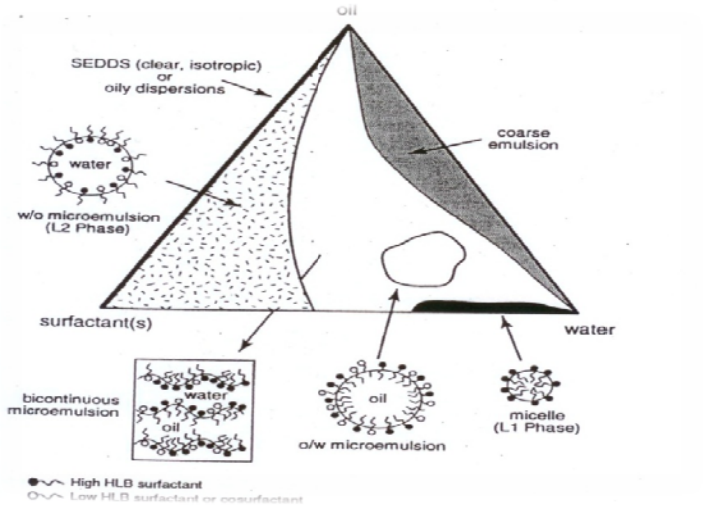

Figure 1 Phase Diagram.

Care must be taken to ensure not only that the temperature is precisely and accurately controlled, but also that observations are not made on metastable system. These multiphase systems can be conveniently described using the Winsor classification.

Formulation of SMEDDS

SMEDDS formulation containing following components

1) Oil phase

2) Primary surfactant

3) Secondary surfactant (co-surfactant)

4) Co-Solvent

These isotropic systems are usually easier to formulate than ordinary emulsion. The type of associated structure formed from these components at particular temperature depends not only on the chemical nature of each component but also on their relative concentration.

1) Oil phase

In order to make SMEDDS systems pharmaceutically acceptable, it is necessary to prepare such systems by using nontoxic and safe components. The formation of bicontinuous micro emulsions with mineral oils has been intensively investigated in model experiments and for application in industrial products. Because Oil from natural sources and their derivatives, e.g. triglycerides and fatty acid methyl esters are easily degraded by microorganism and considered to be harmless to the environment.

Example: Castor oil, Sunflower oil, Olive oil, Seseam oil, Hydrogenated specialty oils

2) Surfactant

A surfactant molecule is formed by two parts with different affinities for the solvents. One of them has affinity for water (polar solvents) and the other has for oil (non-polar solvents). A little quantity of surfactant molecules rests upon the water-air interface and decreases the water surface tension value (the force per unit area needed to make available surface). That is why the surfactant name: “surface active agent”. Surfactants used to stabilize microemulsion system may be non-ionic, zwitterionic, cationic, or anionic surfactants. Combinations of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region .For example Propylene glycol monocaprylate (Capryol 90) ,Polyglycolized glycerides (Gelucire 44/14, 50/13),Polyoxyl-40 hydrogenated castor oil (Cremophor RH 40),Oleoyl macrogol-8 glycerides (Labrafil M 1944 CS),Linoleoyl macrogolglycerides (Labrafil M 2125 CS),PEG-8 caprylic/capric glycerides

(Labrasol),Polyoxyethylene glyceryl trioleate (Tagat TO), Polyoxyethylene(20)sorbitan monooleate (Tween 80)

3) Co-surfactant

The role of a Co-surfactant is that, to increase the fluidity of the interface, destroy liquid crystalline or gel structure which would prevent the formation of microemulsion, and also adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic. Most single-chain surfactants do not lower the oil-water interfacial tension sufficiently to form micro emulsions nor are they of the correct molecular structure. Further under certain condition, a combination of oil, water and surfactant will result in a phase where there are orderly planes of oil and water separated by monomolecular layer of surfactant. This type of phase is known as liquid crystal (lamellar phase). Liquid crystals formation can be detected by large increase in viscosity. Co-surfactant is added to further lower the interfacial tension between the oil and water phase, fluidize the hydrocarbon region of the interfacial-film, and to influence the film curvature. Abe et al (1986) concludes that the role of co-surfactant is to destroy liquid crystalline or gel structures that form in place of a microemulsion phase. Typical co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids and also conclude that surfactant free microemulsion in system cannot be made except at high temperature.

4) Co-solvents

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suitable for

oral delivery and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems. On the other hand, alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SEDDS leading to drug precipitation. Thus, alcohol−free formulations have been designed, but their lipophilic drug dissolution ability may be limited.

Evaluation of SMEDDS

Differential scanning calorimetry Differential scanning calorimetry for SMEDDS can be determined using DSC 60. Liquid sample and Solid sample should be placed in the aluminum pan and result can be recorded. Any type of chemical interaction should be determined using DSC.

Thermodynamic stability studies

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 excipients matrix. In addition, poor formulation physical stability can lead to phase separation of the excipients, 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 3500 rpm for 30 min. Those formulations that does not show any phase separations 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.

Fourier transform-infrared spectroscopy

Fourier transform-infrared for SMEDDS can be determined using FT-IR. Liquid sample should be placed in the liquid sample holder and result can be recorded.

Macroscopic evaluation

Macroscopic analysis was carried out in order to observe the homogeneity of microemulsion formulations. Any change in color and transparency or phase separation occurred during normal storage condition (37±2ºC) was observed in optimized microemulsion formulation.

Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion 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 a formulation 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 2 min).

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.

Determination of Self emulsification time

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus 2. 300 mg of each formulation added drop wise to 500ml purified water at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.

Turbidimetric Evaluation

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 turbidimeter. 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).

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 a high viscosity then it is w/o type of the system.

Solubility studies

Unknown amount of selected vehicles was added to each cap vial containing an excess of drug. After sealing, the mixture was heated at 40ºC in a water bath to facilitate the solubilization. Mixing of the systems was performed using a vortex mixer. Formed suspensions were then shaken with a shaker at 25ºC for 48 hours. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 minutes, and excess insoluble LOV was discarded by filtration using a membrane filter (0.45 µm, 13 mm, Whatman, India).

The concentration of drug was then quantified by U.V.Spectrophotometer.

Droplet size determination

It is a precise method for evaluation of stability. Size of droplet is measured by photon-correlation spectroscopy (PSC) with Zetasizer. All measurements are carried out at scattering angle of 90° and 25°C temperatures. Prior to measurement, microemulsion is diluted in two-steps with pure water then it is filtered through a 0.22um filter just before it is added to cuvette. In first step it is diluted with equal amount of water. In second step the mixture is further diluted to appropriate concentration for the measurement. That depends on droplet size (Usually diluted 100-200 times).

Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

Factors affecting SMEDDS formulation

1. Drugs which are administered at very high dose are not suitable for SMEDDS, unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SMEDDS.

2. The polarity of lipid phase is one of the factors that govern the release from drug from the microemulsion.HLB, chain length degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase.sang-cheol chi et al.who observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity f the oil phase used. The highest release was obtained with the formulation that had oily phase with highest polarity.

3. The ability of SMEDDS to maintain the drug in solubilized of the drug in oily phase. if the surfactant or co-surfactant is contributing to greater extent for drug solubilization, here could be a risk of precipitation, as dilution of SMEEDS will lead to lowering of solvent capacity of surfactant or co-surfactant.

Recent approaches in SMEDDS

1. Self-microemulsifying drug delivery system (SMEDDS) of simavastin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic

2. Enhanced bioavailability up to 1.88 of silymarin was achieved by SMEDDS.

3. The two novel SMEDDSs containing Labrasol with different dilutions on tight junction were studied and found that Labrasol at a concentration of 0.1 and 1% was shown to increase the permeability of mannitol by 4.6-fold and 33.8-fold, respectively.

Applications of SMEDDS

1. Solubilization in SMEDDS

Due to their frequently high content oil, as well as of surfactant, SMEDDS are usually efficient solubilizers of substances of a wide range of lipophilicity. Thus, the solubilizing capacity of a w/o microemulsion for water soluble drugs is typically higher than that of an o/w microemulsion, while the reverse is true for oil soluble drugs. Furthermore, the solubilization depends on the SMEDDS composition.

2. Sustain release from SMEDDS

Due to the wide range of structures occurring in them, SMEDDS display a rich behavior regarding the release of solubilized material. Thus in. case of O/W microemulsion, hydrophobic drugs solubilized mainly in the oil droplets, experience hindered diffusion and are therefore released rather slowly (depending on the oil/water partitioning of the substance). Water soluble drugs, on the other hand, diffuse essentially without obstruction (depending on the volume fraction of the dispersed phase) and are release fast. For balanced micro emulsions, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinuous nature of microemulsion "structure". Apart from the microemulsion structure, the microemulsion composition is important for the drug release rate.

3. Increase the bioavailability of drug

Many of drugs were lipophilic in nature so, it should be insoluble in water. Lipophilic drug should have low bioavailability. In SMEDDS, drugs should be combining with the oil and make a complex. Oil is easily absorbed from the gut and increase the solubility of drugs. So increase the bioavailability of the drug. Ex. Julianto et al, was increase the 3 fold bioavailability from SEDDS which is composed of the Tween 80 and palm oil.

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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