WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 16, 588-617. Review Article ISSN 2277– 7105

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS: A NOVEL APPROACH TO DELIVER DRUGS

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Article Received on
02 October 2022,
Revised on 23 Oct. 2022,
Accepted on 13 Nov. 2022
DOI: 10.20959/wjpr202216-26243

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ABSTRACT

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. Improving oral bioavailability of low poorly water soluble drugs using self-emulsifying drug delivery systems (SEDDS) possess significant potential. Oral bioavailability of hydrophobic drugs can be improved using SEDDS, and appears most promising. SEDDSs possess unparalleled potential in improving oral bioavailability of poorly water soluble drugs. 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. Ideally the formulation allows the drug to remain in a dissolved state throughout its transit through the gastrointestinal tract. We found that SEDDSs could efficiently improve oral absorption of the sparingly soluble drugs by rapid self-emulsification and, subsequently, dispersion in the absorption sites. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizer within a colloidal dispersion. This objective can be achieved by formulation of the drug in a self-emulsifying system or alternatively by taking advantage of the natural process of triglyceride digestion. In practice 'Lipid' formulations range from pure oils, at one extreme, to blends which contain a substantial proportion of hydrophilic surfactants or cosolvents.

KEYWORDS: Solid carrier, Surfactant, lipid emulsifying delivery, characterization, bioavailability enhancement.

INTRODUCTION

Self emulsifying drug delivery system (SEDDS) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. In recent years, the formulation of poorly soluble compounds has presented interesting challenges for formulation scientists in the pharmaceutical industry. Up-to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. Self emulsifying lipid formulations have improved the bioavailability of poorly water soluble & highly permeable compound. This bioavailability enhancing property has been associated with a number of in vivo properties of lipid formulation including:

• The formation of fine dispersions and micellar suspensions to prevent precipitation and re-crystallization of the drug compound.

• The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to flavor improved drug absorption.

• The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.

• Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SMEDDS requires the use of a co-surfactant to generate a microemulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 mm and the dispersion has a turbid appearance. Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption. SELF-system exists: self emulsifying drug delivery systems (SEDDSs) micro-emulsifying drug delivery systems (SMEDDSs). Both SEDDSs and SMEDDSs have distinct features associated with improved drug delivery properties. SMEDDSs, however, have a smaller lipid droplet size (<200 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs. The choice of whether a SEDDS or a SMEDDS is the preferred formulation option often depends on the

interplay between the intrinsic properties of the drug compound and its solubility and dissolution profile during in vitro screening with a number of excipients.

Table 1: Comparison of the basic SEDDS classes characteristics.

SEDDS	MICRO-SEDDS	NANO-SEDDS
Simple binary systems of APIs and excipients that are capable of self-emulsification when in contact with GIT fluids or system of APIs, surfactant and oil/s.	Systems of APIs, surfactants co-surfactants, oils.	Systems of APIs, surfactants cosurfactants and or co-solvents, oils.
The oil drops of the dispersion can reach dimensions in the range of 200 nm - 5µm. Macroscopically a cloudy dispersion is observed.	The oil drops of the dispersion reach dimensions in range of up to 200 nm Macroscopically a clear to slightly opalescent dispersion is observed	The oil drops of the dispersion reach dimensions in range of up to 100 nm Macroscopically a clear to dispersion is observed.
These systems are not thermodynamically stable when in contact with water or GIT fluids. Formulation and optimization may require phase diagrams construction.	These systems are thermodynamically stable when in contact with water or GIT fluids. Formulation and optimization require phase diagrams construction.	These systems are thermodynamically stable when in contact with water or GIT fluids. No phase separation is observed. Formulation and optimization require phase diagrams construction.

In terms of dosage form, SELFs are principally liquid or semi-solidformulations and, therefore, ideal for soft or hard capsule filling. Currently, drugs that utilize SEDDs are exclusively developed in soft or hard gelatin capsules (Table 2). This is because, until recently, getting a SELF into tablet form was a formulation challenge because of the nature of excipients and formulation techniques. That is not to say that formulating for a solid dosage form that utilizes a SELF is impossible, but the starting point for such a formulation requires the use of semi-solid excipients.

Table 2: Examples of pharmaceutical products formulated as selfemulsifying systems.

Drug Name	Compound	Dosage form	Company
Neoral	Cyclosporin	Soft gelatin capsule	Novartis
Norvir	Ritonavir	Soft gelatin capsule	Abbott Laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffman la Rochi Inc.
Agenerase	Amprenavir	Soft gelatin capsule	GlaxoSmithKline
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi-Aventis
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi-Aventis

Table 3: Advantages and disadvantages of SEDDS.

Advantages	Disadvantages
Fast action APIs dose lowering Bioavailability improvement Simple production Potential for peptide APIs that are not stable in GIT In many cases GIT digesting processes are not affecting these systems High APIs loading capacity	Usually unconventional for API solubilization methods are used. Validation of SEDDS system is needed for industrial scale up. Ascertainment of exact and reproducible IVIV correlation is needed. High risk of chemical type instability is present, surfactants high concentrations can cause f adverse GIT reactions

Novelty Statement

This review on Self Emulsifying Drug Delivery Systems (SEDDS) is written as these drug delivery systems have unparalleled prospect in enhancing bioavailability of low soluble drugs of biopharmaceutical classification. An extensive and updated description of literature reports on different types of self emulsifying formulations, techniques employed, characterization, optimization and application strategies are discussed comprehensively to direct the formulation scientists in formulating a stable, safe and effective self emulsifying formulation. The figures are self designed to prove the concept, mechanism and meaning of SEDDS.

Self Emulsifying Drug Delivery System[1,2,3]

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, solid lipid nanoparticles and liposomes. 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 a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several-microns. "Self micro- emulsifying drug delivery systems" (SMEDDS) indicates the formulations forming transparent micro emulsions with oil droplets ranging between 100 and 250 nm. "Self-nano-emulsifying drug delivery systems" (SNEDDS) is a recent term with the globule size ranges less than 100 nm. SELFs have been transformed into solid dosage forms using this techniques such as melt granulation, where the lipid excipient acts as a binder and solid granules are produced on cooling. Solvents or supercritical fluids can be used with that semisolid excipients, which are solubilized and then the solvent will evaporated to produce a waxy powder. However in many cases, because of the nature of lipid excipients, the SELF system is a liquid-based formulation rather than a semi-solid formulation and, therefore, an

alternative approach are required. This article describes the development and optimization of a solid SELF system to produce a tablet from a liquid SELF. The concept works by the adsorption/absorption of a liquid SELF onto a neutral carrier (i.e., neutral silicate).

Overall surprisingly straightforward, developing this solid dosage form technique has required extensive investigation of critical success parameters including as follows:

•Extensive screening of different neutral carriers to evaluate their ability to adsorb maximum levels of the liquid SELF.

•Maximum loading value of the carrier and effect on tablet compression.

•Absorption onto the carrier and effect on flow ability — an essential feature for tablet compression.

• Evaluation of the integrity of the system with a poorly soluble API to examine the effect of transforming a liquid into a powder on drug solubility and dissolution rate.

Need of SEDDS[2,3,5]

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that predissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, 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). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix.

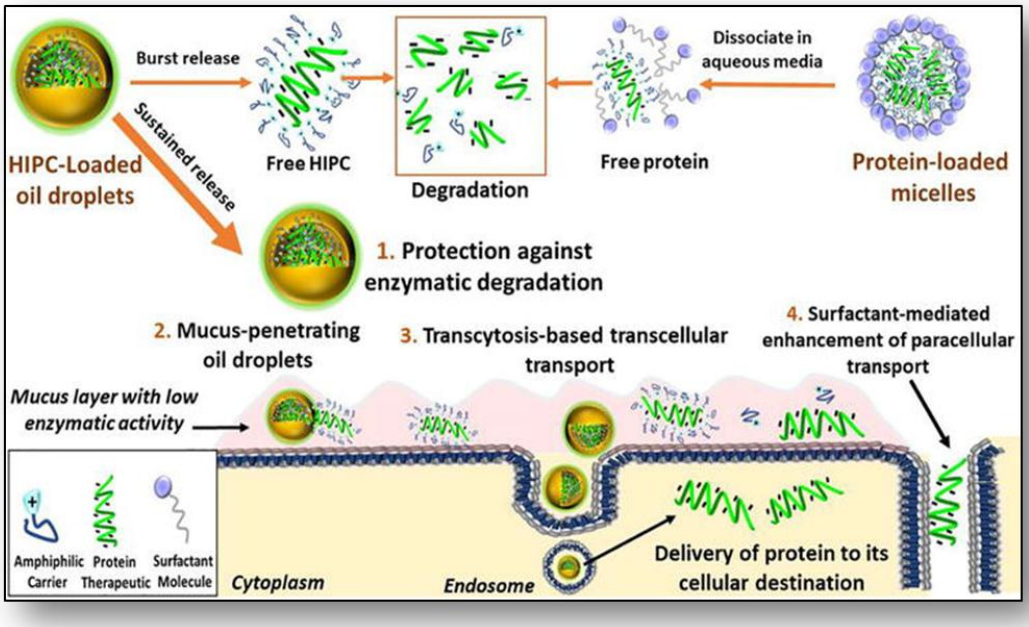


Figure: Self Emulsifying Drug Delivery System.

Limitations of SEDDS[3,4,5]

Chemical instabilities of drug and high surfactant concentrations

- The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT
- Moreover, volatile co-solvent in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drug.

Excipients used in SMEDDS[4,6,7]

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self-micro emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- microemu- lsifying systems.

Oils

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self

emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Furthermore, edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS. This is in accordance with findings of Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT. E.g.: Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Castor oil etc.

Surfactants

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. 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 surfactants. However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule.

The four main groups of surfactants are defined as follows,

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3-) or sulphate (ROSO3-).

Examples: Potassium laurate, sodium lauryl sulphate.

Cationic surfactants: where the hydrophilic group carries a positive charge.

Example: quaternary ammonium halide.

Ampholytic surfactants: (also called zwitter ionic surfactants) contain both a negative and a positive charge.

Example: sulfobetaines.

Nonionic surfactants: where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

Co-solvents[7,8,9]

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components

Co-surfactant

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion. E.g. span, capyrol 90, capmul.

Recent dosage form development in SEDDS

1. Dry emulsions

2. Self- emulsifying capsules
3. Self- emulsifying sustained/controlled-release tablets
4. Self- emulsifying sustained/controlled-release pellets
5. Self emulsifying solid dispersions
6. Self emulsifying beads
7. Self emulsifying Sustained release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories
10. Self emulsifying implants

Mechanism of self emulsification[2,4,6]

Self emulsifying process is related to the free energy, $\Delta G = \Sigma N\pi r2\sigma$ (1) Here, N is the number of droplets with radius r and σ is the interfacial energy. It is apparent from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The systems commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. Mustafa and Groves developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil surfactant system in a water stream, using phosphate nonyl phenoloxylate (PNE) and phosphated fatty alcohol ethoxylate (PFE) in *n*-hexane, and suggested that the emulsification process may be associated with the ease with which water penetrates the oil–water interface, with formation of liquid crystalline phase resulting in swelling at the interface, thereby resulting in greater to relate the phase behavior to the spontaneity of emulsification, with liquid crystals formation, tending to form emulsion more readily, as indicated by the lower equilibration times. Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behavior of the system. For example, if one increases the temperature of the oil in the water system stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification. 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 phases and can be described by

the equation:

$$DG = S\,N_i\,p\,r_i\,2s$$

Where, "DG" =free energy associated with the process (ignoring the free energy of mixing), "N" = number of droplets; "r"= radius of droplets and "S" = interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

Dosage form of SEDDS[4,7,9]

Self-emulsifying capsule

When capsules carrying liquid solution SE preparations are delivered, microemulsion droplets form in the GIT and disperse to reach the area of absorption. If the microemulsion's phase separation is permanent, no increase in medication absorption may be expected. To solve this problem, sodium dodecyl sulfate was added to the SE formulation.

Self-emulsifying sustained/controlled release

The use of surfactants and lipids in the preparation of SE tablets has shown tremendous promise. SE pills are really helpful in preventing negative effects. Incorporating indomethacin into SE tablets, for example, may improve the drug's penetration across the GI mucosal membrane, thus lowering GI bleeding.

Controlled/sustained release self-emulsifying pellets

Pellets can provide variety of advantages over conventional solid dosage forms, including production flexibility, lower intra- and inter-subject fluctuation in plasma profiles, and less GI discomfort without compromising drug absorption. Solid dispersions that self-emulsify: solid dispersions may increase the dissolving rate and bioavailability of drugs that are water insoluble, but they still have manufacturing and stability concerns. Using SE excipients can help you overcome these obstacles.

Semisolid SEDDS

Semisolid SEDDS are synthesized in situ utilizing lipidic ingredients comparable to those used in liquid SEDDS, but with a higher melting point than room temperature. These

formulations are unique in that they do not contain cosurfactants, but only comprise lipids and surfactants. For the manufacturing of semisolid SEDDS lauryl macrogel-glycerides including gelucire 44/14, gelucire 50/13, derivatives of polyoxyethylene hydrogenated castor oil including cetyl alcohol derivative, Nikkol HCO50, and polyoxyethylene polyoxypropylene block polymer are the most frequently used surfactants and lipids. Such preparations have a greater viscosity than the comparable liquid SEDDS, resulting in increased medication stability and mobility during handling. However, because of lipids with high melting point, these formulations generally show poor emulsification efficiency in vivo, likely contributing to uneven drug absorption patterns. Several cases on the semisolid SEDDS, such as carvedilol 93 and atorvastatin 94, have been for increasing their oral bioavailability. It was also revealed that semisolid SE formulations produced with glyceryl mono/dicaprylate, diethylene glycol monoethyl ether, propylene glycol monocaprylate, and gelucire 44/14, have improved physicochemical characteristics, due to the supersaturation which prevents drug precipitation, these formulations showed significant levels of resistance to dilution and stability.

Self-emulsifying hybrid microparticles[8,9,10]

These are colloidal solid SE systems made up of a mix of medium chain triglycerides and silica microparticles with particle sizes ranging from 3 to 100 nm. The liquid oily formulations are encapsulated in microparticles in this method, which may then be given in hard gelatin capsules or compacted into tablets. Spray drying of lipidic emulsions having positively charged lipophilic surfactants and colloidal silica particles in aqueous phase produces microparticles. Under in vivo circumstances, high drug loading, higher drug absorption due to the presence of cationic charge on the surface, and improved drug stability are all benefits of such systems. Drugs like celecoxib, telmisartan, and theophylline for which silica-based lipidic SE micro- particles have been tested to see whether they might improve bioavailability. In beagle dogs, formulations of SE lipid-hybrid microparticles of celecoxib containing Capmul MCM and Aerosil 380 showed a more than twofold increase in fed state oral bioavailability and a 6.5-fold increase in fasted state oral bioavailability when compared to a conventional lipidic solution, as well as a significant reduction in arthritis-like conditions.

Self-emulsifying nanoparticles

Oily liquid compositions are enclosed in SE nanoparticles. Such formulations are created utilizing a solvent injection process and an appropriate blend of polymers like polylactic acid (PLA), polyglycolic acid (PGA), and polyglycolic acid-coglycolic acid (PLGA). The nano-particles give a regulated drug delivery profile, better stomach fluid stability, and increased oral bioavailability. When these formulations come into touch with GI fluids, they create o/w microemulsions in situ. 5- Fluorouracil and paclitaxel are two medicines that have recently been suggested to be made into SE nanoparticulate systems in order to investigate their oral bio- availability increase. As evidenced by MTT testing, TUNNEL method, and immunehisto-chemical staining, the SE nanoparticles of 5-FU using PLGA/O-carboxymethyl chitosan showed dramatically improved cellular absorption of drug through the intestinal lymphatic routes, decreased cytotoxicity, and noteworthy reduction in gliomas. With the help of chitosan and glyceryl monooleate as emulsion solvent evaporation, SE nanoparticles of paclitaxel were shown to have a fourfold increase in cellular absorption and much decreased cytotoxicity in the MTT experiment.

Self-emulsifying controlled release tablets

Self-emulsifying controlled release tablet (SECRET) is a more recent technical advancement in the S-SEDDS field for producing a controlled drug release profile. SECRET is a patented proprietary platform technology created by AlphaRx Inc. (Markham, Canada), in which tablets are formed with the help of liquid SE formulations by adsorbing onto the surface of rate-controlling polymers like HPMC, HPC, and others. These aids in the long-term release of the medication from the polymer matrix. Including systems have important meritorious features in formulation creation, such as site-specific delivery and improved intestinal wall permeability and solubility to aid medication dispersion in the gastrointestinal tract. The coenzyme Q10 SE controlled release hydrophilic matrices which use Avicel-112 and Kollidon V64 as release controlling polymers, improved drug stability and controlled release properties significantly. The composition of SE tablets of carvedilol includes Aeroperl, MCC, HPMC, that significantly increase in vitro drug absorption in HCT-116 cell lines, perhaps owing to P-gp efflux inhibition. The capacity of solid SMEDDS tablets containing candesartan cilexetil dramatically increases the pace and extent of drug dissolution, that proves the better oral bioavailability. Diclofenac SE pellets produced with natural ingredients like goat fat and Tween 80 similarly showed a prolonged release profile of drug release.

Self-emulsifying controlled release capsules

These are made by coating liquid-filled soft-gelatin capsules with a thin layer of semipermeable polymeric material. The lipidic SE formulations give the necessary therapeutic activity for a prolonged length of time due to their semipermeable character. An inflatable layer can also be added to the semipermeable layer to adjust the rate of medication release from the capsule shell. Cardiovascular medications, antiretrovirals, anticancer treatments, corticosteroids, and immune suppressants such as nimodipine, cyclosporine, ritonavir, dexamethasone, vinblastine, and mepitiostane have all been reported to benefit from this method. The semipermeable coating is made up of cellulose acetate, cellulose acetaldehyde dimethyl acetate, cellulose acylate, and polyurethanes, while the expandable coat on the gelatin shell is made up of Carbopol, sodium carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), HPC, HPMC, and other materials. By converting SE formulations into SSEDDS using solidifying adsorption carriers, efficient delivery of SE formulations may be achieved.

Characterization of SEDDS[3,8,9]

Visual evaluation

Visual observation helps in the assessment of self-emulsification. The existence of a clear, isotropic, transparent solution after water dilution of SEDDS suggests microemulsion production, whereas an opaque, milky white appearance indicates macroemulsion evolution. A lack of precipitation and/ or phase separation suggests that the formulation is stable.

Analysis of droplet size

The size of the droplet is determined by the surfactant's type and concentration. The micro-emulsion generated during dilution of SMEDDS with water has a very narrow droplet size distribution, which is critical for optimal drug release, in vivo absorption, and stability. Droplet size analysis is done using DLS methods.

Zeta potential measurement

The zeta potential reflects the emulsion's stability following dilution. If the zeta potential is larger, the formulation remains stable. When compared to particles with either surface charge, particles with a zwitterion charge exhibit greater biocompatibility and a longer blood residence period.

Emulsification time

The amount of time it takes to emulsify a formulation is determined by the oil/surfactant and oil phase ratio. This is determined using a basket dissolution equipment, which observes the development of a clear solution under agitation following drop wise formulation addition to a water-filled basket.

Cloud point determination

The cloud point of a homogeneous solution is the temperature at which it drops its transparency. Above the cloud point, the surfactant normally loses its ability to form micelles. It is determined by progressively raising the temperature of the formulation and spectrophotometrically detecting the turbidity. The cloud point of the surfactant is the temperature at which the percentage transm-ittance decreases. To maintain self-emulsification, formulations should have a cloud point higher than 37.5.

Viscosity measurements

A rheometer, Brookfield viscometer having a cone and plate with rotating spindle is used to assess the viscosity of diluted SMEDDS formulations that are microemulsions.

Liquefaction time

This analysis is performed to determine how long it takes for S-SEDDS to melt in a simulated GI environment without moving. The dosage form, which is threaded to the bulb of a thermometer, is covered in a transparent polyethylene film. The thermometer should then be placed in a round bottom flask with 250 mL of simulated stomach juice without pepsin and held at 37_C. After that, the time it takes for the liquefaction to happen is noted.

Nuclear magnetic resonance (NMR) studies

These methods are utilized to investigate the dynamics andstructure of microemulsions. Self-diffusion assessments utilizing several tracer approaches, most often radio labeling, provide information on the components' mobility and microenvironment. The magnetic gradient on the samples is used in the Fourier transform pulsed-gradient spin-echo (FTPGSE) methods, which enables for the simultaneous and quick measurement of the self-diffusion coefficients of several components. The Stokes–Einstein equation may be used to compute the self-diffusion coefficient. D ¼ KT=6pgr where T is the absolute temperature, g is the viscosity, K is the Boltzmann constant, and r is the radius of droplet.

Scattering techniques

For the investigation of microemulsion, scattering approaches have been used. Small-angle X-ray scattering (SAXS), DLS, PCS, and small angle neutron scattering (SANS) are some of the techniques used. Structural data provided by SAXS on macromolecules vary in size from 5 to 25 nm, as well as repetition distances in partly ordered systems up to 150nm in partially ordered systems. It is used to determine the structure of particle systems at nanoscale or at microscale, including size of particles, dispersion, morphologies, and the surface-to-volume ratio, among other things. To use SANA is to find droplet shape and size. Micelles, oil-swollen micelles, and mixed micelles, are described by the term 'droplet'. The interference effect of wavelets dispersed from diverse materials in a sample is used in small-angle neutron scattering investigations. The dilution of the sample necessary to reduce interparticle interactions is a fundamental disadvantage of these approaches. The structure and content of the pseudo ternary phases can be altered by this dilution. Despite this, effective determination has been achieved utilizing a dilution procedure that preserves the droplet identity. Incorporating denudated molecules or prorogated, SANS allows for selective increase of the scattering ability of distinct microemulsion pseudo phases. The variation in the frequency of the scattering by the droplets due to Brownian motion is studied using DLS and PCS.

Test of thermodynamic stability

Physical stability is essential for a formulation's performance, as precipitation of the chemical in the excipient matrix might have a detrimental influence. Excipient step separation can occur as a result of inadequate formulation physical stability, lowering bioavailability, and decreasing therapeutic effectiveness. Brittleness, softness, and delayed or partial drug release may arise from incompatibilities among the formulation and the gelatin shell of the capsule. The following cycles are used to carry out these investigations.

Turbidimetric test

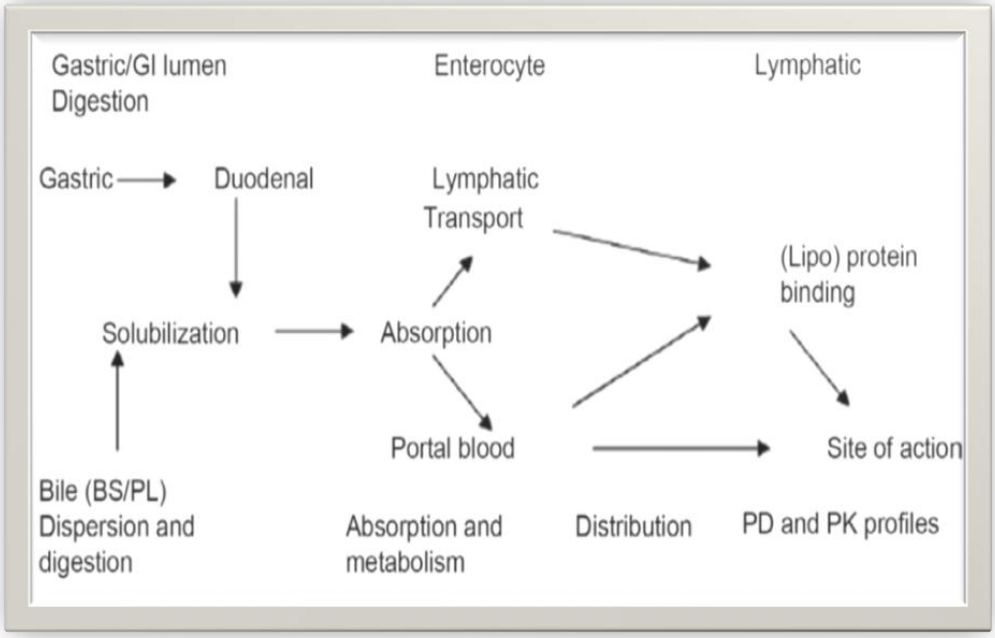
Turbidity is a measurable characteristic that may be used to estimate droplet size and self-emulsification time. After agiven amount of SEDDS is administered to a fixed amount of suitable medium under continual stirring at 50 rpm on a magnetic stirrer at optimal temperature, the turbidity is measured using a turbidity meter. As the time required for complete emulsification is too short, the rate of turbidity shift, or rate of emulsification, cannot be measured. Turbidimetric analysis is used to track the growth of droplets following emulsification.

Determination of self-emulsification time

Using a primitive nephelometer and a rotating paddle to assist emulsification, we investigated the efficiency of emulsification of several formulations of Tween 85 /mediumchain triglyceride systems. This allowed the emulsification period to be measured. Samples were obtained for particle size using photon similarity spectroscopy after emulsification, and self-emulsified and homogenized systems were compared. The self-emulsification process was studied using light microscopy. The process of emulsification was precisely defined as the erosion of a thin cloud of microscopic particles off the surface of big droplets, rather than a steady decrease in droplet scale

Limitations[7,10,11]

The absence of reliable predictive in vitro models for the assessment of SEDDSs and other lipid-based formulations is one of the barriers to their development. Traditional dissolution procedures are ineffective because these formulations may be dependent on gut digestion prior to drug release. An in vitro model of the duodenum's digestion processes has been constructed to imitate this. Before the strength of this in vitro model can be assessed, it must be refined and validated. In addition, because development will be based on in vitro–in vivo correlations, several prototype lipid-based formulations must be produced and evaluated in vivo in an appropriate animal model. Chemical instability of medications and high surfactant concentrations in formulations (about 30–60%) that irritate the GIT are a few other downsides. Furthermore, it is known that volatile cosolvents in traditional self-micro emulsifying formulations diffuse into the shells of soft or hard gelatin capsules, causing lipophilic drugs to precipitate. Due to the dilution impact of the hydrophilic solvent, the drug's precipitation propensity may be increased when diluted. Simultaneously, validating formulations with several components becomes more difficult.



Solubility of active drug in SEDDS[7,12]

The most significant factors for optimizing oral therapeutic effectiveness are pharmaceutical ingredient solubility, dissolution rate, and permeability. SEDDS' dissolution rate is also an essential characteristic since it can alter medication release kinetics and gastrointestinal absorption The water solubility and gastrointestinal permeability are the categories of API as described by the BCS. The dissolution of orally administered drugs must be done in the aqueous environment of the gastrointestinal tract, but they must also have a lipophilic feature to pass through the membrane barriers. The physicochemical compatibility of the medication and the system determines the features of APIs- SEDDS. The oily or surfactant phases are utilized to dissolve the drug of SEDDS. Despite this, the medication can pass through the surfactant interfacial layer. The drug's interaction with the self-emulsification process can also affect API encapsulation efficacy. One of the simplest procedures for determining the major features of the produced nanoemulsion and its continuous phase is the dye solubilization test (DST). While testing, a water-soluble dye was sprinkled onto the surface of the produced emulsion. The quality of the emulsion's internal and external phases can be established by looking at dye dispersion or clump formation. Poor water-soluble drugs pose a significant formulation challenge because of their high hydrophobicity that restricts them to be dissolved in the solvents medium. Hydrophobic drugs are usually dissolved more effectively by synthetic hydrophilic oils and surfactants than by conventional vegetable oils. The incorporation of solvents such as PG, ethanol, and PEG to the lipid vehicle may also help

to increase the solubility of drug. The success of adding a medicament to a SEDDS is highly reliant on the system's or drug's drug/physicochemical capability. The drug interferes with the self-emulsification process to some extent in the majority of cases, resulting in a change in the optimal surfactant to oil ratio. The efficiency of SEDDS can be changed by preventing charge transport across the system through direct complexation of the drug. The drug molecule is with part of the mixture's components via its interaction with the LC phase, or by penetrating the surfactant interfacial monolayer. The impact of the self-emulsification process on the drug may result in a shift in droplet size distribution that varies with the drug's concentration. It is worth noting that in more sophisticated preparations, emulsions with smaller oil droplets are more vulnerable to changes produced by the introduction of therapeutic ingredients. As a result, phase diagram experiments and pre-formulation solubility studies are essential for the development of a suitable SEDDS.

Drug properties suitable for SEDDS

1. Dose should not be so high
2. Drug should be oil soluble
3. High melting point drug is poorly suited to sedds
4. Log P Value should be high.

Solid self-emulsifying drug delivery system (S-SEDDS)[4,8,11]

S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nano-particle technology). In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry Emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature.

Solidification techniques for transforming liquid / semisolid SEDDS to solid SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. In parallel with the advances in capsule technology proceeding, liquid-Oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic

principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by. The advantages of capsule filling are simplicity of manufacturing, suitability for low dose highly potent drugs and high drug loading (up to 50% (w/w) potential.

Spray drying

This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.

Spray cooling

Spray cooling also referred to as spray congealing is a process whereby the molten formula is sprayed into a cooling chamber. Upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms, tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary pressure, two-fluid or ultrasonic atomizers.

Adsorption to solid carriers

SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents (e.g., silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross-linked polymethyl methacrylate). The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxylglycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers.

Melt granulation

Melt granulation or pelletization is a one step-process allowing the transformation of a powder mix (containing the drug) into granules or spheronized pellets. The technique needs high shear mixing in presence of a meltable binder. This is referred to as "pump-on" technique. Alternatively, the binder may be blended with the powder mix in its solid or semi-solid state and allowed to melt (partially or completely) by the heat generated from the friction of particles during high shear mixing referred to as "melt-in" process. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets.

Melt extrusion/extrusion spheronization

It is a solvent-free process that allows high drug loading (60%) as well as content uniformity. Applying extrusion-spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared.

Table 4: Techniques to incorporate liquid and semi-solid SEDDS into solid dosage forms.

Technique	Descriptions	Advantages	Other Exipient
Direct Capsule Filling	Hard or soft gelatin capsules are filled with liquid and semisolid SEDDS formulations; the ΔT of the process is usually 2ºC above the temperature of the incrementation of the apparent viscosity after cooling	Simple process suitable for low dosed strong APIs; low operational costs; Potentially high loading with APIs; good compatibility between lipids and capsule shell	
Adsorption on solid carriers	Liquid SEDDS formulations are being adsorbed on solid carriers with the aim to obtain free flowing powders for capsule filling or tableting.	Very good uniformity of content; Simple technique, low operational costs.	Calcium silicate; Magnesium aluminosilicate; SiO2; carbone nanotubes
Melt extrusion	Semisolid formulations are extruded after fusion in order to obtain a product with uniform density and	High APIs loading; good uniformity of content; Suitable for low dosed strong APIs. No solvent is	Solutol HS-15.; PEG-30-di-(polyhydroxystearate) Gelatin; microcrystalline

	shape.	needed.	cellulose, Gelucire® 44/14, hypromellose, ethylcellulos
Spray drying and spray cooling	Formulation of lipids, solid carriers, surfactants and APIs is spray dried or spray cooled; can work with dry emulsions.	Simple process; method for dry emulsion preparation that are stable, no organic solvents are needed.	MCT, sugar, gelatine, silicon dioxide, Polyoxyl glycerides
Pelletisation or meltgranulation	One-step process, high shear mixing; Depends on APIs: distribution be size shape, solubility in the binding excipient; melting point of and thermoplastic behavior of the binding excipient; binding excipient concentration.	Simple process (one step); No solvents needed; Potentially high APIs loading (up to 85%).	Gelatin, Solutol HS-15.; PEG-30-di(polyhydroxystearate) Lactose, microcrystalline cellulose; silica and magnesium aluminometasilicate

Biopharmaceutical aspects[6,9,14]

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including….

1. Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.

2. Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solublization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micelle structures and a further increase in solubilization capacity.

3. Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly *via* a reduction in first-pass metabolism.

4. Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the pglycoprotein efflux pump, and may also reduce the extent of enterocyte -based metabolism.
5. Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties.

For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

The effect of excipients on efflux transport[8,14,16]

Drug efflux mediated by broad-specificity xenobiotic transporters present in the intestinal epithelium may be an important factor in the poor or variable absorption of orally administered drugs. In the search for less toxic multidrug resistance (MDR) modulators. Bile salts, fatty acids, phospholipids, and surfactants were potent absorption enhancers and efflux-reducing agents in Caco-2 cells and the rat intestine. Other researchers also investigated the non-ionic surfactants, such as Tween 80, Pluronic P85, and Cremophor EL *in vitro* and *in vivo* in animals and in humans for their potential ability to reverse MDR caused by p-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP). Cremophor, Tween 80, and Solutol HS-15 have been proven to reverse the MDR phenotype in cultured cells at concentrations likely to be achieved clinically TPGS (d-a-tocopheryl plyethylene 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 in liver transplant patients as well as significantly improving absorption and reducing the daily drug cost. Inhibition of MDR-related pumps by various percipients has been proposed to occur due to binding competition, ATP depletion, and membrane perturbation. For example, Tween 80 has been shown to modulate anthracycline and Vinca alkaloid resistance in MDR cells by inhibiting the binding of these drugs to. The ability of Pluronic copolymer, one poly (ethylene oxide) block copolymer, to antagonize P-gp and sensitize MDR cells appears to be a result of ATP depletion, and inhibition of P-gp and MRP drug efflux proteins. Studies with MDR modifiers such as bile salts indicated that perturbations of the cell membrane structure may influence P-gpmediated drug transport. These modifiers may influence cytotoxic drug action by producing structural changes to the lipid domains in the plasma membrane. The membrane

perturbation caused by pharmaceutical excipients, such as Tween 20, Tween 80, Brij 30, and Myrj 52, may result in a change in the fluidity of Caco-2 cell membranes, and thus inhibit the activity of membrane-spanning proteins, such as P-gp and MRPs which substantially reduce the basolateral to apical efflux of epirubicin across Caco-2 monolayers. Tween 20, Tween 80, Brij 30, and Myrj 52 may also inhibit protein kinase C (PKC) activity, reduce phosphorylation of P-gp, and modulate P-gp mediated drug efflux. Inhibition of the effluxand /orenterocyte-based metabolism will increase the concentration and residence time of the intact drug in the cell. This may result in increased drug available for partitioning into the lymphatic.

Role of lipolysis[7,8,18]

Digestion of dietary triglyceride in the small intestine is very rapid, and many other non-ionic esters, such as mixed glycerides and surfactants, will be substrates or pancreatic lipase. Digestion of formulations will inevitably have a profound effect on the state of dispersion of the lipid formulation, and the fate of the drug. Fortunately, the liberation of free fatty acid during lipolysis can be titrated using NaOH in a pH stat, allowing quantitative data about the kinetics of digestion to be obtained. The location of the drug can be assayed in fractions after ultracentrifugation of the products of digestion, which allows investigation of the likely fate of the drug after lipolysis. The inclusion of highly lipophilic compounds in SEDDS is often reported to result in strongly enhanced oral absorption although it is still controversial whether further lipolysis of the dispersed lipid material is required for final transfer to the enterocyte membranes. In order to assess the relative roles of lipid vehicle dispersion and vehicle digestibility in the oral absorption of penclomedine (Pcm), a series of formulations of Pcm in medium chain triglyceride (MCT)/ TPGS was developed having three sizes (160 nm, 720 nm, and mm-sized (‘crude’ oil)); with or without the inclusion of tetrahydrolipstatin (THL), a known lipaseinhibitor. Oral absorption of Pcm was studied after administration of small volumes of these formulations to conscious rats. Formulations with a particle size of 160 nm had the highest relative bioavailability (set at F = 1), whereas administration in particle 720 nm in size resulted in a slightly lower bioavailability (F = 0.79). Co-inclusion of THL yielded similar bioavailability for these two SEDDS. ‘Crude’ oil formulations had an F = 0.62 (without THL) and 0.25 (with THL). Only in the case of Pcm administered as un-dispersed MCT was the absorption more dependent on the action of lipase as the bioavailability was inhibited two-fold by the co-incorporation of THL.

Table 5: Comparison of the basic SEDDS classes characteristics.

SEDDS	MICRO-SEDDS	NANO-SEDDS
Simple binary systems of APIs and excipients that are capable of self-emulsification when in contact with GIT fluids or system of APIs, surfactant and oil/s.	Systems of APIs, surfactants co-surfactants, oils.	Systems of APIs, surfactants co-surfactants and or co-solvents, oils.
The oil drops of the dispersion can reach dimensions in the range of 200 nm - 5µm. Macroscopically a cloudy dispersion is observed.	The oil drops of the dispersion reach dimensions in range of up to 200 nm Macroscopically a clear to slightly opalescent dispersion is observed	The oil drops of the dispersion reach dimensions in range of up to 100 nm Macroscopically a clear to dispersion is observed.
These systems are not thermodynamically stable when in contact with water or GIT fluids. Formulation and optimization may require phase diagrams construction.	These systems are thermodynamically stable when in contact with water or GIT fluids. Formulation and optimization require phase diagrams construction.	These systems are thermodynamically stable when in contact with water or GIT fluids. No phase separation is observed. Formulation and optimization require phase diagrams construction.

Application[9,11,14]

SEDDS formulation is composed of lipids, surfactants, and co-solvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism. Table shows the SEDDSs prepared for oral delivery of lipophilic drugs in recent years. As medicines can be loaded in the inner phase and supplied via lymphatic bypass sharing, SEDDSs protect drugs from enzymatic hydrolysis by in the GI tract and decrease presystemic clearance in the GI mucosa and hepatic first pass metabolism**.**

Table no. 6: Application of selfemulsifying drug delivery systems.

Type of delivery system	Drug	Oil	Surfactent	Cosolvent	Improvement
SEDDS (Gelled)	Ketoprofen	Captex 200	Tween 80	Capmul MCM	Silicon dioxide was used for gelling agent. As the concentration of silicon dioxide increases, it causes an increase in the droplet size of emulsion and slows the drug diffusion
SEDDS	Carvedilol	Labrasol	Labrafil M 1944CS	Transcutol P	It improves the oral bio availability of carvedilol up to 413% when compared to conventional tablet
SMEDDS	Simvastatin	Caproyl 90	Cremophore EL	Carbitol	The release rate of Simvastatin from SMEDDS was higher as conventional tablet. The oral bio availability of SMEDDS is about 1.5- fold higher than conventional tablet
Self-emulsifying tablet	Diclofanac Sodium	Goat fat	Tween 65	-------	SEDDS tablets were formulated by pour molding using plastic mould. the tablet containing higher tween 65: goat fat content ratios give better release rate
Self-emulsifying pallets	Methyl and propyl perabens	Mono and di glycerides of capric and caprylic acids.	Tween 80	-------	The self emulsifying formulation improves the rate of drug release from the pellets by applying a water – insoluble polymer containing a water-soluble plasticizer, it reduces the rate of drug release

CONCLUSIONS

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 SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs. From the above review we can conclude that Self-emulsifying drug delivery systems are approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs. microencapsulated emulsions, pellets that are self-emulsifiable, solid SESs and lipid/cross linked polymeric matrices are just a few examples. Upon water dilution, all of such formulations will yield fine oil droplets or micelle dispersions. Currently, pharmacological products developed as SEDDS, such as CsA, ritonavir, and saquinavir, are freely accessible on the market. As roughly 40% of novel drug compounds are hydrophobic, it predicts that further drug products for the pharmaceutical industry will be formed as SEDDS in the coming years.

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