A Review on SEDDS and Solid SEDDS: an Emerging Dosage Forms for Poorly Soluble Drugs

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ABSTRACT

Oral route is the easiest and most convenient route for drug administration. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter and intra subject variability, lack of dose proportionality. It is estimated that 40% of active substances are poorly water soluble. The solubility of such drugs is increased by formulating self emulsifying drug delivery system (SEDDS). Self emulsifying drug delivery systems have gained exposure for their ability to increase solubility and bioavailability of poorly water soluble drugs. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants, which emulsify to produce fine oil-in-water emulsions upon gentle agitation. SEDDS typically produce emulsions with a droplet size between 100–300 nm. Solid SEDDSs are being developed from liquid/semisolid SEDDS mainly by adsorption on solid carriers, spray drying, lyophilization, melt extrusion, and nanoparticle technology. This review focuses on newer approaches for development of SEDDS and Solid SEDDS.

Keywords: Self emulsifying drug delivery system, Co-solvents, surfactants, Solid SEDDS.

INTRODUCTION

Oral route has been the major route of drug delivery for the chronic treatment of human diseases. However, oral delivery of 50% of the drug compound is hampered because of the high lipophilicity of the drug itself [1]. In drug discovery, about 40% of the new drug candidates display low solubility in water, which leads to poor bioavailability, high intra subject/inter subject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity. Therefore producing suitable formulations is very important to improve the solubility and bioavailability of such drugs [2]. Self-emulsifying systems are a useful means of improving the bioavailability of poorly water soluble drugs, particularly the self-micro emulsifying drug delivery systems are well known for their potential as alternative strategies for delivery of hydrophobic drugs[3]. SEDDS are isotropic mixtures of drug, oil/lipid, surfactant and/or co-surfactant, which form fine emulsion/lipid droplets on dilution with physiological fluid. The drug therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state[4].

Advantages

- Improvement in oral bioavailability[5].
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- Inter-subject and intra-subject variability and food effects are reduced[6].
- Ease of manufacture and scale-up
- No influence of lipid digestion process
- Increased drug loading capacity[7].
- Advantages over emulsions
  - SEDDS overcomes the drawback of the layering of emulsions after sitting for a long time.
  - Micro emulsions formed by the SEDDS exhibit good thermodynamic stability and optical transparency[8].
  - SEDDS can be formulated into capsules or tablets, whereas emulsions can only be given as an oral solution.
  - Emulsion cannot be autoclaved, while SEDDS can be autoclaved[9].

Approaches of Delivery Systems

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including co-solvents, which emulsify under conditions of gentle agitation,

similar to those which would be encountered in the gastro-intestinal tract. Hydrophobic drugs can often be dissolved in SEDDS allowing them to be encapsulated as unit dosage forms for per oral administration. Generally, self-emulsifying formulations form a fine emulsion when exposed to aqueous media under conditions of gentle agitation. The resulting oil-in-water emulsions are thermodynamically stable due to relatively small volume of the dispersed oil phase, the narrow range of droplet size distribution and the polarity of the oil droplets. Oral administration of SEDDS, which can be conveniently encapsulated in soft gelatin capsules, the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification. Improvement in the extent and rate of absorption of lipophilic compounds from self-emulsifying formulations is more as compared to traditional oral formulations. The potential of lipoids self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) for improving the extent and reproducibility of the oral absorption of Halofantrine was investigated as such and formulations have been reported to improve the rate and extent of absorption of lipophilic drugs. In recent study, the self-emulsifying properties of Glyceryl Monooleate (GMO) formed a hydrophobic core, presumably micellar, to enhance the solubility of Paclitaxel (PTX) and provide a foundation for chitosan aggregation. The near 100% loading and entrapment efficiencies of PTX in this formulation are attributed to the self-emulsifying properties of GMO-mono glycerides (like GMO), a polar lipids with poor water solubility that exhibit properties resembling non-ionic surfactants have been comprehensively described[10].

Biopharmaceutical Aspects

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:

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

b) 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 phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization 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 micellar structures and a further increase in solubilization capacity.

c) 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.

d) 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 p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.

e) 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[11].

Enhanced drug absorption by lymphatic delivery

Drug candidates for lymphatic transport should have a log P >5 and, in addition, a triglyceride solubility >50 mg/ml. The importance of lipid solubility was illustrated by a comparing the lymphatic transport of DDT (log P 6.19) with hexachlorobenzene (HCB, log P 6.53). While both compounds have similar log P values, the difference in lymphatic transport on administration in oleic acid, 33.5% of the dose in the case of DDT and 2.3% with HCB, was attributed to the 13-fold difference in triglyceride solubility[12]. However, combination of a high log P and high triglyceride solubility does not always guarantee significant lymphatic transport. Penclomedine, an experimental cytotoxic agent with a log P of 5.48 and a triglyceride solubility of 175 mg/ ml, was poorly transported in the intestinal lymph. Khoo et al. showed significant lymphatic transport of the poorly lipid soluble (~1 mg/ml) HCl salt of halofantrine (Hf-HCl), following oral post-prandial administration to dogs. The authors suggest that the high level of lymphatic transport of Hf-HCl (43.7% of dose), which was similar to that of the lipid soluble Hf base, was due to conversion of Hf-HCl in the intestinal lumen, during lipolysis, to the more lipophilic free base, which then becomes associated with chylomicron production. Although enhanced lymphatic transport has been suggested as a potential mechanism of enhanced bioavailability, few studies have investigated the lymphotropic potential of SEDDS. However, one such study by Haus et al. investigated the effects of a range of lipid-based formulations on the bioavailability and lymphatic transport of ontazolast, following oral administration to conscious rats.

The effect of excipients on efflux transport

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. Bile salts, fatty acids, phospholipids, and surfactants (less toxic multidrug resistance (MDR)

modulators) are potent absorption enhancers and efflux-reducing agents in Caco-2 cells and the rat intestine. Non-ionic surfactants, such as Tween 80, Pluronic P85 and Cremophor EL are proven 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). Recently, 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- 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 excipients 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 P-gp. 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].

Role of Lipolysis

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 lipase4. 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 various 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 lipase-inhibitor. 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 undispersed MCT was the absorption more dependent on the action of lipase as the bioavailability was inhibited two-fold by the co-incorporation of THL. A single-dose comparative bioavailability study was conducted to evaluate the bioavailability of tocotrienols from two self-emulsifying formulations, one of which produced an emulsion that readily lipolysed under in vitro conditions (SES-A), while the other produced a finer dispersion with negligible lipolysis (SES-B) in comparison with that of a non-self-emulsifying formulation in soya oil (NSES-C). The results showed that both SES-A and -B achieved a higher absorption than NSES-C. Both SES-A and -B also achieved a faster onset of absorption. However, SES-A and -B had comparable bioavailability, despite the fact that SES-B was able to form emulsions with a smaller droplet size. Thus, it appears that the droplet size as well as the rate and extent of lipolysis of the emulsion products formed are important for enhancing the bioavailability of tocotrienols from the self-emulsifying systems[13].

Selection of Drug Candidate for SEDDS Formulation

The biopharmaceutical classification system (BCS) defines bioavailability as interrelated functions of drug compound permeability and solubility. Drug compounds are categorized accordingly by the BCS classification in which BCS category 'II' Compounds or those possessing poor water solubility and high membrane permeability tend to exhibit most substantial enhancements in bioavailability when formulated in solubilizing lipid excipients. BCS is useful for identifying drug candidate compounds for which oral lipid based formulations which could be expected to improve bioavailability. Lipid based formulations can potentially improve bioavailability for properly selected compounds in every BCS category.

Table 1: Selection of drug according to BCS with relative advantages

BCS	Aqueous Solubility	Membrane Permeability	Potential Advantage of Lipid-based systems
I	High	High	Potential for controlled release; possible benefit for drugs subject to efflux or chemical degradation
II	Low	High	Enhanced bioavailability primarily through solubilization in GIT
III	High	Low	Potential for controlled release; possible benefit for
IV	Low	Low	drugs subject to efflux or chemical degradation

Administering the class II drug compounds as a lipid solution enhances bioavailability primarily by overcoming the absorptive barriers of poor aqueous solubility and show dissolution in the GI. The exact mechanism(s) by involve transfer into the bile-salt mixed micellar phase, from which

absorption across the intestinal epithelium readily occurs. Another pathway by which lipids may improve bioavailability include are mitigation of intestinal efflux via the P-gp transporter, reduction in intestinal first-pass metabolism by membrane bound cytochrome enzymes, and permeability enhancing changes in intestinal membrane fluidity. Lipids can also direct lipid-soluble drugs into the intestinal lymph, from which drugs enter the systemic blood circulation directly, these by circumventing potential hepatic first-pass metabolism[14].

Excipients Used In SEDDS/SMEDDS

The excipients used in SEDDS or SMEDDS are oils, surfactants, co-solvents, co-surfactants and sometimes polymers in the prolonged release formulations.

Oils

The oils 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 28-30. 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.28-30. Novel semi synthetic medium chain derivatives, which are amphiphilic, with surfactant properties are effectively replacing the regular medium chain triglyceride oil in the self-emulsifying oil formulation[15].

Surfactants

Surfactant molecules can be classified based on the nature of the hydrophilic group within the molecules. The four main groups of surfactants are

- Anionic
- Cationic
- Ampholytic (zwitterionic surfactants)
- Non-ionic.

The most widely recommended surfactants are non-ionic surfactants with relatively high(HLB)[16]. The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and Polyoxyethylene 20 oleate (Tween 80). Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible change in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30-60% w/w in order to form stable SEDDS. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead

to the formation of SMEDDS[17]. There is a relationship between the droplet size and the concentration of surfactant being used. In some cases, increasing the surfactant concentration could lead to droplet with smaller mean droplet size. In contrast to this, the mean size may increase surfactant concentrations in some cases[18] .

Co-Surfactants

Generally co-surfactant of HLB value 10-14 is used. Organic solvents like ethanol, propylene glycol(PG), polyethylene glycol(PEG) are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Alternately alcohols and other volatile co-solvents show a disadvantage that by evaporation they get entered into soft/hard gelatin capsule shells resulting in precipitation of drug. On the other hand formulations which are free from alcohols have limited lipophilic drug dissolution ability. Hence, proper choice of components has to be made for formulation of efficient SMEDDS[19].

Co-Solvents

The production of an optimum SEDDS require relatively high concentrations (generally more than 30% w/w) of surfactant, organic solvents as ethanol, PG and PEG are suitable for oral delivery. These solvents can even act as co surfactants in micro emulsion system[20].

Formulation of SEDDS

The formulation of SEDDS is simple and as all that is required is to incorporate the drug into a suitable oil/surfactant mix. The pre-concentrate may then be presented as a dosage form such a liquid filled soft gelatin capsules, alternatively hard gelatin capsules may be used if a gelatin band is included to prevent leakage.

Factors affecting formulation of SEDDS

➢ Nature of the oil/surfactant pair and surfactant concentration.

➢ Surfactant concentration and oil/surfactant ratio; surfactant to co-surfactant ratio. Temperature at which self emulsification occur.

➢ Drugs which are administered at very high dose are not suitable for SEDDS.

➢ The ability of SEDDS to maintain the drugs in solubilized form is greatly influenced by the solubility of the drug in oily phase.

➢ Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilizing and colloidal stabilizing environment of the gut[21]. The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions. The polarity of the droplet is governed

by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of micronized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time period.

Mechanism of Self-Emulsification

The self emulsification takes place when the entropy change that favors dispersion is greater than 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 emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion is either low or positive or negative[22]. 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 droplet[23]. The addition of a binary mixture (oil/non-ionic surfactant) to water, followed by the solubilization of water with in the oil phase as a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will lead 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[24]. Moreover, the presence of the drug compound may alter the emulsion characteristics, probably by interacting with the LC phase. Nevertheless, the correlation between the LC formation and spontaneous emulsification has still not been established[25].

Improvement of oral absorption by SEDDS

The release of the drug compound from SEDDS 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, particle size and polarity of the resulting oil droplets determine the efficient release of the drug compound from SEDDS. 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. Various modes of enhanced drug absorption can be hypothesized as follows,

➢ Drugs may be absorbed through lymphatic via chylomicron synthesis of the fatty components of digestible oil phase of emulsion. A lipophilic drug, which preferably remains in the oil droplet, may in fact be absorbed via bile salt micelles along with metabolites of lipid carrier.

➢ Bates and Sequeria suggested that inhibition of gastric motility caused by the presence of lipid phase of emulsion might allow more time for dissolution and absorption of drugs from lipid phase.

➢ Increased mucosal permeability via incorporation of lipids from mixed micelles and enhanced mesenteric lymph flow may be responsible for the enhanced drug absorption.

➢ A hydrophilic drug is less likely to be absorbed through the lymphatic's (Chylomicron) and instead may diffuse directly into the portal supply. Hence in this case increased dissolution from the large surface area afforded by emulsion may be a contributing factor for enhanced absorption of drugs. A relative consideration is the presence of large amount of surfactants in the formulation which may play role in increasing the absorption of drugs.

➢ Many studies carried out in animals for the assessment of the oral bioavailability of hydrophobic drugs formulated in o/w emulsions indicated better absorption profiles. But, due to their poor physical stability need in large volume.

A three-fold higher values in C_{max} and AUC of a lipophilic naphthalene derivative as compared to other dosage forms observed the improvement in oral bioavailability of anti-inflammatory drug ontazolast administered in rats as lipid based formulations such as emulsion, glycerol oleate solution and SEDDS compared to Suspensions. A multiple dosage studies were conducted on humans diagnosed with HIV infection who were given orally an HIV protease inhibitor either as a SEDDS or as an elixir. Greater AUC values were reported for patients given the SEDDS as compared to the ones given the elixir.

Effect of surfactant on absorption

Surfactants increase the permeability by interfering with the lipid bilayer of the single layer of the epithelial cell membrane, which with the unstirred aqueous layer, forms the rate-limiting barrier to drug absorption/diffusion. Therefore, most drugs are absorbed via the passive transcellular route. Surfactants partition into the cell membrane and disrupt the structural organization of the lipid bilayer leading to permeation enhancement. They also exert their absorption enhancing effects by increasing the dissolution rate of the drug.

Effect of lipids

Lipids exert their effects through several complex mechanisms that leads to alteration in the biopharmaceutical properties of the drug, such as increased dissolution rate of the drug and solubility in the intestinal fluid, protection of the drug from chemical as well as enzymatic degradation in the oil droplets and the formation of lipoproteins which promotes the lymphatic transport of highly lipophilic drugs. The absorption profile and the blood/lymph distribution of the drug compound are affected by the acid chain length of the triglyceride, saturation degree, and volume of the lipid administered. Short and medium chain fatty acids (with a carbon chain length shorter than 12 carbon atoms) are transported to the systemic circulation by the portal blood and

are not incorporated to a great extent in chylomicrons. In contrast, long chain fatty acids and monoglycerides are re-esterified to triglycerides within the intestinal cell, incorporated into chylomicrons and secreted from the intestinal cell by exocytosis into the lymph vessels. In addition to the stimulation of the lymphatic transport, lipophilic drugs with lipids may enhance drug absorption into the portal blood when compared to non-lipid formulations.

Characterization of SEDDS

Particle size

The droplet size of the emulsion is a crucial factor. Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation.

Polarity

The HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by polarity.

Zeta potential

The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive n-potential value of about 35-45 mV. This positive n-potential value is preserved following the incorporation of the drug compounds.

Drug precipitation /stability on dilution

The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilization then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant, hence it is very important to determine stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of 0.1N HCl solution[26].

Drawbacks of SEDDS

The drawbacks of SMEDDS include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates

GIT[27,28]. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules[29, 30]. resulting in the precipitation of the lipophilic drugs. There is a long list of water soluble, insoluble and surfactants, which can be used as solubilizing excipients. Grinding is regularly used in the pharmaceutical industry[31,32,33]. to reduce particle size but it generates heat, sound and vibration energy. It must be performed at a temperature below the melting temperature. Cryogenic grinding is chosen because it is a process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues) and unstable compounds (vitamins, volatile substances, etc.) However, grinding induces mechanical activation and generation of energy can lead to physical and chemical changes in crystalline solid which can affect its efficacy[34].

Newer Approaches to Self Emulsifying Drug Delivery Systems

The self-emulsifying drug delivery systems offers advantages in addressing the challenges of drug solubility and absorption; the next challenge remains the delivery of the drug in an acceptable dosage form. The oral dosage forms are the preferred drug administration route, and lipid formulations offer flexibility for oral dosage forms because they can be formulated as solutions, semisolid, and solid forms. Conventional self-emulsifying drug delivery systems, however, are mostly prepared in a liquid form, which can produce some disadvantages, for example, low stability, irreversible drugs/excipients precipitation, large volume of dose, difficulty in handling and portability, and few choices of dosage forms. To address these problems, solid-SEDDSs (S-SEDDSs) have been investigated as alternative approaches. Such systems require the solidification of liquid self-emulsifying systems into powders to produce various solid dosage forms (SE capsules, SE tablets, SE pellets, SE beads, and so on). The liquid SEDDS can be converted into solid dosage form without affecting drug release property. Self emulsification happens in GIT by the released contents. Thus, S-SEDDSs combine the advantages of SEDDS (i.e., enhanced solubility and bioavailability) with those of solid dosage forms (e.g., high stability and reproducibility, compact dosage form, ease of handling and portability, and better patient compliance). Knowing the advantages of solid dosage forms, S-SEDDSs have been extensively investigated in recent years, as they frequently correspond to more effective alternatives to conventional liquid SEDDS. Examples include the development of S-SEDDS of Dexibuprofen, Nimodipine, and Hydrochlorothiazide. From the perspective of dosage forms, S-SEDDSs mean solid dosage forms with self-emulsification properties. S-SEDDSs focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques.

Solidification Techniques for Transforming Liquid SEDDS to Solid-SEDDS (S-SEDDS)

Solid SEDDSs are being developed from liquid/semisolid SEDDS mainly by adsorption on solid carriers, spray drying, Lyophilization, melt extrusion, and nanoparticle technology. Such powders/nanoparticle, which are referred to as SE nanoparticle /dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms or, alternatively, filled into capsules (i.e., SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDSs are directly filled without any solidifying excipient. Other solid SE dosage forms that have emerged in recent years include SE pellets/tablets, SE microspheres/nanoparticle, and SE suppositories/implants.

Adsorption on Solid Carriers

Free flowing powders may be obtained from liquid SE formulations by adsorption on solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto inert carriers and mixing them in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. 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, for example, silica, silicates, magnesium trisilicate, magnesium aluminium silicate (Neusilin) microporous calcium silicate (Florite TM RE) magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose, and cross-linked polymethyl methacrylate. The self-emulsifying powder was prepared by adsorbing the liquid SEDDS onto neusilin as carrier to improve the solubility of poorly soluble lercanidipine hydrochloride. Cross-linked polymers create favourable environment to sustain drug dissolution. Nanoparticle adsorbents comprise porous silicon dioxide, carbon nanotubes, carbon nanohorns, charcoal, and so forth.

Spray Drying

In this technique, the liquid SEDDS is added to a solution of suitable solid carrier with stirring to obtain the o/w emulsion. This is then atomized into a spray of droplets in 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. The atomizer, the temperature, the most suitable airflow pattern, and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

Lyophilization Technique

Lyophilization or freeze-drying involves transfer of heat and mass to and from the product under preparation. Freeze drying of an oil-in-water emulsion can be an alternative method for the production of dry emulsions. Lyophilization has been thought as a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen, and sublimed to obtain a lyophilized molecular dispersion. The potential applications of Lyophilization in manufacturing of solid dispersions have successfully been investigated. A slow cooling rate and addition of amorphous cryoprotectants has been reported to have the best stabilizing effects during Lyophilization of oil-in-water emulsions. Maltodextrins are also useful matrix forming agent in the formulation of freeze-dried tablets.

Melt Granulation

Melt granulation is a technique in which powder agglomeration is obtained through the addition of a lipid as binder that melts or softens at relatively low temperatures.

Melt Extrusion/Extrusion Spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure 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 the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-Spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogenous powder; wet massing with binder; extrusion into rope-like extrudate; Spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating[35].

Advantages of S-SMEDDS

- Spontaneous formation
- Ease of manufacture
- Thermodynamic stability and
- Improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- Greater bioavailability
- Less drug need to be used
- For many drugs taken by mouth

- Faster release rates and it improve the drug acceptance by consumers
- Selective drug targeting toward a specific absorption window in the GI tract and
- Drug protection from the hostile environment in the gut
- 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
- This may lower cost. (Ren J et al 2002)

CONCLUSION

SMEDDS formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. Self-emulsifying drug delivery system can be use for the formulations of drugs compounds with poor aqueous stability. Development of this technology SEDDS will continue to enable novel applications in drug delivery system. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. Solid SEDDS is more stable than liquid SEDDS. If solid SEDDS form of drug is used instead of plain drug in existing commercially available dosage form, there will be improvement in solubility and not much modification would be needed in manufacturing process.

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