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DEVELOPMENT OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM AND DOSAGE FORMS

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ABSTRACT

Drugs are most often administered by the oral route. However, more than 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. Recently, much attention has been focused on self emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Solid SEDDS, one of the lipid-based drug delivery systems prepared by the incorporation of liquid excipients into powders by solidification, is a promising drug delivery system for poorly water soluble compounds as it combines the advantages of liquid SEDDS (solubility and bioavailability enhancement) with those of solid dosage forms (high stability with various dosage forms options). This article reviews the recent advancement in solid SEDDS with emphasis on solidification technique, solid SEDDS dosage forms, their associated problems and future directions for the research.

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INTRODUCTION

It is generally accepted that many of today's new chemical entities (NCEs) are poorly water-soluble and pose a challenge in developing an optimum solid oral dosage form. However, oral delivery of approximately 40% of the drug compounds is limited because of low aqueous solubility, which leads to limited oral bioavailability, high intra and inter subject variability and lack of dose proportionality[1]. Over recent years, much attention has been focused on lipid formulations, with particular emphasis on liquid self-nanoemulsifying (SNEDDS), self-microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs[2,3]. However, these delivery systems had a few limitations, such as stability, the manufacturing methods, the interaction between the filling and the capsule shell, and the storage temperature[4].

To address these problems, S-SEDDS have been investigated, as alternative approaches. Such systems require the solidification of liquid self-emulsifying (SE) ingredients into powders/nanoparticles to create various solid dosage forms SE tablets[5,6] and SE pellets[7,8]. Thus, S-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance).

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

Self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants[9]. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil in water (o/w) emulsions. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification[10]. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm[11].

EXCIPIENT SELECTION

Self-emulsification has been shown to be specific to: the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; and the temperature at which self emulsification occurs[12].

Oils

The oil represents one of the most important excipients in the SEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate selfemulsification 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[12]. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations[13].

Surfactants

Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SEDDS. There is a relationship between the droplet size and the concentration of the surfactant being used. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation[11].

Cosolvents

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants[14]. More commonly it has been assumed that cosolvents could be included to increase the solvent capacity of the formulation for drugs which dissolve freely in cosolvents. However to enhance the solvent capacity significantly the cosolvent must be present at high concentration and this is associated with the risk of drug precipitation when the formulation is dispersed in water. Cosolvents lose their solvent capacity quickly following dilution[15].

CHARACTERIZATION OF SEDDS

The very essence of SEDDS is self-emulsification, which is primarily assessed visually to determine the rapid equilibrium reached by the dispersion and the reproducibility of this process. The efficiency of self-emulsification can be estimated by determining the rate of emulsification and droplet size distribution[11].The charge on the oil droplets of SEDDS is another property that needs to be assessed. Phase diagram was constructed with the objective of studying the relationship between the phase behavior and the composition of the components[16]

SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in

SEDDS are not solids at room temperature. In recent years, as they frequently represent more effective alternatives to conventional liquid SEDDS. From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoarticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, Nanoparticle technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles/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 SEDDS are directly filled without any solidifying excipient. To some extent, S-SEDDS are combinations of SEDDS and solid dosage forms, so many properties of S-SEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SEDDS and solid dosage forms[17].

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SEDDS TO S-SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations;

Capsule filling is the simplest and the most common technology to encapsulate liquid or semi-solid lipid-based formulations for the oral route. For semi-solid formulations, it is a four step-process: (i) heating of the semisolid excipient to at least 20 °C above its melting point (ii) incorporation of the active substances (with stirring) (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The filling temperature is one of the key parameters for capsule filling. It should be at least 2°C above the temperature at which the apparent viscosity of the drug-excipient mixture significantly increases during cooling (temperature assessed by thermorheology studies). The maximum filling temperatures are 70°C for hard shell capsules and 40°C for soft gelatin capsules[18].

TECHNIQUES TO PRODUCE SOLID PARTICLES

Spray drying

Essentially, 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[17].

Adsorption on solid carriers

The adsorption process is simple and involves addition of the liquid formulation onto the carrier of choice by mixing in a blender. The carriers used for this purpose include calcium silicate, magnesium aluminometasilicate, silicon dioxide, or carbon nanotube. These carriers should be selected for their ability to adsorb a great quantity of liquid excipients (to allow for a high drug loading and high lipid exposure) and for the flowability of the mixture after adsorption. The resulting free flowing powder may then be filled directly into capsules or alternatively mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% w/w) onto suitable carriers[18].

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted[19].

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity[18]. 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[20]. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion– spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets).

The extrusion–spheronization process requires the following steps[21]

a) Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder

b) Extrusion into a spaghetti-like extrudate

c) Spheronization from the extrudate to spheroids of uniform size

d) Drying Sifting to achieve the desired size distribution and coating (optional).

DOSAGE FORM DEVELOPMENT OF SSEDDS

Dry emulsions:

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation[22], freeze-drying[23] or spray drying. Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used[24]. Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders[25].

Self emulsifying capsules:

After administration of capsules containing conventional liquid SE formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation[26]. With the similar purpose, the supersaturatable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects[27,28].Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self micro emulsification upon mixing with water[29,30]. Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: micro porous calcium silicate (Florite™ RE); magnesium aluminum silicate (Neusilin® US2) and silicon dioxide (Sylysia® 320).

Eventually these solids were filled into hard capsules[31]. In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms[32].

Self emulsifying sustained/controlled release tablets:

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal and Khan evaluated the effect of some processing parameters (colloidal silicates- X_1, magnesium stearate mixing time- X_2, and compression force- X_3) on hardness and coenzyme Q_{10} (CoQ_{10}) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X_1= 1.06 %, X_2= 2 min, X_3= 1670 kg) were achieved by a face-centered cubic design[33]. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil™ 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release[34]. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol™ (a copolymer of alkyl phenol and formaldehyde).

Self-emulsifying sustained/controlled-release pellets:

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability[35]. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Serratoni et al. prepared SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80. This research demonstrated that combinations of coating and SES could control in vitro drug release by providing a range of release rates; and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution[36]

Self emulsifying solid dispersions:

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients[37,38]. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling[39]. SE excipients like Gelucire 144/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field[40].

Self emulsifying beads:

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the micro-channels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES loaded PPB[41].

Self-emulsifying sustained-release microspheres:

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, You et al. prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique. ZTO release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration– time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS[42].

Self emulsifying nanoparticles:

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. These approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%[43].

Self-emulsifying suppositories:

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption[44]. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C_6–C_{18} fatty acid glycerol ester and a C_6–C_{18} fatty acid\macrogol ester[45].

Self emulsifying implants:

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl)-1- nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses[46].

CONCLUSION

S-SEDDS substantially improved solubility/ dissolution, absorption and bioavailability of poorly water-soluble drugs. S-SEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable.

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