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DEVELOPMENT OF SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Self-emulsifying drug delivery system (SEDDS) is one of the most popular and commercially viable formulation approaches to improve solubility of water-insoluble drugs. However, SEDDS are normally prepared as the liquid form that has several limitations. SEDDS is converted into solid self-emulsifying drug delivery systems (S-SEDDS) by solidification technique, which maintains the advantages of L-SEDDS whilst enhancing storage stability. Thus the aim of this review is to discuss solid carriers, various methods of preparation and the stability of S-SEDDS for providing more options for future drug research.

KEYWORDS: solid self-emulsifying drug delivery systems, S-SEDDS, method, stability.

INTRODUCTION

In drug research, many new drug candidates exhibit low oral bioavailability due to their poor water solubility. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity. Therefore, producing reasonable formulations is essential to enhance the solubility and oral bioavailability of such drugs.

Over recent years, much consideration has been concentrated on self-emulsifying drug delivery systems (SEDDS) to solve these problems.[1,2,3] SEDDS is composed of drugs, oil,

surfactant and co-surfactant, which can spontaneously form O/W emulsion with the particle size less than 500 nm in the gastrointestinal tract. It can improve the solubility and dissolution rate of insoluble drugs and improve its oral bioavailability. However, SEDDS are normally prepared as liquid form that has several limitations, such as low stability, the complex manufacturing methods, the interaction between the filling and the capsule shell, the great gastrointestinal irritation (generally requirement about 30%-60% of surfactants to achieve good self-emulsifying properties[4]) and the storage temperature.[5] To address these problems, Solid self-emulsifying drug delivery system (S-SEDDS) have been extensively exploited recently, as an alternative approach. Moreover, it can improve drug efficacy and reduce drug side effects. Thus this review throws light on various solid carriers, excipients, methods of preparation and the stability of solid SEDDS to provide more options for future drug research.

FORMULATION OF S-SEDDS

Liquid-SEDDS

SEDDS mainly consists of oil, surfactant and co-surfactant. Oil commonly used include glyceryl monooleate, propylene glycol monocaprylate and oleic acid. Surfactants are mainly non-ionic surfactants with the large value of Hydrophile-Lipophile Balance (HLB). In recent years, some researchers have adopted multiple surfactants in order to obtain better self-emulsifying properties and physical stability, such as Ping Li *et al.*[6] demonstrated the combined use of surfactants (Tween 20 and Cremophor EL) that greatly improved the microemulsions generated upon dilution with the aqueous medium. The main role of co-surfactant in SEDDS system is to increase the solubility of the drug, the interfacial membrane fluidity and regulate the HLB value. It is commonly short, medium chain alcohol, such as propylene glycol, ethanol, etc. Pouton *et al.*[7] introduced the characteristics, types and selection principles of self-emulsifying agents in detail. After selection of oil, surfactant and co-surfactant, pseudo-ternary phase diagrams are usually used to determine the optimal ratio and self-emulsion area for prescription optimization.

Solid carriers

From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid self-emulsifying ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions onto solid carriers, spray drying, melt extrusion, nanoparticles technology, etc.).

Solid carriers can be divided into hydrophilic solid carriers (such as PEG4000, PEG6000, mannitol, etc.) and hydrophobic solid carriers (such as aerosol, microcrystalline cellulose, etc.). Over the years, some researchers had compared the effects of hydrophilic solid carriers and hydrophobic solid carriers in improving the oral bioavailability. Truong *et al*.[8] solidified Erlotinib self-microemulsion by spray drying and found that the $AUC_{0-\infty}$ and C_{max} values of S-SEDDS prepared with dextran were approximately 2.1- and 2.4-fold higher than those of erlotinib powder, respectively. The $AUC_{0-\infty}$ and C_{max} values of S-SEDDS prepared with Aerosil 200 were approximately 3.5- and 4.2-fold higher than those of erlotinib powder, respectively. However, Oh *et al*.[9] demonstrated that using Colloidal silica and dextran were as a hydrophobic and a hydrophilic carrier, respectively, which had no significant effects on the formation of S-SMEDDS such as crystalline properties, dissolution and oral bioavailability of flurbiprofen. Hence, the properties of carrier on the solubilization are not specific, and the existing form of the drug in carrier is an important factor affecting the solubilization.

Moreover, many researchers used new carrier materials to prepare cationic solid SEDDS, which had static electricity between positively charged emulsion droplets and negatively charged biofilm of the gastrointestinal tract, thereby accelerating drug absorption. Sri *et al*.[10] demonstrated the relative bioavailability of the solid SMEDDS of Valsartan prepared with Neusilin US2 was 1.6-fold higher compared to the pure suspension. Katla *et al*.[11] showed that SSMED of losartan prepared with neusilin US2 had good flow property and drug content uniformity.

METHODS OF SOLIDIFICATION

Adsorption to solid carriers

The adsorption process involves addition of the liquid SMEDDS onto solid carriers by mixing in a blender to obtain good flow property of powders. The significant benefit of the adsorption technique are simple, good drug content uniformity and low cost of production. Solid carriers can be high surface-area colloidal inorganic adsorbent substances, micro porous inorganic substances, cross-linked polymers or nanoparticle adsorbents, for instance, silica, silicates, magnesium trisilicate, magnesium hydroxide and cross linked polymethyl methacrylate. Nanoparticle adsorbents include porous silicon dioxide, carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal.[12]

A variety of researches have compared different adsorbents in their adsorption capacity (Table 1), physical characteristics of produced S-SMEDDS, its dissolution curves and oral bioavailabiliy.

Table 1: Literature reports on compositions from different lipid-based formulations solidified by adsorption of liquid SEDDS onto solid carriers.

Lipid-based formulation	Carrier	Lipid- formulation: carrier	Drug	Reference
Capmul MCM L8 (30%); Tween 80:PEG400 (6:1)	Neusilin	0.25:1; 0.5:1; 1:1; 1.5:1; 2:1	Lercanidipine hydrochloride	Kallakunta *et al*[13]
Tween 80 (45%); Labrasol (30%); Captex 355 (5%)	$CaSiO_3$; $MgSiO_3$; $Al_2(SiO_3)_3$; SiO_2	From 0.25:1 to 3:1	griseofulvin	Agarwal *et al*[14]
Miglyol 812 (30%); Cremophor RH 40 (40%); Tween 80 (20%); Transcutol P (10%)	Syloid 244 FP	02:01	Nitrendipine	Wang *et al*[15]
(1) tartaric acid (0.018g); captex 355: oleic acid (0.4877g); span 80 (0.2g); tween 80 (0.1g)	Aerosil 200	01:01	Atenolol	Bhattacharjee *et al*[16]
(2) tartaric acid (0.018g); captex 355: oleic acid (0.5g); span 80 (0.1839g); tween 80 (0.1g)				
Capmul MCM 20%; Tween 80: PEG 400 (1:2)	Neusilin US2	01:01	Chlorthalidone	Dangre *et al*[17]
Capmul MCM (20%) Tween 20 (40%) Cremophor EL (40%)	Aerosil 200	8:4; 8:5.5 and 8:7	Simvastatin	Dixit and Nagarsenker[18]
PEG 30 hydrogenated castor oil (50%); Miglyol 812/Imwitor 988 =70/30 or Imwitor 308 (50%)	magnesium aluminomet-asilicate	1:1; 1.5:1 and 2.3:1	fenofibrate	Shazly and Mohsin[19]
Cremophor RH40 (46%) Labrafil M 2125 CS (38%), Ethanol (11%) Propylene glycol (5%)	Neusilin US2	Various	Cyclosporine A	Sander and Holm[20]

Spray drying

Spray drying is a simple and economical method for producing solid SEDDS by rapidly drying with hot gas and their further processing into tablets or filling into hard capsules. Production of solid SEDDS by spray drying is applicable to various carriers, whether hydrophilic or hydrophobic. Yi *et al*[21] showed that the $AUC_{0-\infty}$ and C_{max} of nimodipine solid SEDDS prepared by spray drying technique were similar compared with the liquid SEDDS

and the $AUC_{0-\infty}$ and C_{max} values of solid-SEDDS were approximately 2.6- and 6.6-fold higher than the conventional tablets, respectively. Balakrishman *et al*[22] demonstrated that the dissolution of dexibuprofen solid SEDDS prepared by spray drying method had no significant difference compared with liquid form SEDDS. This showed that spray drying technique which converts liquid- SEDDS into solid form did not hinder the drug release and drug absorption.

According to literature solid SEDDS were successfully prepared by spray drying technique with various carriers and self-emulsifying properties were preserved (Table 2).

Table 2: Overview of produced solid-SEDDS by spray drying method.

Lipid-based formulation	Carrier	Drug	droplet size of S-SEDDS after redispersion	Reference
ethyl oleate, Cremophor RH 40 and Labrasol	HPMC	Nimodipine	less than 100nm	Yi *et al*[24]
Tween 80, water, R-(+)-limonene, ethanol, and glycerol	Syloid 244 FP	Carotenoid	250nm	Chow *et al*[25]
Miglyol 812, Peceol, Gelucire 44/14, and Solutol HS 15	MD	Naproxen	less than 100nm	Čerpnjak *et al*[26]
Oleic acid, Cremophor RH 40, Tween 80, Labrasol, Labrafil 1944 CS	Neusilin US2	Artemether and Lumefantrine	67.74nm	Bhandari *et al*[27]
Labrafil M 1944 CS, Labrasol, Capryol PGMC	Dextran	Fenofibrate	around 240nm	Kim *et al*[28]
Labrafil 2125 CS, Tween 20, Maisine 35-1	Aerosil 200	Mebendazole	within 250nm	Parakh *et al*[29]

Extrusion and spheronization

The extrusion process was carried out in a ram co-extruder equipped by a mechanical press. The extrudates were spheronized in a radial plate spheronizer. Drying of spheroids was carried out in a fluidized bed dryer. Iosio *et al*.[30] proved co-extrusion/spheronization was a feasible technology to produce bi-layered cohesive self-emulsifying pellets of vinpocetine with good quality and improved in vivo bioavailability. Solid self-microemulsifying pellets containing Sirolimus (SRL) was developed by Hu *et al.*[31] The authors reported that the oral relative bioavailability of SRL-SMEDDS pellets to the commercial tablets was about 136.9%. Wang *et al*[32] produced solid self-emulsifying nitrendipine pellets by extrusion/spheronization technique with uniform size (800–1000 μm), round shape and showed that the $AUC_{0-\infty}$ values of solid-SEDDS was 1.6-fold higher than the conventional tablets and no significant difference compared with the liquid form SEDDS. Thus, pellets produced by extrusion/spheronization preserve self-emulsifying properties of liquid SEDDS, making this method a feasible technology for the solidification of liquid SMEDDS.

Liquisolid compact technique

The liquisolid compact technique is a powdered form of a liquid drug formed by blending the liquid drug formulation with selected carrier material and coating material to form dry looking, non-adherent, free-flowing and readily compressible powdered mixtures.[33] Zhao *et al*.[34] in their study reported that the self-micro-emulsifying tablet of Cyclosporine-A prepared by the liquisolid compact technique exhibited acceptable flowability and compressibility and enhanced the solubility and the in-vitro release. Khalid *et al.*[35] produced Rofecoxib liquisolid tablets by using liquisolid compact technique. The authors showed that addition of 10% Cab-O-Sil® and 5% magnesium oxide improved the flowability of the tested Rofecoxib powders from bad flow to satisfactory flow and Rofecoxib liquisolid tablets showed higher dissolution rates than the three studied commercial tablet. Thus this technique is a new and promising method that can change the dissolution rate of water insoluble drugs.

Spherical Crystallization Technique

Spherical crystallization is a size enlargement method in which limited quantities of an agglomeration promoting liquid are added directly during the crystallization for purpose of getting spherical agglomerates. These agglomerates can be directly compressed into a tablet form without intermediate processing steps. Spherical crystallization can be categorized by different methods such as spherical agglomeration[36], emulsion solvent diffusion, ammonia diffusion system and neutralization technique.[37]

List of various drugs on which Emulsion solvent diffusion (ESD), spherical agglomeration (SA), Ammonia diffusion method (ADM) and neutralization technique (NT) has been tried for improving physicochemical properties in table 3.

Table 3: Summarizes the different techniques and solvents used in preparing spherical agglomeration of drugs.

Drug	Method	Solvent used	Reference
Celecoxib	SA	Acetone, water, chloroform	Khan G.M *et al*[38]
Aspirin	SA	Acid buffer, methanol, chloroform	Gupta VR *et al*[39]
Ibuprofen	ESD	Ethanol, water with sucrose, fatty acid ester	Viswanathan Cl *et al*[40]
Acebutalol HCl	ESD	water, ethanol, Isopropyl acetate	Kawashima Y *et al*[41]
Norfloxacin	ADM	Ammonia water, acetone, dichloromethane	Kawashima Y *et al*[42]
Enoxacin	ADM	Ammonia water, acetone, dichloromethane	Hector GP *et al*[43]
Tolbutamine	ESD, NT	Ethanol, water, Isopropyl alcohol	Sano A *et al*[44]

THE STABILITY OF S-SEDDS

Liquid self-microemulsion emerged crystal separation, stratification and other unstable phenomena in the storage.[45] Thus the liquid-SEDDS is converted into solid-SEDDS that can maintain the advantages of L-SEDDS whilst enhancing storage stability.[46,47] Moreover, a number of researchers compared the stability solid-SEDDS and solid dispersions, such as Milovic *et al*.[48] demonstrated that diatoms with adsorbed liquid carbamazepine (CBZ)-loaded self-emulsifying phospholipid suspension (SEPS) maintain polymorphic form of CBZ without significant influence on the drug dissolution rate and crystallinity, contrary to conventional solid dispersion where increase in crystallinity was observed under accelerated conditions (40°C and 70% RH) for period of 10 weeks. However, Kim *et al*.[49] showed that solid SMEDD of clopidogrel napadisilate (CN) decrease about 7% in the drug content at the end of 4 weeks. On the contrary, SD had no significant drug loss under accelerated conditions of 50°C/75% RH for 4 weeks.

Thus it can be seen that the instability or aging of the solid micro-emulsion is relevant to the surface properties of drug carriers. As the specific surface area increases, drug crystal-nucleation will decrease and preparation will be more stable.

CONCLUSION

S-SEDDS are a promising approach for the formulation of drugs with poor water solubility. The oral delivery of lipophilic drugs can be made possible by S-SEDDS, which has been shown to substantially enhance oral bioavailability. As stated above, numerous studies have proved that S-SEDDS substantially enhanced solubility, dissolution, and oral bioavailability of poorly water-soluble drugs. In addition, S-SEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability. Above all, S-SEDDS are very flexible to develop various solid dosage forms for oral administration.

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