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Preparation and characterization of pelletized solid dispersion of resveratrol with mesoporous silica microparticles to improve dissolution by fluid-bed coating techniques

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ABSTRACT

With hydrophilic surface and high surface area, porous silica has been applied to load insoluble drugs. Compared to solvent equilibrium method, resveratrol (RES)–mesoporous silica microparticles (MSM) solid dispersion prepared by fluid bed demonstrated higher drug loading and more complete dissolution. Pore volume and diameter have more remarkable effects than surface area to the drug loading and *in vitro* dissolution profiles. RES–polyethylene glycol solid dispersion with high drug loading showed fast but incomplete dissolution due to the recrystallization. The combination of fluid bed and MSM was an effective strategy to improve drug loading as well as dissolution for poorly water-soluble drugs.

1. Introduction

With the development of high throughput screening (HTS) from the 1980s, combinatory chemistry and HTS discovered numerous poorly water-soluble new chemical entities (NCEs) as drug candidates [1]. Studies have demonstrated that oral immediate release (IR) drug products constituted more than 50% of the top 200 drug product lists from four developed countries. More than 40% of these products on each list were determined to be poorly water-soluble drugs, and among them more than 30% belong to the Biopharmaceutics Classification System (BCS) II class with good membrane permeability but poor aqueous solubility [2].

In order to solve the dissolution problem of poorly water-soluble drugs, solid dispersion technology with polymers prepared by solvent evaporation method [3], supercritical fluid method [4], spray drying [5], hot-melt extrusion [6], and spray

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freeze drying (SFD) [7] have been extensively investigated. The interaction between drug molecule and carrier may retard drug recrystallization from the solid dispersion system and lead to quick dissolution [8]. The most popular carrier materials used in the solid dispersion are water-soluble polymers (e.g. PEG and PVP), which tend to be hygroscopic or sticky and which result in a reduction in the recovery of the solid dispersion and bring difficulty in the subsequent manufacture processing. Moreover, as milling or mixing with other excipients is often conducted before encapsulated into capsules or tableting, this sometimes facilitates crystallization of drug from the solid dispersion with the reduced dissolution.

In consideration of the disadvantages of solid dispersion with a water-soluble polymer, solid dispersion with porous materials such as silica, carbon nanotube [9], ZnO [10], starch [11] and magnesium carbonate [12] have been developed since 2004. Among these materials, porous silica has received wide attention particularly since silanol groups on the surface may be able to form hydrogen bonds with drug molecules, which results in a decrease in the crystallinity of drugs [13–17]. The differences between solid dispersions with hydrophilic and hydrophobic silica [8], porous and nonporous silica [13], different porous properties silica [18] or manufacturing by different methods [19] have all been thoroughly investigated before and will not be discussed in detail. In order to prepare a solid dispersion with spherical porous silicate, an approach with the help of a Wurster-type fluid bed was published in 2014 [20]. This approach is able to manufacture drug product with a pelletized shape and excellent mobility that is easy to operate in the subsequent pharmaceutical processes (e.g. encapsulation or tableting). It is also easily to adjust the amount of the drug loading by changing the amount of the feeding solution, which will provide drug products to meet different demands in the market. Therefore, this approach may have good potential to be widely used in solid dispersion product development.

The fluid bed technology is mainly applied on coating and granulation processes. For example, the fluid bed coating technology was first introduced to manufacture solid dispersion in 2008, in which PVP and nonpareil pellets were used as carriers to load drugs [21–23]. As shown in the graphic abstract, drugs/excipient to be coated into the pellets or MSNs are dissolved and sprayed via the nozzle. The drug may enter into the pore channels or adsorb onto the surface of the particles, which will mainly depend on the interaction of the drug with the mesoporous particles and the amount/concentration of the feeding solution.

Resveratrol (RES), a polyphenol with many biological activities such as anti-tumor, immune-regulation and anti-aging activities, was chosen as a model drug in this study. It was reported to have a poor solubility and high ability to permeate through the enterocytes [24], and belongs to the BCS II classification system, where the poor aqueous solubility and dissolution affect its clinical application. The aim of this study was to develop high drug-loaded solid dispersion of RES with different mesoporous silica microparticles (MSM) by fluid bed to improve its dissolution profile. Specifically, the effects of the three kinds of MSM on drug loading and the dissolution rate of the solid dispersions prepared by fluid bed were firstly investigated. Moreover, RES–MSM solid dispersions and RES–PEG solid dispersion were prepared by solvent equilibrium method for comparison. Characterization of these solid dispersions included surface morphology, *in vitro* dissolution profile, solid state forms of RES, thermal analysis and surface area analysis.

2. Materials and methods

2.1. Materials

RES (purity ≥ 98%, Xian Caocuixin Biological Science and Technology Co. Ltd., China) was used as the model drug. MSM (CHROMATOREX, Fuji Silysia Chemical Co. Ltd., Japan), which is a mesoporous silica microparticle, was selected as a porous material to load RES. Acetone and ethanol (AR, Tianjin Zhiyuan Chemical Co. Ltd., China) were used as organic solvents to dissolve RES in the preparation process of solid dispersions. PEG 6000 was purchased from Shanghai Aladdin Industrial Co. Ltd., China.

2.2. Instruments

Mini-Glatt fluid bed (Glatt GmbH, Germany) with a 0.5 mm nozzle and two air compressors (SF4FF, Atlas Copco) was used to manufacture RES solid dispersion, and the RES solution on a magnetic stirrer (PC-420, Corning) was pump into the fluid bed by a peristaltic pump (1003, Flocon) with a rubber tube (0.8 mm inner diameter) in the process. Agilent 1200 HPLC-DAD (Agilent, USA) with an Eclipse XDB-C18 HPLC column (150 mm × 4.6 mm, 5 μm, Agilent) was applied to the quantitative analysis of RES. The dissolution study was performed by dissolution-tester 700 (Erweka, Germany).

2.3. Preparation of RES–MSM solid dispersions by solvent equilibrium method

RES was dissolved in ethanol or acetone solvent, and then the MSM was added to the drug solution system. The RES–MSM suspension system reached adsorption equilibrium after stirring on a magnetic stirring apparatus at a low agitation speed for a period of time. Finally, the suspension was filtered and dried in vacuum drier at 40 °C for 24 h to reduce the residual solvent [19]. Samples were stored in a silica-gel drier for the following characterization.

2.4. Preparation of RES–MSM solid dispersions by fluid bed method

MSM of 50 cm^3 was placed in fluid bed first, while RES acetone solution of 100 mg/ml was applied as the feeding solution with the help of peristaltic pump. The process parameters of fluid bed were set as the following: inlet air temperature: 25–30 °C; material temperature: 22–26 °C; spray speed: 0.25–1.0 mg/ml; supply air rate: 0.10–0.25 bar; and atomization pressure: 0.15–0.30 bar.