Research paper

Increased dissolution rate and oral bioavailability of hydrophobic drug glyburide tablets produced using supercritical CO$_2$ silica dispersion technology

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ABSTRACT

The aim of this study was to design a silica-supported solid dispersion of a water-insoluble drug, glyburide, to increase its dissolution rate and oral absorption using supercritical fluid (SCF) technology. DSC and PXRD results indicated that the encapsulated drug in the optimal solid dispersion was in an amorphous state and the product was stable for 6 months. Glyburide was adsorbed onto the porous silica, as confirmed by the SEM images and BET analysis. Furthermore, FT-IR spectroscopy confirmed that there was no change in the chemical structure of glyburide after the application of SCF. The glyburide silica-based dispersion could also be compressed into tablet form. In vitro drug release analysis of the silica solid dispersion tablets demonstrated faster release of glyburide compared with the commercial micronized tablet. In an in vivo test, the AUC of the tablets composed of the new glyburide silica-based solid dispersion was 2.01 times greater than that of the commercial micronized glyburide tablets. In conclusion, SCF technology presents a promising approach to prepare silica-based solid dispersions of hydrophobic drugs because of its ability to increase their release and oral bioavailability.

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1. Introduction

Glyburide (Fig. 1) is an oral blood glucose-lowering agent belonging to the second generation of sulfonylureas commonly used in the treatment of Type 2 Diabetes [1]. Belonging to Class II of the BCS (Biopharmaceutics Classification Systems), glyburide has the characteristics of high permeability and poor solubility. The very low water solubility of glyburide results in poor and variable bioavailability and, consequently, possible side effects, such as variable clinical outcomes (hypoglycemia or hyperglycemia) [2–4]. A large variability in bioavailability has been observed in previous studies and it has been demonstrated that the oral absorption of glyburide is formulation-dependent. Micronized drugs, such as Glynase®PresTab® (usual oral dose: 1.5–3 mg daily), were marketed by Pfizer with increased in vivo dissolution and oral absorption, less variability and a lower dose could be used compared with non-micronized products, such as Micronase® (usual oral dose: 2.5–5 mg daily). Over the last decade, many

scientific attempts have been made to increase glyburide dissolution, including complexation with cyclodextrins [1,5], amorphization [6] and solid dispersion [7–9].

In recent years, several supercritical fluid (SCF) processes, which take advantage of some specific properties of SCF such as environmentally friendly and nontoxic profiles, have emerged as attractive methods for drug particle formation [10–12]. These processes can be carried out under relatively mild conditions and high purity microparticles can be prepared when supercritical carbon dioxide (scCO$_2$) is used. The most typical of these approaches involves the rapid expansion of a supercritical solution (RESS) process (using CO$_2$ as a solvent), which can reduce the particle diameter of poorly water-soluble drugs and further increase the dissolution rate. However, the application of the RESS process is largely limited by the low solubility of most solids of interest in scCO$_2$ [13]. In addition, microparticles prepared by this process tend to aggregate forming big particles due to the large surface area and van der Waals attraction [14,15].

A wide variety of organic and inorganic materials have been produced in the form of particles employing the SCF technology. Among them, carbon dioxide-soluble polymers such as siloxanes and fluoropolymers have received special attention for coating applications involving the RESS process. For example, Desimone
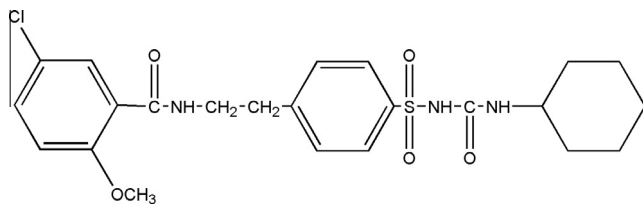
Fig. 1. Chemical structure of glyburide.

et al. reported the first dispersion polymerization of methyl methacrylate in scCO$_2$ using a highly soluble amorphous fluorinated polymer (poly(1,1-dihydroperfluorooctyl acrylate) (p-FOA) as a stabilizer [16]. Gupta et al. found that the adsorption of fenofibrate on high-surface-area silica by the SCF process significantly increased the drug dissolution rate. Moreover, there was no residual solvent in the final formulation [17]. Recently, a new solid dispersion system containing porous silica Sylysia 350 as a carrier has been developed using the scCO$_2$ technology [14]. High solubility and good absorption of a poorly water-soluble drug was achieved when the system was used on solid powders. However, it was not reported whether such a powder system could survive the compression during the tableting process.

The aim of this work was to study the feasibility of using SCF to prepare glyburide solid dispersion products with inert porous silica as a carrier to increase the dissolution and oral bioavailability. In our approach, a glyburide silica-based solid dispersion was obtained under mild conditions (40 °C) and this temperature was much lower than the melting points of the drug. Furthermore, no organic solvent was used throughout the SCF process, and, therefore, the problem of residual solvents associated with the conventional preparation methods of solid dispersions was avoided. The silica is a high purity amorphous anhydrous colloidal silicon dioxide used in many pharmaceutical products [18]. DSC, PXRD, and FT-IR were used to investigate the solid state properties of the formulations and SEM was employed to determine the morphology of solid dispersions. The silica-containing solid dispersions were further developed into a more commercially useful form, tablets, and the dissolution profile and absorption of such tablets were studied and compared those of commercial micronized tablets. To the best of our knowledge, this is the first time that a silica-supported solid dispersion has been converted into a tablet form.

2. Materials and methods

2.1. Materials

Glyburide (purity > 99%) and glipizide (purity > 99%) were provided by Kangya Pharmaceutical Co., Ltd. (China). Liquid CO$_2$ was purchased from Shenyang Liquefied Gas Industry Co., Ltd. (China). Silica (particle size ⩽ 44 μm, CAB-O-SIL®M-5DP, CABOT, Rheinfelden, Switzerland) and lactose (KERRY, USA) were supplied by Fengli Jingqiu Commerce & Trade Co., Ltd. (Beijing, China). Monobasic potassium phosphate, sodium hydroxide, phosphoric acid and sodium borate of analytical grade were used to prepare the buffer solutions. Both acetonitrile (HPLC-grade) and methanol (HPLC-grade) were purchased from Fisher Scientific (Pittsburgh, PA, USA). Formic acid was purchased from DIMA Technology Inc. (DikmaPure, USA).

2.2. Preparation of solid dispersion samples

A schematic diagram of the apparatus is shown in Fig. 2. The physical mixture of silica and glyburide in different ratios ((A) 1:15, (B) 1:7, and (C) 1:3, w/w) was sealed in a porous cellulose

pouch (20 ± 0.5 μm pore size) and kept inside the vessel. After filling the vessel with CO$_2$, the CO$_2$ was liquefied through a chiller and compressed to the operating pressure with a pump. Then, the fluid was preheated to the desired temperature in a heat exchanger before entering the precipitation vessel. The system pressure was controlled at 20 ± 0.2 MPa and the temperature was maintained at 40 ± 1 °C using a heater. Under these conditions, the system was allowed to equilibrate for 120 min and then the vessel was depressurized, and the solid dispersion of glyburide was collected from the cellulose pouch. At the same time, CO$_2$ was cleaned by a CO$_2$-Purifier and recycled by pumping into another gas cylinder. The drug loading (g drug/g formulation) was measured by dissolving a known amount of the formulation in methanol followed by HPLC analysis as described in detail in Section 2.10.

2.3. Differential Scanning Calorimetry (DSC)

Thermal analysis of different formulations was performed in a differential scanning calorimeter (DSC-1, Mettler-Toledo, Switzerland). Samples were weighed accurately into aluminum pans and thermograms were obtained at a heating rate of 5 °C/min over a temperature range of 0–200 °C under a nitrogen gas purge (30 ml/min). Aluminum oxide was used as the internal standard. Pyris software 8.04 (Perkin–Elmer) was used for analysis. The degree of crystallinity (X) was determined from calorimetric data as follows [19]:

$$X = \frac{\Delta H_s - \Delta H_a}{\Delta H_c - \Delta H_a} \times 100\% \tag{1}$$

where ΔH_s, ΔH_a, and ΔH_c are the heats of fusion for the actual, completely amorphous, and completely crystalline formulations, respectively.

2.4. Powder X-ray diffraction (PXRD)

The crystalline state of glyburide before and after the SCF process was evaluated using a X-ray diffractometer (Rigaku Geigerflex XRD, Japan) using Cu Kα radiation (λ = 0.154 nm, voltage: 30 kV, current: 30 mA, 2θ angle range: 5–45°, scan rate: 3.0°/min).

2.5. Morphology determined by scanning electron microscopy (SEM)

A Supra 35 field emission scanning electron microscope (accelerating voltage: 15 kV, ZEISS, Germany) was employed to determine the morphology of the particles. The particles were fixed using mutual conductive adhesive tape on aluminum stubs and covered with gold palladium using a sputter coater.
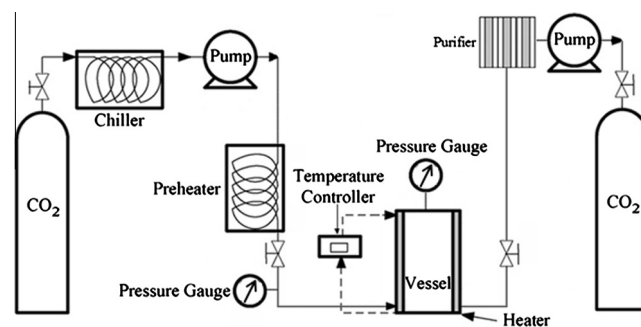

Fig. 2. Schematic of the supercritical CO$_2$ apparatus used for solid dispersion.