Journal of Pharmaceutical and Biomedical Analysis 129 (2016) 367–377

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Effect of milling conditions on solid-state amorphization of glipizide, and characterization and stability of solid forms

Kailin Xu[a], Xinnuo Xiong[a], Yuanming Zhai[b], Lili Wang[a], Shanshan Li[a], Jin Yan[a], Di Wu[a], Xiaoli Ma[a], Hui Li[a,*]

[a] College of Chemical Engineering, Sichuan University, Chengdu 610065, China
[b] Analytical &Testing Center, Sichuan University, Chengdu 610064, China

ARTICLE INFO

Article history:
Received 3 April 2016
Received in revised form 8 July 2016
Accepted 16 July 2016
Available online 18 July 2016

Keywords:
Glipizide
Amorphization
Solid forms
Solid-state transformations

ABSTRACT

In this study, the amorphization of glipizide was systematically investigated through high-energy ball milling at different temperatures. The results of solid-state amorphization through milling indicated that glipizide underwent direct crystal-to-glass transformation at 15 and 25 °C and crystal-to-glass-to-crystal conversion at 35 °C; hence, milling time and temperature had significant effects on the amorphization of glipizide, which should be effectively controlled to obtain totally amorphous glipizide. Solid forms of glipizide were detailedly characterized through analyses of X-ray powder diffraction, morphology, thermal curves, vibrational spectra, and solid-state nuclear magnetic resonance. The physical stability of solid forms was investigated under different levels of relative humidity (RH) at 25 °C. Forms I and III are kinetically stable and do not form any new solid-state forms at various RH levels. By contrast, Form II is kinetically unstable, undergoing direct glass-to-crystal transformation when RH levels higher than 32.8%. Therefore, stability investigation indicated that Form II should be stored under relatively dry conditions to prevent rapid crystallization. High temperatures can also induce the solid-state transformation of Form II; the conversion rate increased with increasing temperature.

1. Introduction

The solid-phase diversity of pharmaceutical molecules (e.g., pharmaceutical polymorphs, pseudo polymorphs, and amorphous solids [1–6]) has been widely investigated in contemporary drug research; in this regard, medical researchers can select the optimal form based on unique physicochemical properties and efficacy to achieve the maximum therapeutic benefit [1,7,8]. Compared with their crystalline counterparts, compounds in the amorphous form exhibit higher Gibbs free energy, which translates to high solubility and fast dissolution [3,4]. Hence, the amorphous form can be used to address bioavailability issues related to poor solubility and dissolution-rate limited absorption of drugs. Various techniques can induce the crystalline forms to solid-state amorphization, including grinding/milling, quench cooling of the melt, freeze drying, spray drying, and dehydration of crystalline hydrates [9,10].

Milling is frequently used in the pharmaceutical industry to reduce the particle size of drugs, improve dissolution properties and bioavailability by increasing the surface area of drugs, and achieve accurate dosing of drugs during administration [11,12]. The high mechanical energy generated during milling may modify the structural state of milled materials, particularly in terms of crystal morphology [13], alteration in chemical stability [12], polymorphic transformation [11], and partial or complete amorphization [14,15]. Among drug amorphization techniques, milling is a mild and environment-friendly method of producing amorphous materials without using solvents or high-temperature melting. Amorphous drugs exhibit higher bioavailability and medicine efficacy than other solid forms; as such, numerous studies have been conducted using the amorphous form, instead of the crystalline form, of a drug [16,17]. However, the intrinsic recrystallization tendency under the amorphous state can affect the stability of amorphous drugs and alter the therapeutic characteristics of drugs during storage, thereby imposing negative effects on medicine efficacy [16]. Therefore, the physicochemical stability of amorphous drugs and the mechanisms underlying their transformation must be investigated under various conditions. Furthermore, the poly-

* Corresponding author at: College of Chemical Engineering, Sichuan University, Chengdu, Sichuan, China.
E-mail address: lihuilab@sina.com (H. Li).

http://dx.doi.org/10.1016/j.jpba.2016.07.026
0731-7085/

morph conversion of drugs generated through milling must be explored.

Glipizide, a second-generation sulfonylurea derivative, can effectively decrease blood glucose levels by stimulating the release of insulin to treat type II diabetes [18,19]. Nevertheless, glipizide presents limited solubility in water (28.89 μg/mL solubility in water at room temperature) and acidic environment [20]. Glipizide can be absorbed rapidly when given orally to healthy people, whereas its absorption is erratic in diabetic patients owing to their impaired gastric motility and/or gastric emptying [21]. The absorption is limited by the dissolution rate due to the poor water solubility of glipizide. Amorphous glipizide is likely to overcome the drawback and will present higher solubility and faster dissolution than the crystalline form. The crystal structure of glipizide has been first reported in 2005, indicating the different intermolecular interactions, including hydrogen-bond networks and π-π stacking effect, exist in the crystal structure [22]. Various studies have focused on drug formulation and preparation to improve the solubility and bioavailability of glipizide [21,23]. Solid-state forms of glipizide were also investigated to enhance its dissolution rate [24], but sharp peaks were still observed in the X-ray powder diffraction (XRPD) patterns of the amorphous form.

A wide range of analytical techniques, including X-ray diffraction, differential scanning calorimetry (DSC), infrared spectroscopy, Raman spectroscopy, and solid-state nuclear magnetic resonance (SS-NMR), have been employed to characterize and monitor the solid forms of drugs [14,16,25]. X-ray powder diffraction (XRPD) is considered as the standard technique for the analysis of solid-state mixtures and quantification of the degree of crystallinity [26]. DSC is widely used for investigating the phase behavior of pharmaceutical solids, including quantification of the amorphous or crystal content [27,28].

This study aimed to obtain the amorphous form of glipizide by ball milling at different temperatures, investigate the effect of milling conditions on amorphization of glipizide, and study the detailed solid-state transformations mechanism in the amorphization of glipizide. In the previous report of co-amorphous form of glipizide with simvastatin, ball milling was not sufficient to produce amorphous glipizide; the pure amorphous glipizide could be obtained only by cryomilling at 4 °C [29]. Nevertheless, the amorphous glipizide was obtained by ball milling at various temperatures in our experiments when the time of milling was rightly controlled. In addition, the different solid-state transformations under varying temperatures were occurred. The solid forms of glipizide were systematically characterized using several analytical techniques. Solid-state transformations in glipizide by mechanical milling and non-mechanical treatments under different conditions were monitored; the relative stability of the solid-state forms of glipizide was investigated for up to 30 d under different levels of relative humidity (RH).

2. Materials and methods

2.1. Materials

Glipizide (99% pure) consisting of Form I was purchased from Chemsky International Co., Ltd. (Shanghai, China). Ultrapure water (18 MΩ resistivity, Millipore system) was used throughout the experiment. All reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of amorphous glipizide

Amorphous glipizide (Form II) was prepared through mechanical milling of commercial glipizide for 3 h at 15 °C. Form III was obtained through mechanical milling of commercial glipizide for 5 h at 35 °C.

2.2.2. Milling experiments

Milling experiments were performed using a planetary mill (PM-D0.4L, Droide Instrument & Equipment (Shanghai) Co., Ltd., China) with an air cycle refrigeration system under different temperatures. Four agate ball milling jars, with a volume of 50 cm^3 and contain 10 balls (ø = 10 mm) of the same material, were used. Each milling was performed using 1.0 g of the powder to ensure homogeneous milling and reproducible results. The rotation speed of the solar disk was set to 400 rpm, and alternate milling periods (typically 10 min) with intervals (typically 5 min) were applied to limit the mechanical heating of the sample. The samples were milled for 20 min–360 min at various temperatures and detected once at 20 min to evaluate the effect of milling on Form I.

2.2.3. Stability of solid forms of glipizide

The stability was investigated at 25 °C under different RH levels. RH of 0% was achieved with P_2O_5 in desiccators; RH of 11.3%, 32.8%, 43.2%, 57.6%, 75.3%, 84.3%, and 97.3% were achieved with the saturated salt solutions of LiCl, $MgCl_2$, K_2CO_3, NaBr, NaCl, KCl, and K_2SO_4 in desiccators, respectively, at 25 °C [30]. The effect of temperature on Forms I, II, and III was also investigated at different temperatures.

2.3. Analytical techniques

2.3.1. Scanning electron microscopy (SEM)

The SEM micrographs of glipizide in solid forms were examined using a JSM–7500 F scanning electron microscope at 5.0 kV. Electrically conductive samples were prepared by coating with a thin layer of gold in vacuum prior to examination.

2.3.2. XRPD

XRPD data were collected at room temperature by using an X'Pert PRO diffractometer (PANalytical) with a PIXcel 1D detector and Cu Kα radiation (λ = 1.5406 Å, generator setting: 40 kV and 40 mA). Diffraction data were collected within the 2θ range of 4° to 50°, with a step size of 0.01313° and a counting time of 30 ms/step.

2.3.3. DSC and thermogravimetric analysis (TGA)

DSC and TGA were performed to characterize the solid forms of glipizide. Weight reduction was determined using a thermogravimetric analyzer (TG209F1 Iris, NETZSCH, Germany), and thermograms were collected using a differential scanning calorimeter (Q200, TA Instruments Co., New Castle, DE, USA). These two techniques were performed with N_2 purge at 20 psi. Temperature was maintained at 30 °C to 400 °C, with a heating rate of 10 °C/min, for TGA, and 30 °C to 500 °C, with a heating rate of 10 °C/min, for DSC.

2.3.4. SS-NMR

SS-NMR of Form I and amorphous glipizide were recorded on a Bruker AV II–500 MHz NMR spectrometer operated at Larmor frequencies of 125.76 MHz for ^{13}C and 500.13 MHz for ^{1}H by using a double-tuned cross-polarization (CP)/magic-angle spinning (MAS) probe equipped with 4 mm rotors. ^{13}C CP and ^{1}H MAS NMR spectra were externally referenced to adamantane and tetramethylsilane, respectively. ^{13}C CP/MAS spectra was recorded using a spectral width of 37.9 kHz, a recycle delay of 3 s, 512 scans, and an acquisition time of 49.9 ms. ^{1}H MAS NMR spectra was recorded using a spectral width of 50 kHz, a recycle delay of 3 s, 256 scans, and an acquisition time of 20.5 ms.