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Stabilized amorphous glibenclamide nanoparticles by high-gravity technique

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ABSTRACT

The stable amorphous glibenclamide nanoparticles was obtained via anti-solvent precipitation using the high-gravity technique in this study. The effects of operating variables on the particle size were investigated. The properties of glibenclamide nanoparticles were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC) and dissolution test. The prepared glibenclamide nanoparticles had a mean size of 220 nm within a narrow distribution. The dissolution rate of glibenclamide nanoparticles was obviously faster than that of the raw glibenclamide or the commercial glibenclamide tablet. It achieved 85% in 5 min, while those of the raw glibenclamide and the commercial glibenclamide tablet achieved 35% and 55% respectively during the same period. The physical stability of the nanoparticles was tested after storing for more than 70 days at room conditions. Their morphology, particle size, crystalline form and dissolution rate almost remained constant during storage.

1. Introduction

Diabetes mellitus is a chronic metabolic disease resulting from insulin deficiency. Since it has become a major public health concern around the world, the researches on the safe and effective anti-diabetic drugs have become a top priority.

Glibenclamide (GCM), N-[4-β-[2-methoxy-5-chlorobenzamido]-ethyl)-benzenesulfonyl]-N-cyclohexyl-urea, is the second generation oral sulfonylurea antidiabetic agent widely used to lower blood glucose levels for the patients with type II diabetes mellitus [1]. It acts mainly by stimulating endogenous insulin release from β-cells of pancreas and is effective in reducing serum glucose concentrations.

GCM belongs to class II compound according to the biopharmaceutics classification system (BSC) due to its low aqueous solubility (~38 μmol L^{-1} at 37 °C) and poor dissolution rate [2,3]. In order to improve the dissolution and bioavailability performance of GCM, several techniques have been used, such as micronization [4,5], use of surfactants [6,7], molecular dispersion [8], inclusion complexation with cyclodextrin [9] and the transformation from crystalline drug into amorphous state [10]. It has been reported that the amorphous state of active pharmaceutical ingredients (APIs) is much more soluble and consequently has better bioavailability than their crystalline counterparts [11,12]. The first amorphization of GCM using melting and quench cooling was carried out in 1991 by Hassan et al. [13]. They observed that the rapid cooling of the melt resulted in an amorphous compound with its solubility 10 times higher than its former crystalline form. Recently, Wojnarowska et al. [14] used two different preparation techniques, the quench cooling of the melt and the cryogrinding milling to convert the crystalline GCM into the amorphous form and analyzed its molecular dynamics.

In addition, another most common way to increase the dissolution rate of water-insoluble drug was to reduce the particle size and increase the surface area of APIs [15]. According to the Noyes–Whitney and Ostwald-Freundlich equations, the size reduction can offer improved dissolution and solubility characteristics [16]. Many techniques had been utilized to reduce the particle size [17]. Among these techniques, liquid precipitation technique has a good prospect, because it is low-cost, rapid and easy to perform, and often enables the small nanoparticles with a narrow unimodal distribution.

Previously, it had been shown that the particles synthesized under the high-gravity environment had a narrow size distribution and the reaction can be accelerated due to the intensified micromixing and mass transfer [18]. Further, the high gravity technique had been proven to be useful in the pharmaceutical industry. In 2004, Chen's group produced benzoic acid nanoparticles of 10 nm in size [19]. In 2006, they obtained amorphous cefurox-

Abbreviations: GCM, glibenclamide; API, active pharmaceutical ingredient; RPB, rotating packed bed; HPMC, hydroxypropylmethylcellulose; DMF, NN-dimethylformamide.

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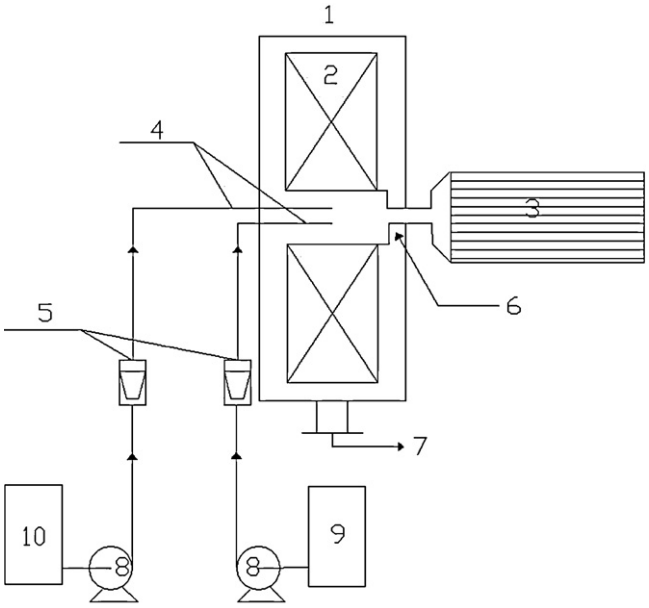

Fig. 1. Schematic representation of high-gravity processes (1: casing; 2: packed rotator; 3: motor; 4: liquid distributors; 5: flow meters; 6: seal ring; 7: outlet; 8: pump; 9, 10: liquid storage containers).

ime axetil particles of 300 nm [20] by an antisolvent precipitation process in a high gravity equipment of rotating packed bed (RPB). The dissolution rate of the processed drug particles was greatly enhanced.

In this work, anti-solvent precipitation process proceeded in a RPB and followed by spray drying, was proposed to generate the amorphous GCM nanoparticles. Conventional water-soluble pharmaceutical excipients, such as HPMC, were used as solid support to prevent the GCM nanoparticles from aggregation and to enhance the dissolution of GCM. The as-prepared product was characterized by SEM, FT-IR, XRD, and DSC. The stability and dissolution performance of amorphous GCM nanoparticles were evaluated.

2. Materials and methods

2.1. Materials

Raw GCM (purity is 99.7%) was purchased from Jinan Zhongke Yitong Chemical Co. Ltd. N, N-dimethylformamide (DMF) of analytical grade was obtained commercially from Beijing Chemical works (Beijing, RPC). Polyvinylpyrrolidone (PVP) was obtained from Tianjin Chenhua Chemicals Co. Ltd. Hydroxypropylmethylcellulose (HPMC) was obtained from Zhejiang Zhongwei medicine manufacturing enterprise. Deionized water was prepared with Hitech-K Flow Water Purification System (Hitech Instruments Co. Ltd, Shanghai, China). Commercial glibenclamide tablets (3.58 wt%) was obtained from Beijing Taipingyang medicine Co. Ltd.

2.2. Preparation of GCM nanoparticles

Anti-solvent precipitation process in a RPB was shown in Fig. 1. The detailed structure of RPB could be referenced [19]. RPB, the key component of high-gravity technique, can form homogeneous mixing environment and make a uniform supersaturation state by greatly enhanced micro-mixing to produce drug particles with good quality. Two liquid streams could be introduced into RPB via distributors and then mixed in the center of RPB to yield particles. The mixture flows in the radial direction under high gravity environment owing to centrifugal force, and finally assembles at the shell and leaves out from the rotator. In a typical procedure, DMF and water were used as solvent and anti-solvent respectively. Raw GCM was dissolved in DMF at the concentration of 50 mg ml^{-1}, and the solution was filtrated through 0.45 μm pore size membranes to remove the impure particulates. Then 0.17% HPMC aqueous solution was prepared. After that, GCM solution and HPMC solution were pumped into RPB at the flow rates of 8 L h^{-1} and 240 L h^{-1} respectively. The two liquid streams mixed well owing to centrifugal force, and the GCM nanoparticles precipitated. The slurry was dried by spray drying (SD-Basic, Labplant, UK) under the following conditions: inlet temperature, 160 °C; outlet temperature, 70–90 °C; spray flow rate, 21 mL min^{-1}. Finally, the GCM nanoparticles were obtained.

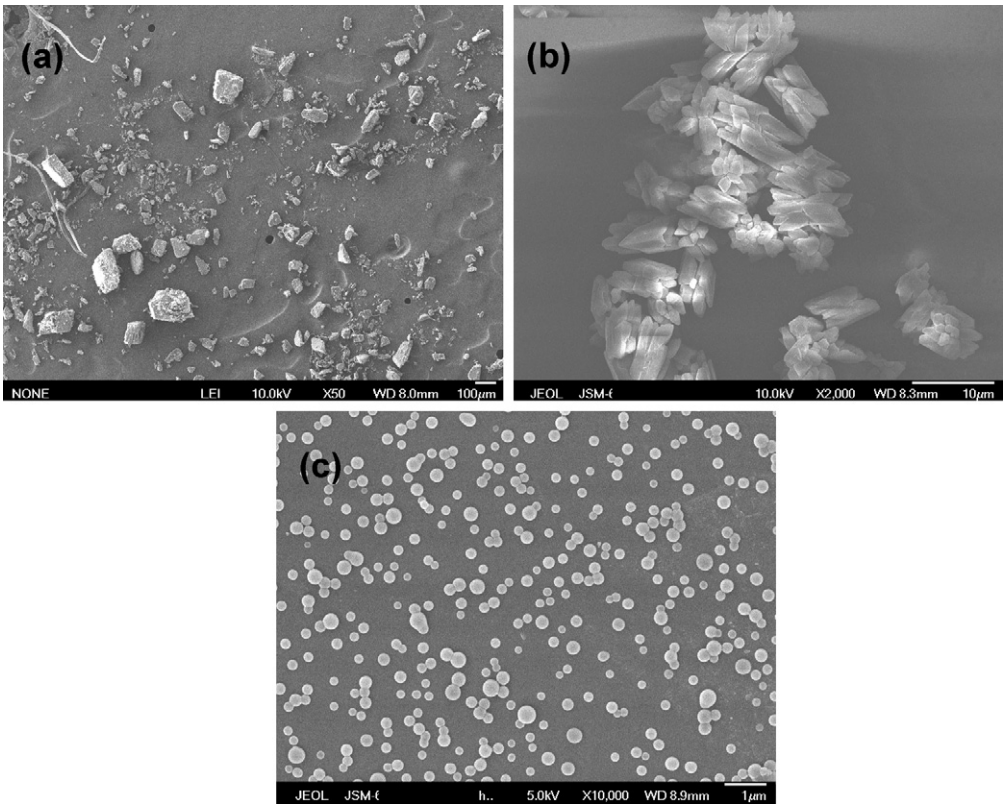

Fig. 2. SEM images of (a) raw GCM; (b) GCM precipitated from deionized water (c) GCM precipitated from HPMC aqueous solution.