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Large-scale preparation of stable irbesartan nanoparticles by high-gravity liquid antisolvent precipitation technique

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ABSTRACT

Irbesartan (IBS), an angiotensin II receptor antagonist mainly used for the treatment of hypertension, is a poorly water-soluble drug. To enhance its solubility and dissolution rate, and thus potentially improve the oral bioavailability, stable amorphous IBS nanoparticles were prepared via high-gravity liquid antisolvent precipitation (HGLAP) technique, without requiring any additives. The effect of various operating parameters on particle size was investigated in detail. IBS nanoparticles with an average size of 295 nm were successfully prepared. Compared to the raw drug, the saturation solubility of IBS nanoparticles was dramatically increased from 3.6 μg/mL to 13.7 μg/mL. The prepared nanoparticles exhibited a good stability and were capable of generating a maximum supersaturation level, reaching up to ~13.5 times of raw drug's saturation solubility. In *vitro* dissolution test, IBS nanoparticles showed a significantly enhanced dissolution rate and 100% of the drug dissolved within 30 min, while the raw drug did not dissolve completely even after 120 min. HGLAP technique offers a great opportunity for the massive production of drug nanoparticles with improved solubility and dissolution rate.

1. Introduction

It is estimated that 40% or more of the newly developed drugs are poorly water-soluble [1]. For drugs with low solubility and high permeability, the dissolution rate in the gastrointestinal tract limits their bioavailability [2]. Nanoparticles are well known to improve dissolution rate and bioavailability of poorly water-soluble drugs owing to their increased surface area [3–6]. Nanoparticles could be obtained by media milling [7,8], high-pressure homogenization [9,10], supercritical fluid technique [11], liquid antisolvent precipitation [12–14], and so forth. Among these techniques, liquid antisolvent precipitation has promising properties, such as its low-cost, convenience in processing, and easy scaling up, especially from an industrial viewpoint.

The driving force of a liquid antisolvent precipitation process is the supersaturation of a solution generated by mixing the drug solution and an antisolvent. Both of the supersaturation level and its spatial concentration are crucial to obtain nanoparticles with a narrow distribution [15,16]. It is well known that micromixing efficiency is a key factor in determining the supersaturation level [16–18]. Uniform spatial supersaturation distribution on molecular scale can only be reached by intense micromixing. Various techniques and equipment are being developed to achieve excellent mixing efficiency to prepare nanoparticles with narrower particle size distribution [18–21].

The high-gravity liquid antisolvent precipitation (HGLAP) technique, which usually implemented by rotating packed bed (RPB), can strongly intensify mixing efficiency and mass transfer during the precipitation process. The magnitude of micromixing and mass transfer rate in RPB are much larger than these in the conventional stirring tank reactor, which contributes to generating higher supersaturation and more uniform spatial concentration. Therefore, it can provide good control of particle size and size distribution. In addition, HGLAP technique is of high industrial interest because of its advantages of low-cost, time-saving, convenience in processing, and ease for scale-up. It has been successfully applied to prepare a variety of pharmaceutical nanoparticles, such as cefixime [12], itraconazole [22], glibenclamide [23], and cefuroxime axetil [24].

Irbesartan (IBS), a biopharmaceutics class II drug with low solubility and high permeability, is primarily used for the treatment of cardiovascular diseases such as hypertension, cardiac insufficiency, and cardiac arrhythmia [25]. However, as a poorly water-soluble drug, IBS features a low dissolution rate, which limits its intestinal absorption and bioavailability [26]. To enhance the bioavailability, numerous works have been devoted to increasing the dissolution rate of IBS, such as the formation of IBS solid dispersions [27,28], β-cyclodextrin complexes [29], nanocomposite particles [30], and micron-sized crystalline particles [31]. However, a large amount of pharmaceutical additive(s) was usually required to obtain dry powder, generally >50% of the pure drug. The drug content was thus much lower than that of the commercially available tablets (APROVEL, drug content of 60%). Therefore, it is of great significance to prepare pure IBS nanoparticles without using any additives.

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The objective of this study was to propose HGLAP technique for large-scale preparation of pure IBS nanoparticles with enhanced solubility and dissolution rate. To the best of our knowledge, no attempts have been done for large-scale production of IBS nanoparticles, especially via HGLAP technique. The effects of operating parameters on particle size were investigated in detail. No additive was added in order to gain concrete information on the effect of HGLAP on the control of drug particle size. The prepared IBS nanoparticles were characterized by particle size, scanning electron microscopy (SEM), fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), differential scanning calorimeter (DSC), and specific surface area analysis. The stability, supersaturation generation, saturation solubility, and in *vitro* dissolution rate of IBS nanoparticles were also evaluated.

2. Materials and methods

2.1. Materials and equipment

Raw IBS (purity >99.4%) was purchased from Liuhe Xiuzheng Pharmaceutical Co. Ltd. (Jilin, China). All reagents used were of analytical grade and obtained commercially from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Liquid antisolvent precipitation process in RPB is shown in Fig. 1. Parameters of the RPB are shown in Table 1. The key part of the RPB (high-gravity machine) is a packed rotator (2). The rotator is packed with stainless steel wire mesh and installed inside the fixed casing. Drug solution and antisolvent are pumped through the liquid distributors (4) introduced into the RPB. After entering the bed, the liquids flow in the radial direction under centrifugal force, passing the packing, finally leave the casing through the liquid exit (9).

2.2. Preparation of IBS nanoparticles

In a typical process, methanol and deionized water were used as solvent (S) and antisolvent (AS), respectively. Raw drug was dissolved in methanol at the concentration of 15 mg/mL. The drug solution was filtrated through a 0.45 μm nylon membrane to remove the possible particulate impurities. The drug solution and deionized water were added into the storage containers 6 and 7, respectively. Then, the two liquids were pumped through the liquid distributors 4 into the RPB, separately. After entering the RPB, the two liquids mixed in the packed bed zone. Nanoparticles were generated simultaneously when the two streams encountered. The as-obtained drug suspension was collected through the outlet and was filtered. The filter cake was then dried in a vacuum oven at 65 °C for 12 h to obtain the drug powder. The dried nanoparticles were sealed in a polyethylene bag under room conditions until further use for characterization and testing.

2.3. Particle size and morphology

Particles morphology was analyzed by JSM-6701 SEM (JEOL, Japan). Samples were coated with gold in an argon atmosphere and then observed by SEM. Particle size distribution (PSD) was analyzed using a Zetasizer-3000HS analyzer (Malvern).

2.4. Specific surface area

Specific surface area was measured by a Micromeritics ASAP 2420 (Micromeritics, USA) using N_2 an adsorption method. Prior to measuring, all of the samples were degassed at least 4 h at room temperature. The calculation was based on the BET equation.

2.5. Chemical composition and physical characteristics

FT-IR spectra were recorded with Nicolet iS10 FT-IR spectrometer (Nicolet, USA) in the range of 525–4000 cm^{-1}. Samples were diluted with KBr mixing powder at 1% and pressed to obtain self-supporting disks.

XRD was performed using a XRD-6000 diffractometer (Shimadzu, Japan). Cu Kα radiation was generated at 30 mA and 40 kV. The scanning speed was 5°/min from 3° to 40° with a step size of 0.02°.

DSC analysis was implemented using a Q200 analyzer (TA, USA). The heating rate was 10 °C/min, and a dry nitrogen purge of 20 mL/min was used. Calibration of the analyzer with respect to temperature and enthalpy was reached using high purity standard of indium.

2.6. In vitro dissolution test

In *vitro* dissolution test was carried out following the USP Apparatus 2 (paddle) method (D-800LS, Tianjin, CN). The paddle speed was 50 rpm, and the dissolution medium was 0.1 mol/L HCl which was maintained at 37.0 ± 0.5 °C. The powder was added into vessels containing 900 mL of the dissolution medium, and 2 mL samples were withdrawn at specific intervals. In the meantime, fresh medium (2 mL) was added to keep constant volume. The samples were filtered using a 0.22 μm filter. The drug concentrations were measured by a UV-2501 spectrophotometer (Shimadzu, Japan) at 245 nm. Each sample was analyzed in triplicate.

2.7. Supersaturation generation

The supersaturation generation capability of IBS nanoparticles was defined as C_{ns}/C_{rs}, where C_{ns} was the supersaturated concentration of IBS nanoparticles, and C_{rs} was the saturation solubility of the raw drug. To measure the value of $C_{rs,}$ an excess amount of the raw drug

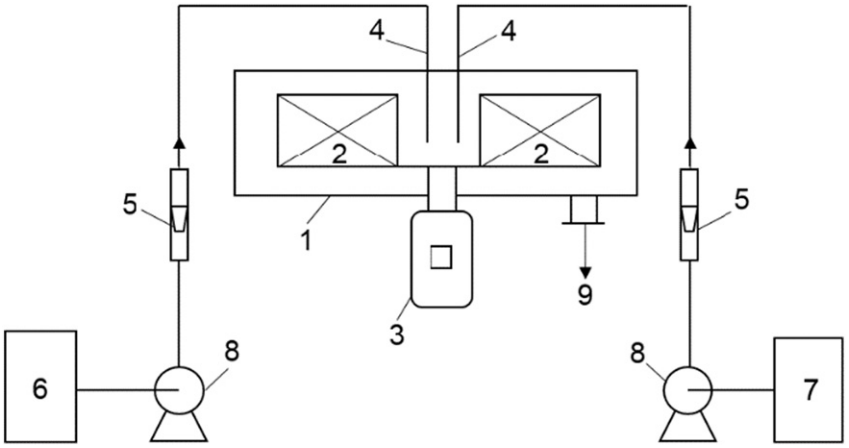

Fig. 1. Schematic representation of HGLAP process. 1-casing; 2-packing; 3-motor; 4-liquid distributor; 5-flow meters; 6, and 7-liquid storage tank; 8-pump; 9- liquid outlet.