Powder Technology 308 (2017) 200–205

Contents lists available at ScienceDirect

Powder Technology

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

A green route to beclomethasone dipropionate nanoparticles via solvent anti-solvent precipitation by using subcritical water as the solvent

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ARTICLE INFO

Article history:
Received 2 November 2016
Received in revised form 2 December 2016
Accepted 4 December 2016
Available online 09 December 2016

Keywords:
Beclomethasone dipropionate
Subcritical water
Green solvent
Green route
Nanoparticles

ABSTRACT

Oral beclomethasone dipropionate (BDP) has been extensively studied in the management of ulcerative colitis in clinical practice in recently years. However, the effective bioavailability and absorption of BDP are limited by its poor water solubility when administered orally. Herein, we report a green process for the synthesis of BDP nanoparticles via solvent anti-solvent precipitation, in which the subcritical water (SBCW) and cold water were used as the solvent and anti-solvent respectively. Polyethylene glycol (PEG), a non-ionic, hydrophilic polymer was introduced as stabilizers in the SBCW process to obtain sub-50 nm BDP nanoparticles with improved dissolution rate. Scanning electronic microscopy (SEM), Fourier transform infrared (FTIR) spectrophotometry, powder X-ray diffraction (XRD) and dissolution tests were performed to investigate the corresponding particle morphology, structure and dissolution rate properties of the BDP nanoparticles. The obtained BDP nanoparticles are <50 nm in diameters with uniform distribution, exhibiting similar chemical structures, lower crystallinity and much higher dissolution rate than the raw BDP drug. These results show that as-synthesized BDP nanoparticles are promising for oral administration of BDP towards the management of ulcerative colitis.

1. Introduction

Beclomethasone dipropionate (BDP) has long been used for the prevention of bronchospasm in patients with asthma, in the form of dry powder inhalers [1]. In recent years, oral BDP has been extensively studied in the management of ulcerative colitis in clinical practice [2,3]. However, when administered orally, the effective bioavailability and absorption of BDP are limited by the poor water solubility of BDP. The development of nanotechnology has attracted much attention in various fields [4–7]. Previous studies on poorly soluble drugs have demonstrated that particle size reduction to nanometer can lead to an increased rate of dissolution and higher oral bioavailability [8–10]. Therefore, it is critical to develop BDP nanoparticles with high dissolution rate for oral applications. Along with others, we have reported the preparation of BDP particles in the range of hundreds of nanometers to several micrometers by solvent anti-solvent precipitation in water-organic solvent systems [11–13]. However, the development of sub-100 nm BDP nanoparticles is still challenging [14,15]. Particularly, sub-50 nm BDP nanoparticles have not been reported as far as we are aware.

Solvent anti-solvent precipitation has been regarded as an effective approach for mass production of nanoparticles [16]. However, conventional process of anti-solvent precipitation are not suitable for preparation of biomaterials, since they usually use organic solvents, which may leave high levels of residual solvent, leading to the need for further purification [17–19]. Subcritical water (SBCW) refers to water heated to any temperature up to its critical temperature of 374 °C and with enough pressure to maintain its liquid state [20]. The polarity of SBCW can be controlled over a wide range by changing temperature under moderate pressures [21,22]. Although water at ambient conditions is too polar to solvate most organics, SBCW acts more like organic solvents so that the solubility of organics is dramatically increased [23]. Therefore, using SBCW as the solvent overcomes the requirements of using toxic organic solvents to dissolve hydrophobic drugs for majority of current solvent anti-solvent precipitation techniques [24–26].

Herein, for the first time, sub-50 nm beclomethasone dipropionate nanoparticles have been successfully synthesized via solvent anti-solvent precipitation by using SBCW as the solvent and cold water as the anti-solvent, respectively. Polyethylene glycol (PEG), a non-ionic, hydrophilic polymer was introduced as stabilizers in the precipitation process to obtain BDP nanoparticle with improved dissolution rate. The morphology, structure and dissolution rate properties of the nanoparticles were investigated by scanning electronic microscopy (SEM),

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http://dx.doi.org/10.1016/j.powtec.2016.12.019
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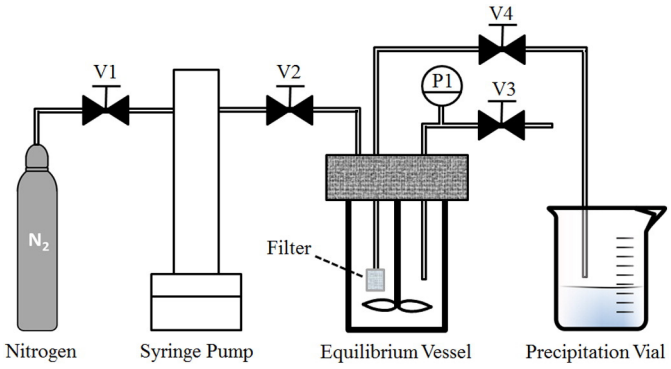

Fig. 1. A schematic diagram of the solvent anti-solvent precipitation by using subcritical water reactor system.

Fourier transform infrared (FTIR) spectrophotometry, powder X-ray diffraction (XRD) and dissolution tests.

2. Experimental

2.1. Materials

The beclomethasone dipropionate ($C_{28}H_{37}ClO_7$, ≥98%) was purchased from Shenzhen Shijingu Bio & Tech Co., Ltd. The melting point and molecular weight of BDP are 119 °C and 521. The ethanol (≥99.7%, for washing) was purchased from Beijing Chemical Works. The nitrogen (≥99.9992%) was purchased from PREMER. The polyethylene glycol-4000 (PEG4000) was obtained from Shandong Ruitai Chemicals Co. Ltd. The average molecular weight of PEG4000 used in this work is 4000 and the melting point of PEG4000 is 58–61 °C. All the chemicals were used as received without purification. The deionized water was prepared by a Hitech-K flow water purification system (Hitech instrument Co., Ltd. Shanghai, China) and used in all experiments.

2.2. Apparatus and procedure

A schematic diagram (Fig. 1) shows the setup of SBCW apparatus. The fittings and tubing were composed of stainless steel (type 316). The temperature, the pressure and the stirring speed of the system were displayed by the 4590 Micro Bench Top Reactor (Parr, USA) attached to a 4848 Reactor Controller (Parr, USA). A microprocessor based control module in the reactor controller was used to provide the precise temperature (±0.1 °C) and the stirring speed control with adjustable tuning parameters. The micro reactor (MR) had an internal volume of 100 mL. A 0.5-μm filter was installed inside of the MR to remove any undissolved particles. The nitrogen used as protective gas was supplied to the system by a syringe pump (ISCO model 260D) to control the pressure.

For the preparation of BDP nanoparticles, a certain amount of BDP powder (10 mg) and water (6 mL) was loaded into the micro reactor (MR), forming turbid solution. Nitrogen was then supplied to the system by a syringe pump (ISCO model 260D) to exclude air and maintain the pressure of the MR at 5 MPa. The system was heated to a selected temperature and the obtained SBCW solution of BDP was stirred at 160 rpm for 10 min. By aerating nitrogen, the SBCW solution of BDP was then deliver into the precipitation vial, after filtrated through a membrane with a pore size of 0.45 μm to remove the possible particulate impurities. The SBCW solution of BDP were mixed with 15 mL of anti-solvent (pure water, or aqueous PEG solution with concentrations of 0.01 wt%, 0.02 wt%, and 0.03 wt%, respectively) under constant magnetic stirring in the precipitation vial, to form BDP nanoparticles. The powders of BDP nanoparticles were obtained by centrifugation (12,000 rpm for 15 min) of the suspension and dried in a vacuum oven at 60 °C.

2.3. Characterization

The morphology studies were performed using a JEOL JSM-6360LV scanning electron microscope (SEM). Typically, a glass slide with the sample was fixed on an aluminum stub using double-sided adhesive tape and sputter coated with Au at 50 mA for 30 s by a Pelco Model 3 sputter-coater under an Ar atmosphere. The particle size distribution of the samples was determined by dynamic light scattering (DLS, Zetasizer, Malvern Instruments Ltd.). A PerkinElmer spectrum GX Fourier transform infrared (FTIR) spectroscopy system was used to record the FITR spectra of solid samples. X-ray diffraction (XRD) patterns of the samples were measured by an XRD-6000 diffractometer (Shimadzu Inc.), consisting of a rotating anode in transmission mode using Cu Kα

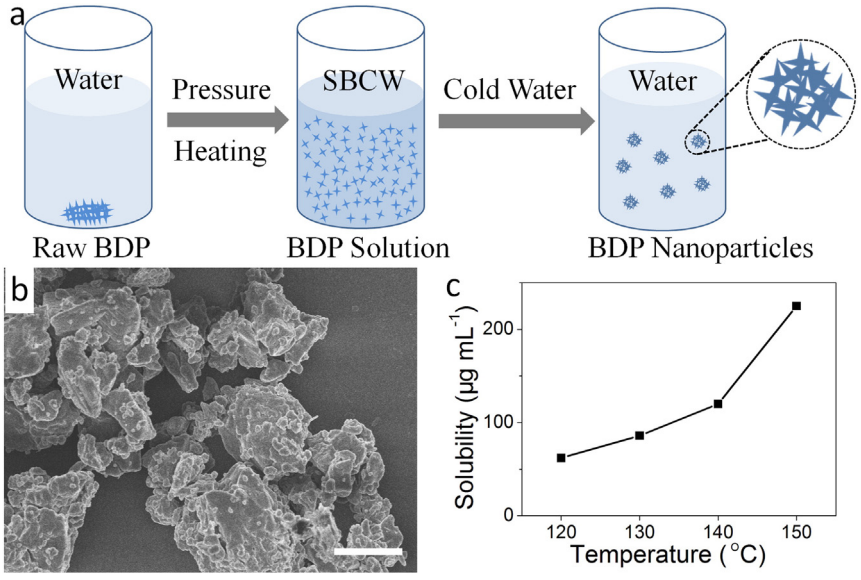

Fig. 2. (a) Schematic diagram of the BDP nanoparticle formation during precipitation by using SBCW as the solvent and cold water as the anti-solvent, (b) a typical SEM image of raw BDP, (c) effect of the SBCW temperature on the solubility of BDP. The scale bar in (b) represents 10 μm.