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

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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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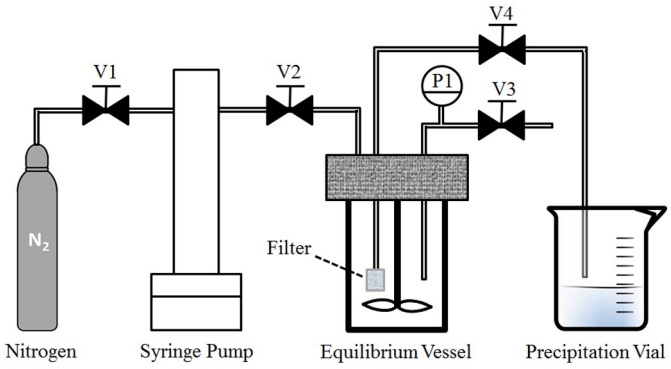


**Fig. 1.** A schematic diagram of the solvent anti-solvent precipitation by using subcritical water reactor system.

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

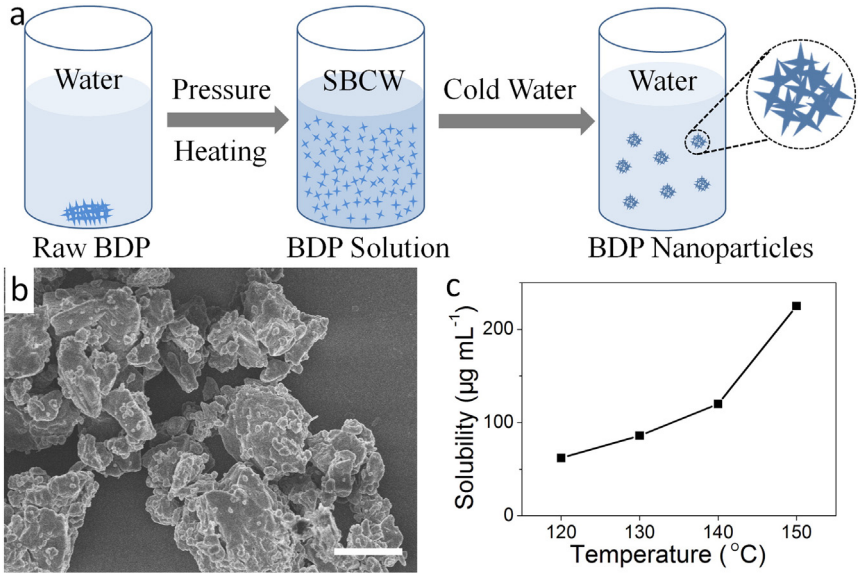


**Fig. 2.** (a) Schematic diagram of the BDP nanoparticle formation during precipitation by using SBCW as the solvent and cold water as the anti-solvent, (b) a typical SEM image of raw BDP, (c) effect of the SBCW temperature on the solubility of BDP. The scale bar in (b) represents 10 μm.

radiation generated at 30 mA and 40 kV. The scanning speed was 5°/min in range of from 5° to 60° with a step size of 0.05°.

### 2.4. Dissolution testing

The dissolution testing for each sample (raw BDP, BDP nanoparticles and BDP/PEG nanoparticles, respectively) was performed on 25 mg dry powder using a dissolution apparatus (D-800LS, Tianjin, China) through the USP Apparatus II (paddle) method [27]. The paddle speed and bath temperature were set to 50 rpm and 37.0 ± 0.5 °C, respectively. A phosphate buffer (pH = 6.8) was used as the dissolution medium. 25 mg of the sample was placed into a vessel containing 900 mL of the dissolution medium. Samples (3 mL) were withdrawn and immediately filtered through a 450 nm syringe filter for analysis at specified time points (2 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 90 min, 120 min). The content of BDP was assessed by UV spectroscopy (Shimadzu UV-2501) at 240 nm. Each dissolution experiment was performed in triplicate.

## 3. Results and discussions

### 3.1. Formation of BDP nanoparticles via SBCW process

Fig. 2(a) shows the major steps for the synthesis of BDP nanoparticles via precipitation by using SBCW as the solvent and cold water as the anti-solvent. The raw BDP are anomalistic aggregates from ten to hundreds of micrometers (Fig. 2b) and are practically insoluble in water at ambient conditions (solubility < 1 μg/mL) [28,29]. Fig. 2(c) shows the experimental solubility data of BDP in subcritical water of various temperature, in which a gradual increase in solubility as the temperature raised from 120 °C to 140 °C, along with a large solubility increase between 140 °C and 150 °C. The correlation of the BDP solubility and temperature of the subcritical water was in agreement with previous reports on other kinds of active pharmaceutical ingredients [30–32], which was attributed to the decreasing of dielectric constant of water [33]. When mixing the BDP solution of SBCW with cold water (0 °C), the solubility of BDP decreased. Therefore, BDP nanoparticles formed due to the supersaturation of BDP molecules.

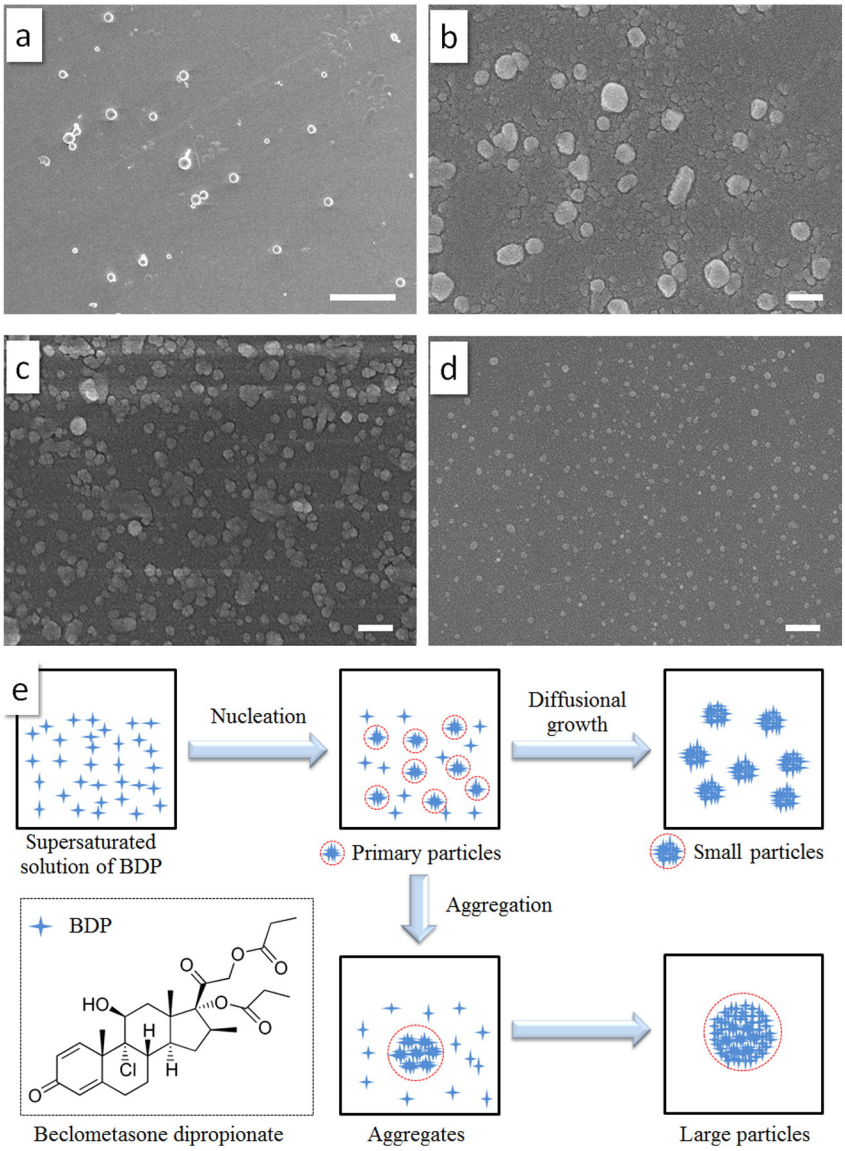


**Fig. 3.** SEM images of BDP particles obtained through the solvent anti-solvent precipitation with SBCW of different temperatures as the solvent: (a) 120 °C, (b) 130 °C, (c) 140 °C, and (d) 150 °C. Cold water at 0 °C was used as the anti-solvent for all samples. The scale bar in (a) represents 10 μm and in (b–d) represents 200 nm. (e) Schematic diagram of the particle diffusional growth process of the primary particles to small BDP nanoparticles and the aggregation process of the primary particles to large BDP nanoparticles, respectively.

### 3.2. Effect of the temperature of SBCW solutions

Fig. 3 presents the BDP particles generated through the solvent anti-solvent precipitation with SBCW of different temperatures (120 °C, 130 °C, 140 °C and 150 °C, respectively) as the solvent and cold water at 0 °C as the anti-solvent. The particle population generated from solvent at lower temperature was lower than particles from solvent at higher temperature. We attributed this phenomenon to the following reason. Since the solubility of BDP shows a positive correlation to the temperature of subcritical water, more BDP molecules were dissolved in the solution when the temperature of solvent was higher, resulting in higher yield of precipitated particles. The BDP particles precipitated from SBCW solution at 120 °C tended to form micro-sized particles (Fig. 3a). BDP nanoparticles appeared when the SBCW temperature was increase to 130 °C, although some large particles/aggregates were also observed (Fig. 3b). When 140 °C SBCW were used, sub-100 nm spherical particles were obtained (Fig. 3c). As the temperature of SBCW increased to 150 °C, the size of obtained BDP nanoparticles decreased to sub-50 nm. However, it was noted that the distributions of obtained BDP nanoparticles in both Fig. 3(c) and (d) were not very uniform. For the precipitation of BDP particles via solvent anti-solvent process, the level of supersaturation was determined by the difference of the BDP solubility under subcritical and ambient water conditions. As depicted in Fig. 3(e), primary BDP particles formed through a burst-nucleation step due to the change of the supersaturation of BDP molecules when mixing the solvent and anti-solvent. The particles then grew to larger particles via diffusional growth and/or aggregation. The increase of SBCW temperature from 120 to 150 °C enhanced the solubility of BDP, leading to an enhanced supersaturation, along with a decreased average particle size. However, the probability of particle collision increased drastically with increased temperature, which in turn leading to the aggregation and formation of large particles. Therefore, the BDP nanoparticles obtained by using SBCW of high temperature (150 °C) exhibited wide size distribution.

### 3.3. Effect of the concentration of the pharmaceutical excipients

Previous studies have demonstrated that the size of the drug particles tightly associated with the rate of dissolution and oral bioavailability [8,9]. Therefore, it is critical to develop BDP nanoparticles with uniform size distribution for oral applications. To prevent the aggregation of primary particles, PEG molecules were used at the stabilizers during the solvent anti-solvent precipitation process of BDP nanoparticles. Since PEG is a wildly used excipient in many types of pharmaceutical formulations approved by food and drug administration (FDA) for clinical, the use of PEG-assisted synthesis of BDP nanoparticles were important reference for practical applications [17,18,34,35]. In this work, the PEG-assisted synthesis of BDP nanoparticles were performed by using SBCW water at 140 °C as the solvent and aqueous PEG solution (0.01 wt%, 0.02 wt% and 0.03 wt%, respectively) as the anti-solvent and the temperature of the aqueous PEG solution was 0 °C. Fig. 4 showed the SEM images of BDP nanoparticles prepared by PEG-assisted anti-solvent precipitation. By adding 0.01 wt% PEG in water as the anti-solvent, the obtained BDP nanoparticles (Fig. 4a) exhibited similar morphology as the particles shown in Fig. 3(c). When the PEG concentration was increased to 0.02 wt%, the obtained BDP nanoparticles were much smaller with narrower particle size distribution (Fig. 4b). The SEM images also demonstrated the degree of agglomeration of the BDP nanoparticles was reduced with an increasing of the PEG proportion. In our experiments, further increasing of the PEG concentration to 0.03 wt% caused slightly reducing of the sized of obtained BDP particles (Fig. 4c). The hydrodynamic diameters of BDP nanoparticles obtained by using various anti-solvents (aqueous PEG solutions with concentrations of 0.01 wt%, 0.02 wt%, and 0.03 wt%) were investigated by DLS measurements (Fig. 4d–f). The average diameters of obtained BDP nanoparticles were 72, 38 and 31 nm, respectively. By increasing the concentration of PEG, smaller BDP particles with narrower particle size distribution were obtained. Therefore, with the help of very small amount of PEG in the anti-solvent (0.02 wt%), sub-50 nm BDP nanoparticle with uniform distribution could be prepared. These results demonstrated that the PEG molecules effectively prevented the growth and aggregation of BDP nanoparticles in the SBCW process. The presence of PEG molecules adsorbed on the surface of the BDP primary particles due to the hydrophobic bond, which enhanced the dispersion of BDP primary particles in the aqueous phase. The aggregation and growth of the BDP particles were limited. When the PEG concentration was

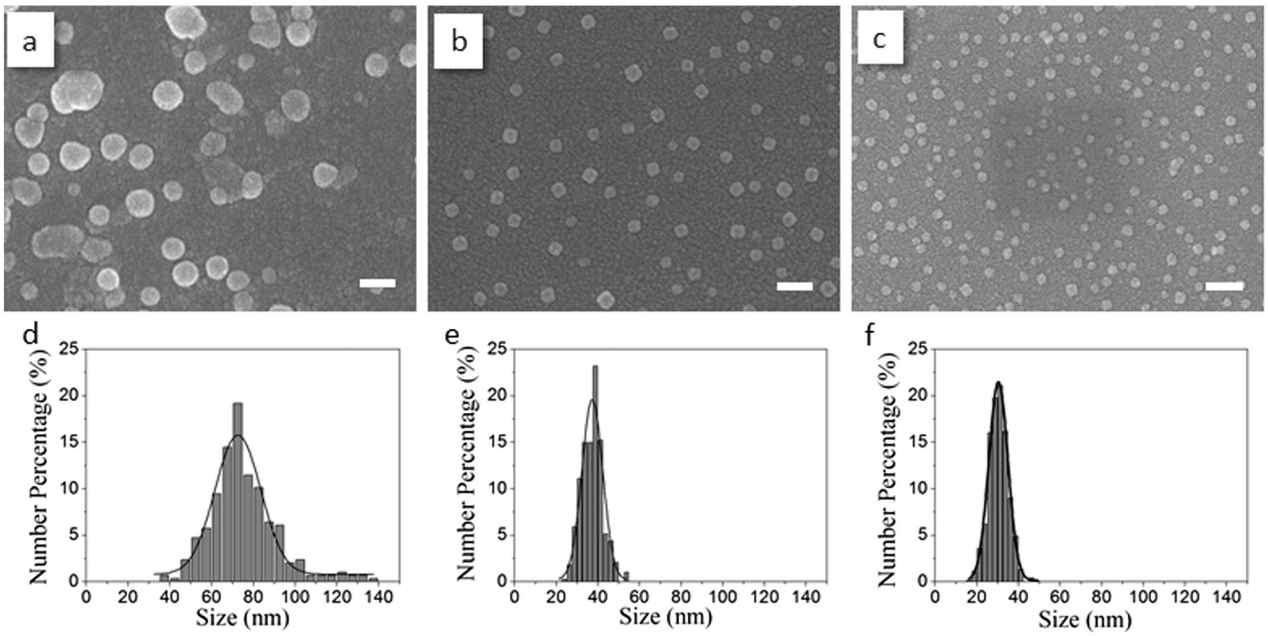


**Fig. 4.** SEM images of the BDP nanoparticles prepared by anti-solvent precipitation using 150 °C SBCW solutions and 0 °C aqueous PEG solutions with different concentrations (a) PEG 0.01 wt%, (b) PEG 0.02 wt%, (c) PEG 0.03 wt%. The scale bars represent 200 nm. DLS results in aqueous solutions of BDP particles obtained by using aqueous PEG solutions with concentrations of (d) 0.01 wt%, (e) 0.02 wt%, and (f) PEG 0.03 wt% as the anti-solvents.

raised, there were enough PEG molecules to stabilize the BDP particles and the size decrease of obtained particles was no longer apparent.

### 3.4. FTIR and XRD analysis

To investigate the components and structures of BDP nanoparticles, the FTIR spectra of raw BDP drugs (Fig. 2b), Micro-BDP particles (Fig. 3a), Nano-BDP particles (Fig. 3c) and Nano-BDP/PEG particles (Fig. 4c) were measured. The FTIR results shown in Fig. 5 demonstrated that the SBCW process did not affect the chemical composition of BDP, since all the samples exhibited very similar FTIR spectra with same characteristic peaks. Compared with the FTIR spectra of Nano-BDP particles obtained by using pure water as the anti-solvent, none additional FTIR peaks were observed from the Nano-BDP/PEG particles obtained from PEG-assisted approaches, suggesting that the content of PEG molecules absorbed on the surface of Nano-BDP/PEG particles were very low. These results demonstrated that most of the PEG molecules were removed during experimental step of centrifugation to obtain powder of BDP nanoparticles.

Apart from the particle size, crystallinity is also a key factor for oral drugs. Fig. 6 presents the XRD patterns of raw BDP drugs, Micro-BDP particles, Nano-BDP particles and Nano-BDP/PEG particles, respectively. The raw BDP drugs showed an orthorhombic system according to database of JCPDS-ICDD 2004 (International Centre for Diffraction Data). The Micro-BDP particles showed similar peaks as the raw BDP drugs, while the Nano-BDP particles exhibited much lower crystalline than raw BDP. The Nano-BDP/PEG nanoparticles showed the lowest crystalline of BDP in these four samples. It has been demonstrated that a pharmaceutical with poor water solubility usually exhibit better bioavailability when its crystallinity is low [12,36]. Therefore, the low crystalline of Nano-BDP/PEG particles should be benefited for their potential applications as oral drugs.

### 3.5. Dissolution testing

The dissolution tests of the samples were performed following a stand USP Apparatus II method and the results were presented in Fig. 7. As expected, the BDP nanoparticles (Fig. 4c) exhibited much higher dissolution rate than both Micro-BDP particles (Fig. 3a) and raw BDP (Fig. 2a). After 40 min, the dissolved amount of BDP drugs from the spherical BDP nanoparticles was ~60%, while only ~30% and ~10% BDP drugs dissolved from Micro-BDP particles and raw BDP, respectively. The enhanced dissolution rate of Micro-BDP particles compared with raw BDP was attributed to the decreased sized of the drug particles. The extremely high dissolution rate of BDP nanoparticles was attributed to the ultra-small size, low crystallinity of the particles.

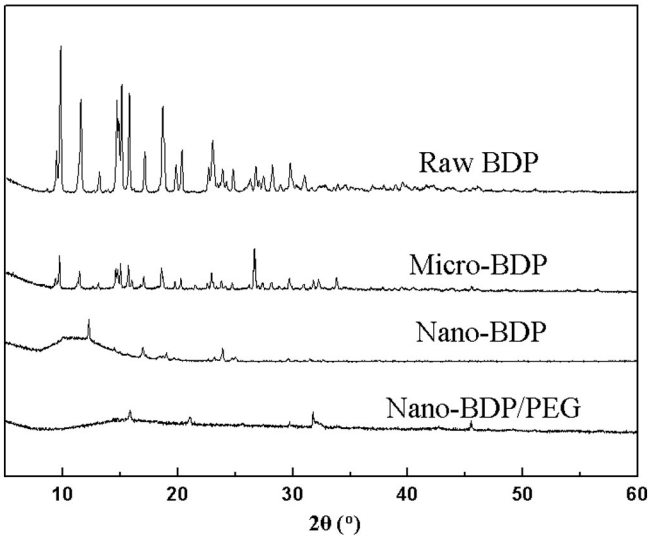


**Fig. 6.** XRD patterns of raw BDP drugs, Micro-BDP particles, Nano-BDP particles and Nano-BDP/PEG particles.

## 4. Conclusions

A green solvent, the SBCW, was used for the preparation of BDP nanoparticles via solvent anti-solvent precipitation. BDP nanoparticles were prepared via an easy-handle approach by using SBCW and cold water as the solvent and anti-solvent respectively. Sub 50-nm BDP nanoparticles were obtained by PEG-assisted precipitation. According to the FTIR analysis, the chemical structures of BDP were stable during the SBCW process up to 150 °C. The obtained BDP nanoparticles exhibited high dissolution rate due to their ultra-small size, low crystallinity. In addition, solvent anti-solvent precipitation is a feasible pathway to obtain BDP nanoparticles. The use of SBCW as the solvent overcomes the limitations of using toxic organic solvents during solvent anti-solvent precipitation, offing a green method of manufacturing BDP nanoparticles, as well as nanoparticles of other poor water soluble drugs and it is easy to scale-up.

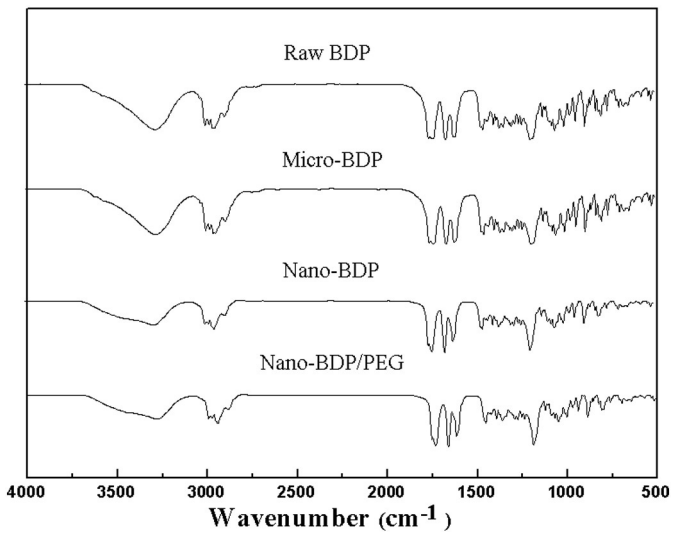


**Fig. 5.** FTIR spectra of raw BDP drugs, Micro-BDP particles, Nano-BDP particles and Nano-BDP/PEG particles.

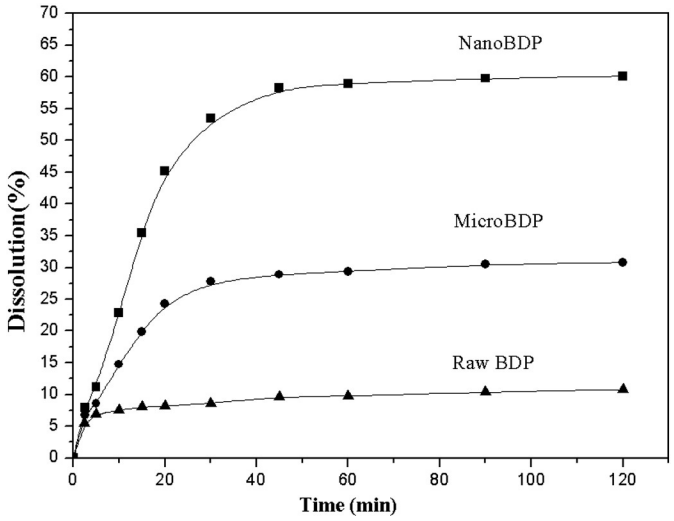


**Fig. 7.** Dissolution profiles of raw BDP, Micro-BDP particles and ultrafine Nano-BDP particles.

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