Powder Technology 321 (2017) 197–203

Contents lists available at ScienceDirect

Powder Technology

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

Nanonization of ciprofloxacin using subcritical water-ethanol mixture as the solvent: Solubility and precipitation parameters

Yuan Pu [a,b], Jundian Lu [a,b], Dan Wang [a,b,*], Fuhong Cai [c], Jie-Xin Wang [a,b], Neil R. Foster [a,d], Jian-Feng Chen [a,b]

[a] Beijing Advanced Innovation Center for Soft Matter Science and Engineering, State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing 100029, China
[b] Research Center of the Ministry of Education for High Gravity Engineering and Technology, Beijing University of Chemical Technology, Beijing 100029, China
[c] College of Mechanical & Electrical Engineering, Hainan University, Haikou 570228, China
[d] Department of Chemical Engineering, Curtin University, Perth, Western Australia 6102, Australia

ARTICLE INFO

Article history:
Received 25 April 2017
Received in revised form 7 August 2017
Accepted 9 August 2017
Available online 12 August 2017

Keywords:
Ciprofloxacin
Subcritical water-ethanol
Solubility model
Nanoparticles
Green chemical engineering

ABSTRACT

Ciprofloxacin (CIP) has been widely used to treat many types of bacterial infections. Herein, we reported a green approach for preparation of CIP nanoparticles via solvent anti-solvent precipitation by using subcritical water-ethanol mixture as the solvent. The solubility of CIP in subcritical water-ethanol mixture (with various ethanol ratio of 0, 5, and 20 wt%) at the temperature range from 100 °C to 170 °C and constant pressure of 4 MPa were measured. The chemical structure of CIP was stable after processed in subcritical water-ethanol mixture at up to 170 °C, confirmed by Fourier transformed infrared analysis. The obtained solubility data of CIP were correlated using a modified Apelblat model and the results of the predicted solubility show good agreement with the experimental value. The nanonization of CIP via solvent anti-solvent precipitation process that used the tunable solvent power of subcritical water-ethanol mixture was conducted. Two kinds of no-ionic, hydrophilic polymer, including polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG), were introduced as stabilizers in the precipitation process to obtain CIP nanoparticle with improved dissolution rate. These results show that as-synthesized CIP nanoparticles are promising for oral administration of CIP drugs.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Ciprofloxacin (CIP), a representative member of the quinolones, has been widely used to treat different types of bacterial infections, such as diverse gram-negative infections, urinary tract infections, typhoid fever, pyelonephritis, gonococcal infections, acute sinusitis, just to name a few [1,2]. In nearly all cases, the CIP drug must be dispersed well in solution to be absorbed into the bloodstream from the gastrointestinal tract [3,4]. However, poor aqueous solubility of CIP has been an industry wide problem for its development and clinical application. Recent developments in nanotechnology allow the manipulation of materials at the nanoscale, providing varieties of nanomaterials for diagnosis and therapy [5–9]. Along with others, we have demonstrated that particle size reduction to nanometer can lead to an increased rate of dissolution and higher oral bioavailability [10–14]. Therefore, it is critical to develop CIP nanoparticles with high dissolution rate for oral applications. Solvent anti-solvent precipitation is the most straightforward technique for producing nanoparticles, in which the water insoluble drug is usually dissolved in an organic solvent [15]. However, most drugs produced by precipitation techniques employing organic solvents show trace amounts of solvents even after purification [16].

Subcritical water (SBCW), also known as superheated water (SHW), hot compressed water (HCW), pressurized hot water (PHW), or near-critical water (NCW), refers to liquid water at temperatures between the atmospheric boiling point of 100 °C and the critical temperature of 374 °C, which maintains its liquid state under pressurized condition [17]. Although water at ambient conditions is too polar to solvate most organic compounds, the polarity of SBCW can be controlled over a wide range by changing temperature under moderate pressures, acting more like organic solvents so that the solubility of organics could be dramatically increased, making them an ideal candidate as the solvent for precipitation processes [18–21]. Previous reports have indicated that the dielectric constant (ξ) of ambient water is very high (ξ = 78.5), while the dielectric constant of SBCW can be decreased to a value as low as 27 at 250 °C [22]. Furthermore, high solubility of organic compounds is feasible at lower temperatures if cosolvents are used in conjunction with an adjustment of the extraction temperature in reducing the polarity of water [23]. This approach is preferred for solutes that are thermally labile. Ethanol is a suitable cosolvent as it is nontoxic and can be safely disposed of along with the rest of the aqueous media [24,25]. However, as far as we are aware, few studies have

* Corresponding author at: State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing 100029, China.
E-mail address: wangdan@mail.buct.edu.cn (D. Wang).

http://dx.doi.org/10.1016/j.powtec.2017.08.038
0032-5910/© 2017 Elsevier B.V. All rights reserved.

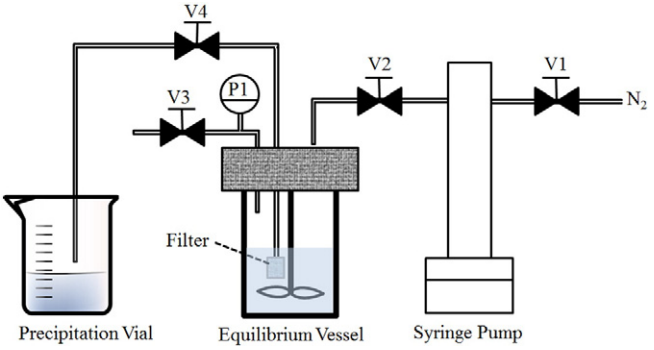

Fig. 1. A schematic diagram of the subcritical water-ethanol mixture system.

utilized subcritical water-ethanol mixture for the nanonization of water insoluble drugs.

Herein, we reported a green approach for preparation of CIP nanoparticles via solvent anti-solvent precipitation by using subcritical water-ethanol mixture as the solvent. The solubility of CIP in subcritical water-ethanol mixture at the temperature range from 100 °C to 170 °C and constant pressure of 4 MPa were firstly measured and correlated using a modified Apelblat model. The nanonization of CIP via solvent anti-solvent precipitation process that used the tunable solvent power of subcritical water-ethanol mixture was conducted. Two kinds of non-ionic, hydrophilic polymer, including polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG), were introduced as stabilizers in the precipitation process to obtain CIP nanoparticle with improved dissolution rate. The products were characterized by Fourier transform infrared spectrophotometry (FTIR), scanning electronic microscopy (SEM), dynamic light scattering (DLS), and dissolution tests.

2. Experimental

2.1. Materials and instruments

The ciprofloxacin (98%, $C_{17}H_{21}ClFN_3O_4$) raw drug, polyvinylpyrrolidone ($(C_6H_9NO)_n$, K30, abbreviated to PEG), poly(ethylene glycol) ($HO(CH_2CH_2O)_nH$, average Mn 4000, abbreviated to PEG) and ethanol (99.7%) were purchased from Shanghai Macklin Biochemical Co., Ltd. Nitrogen (≥99.999%) gas was purchased from Beijing Yanglilai Technology Co., Ltd. All the chemicals were used as received without further purification. Deionized water prepared by a Hitech Laboratory Water Purification System (DW100, Shanghai Hitech Instruments Co., Ltd.) was used for all experiments.

Table 1
Solubility parameters of ciprofloxacin (CIP) in subcritical water-ethanol mixture of ethanol ratio at 0, 5, and 20 wt% from modified Apelblat equation.

Solvent[a]	A	B	C
1	405.5	−32,856.3	−53.7
2	−486.7	19,488.6	73.5
3	−385.4	14,612.3	58.9

[a] Solvents were subcritical water-ethanol mixture of ethanol ratio at 0, 5, 20 wt% for 1, 2, 3, respectively.

2.2. Solubility determination of CIP in subcritical water-ethanol mixture

The solubility data of CIP in subcritical water-ethanol mixture at various temperatures were determined by a batch method reported in a previous publication [26]. The operating pressure was 4 MPa. The external ring magnet oscillated at 600 rpm. The temperature of the subcritical water-ethanol mixture (with various ethanol ratio of 0, 5, and 20 wt%) were maintained at a certain temperature (100, 110, 120, 130, 140, 150,160 and 170 °C) for 20 min. The CIP sample (100 mg) was weighed by using an electronic balance and loaded into a solubility vial together with a small magnet. Since excess CIP was added into the water-ethanol mixture to form saturated solution of CIP in our experiments, a threaded tube fitting with 0.45 μm filter stone pore was used to retain undissolved CIP particles in the solubility vial. The CIP dissolved in the subcritical water-ethanol mixture were collected in a collection vial. The solution of CIP in water-ethanol mixture were dried and then diluted with 100 mL of analytical grade ethanol and the absorbance was measured under a UV spectrophotometer (Varian model Cary 50 Conc) at 279 nm. A stock solution for CIP was prepared in ethanol solution. With appropriate dilution, a set of standard

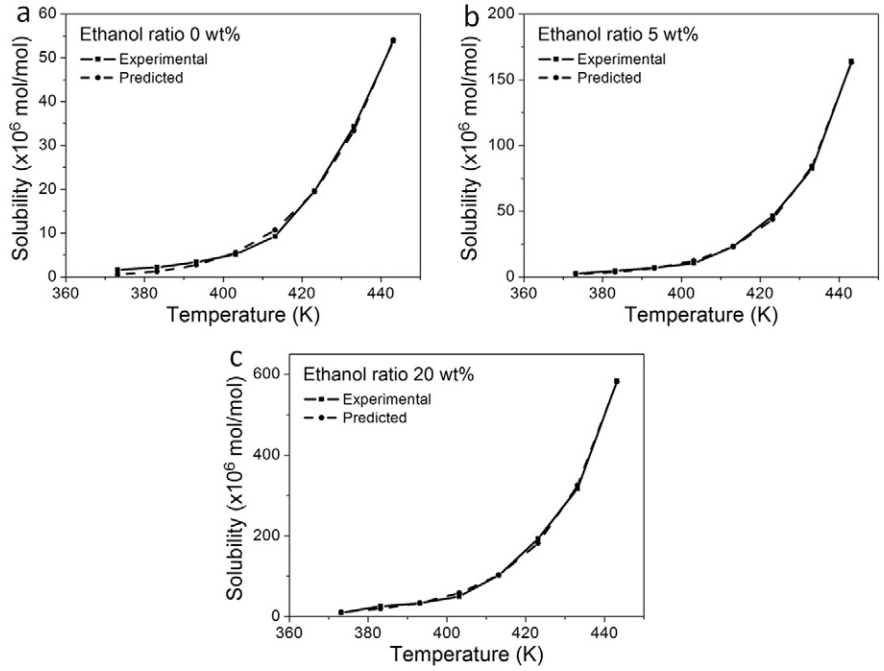

Fig. 2. Experimental and predicted mole fraction solubility of CIP in subcritical water-ethanol mixture as a function of temperature. The ethanol ratios were 0, 5, and 20 wt% in (a), (b) and (c).

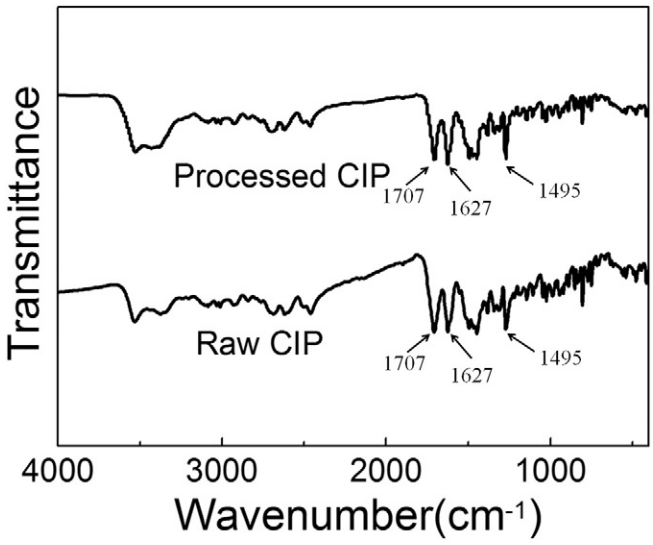

Fig. 3. FTIR spectra of raw CIP and processed CIP in subcritical water-ethanol mixture at 170 °C.

solutions were obtained and a solubility curve relating absorbance against concentration was plotted. The concentration of each fraction of the experiments was calculated by reading the absorbance of the solution in UV spectrophotometer. The solubility of investigated solutes was calculated using Eq. (1)

$$x_{sol} = \frac{m_d/M_d}{m_d/M_d + m_w/M_w} \quad (1)$$

where x_{sol} represents the solubility (mol/mol) of the solute, m_d and m_w are the respective mass (g) of the solute (solid) and water. M_d and M_w represent the molar mass (g/mol) of the solid and water respectively.

2.3. Solvent anti-solvent precipitation of CIP nanoparticles

The CIP nanoparticles were synthesized via anti-solvent precipitation of CIP by using subcritical water-ethanol mixture as the solvent. The setup of the subcritical water apparatus was following our previous reported approach and shown schematically in Fig. 1 [27]. In a typical experiment, for the preparation of CIP nanoparticles, 200 mg CIP raw drug and 50 mL water were loaded into a micro reactor (4590 Micro Stirred Reactors 100 mL, Parr Instrument Company, USA), which was combined with controller systems (A 4848 Reactor Controller, Parr Instrument Company, USA) to display the temperature, the pressure and the stirring speed of the system. With nitrogen filled by a syringe pump (260D Syringe Pump, Teledyne Isco), the air in the micro reactor was excluded and the pressure was maintained at 4 MPa. The mixture in the micro reactor was then heated to 150 °C ($T_{solvent}$ = 150 °C) and stirred at 150 rpm for 20 min, forming saturated solution of CIP in subcritical water-ethanol mixture. After that, the solution in the micro reactor was then delivered into the particles collection vial by aerating nitrogen. 150 mL of anti-solvent (pure water, or aqueous PEG solution with concentrations of 0.05 wt%, 0.10 wt%, and 0.15 wt%, respectively) at 0 °C ($T_{anti\text{-}solvent}$ = 0 °C) in the collection vial was used as anti-solvent and mixed with the CIP solution under magnetic stirring at 600 rpm. The suspension solution of CIP nanoparticles was obtained due to the decreased solubility of CIP and supersaturation of CIP molecules. The powders of CIP nanoparticles were obtained by centrifugation and dried in a vacuum oven at 60 °C.

2.4. Characterization of CIP nanoparticles

The Fourier transform infrared (FTIR) spectra of samples were measured by a PerkinElmer Spectrum GX FTIR Spectrometer. For morphology studies, the powder of samples were sputter coated with Au at 50 mA for 30 s by a Pelco Model 3 sputter-coater under an Ar atmosphere and then observed by a JEOL JSM-6360LV scanning electron microscope (SEM). The particle size distribution of the samples was determined by dynamic light scattering (DLS, Zetasizer, Malvern Instruments Ltd., UK). Briefly, 2 mg of the CIP particles were dispersed into 5 mL of water, followed by ultrasonic treatment for 2 min. The obtained turbid liquid was filtered by a 0.45 μm filter and then examined by the DLS analyzer.

2.5. Dissolution testing

The USP Apparatus II (paddle) method was used to perform the dissolution tests of samples [28,29]. Briefly, 25 mg of samples was placed into a vessel containing 900 ml of dissolution medium (phosphate buffer, pH = 6.8) with water bath at 37.0 ± 0.5 °C. The paddle speed was set to 100 rpm. Afterwards, 5 mL of solution were withdrawn at specific intervals (i.e. 5, 10, 15, 20, 30, 60, 90, 120, 150, 180 min) and immediately filtered through a 0.45 μm syringe filter. The absorbance of the filtrate at 279 nm was measured using a Shimadzu UV-2501 UV–Vis Recording Spectrophotometer. For each sample, the experiments were repeated at least three times to ensure accuracy in the results.

3. Results and discussions

3.1. Solubility of CIP in subcritical water-ethanol mixture

The experimental solubility data of CIP in subcritical water-ethanol mixture of various ethanol ratio (0, 5, 20 wt%) at 100–170 °C were presented in Fig. 2. As can be seen, the solubility of CIP increased as the temperature of solvent, with a gradual increase as the temperature raised from 100 °C to 140 °C and a large increase between 140 °C to 170 °C. The solubility of CIP also increased as the ethanol ratio increasing, at each temperature point. A modified Apelblat equation from Eq. (2) was used to correlate the temperature dependency of the aqueous solubility of the CIP in subcritical water-ethanol mixture [26].

$$\ln(x_{sol}) = A + \frac{B}{T} + C \times \ln(T) \quad (2)$$

where x_{sol} is the mole fraction solubility of CIP; T is the absolute temperature of subcritical water-ethanol mixture; A, B and C are the empirical parameters.

Table 1 shows the empirical parameters of A, B and C for each solvent (namely, subcritical water-ethanol mixture of ethanol ratio at 0, 5, and 20 wt%). As can be seen in Fig. 2, the predicted solubility data of CIP subcritical water-ethanol mixture from Eq. (2) provided good agreement with the experimental data at the temperature range of 100 °C to 170 °C.

Considering that the chemical structure of CIP may change at high temperature (up to 170 °C) during the treatment, Fourier transformed infrared (FTIR) spectrum of the CIP sample treated in the subcritical water-ethanol mixture at 170 °C for 20 min, which was the harshest condition in our experiments, was performed, along with the FTIR spectrum of raw CIP sample as a control. As the results shown in Fig. 3, the characteristic peaks (at 1495, 1627, 1707 cm^{-1}) [2] of CIP were observed from both FTIR spectra of raw CIP and processed CIP at 170 °C for 20 min in subcritical water-ethanol mixture, with no significant changes or shifts. These results demonstrated that CIP was stable in subcritical water-ethanol mixture at high temperature up to 170 °C.

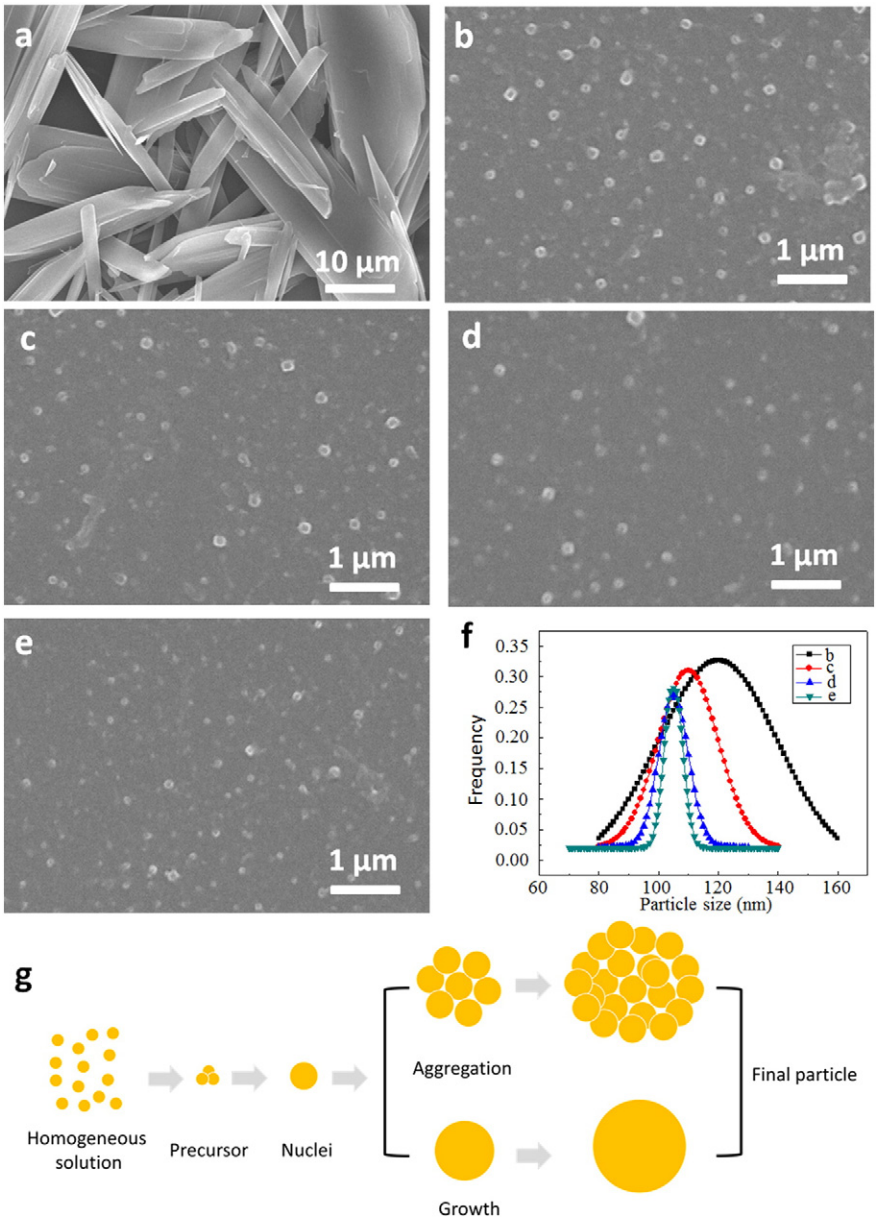

Fig. 4. SEM images of raw CIP (a) and CIP nanoparticles obtained from subcritical water-ethanol mixture of different ethanol ratio as the solvent (b) 0 wt%, (c) 5 wt%, (d) 10 wt%, (e) 20 wt%; (f) DLS results of the samples in (b–e); (g) schematic diagram of stages of particle formation.

3.2. Formation of CIP nanoparticles via solvent anti-solvent precipitation

Fig. 4 presents the SEM images raw CIP drugs and CIP nanoparticles generated through the solvent anti-solvent precipitation by using subcritical water-ethanol mixture of different ethanol ratio (0, 5, 10, and 20 wt%, respectively) at 150 °C as the solvent and pure water at 0 °C as the anti-solvent, which were denoted as NanoCIP-0, NanoCIP-5, NanoCIP-10 and NanoCIP-20. The volume ratio of the solvent and anti-solvent was 1:3 for all the experiments. Compared with raw CIP, which exhibited blocky structure with a wide size distribution up to dozens of micrometers (Fig. 4a), the CIP precipitated from subcritical water-ethanol mixture and cold water were nanoparticles with uniform distribution and average size of <100 nm (Fig. 4b–e). The CIP nanoparticles appeared to be smaller when the ethanol ratio of the subcritical water-ethanol mixture increased from 0 to 20 wt% (Fig. 4b–e). According to the DLS results (Fig. 4f), the average sizes of CIP nanoparticles were 120 nm, 109 nm, 105 nm and 105 nm for NanoCIP-0, NanoCIP-5, NanoCIP-10 and NanoCIP-20, which were consistent with the SEM results. The formation of CIP nanoparticles during the precipitation were described with schematic illustration shown in Fig. 4g. When the CIP solution in subcritical water-ethanol mixture were pumped into the cold water, the mixture solution was supersaturated with CIP molecules, and primary CIP particles formed through a burst-nucleation step. The growth of the CIP nanoparticles were then in progress via diffusional growth or aggregation. In the solvent anti-solvent precipitation of CIP, the level of supersaturation was determined by the difference of the CIP solubility in the solvent and anti-solvent. As the SEM images shown in Fig. 4b–d, when the ethanol ratio of the subcritical water-ethanol mixture increased from 0 to 10 wt%, the solubility of CIP in the solvent increased, leading to an enhanced supersaturation, which resulting a decreased average particle size. However, when the ethanol ration in the solvent increased to 20 wt%, the obtained CIP nanoparticles exhibited broader size distribution, which was resulted by the combined effect of supersaturation level of CIP in the solvent and anti-solvent (Fig. 4d–e). As the increasing of ethanol ratio in the solvent, the ethanol ratio in the mixture of the solvent and anti-

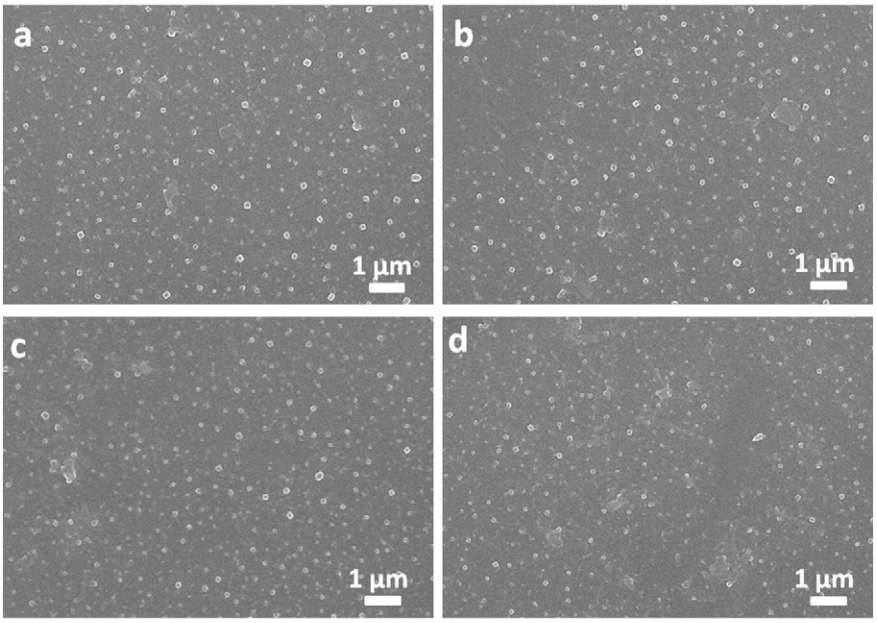

Fig. 5. SEM images of the CIP nanoparticles prepared by precipitation using 150 °C subcritical water-ethanol mixture with ethanol ratio of 10 wt% as the solvent and 0 °C aqueous PVP solutions with different concentrations (a) PVP 0.05 wt%, (b) PVP 0.10 wt%, (c) PVP 0.15 wt% and (d) PEG 0.20 wt% as the anti-solvent.

solvent increased, leading to higher solubility of CIP. Some of the CIP re-dissolved, causing the differentiation of particle size.

3.3. Surfactant-assisted synthesis of CIP nanoparticles

It has been generally accepted that the particle size reduction can lead to an increased rate of dissolution and higher oral bioavailability for poor water soluble drugs [30]. Therefore, it is critical to develop CIP nanoparticles. The use of low polarity polymers as stabilizers in the precipitation process has been demonstrated to be an efficient approach to prepared nanoparticles with uniform distribution [31,32]. In this work, two kinds of non-ionic, hydrophilic polymer, including PVP and PEG, were introduced as stabilizers in the precipitation process to obtain CIP nanoparticles, and both of them were among the most widely used amphoteric water-soluble polymers in a variety of pharmaceutical formulations due to its low toxicity and chemical stability [33]. For PVP-assisted nanonization of CIP, the temperatures of subcritical water-ethanol mixture with ethanol ratio of 10 wt% and aqueous PVP solution of various mass concentrations were 150 °C and 0 °C. The mass concentrations of PVP in the anti-solvent were 0.05, 0.10, 0.15 and 0.20 wt% respectively. Fig. 5 showed the SEM images of CIP nanoparticles obtained by PVP-assisted solvent anti-solvent precipitation by using subcritical water-ethanol mixture as the solvent, in which the CIP nanoparticles were highly dispersed with uniform size distribution. The hydrodynamic diameters of CIP nanoparticles obtained by using various PVP solutions with concentrations of 0.05, 0.10, 0.15 and 0.20 wt% were investigated by DLS measurements. DLS measurements showed that the average diameters of CIP nanoparticles obtained by

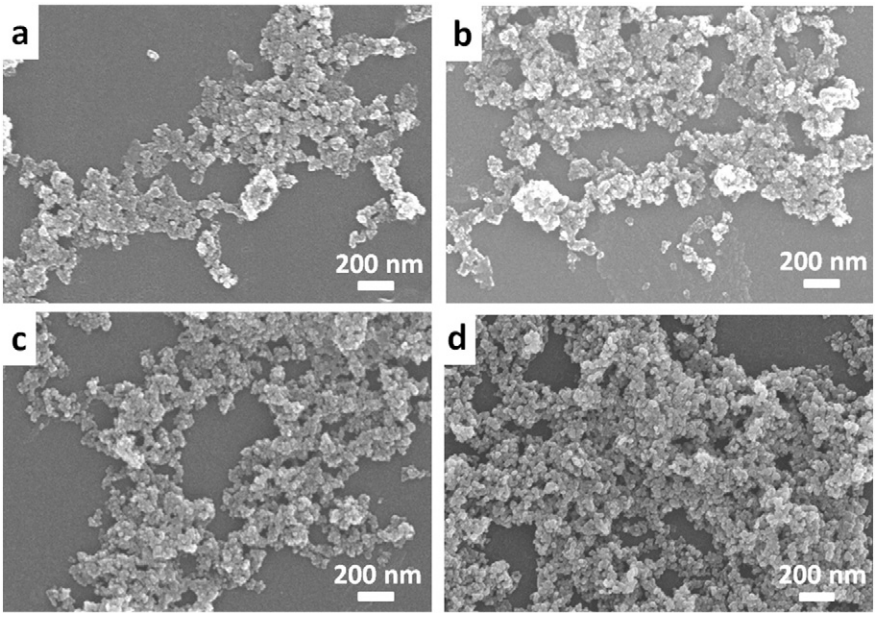

Fig. 6. SEM images of the CIP nanoparticles prepared by precipitation using 150 °C subcritical water-ethanol mixture with ethanol ratio of 10 wt% as the solvent and 0 °C aqueous PEG solutions with different concentrations (a) PEG 0.05 wt%, (b) PEG 0.10 wt%, (c) PEG 0.15 wt% and (d) PEG 0.20 wt% as the anti-solvent.

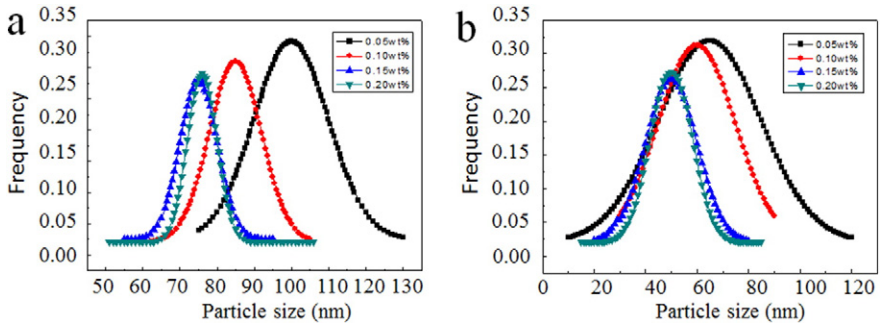

Fig. 7. Size distribution results measured by DLS for nanoparticles prepared by PVP-assisted (a) and PEG-assisted (b) solvent anti-solvent precipitation.

using PVP aqueous solutions as anti-solvents were 101 nm, 86 nm, 72 nm and 75 nm, respectively (Fig. 7a). These results demonstrated that the PVP molecules effectively prevented the growth and aggregation of CIP nanoparticles in the solvent anti-solvent precipitation process.

Fig. 6 showed the SEM images of CIP nanoparticles obtained by PEG-assisted solvent anti-solvent precipitation. The individual CIP nanoparticle obtained by PEG assisted methods was much smaller than those obtained by using pure water or aqueous PVP solution as the anti-solvent, although the final products of CIP nanoparticles powder showed apparent aggregations. According to the DLS measurements shown in Fig. 7b, the average diameters of CIP nanoparticles obtained by using PEG aqueous solutions as anti-solvents were 65 nm, 60 nm, 50 nm and 50 nm, respectively, indicating that the PEG molecules could also effectively prevent the growth and aggregation of CIP particles in the solvent anti-solvent precipitation process, resulting CIP nanoparticles.

3.4. Dissolution testing

The profiles of the raw CIP powder, CIP nanoparticles obtained by precipitation in PVP (NanoCIP-75 nm, Fig. 4c) and PEG (NanoCIP-50 nm, Fig. 5c) aqueous solution were compared in Fig. 8. The dissolved amount of drug from CIP nanoparticles obtained by in PVP and PEG aqueous solution increased to 50% and 80% after 120 min, while only 8% of the raw CIP dissolved. The increased dissolution rates of the products are primarily attributed to the reduced particle size. Therefore, nanonization of CIP using subcritical water-ethanol mixture as the solvent can decrease the particle size, enhancing the dissolution rate of CIP in water.

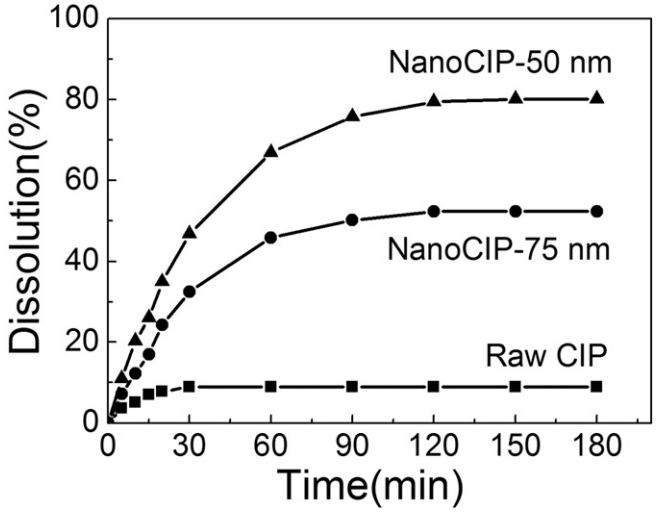

Fig. 8. Dissolution profiles of raw CIP, NanoCIP-75 nm and NanoCIP-50 nm nanoparticles.

4. Conclusions

A green approach for preparation of CIP nanoparticles via solvent anti-solvent precipitation by using subcritical water-ethanol mixture as the solvent was developed. The solubility of CIP in subcritical water-ethanol mixture (with various ethanol ratio of 0, 5, and 20 wt%) at the temperature range from 100 °C to 170 °C and constant pressure of 4 MPa were measured. The solubility of CIP increased exponentially as the temperature of the subcritical water-ethanol mixture increased from 100 °C to 170 °C. The obtained solubility data of CIP were correlated using a modified Apelblat model and the results of the predicted solubility showed good agreement with the experimental value. The nanonization of CIP via processes that used the tunable solvent power of subcritical water-ethanol mixture was conducted. CIP nanoparticles were obtained through solvent anti-solvent precipitation by using subcritical water-ethanol mixture of different ethanol ratio (0, 5, 10, and 20 wt%, respectively) at 150 °C as the solvent and pure water at 0 °C as the anti-solvent. Two kinds of non-ionic, hydrophilic polymer, including PVP and PEG, were introduced as stabilizers in the precipitation process to obtain CIP nanoparticles with average size of 75 nm and 50 nm, respectively. The dissolution of CIP nanoparticles was significantly improved versus the raw CIP powder. Therefore, the subcritical process provides a green method of manufacturing CIP nanoparticles while controlling their size and morphology with potential application value.

Acknowledgements

This work was supported by grants from the National Key Research and Development Program of China (2016YFA0201701/2016YFA0201700), the National Natural Science Foundation of China (51641201, 21622601), the Fundamental Research Funds for the Central Universities of China (BUCTRC201601), and the “111” project of China (B14004). Dr. Fuhong Cai was grateful to the scientific research fund of Hainan University (kyqd1653).

References

[1] R. Wilson, T. Welte, E. Polverino, A. De Soyza, H. Greville, A. O'Donnell, J. Alder, P. Reimnitz, B. Hampel, Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study, Eur. Respir. J. 41 (2013) 1107–1115.
[2] Q. Wu, Z. Li, H. Hong, K. Yin, L. Tie, Adsorption and intercalation of ciprofloxacin on montmorillonite, Appl. Clay Sci. 50 (2010) 204–211.
[3] K. Dillen, J. Vandervoort, G. Van den Mooter, L. Verheyden, A. Ludwig, Factorial design, physicochemical characterisation and activity of ciprofloxacin-PLGA nanoparticles, Int. J. Pharm. 275 (2004) 171–187.
[4] N. El-Gendy, V. Desai, C. Berkland, Agglomerates of ciprofloxacin nanoparticles yield fine dry powder aerosols, J. Pharm. Innov. 5 (2010) 79–87.
[5] D. Wang, L. Zhu, J.-F. Chen, L. Dai, Liquid marbles based on magnetic upconversion nanoparticles as magnetically and optically miniature reactors for photocatalysis and photodynamic therapy, Angew. Chem. Int. Ed. 55 (2016) 10795–10799.
[6] D. Wang, L. Zhu, C. McCleese, C. Bruda, J.-F. Chen, L. Dai, Fluorescent carbon dots from milk by microwave cooking, RSC Adv. 6 (2016) 41516–41521.

[7] D. Wang, J.-F. Chen, L. Dai, Recent advances in graphene quantum dots for fluorescence bioimaging from cells through tissues to animals, Part. Part. Syst. Charact. 5 (2015) 515–523.
[8] D. Wang, J. Liu, J.-F. Chen, L. Dai, Surface functionalization of carbon dots with polyhedraloligomericsilsesquioxane (POSS) for multifunctional applications, Adv. Mater. Interfaces 3 (2016) 1500439.
[9] D. Wang, Z. Wang, Q. Zhan, Y. Pu, J.-X. Wang, N.R. Foster, L. Dai, Facile and scalable preparation of fluorescent carbon dots for multifunctional applications, Engineering 3 (2017) 402–408.
[10] F. Kesisoglou, S. Panmai, Y. Wu, Nanosizing-oral formulation development and biopharmaceutical evaluation, Adv. Drug Deliv. Rev. 59 (2007) 31–44.
[11] K. Riehemann, S.W. Schneider, T.A. Luger, B. Godin, M. Ferrari, H. Fuchs, Nanomedicine-challenge and perspectives, Angew. Chem. Int. Ed. 48 (2009) 872–897.
[12] N. Rasenack, H. Steckel, B.W. Müller, Micronization of anti-inflammatory drugs for pulmonary delivery by a controlled crystallization process, J. Pharm. Sci. 92 (2003) 35–44.
[13] Z. Wang, J.F. Chen, Z.G. Shen, J. Yun, Preparation of ultrafine beclomethasone dipropionate drug powder by anti-solvent precipitation, Ind. Eng. Chem. Res. 46 (2007) 4839–4845.
[14] X.S. Li, J.X. Wang, Z.G. Shen, P.Y. Zhang, J.F. Chen, J. Yun, Preparation of uniform prednisolone microcrystals by a controlled microprecipitation method, Int. J. Pharm. 342 (2007) 26–32.
[15] M. Kakran, N.G. Sahoo, L. Li, Z. Judeh, Fabrication of quercetin nanoparticles by antisolvent precipitation method for enhanced dissolution, Powder Technol. 223 (2012) 59–64.
[16] U. Wais, A.W. Jackson, T. He, H. Zhang, Nanoformulation and encapsulation approaches for poorly water-soluble drug nanoparticles, Nano 8 (2016) 1746–1769.
[17] A.G. Carr, R. Mammucari, N.R. Foster, A review of subcritical water as a solvent and its utilisation for the processing of hydrophobic organic compounds, Chem. Eng. J. 172 (2011) 1–17.
[18] Y. Pu, X. Wen, Y. Li, D. Wang, N.R. Foster, J.-F. Chen, Ultrafine clarithromycin nanoparticles via anti-solvent precipitation in subcritical water: effect of operating parameters, Powder Technol. 305 (2017) 125–131.
[19] A.G. Carr, R. Mammucari, N.R. Foster, Particle formation of budesonide from alcohol-modified subcritical water solutions, Int. J. Pharm. 405 (2011) 169–180.
[20] S.K. Poornachary, G. Han, J.W. Kwek, P.S. Chow, R.B.H. Tan, Crystallizing micronized particles of a poorly water-soluble active pharmaceutical ingredient: nucleation enhancement by polymeric additives, Cryst. Growth Des. 16 (2016) 749–758.
[21] Y. Pu, Y. Li, D. Wang, N.R. Foster, J.-X. Wang, J.-F. Chen, A green route to beclomethasone dipropionate nanoparticles via solvent anti-solvent precipitation by using subcritical water as the solvent, Powder Technol. 308 (2017) 200–205.
[22] G. Akerlof, Dielectric constants of some organic solvent-water mixtures at various temperatures, J. Am. Chem. Soc. 54 (1932) 4125–4139.
[23] M.S.S. Curren, J.W. King, Solubility of triazine pesticides in pure and modified subcritical water, Anal. Chem. 73 (2001) 740–745.
[24] D. Gao, T. Kobayashi, S. Adachi, Kinetics of sucrose hydrolysis in a subcritical water-ethanol mixture, J. Appl. Glycosci. 61 (2014) 9–13.
[25] W.H. Teoh, S.A.B.V. de Melo, R. Mammucari, N.R. Foster, Solubility and solubility modeling of polycyclic aromatic hydrocarbons in subcritical ethanol and water mixtures, Ind. Eng. Chem. Res. 53 (2014) 10238–10248.
[26] Y. Pu, F. Cai, D. Wang, Y. Li, X. Chen, A.G. Maimouna, Z. Wu, X. Wen, J.-F. Chen, N.R. Foster, Solubility of bicalutamide, megestrol acetate, prednisolone, beclomethasone dipropionate, and clarithromycin in subcritical water at different temperatures from 383.15 to 443.15 K, J. Chem. Eng. Data 62 (2017) 1139–1145.
[27] X.-Y. Chen, Y.-L. Shang, Y.-H. Li, J.-X. Wang, A.G. Maimouna, Y.-X. Li, D. Zou, N.R. Foster, J. Yun, Y. Pu, Green preparation of uniform prednisolone nanoparticles using subcritical water, Chem. Eng. J. 263 (2015) 20–26.
[28] Z.B. Zhang, Z.G. Shen, J.X. Wang, H. Zhao, J.-F. Chen, J. Yun, Nanonization of megestrol acetate by liquid precipitation, Ind. Eng. Chem. Res. 48 (2009) 8493–8499.
[29] H.X. Zhang, J.X. Wang, Z.B. Zhang, L. Yuan, Z.G. Shen, J.-F. Chen, Micronization of atorvastatin calcium by antisolvent precipitation process, Int. J. Pharm. 374 (2009) 106–113.
[30] H. Chen, C. Khemtong, X. Yang, X. Chang, J. Gao, Nanonization strategies for poorly water-soluble drugs, Drug Discov. Today 16 (2011) 354–360.
[31] F.M. Veronese, G. Pasut, PEGylation, successful approach to drug delivery, Drug Discov. Today 10 (2005) 1451–1458.
[32] A. Pongpeerapat, K. Itoh, Y. Tozuka, K. Moribe, T. Oguchi, K. Yamamoto, Formation and stability of drug nanoparticles obtained from drug/PVP/SDS ternary ground mixture, J. Drug Delivery Sci. Technol. 14 (2004) 441–447.
[33] W.R. Wasylaschuk, P.A. Harmon, G. Wagner, A.B. Harman, A.C. Templeton, H. Xu, R.A. Reed, Evaluation of hydroperoxides in common pharmaceutical excipients, J. Pharm. Sci. 96 (2007) 106–116.