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Subcritical water processing for nanopharmaceuticals

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ABSTRACT

Nanonization of poorly water-soluble drugs offers an efficient approach for enhancing the bioavailability of drugs where the solubility and dissolution rate are the main limitations. The solvent anti-solvent precipitation methods have been the most straightforward technique for producing ultrasmall drug nanoparticles with narrow size distributions. By using subcritical water (SBCW) as the solvent, the use of organic solvents could be eliminated, providing a green route to nanopharmaceuticals. In this review, we aim to give a comprehensive overview and latest progress on SBCW processing for nanoparticles of poorly water-soluble drug compounds. The effects of processing parameters and stabilizers on the properties of the nanoparticles are summarized. Perspectives on existing challenges and opportunities for scale-up and commercialization of the SBCW technology are discussed.

1. Introduction

Most of conversional and newly developed drugs are poorly water-soluble compounds, which are difficult to be formulated as highly potent drug products using conventional formulation techniques [1–4]. The adoption of nanoscience and nanotechnology in pharmaceutical to prepare nanopharmaceuticals has emerged as an efficiency strategy to improve bioavailability of oral drugs with poorly-water solubility [5–8]. The solvent anti-solvent (SAS) method by dissolving the drug in a solvent and adding the solvent to an anti-solvent that cause precipitation of drug nanoparticles, has been the most straightforward technique for producing ultrasmall size drug nanoparticles with narrow size distributions [9–12]. However, the use of organic solvents in general is unfavorable for the production of pharmaceutical drugs [13]. For example, according to the International Council for Harmonisation guidelines, the toxicity of organic solvents and their residue in the final products should be carefully evaluated [13–15]. The potential environment pollution caused by the large consumption of organic solvents during the manufacture process is another consideration [16]. The development of “green chemical engineering” pursues high performance, cost effective and environmental friendly processes and products for social use [17–23]. As a newly developed process intensification technology, subcritical water (SBCW) technology presents a green route for the formation of organic nanoparticles and drug design, which have become attractive in recent years [13,14,24–26]. Our group at Beijing University of Chemical Technology is among the earliest research groups to perform the possibility to eliminate the use of organic solvent in the manufacture of nanoparticles for poorly water-soluble compounds by using SBCW as the solvent and liquid water as anti-solvent [27–32]. In contrast to conversional SAS methods, the nanoparticles obtained through SBCW processing are organic solvent-free, which would simplify the treatment procedure and increase economic benefit of in manufacturing processes of nanopharmaceuticals.

In this article, we present a focused review on the design and synthesis of nanoparticles for poorly water-soluble drugs based on the process intensification of SBCW processing. In such a context, the fundamentals of SBCW processing for organic nanoparticles and recent advancements in this field are demonstrated. The properties affecting the solubility of organic drug compounds in SBCW and the effects of operating parameters such as the volume ratios of the solvent (SBCW) and anti-solvent (liquid water), temperatures and use of various stabilizers on the products of drug nanoparticles were summarized, based on our expertise and experimental outcomes. Finally, challenges and opportunities are provided based on our own understanding of this field.

2. Properties of SBCW

It is generally known that water exists as a solid, liquid or gas depending on the temperature and pressure. Fig. 1a shows the phase behavior of H_2O in a pressure-temperature diagram [33]. At a constant

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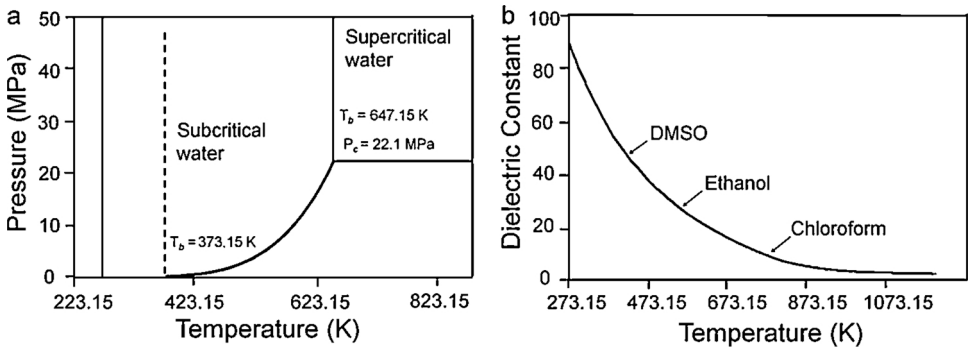

Fig. 1. (a) Pressure-temperature phase diagram of water: T_c = 647.15 K (critical temperature), Pc = 22.1 MPa (critical pressure), T_b = 373.15 K (boiling point) [33]. (b) Comparison of the temperature-sensitive dielectric constant of water at saturated liquid pressure with the dielectric constants of different solvents at room temperature [13].

temperature, the density of H_2O increases with increasing pressure. When the pressure is constant, the density of water decreases with increasing temperature. As both temperature and pressure increase, the coexistence curve of the gas-liquid equilibrium moves upward, while the phase boundary disappears and the densities of both liquid and gas phases become equal at the critical point [33–35]. The SBCW is defined as water that maintains liquid state by pressure at a temperature higher than its natural boiling point of 373.15 K and lower than its critical temperature of 647.15 K. The SBCW is also known as hot compressed water (HCW) superheated water (SHW), pressurized hot water (PHW) or near-critical water (NCW) [36–38], and in fact, it is very common in our daily life, presenting in a pressure cooker in which the food is cooked rapidly due to the higher real temperature than regular boiling water [39]. As the data shown in Fig. 1b, the dielectric constants of water at saturated liquid pressure decrease as the temperature increases, due to the disruption of the hydrogen bonding network of H_2O caused by the thermal motion of molecules. Typically, bulk water at room temperature exhibits a high dielectric constant of 80 [40] and when the temperature of water is raised to 423.15 K, the dielectric constant falls to 47, similar as that of diemthyl sulfoxide (DMSO) at ambient conditions (Fig. 1b). [13] Further, the dielectric constant of SBCW at 573.15 K is close to that of ethanol at room temperature [41]. Therefore, the SBCW has the ability to serve as a solvent for non-polar organics and has been used widely in selectively extraction of hydrophobic organic compounds from biomasses [42–44]. Besides that, the increase of ionic product for water at subcritical state drives the formation of hydronium (H_3O^+) and hydroxide (OH^-) ions, making SBCW perfect for either acid or base catalyst, such as hydrolysis proteins [45]. Tremendous progresses have been achieved on the fundamental investigations and applications of SBCW processing for extraction and hydrolysis of organic compounds, with a series of specialized review articles published [46–50]. In the subsequent sections, we will focus on the “nanopharmaceuticals engineering” part of the SBCW story, which has only just begun.

3. Nanopharmaceuticals

Nanopharmaceuticals are drug nanoparticles or nanodispersions engineered on the nanoscale with sizes between several nm to hundreds of nm. By reducing the size of poorly water-soluble drug particles to nanoscale, they usually exhibit unique thermodynamic and kinetic characteristics that neither the bulk material nor the atoms/molecules of that same material display [51–53]. Traditional solid powder with size in micrometer range or above, have a certain saturation solubility, depending on the chemical nature of the solute, the dissolution medium and the temperature. However, for solid particles at nanoscale, the saturation solubility of the solute at constant temperature and pressure is also a function of the particle radius on the basis of Ostwald-Freundlich equation [54]:

$$S = S_\infty exp\left(\frac{2\gamma M}{r\rho RT}\right)$$

Where S is the drug solubility, S_∞ is the solubility of large particles, γ = interfacial surface tension, M = molecular weight of the compound, R = gas constant, T = absolute temperature, ρ = density of the solid, and r = radius of the particle.

As predicted by Ostwald-Freundlich equation, the solubility of drug can be enhanced when the particle radius is decreased. This effect is unobvious for large drug particles but will be significantly more pronounced for nanoparticles [55,56]. The increased saturation solubility of drug nanoparticles in turn results in enhanced concentration gradient between gut lumen and blood, which is positive for the absorption of oral drugs by passive diffusion [57]. Drug dissolution from formulations is another important factor influencing the bioavailability of oral drugs. Especially for drugs with a short absorption window, they might have passed their absorptive sites (intestinal tract) before they dissolve [55–57]. The dissolution of solid drug particles in aqueous medium is described by the Noyes-Whitney equation:

$$\frac{dc}{dt} = D \times A\left(\frac{c_s - c_x}{h}\right)$$

Where c represents the concentration of drug molecules, t is the time and $\frac{dc}{dt}$ indicate the dissolution rate of drug particles. D = diffusion coefficient, A = surface area of the particle, c_s = saturation solubility, c_x = bulk concentration and h = diffusional distance.

On the basis of Noyes-Whitney equation, by downsizing the poorly water-soluble drug particles, the saturation solubility (c_s) and surface area (A) increases, resulting in increased dissolution rate ($\frac{dc}{dt}$). Therefore, nanonization of poorly water-soluble drugs is a suitable way to successfully enhance the bioavailability of drugs. To date, many techniques for manufacturing drug nanoparticles have emerged, which can be classified into two strategies. One is the top-down approach, in which the large-size drug powders are broken down to small particles using technologies such as ball milling and high pressure homogenization [51]. A number of marketed nanopharmaceutical products are available by top-down technologies, however, there are still some inherent drawbacks, including contamination of impurities and chemical degradation. In addition, it is very difficult to produce small, uniform, and non-aggregated nanoparticles by using traditional top-down methods. The products are usually hundreds of nm in size [52]. Alternatively, nanopharmaceuticals can be synthesized *via* bottom-up approachs, such as SAS precipitation, spray drying, cryogenic and microemulsion methods [3]. The SAS precipitation is the most straightforward technique for producing nanoparticles [58]. Fig. 2 shows the general process of the particle formation in solution by SAS precipitation, involving the mixing of the reactants, formation of precursor, critical nuclei, followed by the stabilization, growth and/or aggregation of organic particles [59]. Typically, the formation of nanoparticles in solution is the result of relative diffusion of solutes, and the main factor is the difference of diffusion concentration. For the conventional SAS processes to prepare organic nanoparticles, the solute is generally

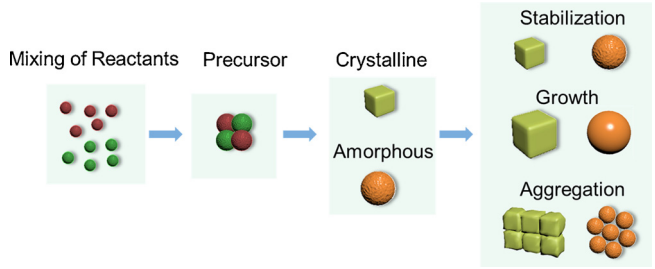

Fig. 2. The general process of particle formation in solution exhibiting the mixing of the reactants, formation of precursor, critical nuclei, stabilization, growth, aggregation of solid particles in solution.

dissolved in organic solvents and the supersaturation for the induction of the initial precipitation or crystallization reaction is produced by mixing the solution with a second fluid phase in which the substance is poorly soluble or insoluble [60]. Accordingly, the toxicity of organic solvents and their residue in the final products should be carefully evaluated. The rigorous organic solvent removal is often required. As a newly developed technology, the SBCW processing for nanopharmaceuticals, that is using SBCW as the solvent and water as the anti-solvent, provides the possibility to eliminate the use of organic solvent in the manufacture of drug nanoparticles, and can be considered to fall under the banner of green chemistry [61].

4. Solubility of hydrophobic compounds in subcritical water

The solubility data of solid solute in certain SBCW medium is the fundament to the development of SBCW processing for organic nanoparticles. To date, the solubility data of several kinds of organic solutes in SBCW under various conditions have been reported [13,14,24–26,28–31]. The total regularity is that the solubility values of organic solutes in SBCW are closely related to the temperature and chemical structure of the solutes and was not obvious to the pressure. For detailed information, the interested readers are referred to specialized review articles and research papers [13,46,50]. Herein, we give only a brief summary of our results to show the general situation of the research route [32]. Fig. 3 shows the diagram of a typical SBCW apparatus established in our lab, which involves a syringe pump system, a equilibrium vessel with temperature control oven and a precipitation vial [31]. The system was connected with a series of stainless steel fittings and tubing lines controlled by different valves, The experimental details for the measurements of solubility of various drug molecules could be referred in our previous published article [32].

Fig. 4 presents the experimental solubility data of five kind of drugs including bicalutamide (BC), megestrol acetate (MA), prednisolone (PDL), beclomethasone dipropionate (BDP), and clarithromycin (CLA) in SBCW [32]. Maintaining the confining pressure at 5.5 MPa, we determined the solubility of the solutes in SBCW in different temperature

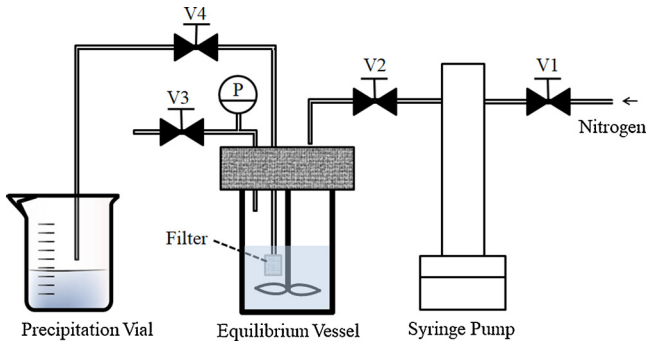

Fig. 3. A schematic diagram of the subcritical water-ethanol mixture system. V1-V4 represent different valves of the system. P is the pressure reader [31].

from 383.15 to 443.15 K [32]. All the five solutes exhibited strong dependence of solubility on the temperature of SBCW. In the temperature range of 383.15 to 413.15 K, the solubility of the solutes in SBCW increased slowly, but that of 413.15 and 443.14 K increased rapidly [32]. The experimental solubility data fitted well with the modified Apelblat equation:

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

where x_{sol} is the mole fraction solubility of investigated solute; A, B and C are the empirical parameters; T is the absolute temperature.

The empirical parameters of A, B, and C for each solute and the respective root-mean-square error (RMSE) are shown in Table 1. The verification results show that the prediction data of the modified Apelblat model accord well with the observed data, and the prediction results can actually provide some guiding significance for the SBCW processing of nanopharmaceuticals.

5. Nanoprecipitation of hydrophobic compounds

The use of SBCW for the manufacture of drug nanoparticles can lead to 'green' processes, which have become attractive in recent years [13,24–32]. Fig. 5 shows the major steps for the synthesis of organic nanoparticles via SAS precipitation by using SBCW as the solvent and cold water as the anti-solvent [30]. As described in Section 4, the solubility of drugs are significantly enhanced in SBCW than that of in cold water. The mixing of the SBCW solution and cold water results in supersaturation of the drug molecules. Primary drug particles appear through the burst-nucleation step and large particles then form via diffusional growth and/or aggregation of the primary particles [29,30]. It is generally accepted that within a short reaction time, the diffusional growth usually produces smaller particles than aggregation does [62,63]. Therefore, the control of supersaturation process is critical for the preparation of drug nanoparticles with controllable and uniform size distribution. As a representative, Chen et al. reported the SBCW processing of PDL nanoparticles, which were smaller than 100 nm with spherical morphologies and regular shapes [28]. The particle size and morphology can be controlled by tuning the excipients added and temperatures of the SBCW and water. The morphology of PDL particles changed from rods to spheres when the temperature of the SBCW solution increased from 383.15 K to 433.15 K. The colder the anti-solvent was, the smaller the obtained PDL particles were [28]. By adding stabilizers such as polyethylene glycol (PEG) to prevent the agglomeration among the nanoparticles, the average size of PDL particles could be decreased to as small as 29 nm in diameter [28]. Furthermore, Pu et al. expanded the use of SBCW processing for nanopharmaceuticals and first investigations were made with respect to broad-spectrum antibacterial agents such as BDP, CIP and CLA [29–31]. Taking the CLA as an example, the scanning electron microscope (SEM) images raw CLA is shown in Fig. 6a, which exhibits an irregular shape with sizes of several micrometers [29]. The CLA particles precipitated from SBCW solution of 382.15 K are rod-shaped particles of 150–200 nm in wide and several micrometers in length (Fig. 6b) [29]. Under optimized experimental conditions of SBCW processing, which was using 1.5 ml of SBCW at 423.15 K as the solvent and 15 ml of aqueous polyvinyl pyrrolidone (PVP) solution (0.4 wt%) as the anti-solvent, sub-50 nm CLA nanoparticles are obtained (Fig. 6c), which show much higher dissolution rate (over 85% at 60 min) than those of the raw CLA and submicron CLA (Fig. 6d) [29]. Although the SBCW processing for nanopharmaceuticals may require more critical equipment and higher energy consumption than the conversional SAS precipitation using organic solvents, it offers an organic solvent free route, which do not need rigorous solvent removal of the products.

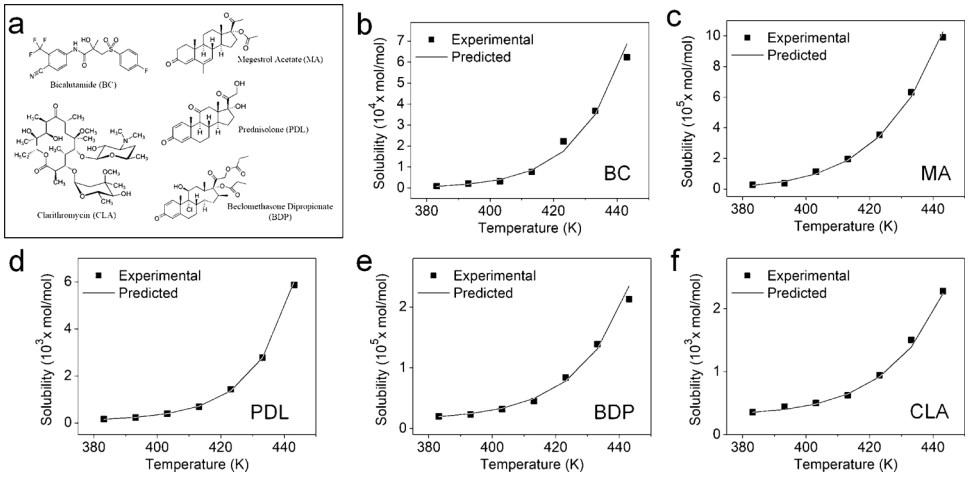

Fig. 4. (a) Chemical structures of bicalutamide (BC), megestrol acetate (MA), prednisolone (PDL), beclomethasone dipropionate (BDP), and clarithromycin (CLA). Experimental and predicted mole fraction solubility of BC (b), MA (c), PDL (d), BDP (e) and CLA (f) as a function of temperature [32].

Table 1
Solubility parameters of BC, MA, PDL, BDP and CLA from modified Apelblat equation [32].

Solute	A	B	C	RMSE
BC	−32.54	−9493.72	7.66	0.19
MA	158.04	−19095.72	−20.37	0.18
PDL	−1190.29	60560.21	172.06	0.04
BDP	−1071.83	56106.38	153.36	0.09
CLA	−1042.97	56275.04	149.31	0.06

6. Conclusion and perspective

The replacement of conversional used organic solvents with SBCW to dissolve hydrophobic organic compounds performs the possibility to eliminate the use of organic solvent in the manufacture process of nanopharmaceuticals via SAS preciptaion. We have presented a focused review on the fundamentals and methods for the synthesis of nanoparticles of poorly water-soluble drugs by SBCW processing. Even this short review article has revealed the potentially significant value of this technique for manufacture of drug nanoparticles without the use of toxic organic solvents. However, the applications of SBCW for nanopharmaceuticals are still at its early stage with some important issues

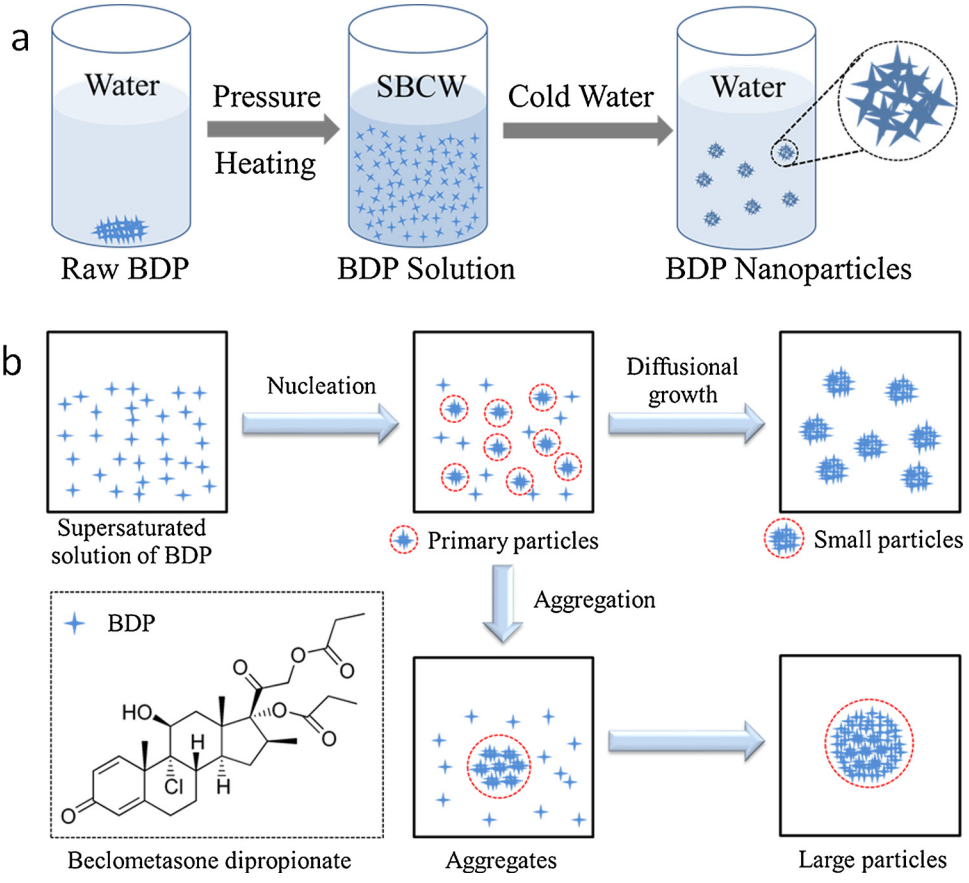

Fig. 5. (a) Schematic diagram of the BDP nanoparticles formation during the SAS precipitation by using SBCW as the solvent and cold water as the anti-solvent. (b) Schematic diagram of the particle diffusional growth process of the primary particles to small BDP nanoparticles and the aggregation process of the primary particles to large BDP nanoparticles, respectively [30].

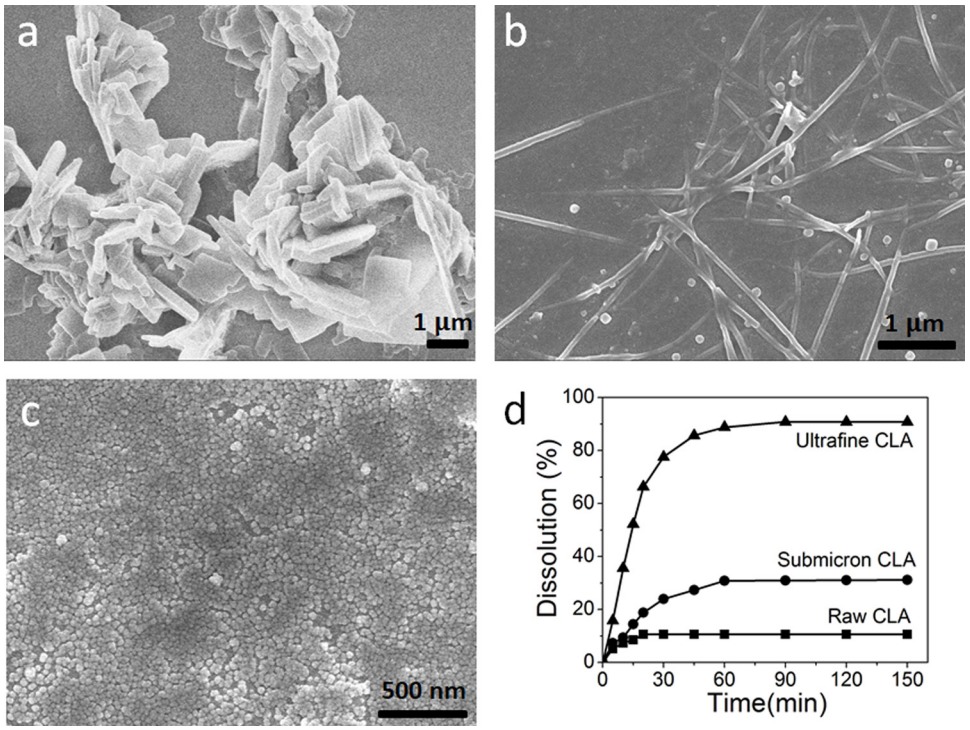

Fig. 6. SEM images of (a) unprocessed raw CLA drug particles, (b) submicron CLA particles obtained by using SBCW of 383.15 K as the solvent and deionized water (293.15 K) as the anti-solvent, (c) CLA nanoparticles prepared by using SBCW of 423.15 K as the solvent and aqueous PVP solutions (0.4 wt%, 293.15 K) as the anti-solvent. (d) Dissolution profiles of raw CLA, submicron CLA particles and CLA nanoparticles. [29]

remained to be addressed:.

(1) Several aspects affecting particle size distribution such as molecule scale and nanoscale micromixing processes are challenging when scaling-up these processes. The issues related to scale-up and cost of the whole process must be considered at an earlier stage of development. An ideal reactor to obtain nanoparticles with uniform size distribution, should be able to realize fast micromixing to meet the requirements of homogeneous micromixing before nucleation. Otherwise, it is difficult to control the particle formation. Therefore, intensified micromixing and mass transfer are highly required for the engineering of drug nanomaterials. In particular, the high gravity technology based on the use of rotating packed bed (RPB) reactor, has been demonstrated to be an efficient tool for process intensification [63–67]. The realization of SBCW processing in RPB reactors is attractive and should be an interesting topic for follow-up studies.

(2) Despite the fact that there are several publications of SBCW processing for nanopharmaceuticals, an absence of standardized methodologies (pressure, reactor size, etc.), makes it difficult to compare the product yield of the drug nanoparticles from different literatures. Therefore, a more extensive and complete characterization including the process parameters, solubility, product yield, nanoparticle morphology, bioavailability, etc., is recommended for drug nanoparticles to determine the effectiveness and practicability of the SBCW processing technology. For organic solutes with low melting points, the usable temperature range of the SBCW is limited and the yield of organic nanoparticles is low. High solubility of organic compounds is feasible at lower temperatures if co-solvents are used.

(3) Besides sizes, the crystalline structures of drug nanoparticles also play important role for the dissolution rates and pharmacological functions in living organisms. Amorphous nanoparticles usually exhibited higher solubility than their crystalline counterparts [68]. However, it remains difficult to produce drug nanoparticles with amorphous structures since most of the poorly water-soluble drugs have a high propensity to crystallize. As for the development of nanopharmaceuticals, there are still concerns about the possible side effects derived from nanoscale [69]. Detailed assessments of drug nanoparticles remain to be investigated, including but not limited to the *in vivo* distribution of the drug nanoparticles and the metabolic mechanism in various animal models.

In general, the combination of nanotechnology and pharmaceuticals [70,71], along with the pioneering researches by Prof. Langer et al. in particular [72–75], are revolutionizing medical therapies. We are honored to join in the wave of the technological revolution and contribute to the development of this filed. Looking forward to the future, we sincerely hope that this mini-review can give some inspiration in the next few years for research that focus on the application of SBCW processing for organic nanoparticles and inspire new endeavors to promote nanopharmaceuticals for large-scale commercial application.

Notes

The authors declare no competing financial interest.

Acknowledgments

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