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Green preparation of uniform prednisolone nanoparticles using subcritical water

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HIGHLIGHTS

- Subcritical water (SBCW) process was a new green environmental-friendly method for preparing drug nano-particles.
- Prednisolone particles with narrow size distributions were produced from the SBCW process.
- Particle morphology was significantly dependent on operating conditions.
- Prednisolone particles displayed obviously higher dissolution rates than the raw drug.

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ABSTRACT

Drugs with poor solubility in water, which indicates poor oral bioavailability, account for a considerable portion of new pharmaceutical candidates. Nanonization is a technique that overcomes this problem. However, current nanoionization methods have many disadvantages, including high energy demands, broad particle size distributions and the use of organic solvents. We report a new green method for preparing drug nano-particles by combining a subcritical water (SBCW) process with an anti-solvent precipitation method. The nano-particles processed through SBCW technology have a spherical morphology, a regular shape and a homogeneous particle size. Prednisolone nanoparticles averaging 31 nm in diameter were produced using this approach, and these particles were 10 times smaller size than the unprocessed drug. The resulting particle morphology depended strongly on operating conditions such as the temperature of the SBCW solution, the temperature of the anti-solvent and the concentration of the pharmaceutical excipients. Consequently, uniform prednisolone nanoparticles were produced through an environmentally friendly method.

1. Introduction

More than 40% of pharmaceutical candidates exhibit poor water solubility [1,2]; therefore, the dissolution bioavailability of those drugs remains insufficient and far below the therapeutic level [3,4]. Improving the water solubility of drug candidates has become an important project during drug development in pharmaceutical companies. Several approaches are available for improving the water solubility of active pharmaceutical ingredients (API), such as complexation with cyclodextrins [5], forming salts with ionizable drugs [6], micellar solutions [7], and the solubilization of drugs in co-solvents [8]. Among these methods, nanonization is an effective and versatile method for improving the water solubility and bioavailability of water-insoluble drugs [3,9–13], This method is simple in principle because the particle size is reduced to the nanometer range; in addition, this method is easy to manipulate, granting it great potential.

Many approaches for producing nanoparticles utilize various processes, such as media milling [14], high-pressure homogenization [15] anti-solvent precipitation [16,17], and supercritical fluid techniques [18,19]. The media milling method requires grinding processes and corrosive media, which can easily cause contaminate to the drugs [20,21]. All mechanical commutation methods require large amounts of energy and exhibit some disadvantages, such as electrostatic effects and broad particle size distributions [22]. Anti-solvent precipitation has remained an effective way for preparing nano-sized drug particles. With this method, the drug

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is initially dissolved in a solvent, and this solution is quickly combined with the anti-solvent. Precipitation occurs immediately through the rapid desolvation of the drug. However, the solvents used during these procedures are toxic; therefore, a thorough removal of these organic solvents removal is often required, which is expensive and time-consuming.

Subcritical water (SBCW) processes are new alternative supercritical fluid techniques that are promising for the preparation of drug nanoparticles [23,24]. SBCW or "hot" water is a liquid water phase under pressure at temperatures between the usual boiling point (100 °C) and the critical temperature (300 °C), and non-polar organic solvents are miscible in these phases. As the temperature of the water increases, the intermolecular hydrogen bonds begin to weaken, reducing the polarity. Consequently, the polarity of water at these temperatures becomes equivalent to that of common organic solvents [25,26]. When the nanoparticles are produced, the contact between the SBCW solution and the room-temperature water decreases the polarity of the solvent. The change in polarity can induce supersaturation in the solution, leading to a rapid precipitation of the solute. Compared to the anti-solvent precipitation process, the SBCW process is non-toxic and does not require rigorous solvent removal. Therefore, the combination of a subcritical water (SBCW) process with an anti-solvent precipitation process might be an ideal candidate for forming particles in an environmentally friendly manner. To our knowledge, few works have detailed the preparation of nanoparticles through subcritical water technologies. These works describe the preparation of particles composed of drugs, such as griseofulvin [23] and budesonide [27], from pure and modified subcritical water solutions, generating particles a few micrometers in diameter. Recently, the use of hydrophilic microparticles has become one of the most novel and advanced release systems, and these systems are key when designing a formulation for oral drug delivery. For instance, aqueous solutions containing a hydrophilic stabilizer could be used as an anti-solvent. In recent years, several papers have described the formation of particles composed of an API through subcritical water technologies, but our report is the first report applying these methods toward micronizing prednisolone to particle sizes below 100 nm. To obtain smaller particles, a lower injection velocity is used to introduce the SBCW solution to the anti-solvent, and a hydrophilic stabilizer is incorporated in the anti-solvent. The controlled injection velocity is the key factor for generating smaller particles the aspect making our procedure different from other methods. In this paper, polyethylene glycol (PEG) was selected as a stabilizer due to its non-toxic nature, ease of manufacture and common use as a carrier for partially water-insoluble drugs [27].

Prednisolone (PDL) is a synthetic adrenal corticosteroid, which is a derivative of cortisol, used to treat various inflammatory and auto-immune conditions [28] such as asthma [29], uveitis, acute rheumatoid arthritis, autoimmune pericarditis and allergic or inflammatory conditions of the nose and eyes [30]. This compound is also used to treat sarcoidosis through an unknown mechanism. PDL is poorly soluble in water, and it exists in at least two polymorphic forms and two pseudopolymorphic forms [31]. Its low solubility and dissolution rate in the gastrointestinal tract limits its effective absorption and bioavailability. Therefore, stringent control over the particle size distribution must be achieved.

The objective of this paper was to prepare nanoparticles from PDL while using subcritical water solutions. The effect of the operating parameters, such as the temperature of the SBCW solution and regular water (as anti-solvent) and the concentration of PDL in the SBCW solution, were explored. The corresponding physical stability and dissolution properties of the PDL microcrystals were characterized through scanning electronic microscopy (SEM), Fourier transform infrared spectrophotometry (FT-IR), powder X-ray diffraction (XRD) and dissolution tests.

2. Experimental section

2.1. Materials

The prednisolone (⩾98%, CAS No. 50-24-8) was purchased from Shandong Taihua Bio & Tech co., Ltd. The ethanol (⩾99.7%, for washing) was purchased from Beijing Chemical Works. The nitrogen (⩾99.9992%) was purchased from PREMER. The polyethylene glycol 4000 (PEG) was obtained from Shandong Ruitai Chemicals Co. Ltd. The deionized water was prepared by a Hitech-K flow water purification system (Hitech instrument Co., Ltd. Shanghai, China) and used during all experiments.

2.2. Experimental procedure

A schematic of the experimental apparatus is shown in Fig. 1. The fittings and tubing were composed of stainless steel (type 316). A Druck pressure transducer and indicator were fitted, and a Binder GC-8A chromatography oven was used to the precise temperature control (±0.1 K) necessary for solubility analyses. A Sartorius BSA224 electronic balance with a metering accuracy of ±0.1 mg was used to determine the masses of the relevant compounds.

The solubility vessel (SV) had an internal volume of 6.4 ml. At each end of the SV, a threaded tube fitting containing a 0.5-μm filter stone, which was used to remove any undissolved particles in the SV, was installed. For each run, the SV was loaded with excess PDL. The vessel was filled with water through a syringe pump (ISCO model 260D) at a constant flow rate. An ISCO model 260D

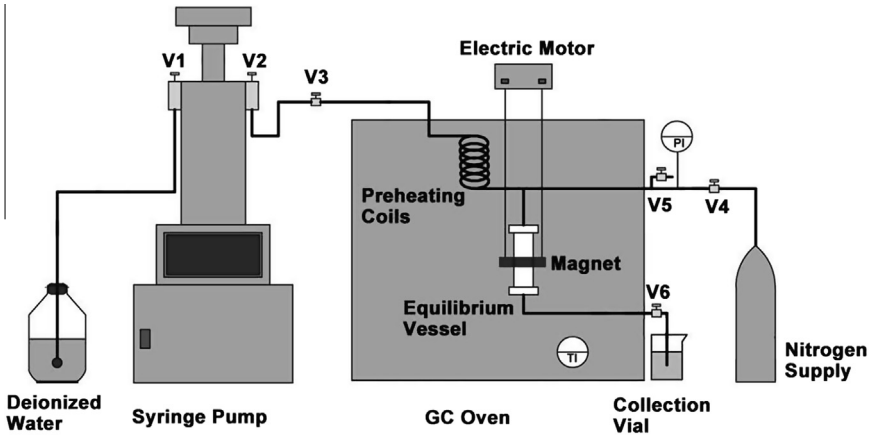

Fig. 1. Schematic diagram of the particle formation in subcritical water.