PRODUCTION OF PEG SUBMICRON PARTICLES BY THE SOLUTION ENHANCED DISPERSION WITH ENHANCED MASS TRANSFER BY ULTRASOUND IN SUPERCRITICAL CO_2 (SEDS-EM)

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ABSTRACT
In this study, a novel method, solution enhanced dispersion in supercritical CO_2 with enhanced mass transfer (SEDS-EM), is applied for the production of PEG submicron particles. To form a fixed morphology of PEG particles, PLA is used as a frame material. The solution can be generated into very small droplets during SEDS-EM, which induces the enhanced mass transfer in the supercritical CO_2 and the prevention of agglomeration of particles. The effects of ultrasound and the amount of PEG in the composite on the morphology and size of PEG-PLA nanoparticles have been examined.

Keywords: supercritical CO_2, SEDS, ultrasound, nanoparticle, resveratrol

1. INTRODUCTION

The side effects and low efficacy appear sometimes after the oral administration of some drugs in the gastrointestinal tract because of their toxicity, low bioavailability, physical and chemical instability, enzymatic degradation and poor absorption.[1] In the recent years, many efforts have been made to develop proper ways or formulations to solve these problems. In particular, polymeric composites of these drugs have been found to succeed in preparation of sustained drug delivery systems with high therapeutic performance. The release of these drugs is controlled due to the existence of biodegradable and biocompatible materials. Many methods and techniques to prepare such composites and particles in the pharmaceutical industry are established. Among them, the techniques based on supercritical fluids (SCF) as an antisolvent are considered advanced ways to obtain size controllable, tiny and free-solvent residual particles. These techniques consist of several main processes, such as supercritical antisolvent precipitation (SAS), aerosol solvent extraction system (ASES), and solution enhanced dispersion by supercritical fluid (SEDS) and supercritical antisolvent with enhanced mass transfer (SAS-EM). [2-5] Recently, a novel SEDS technique of solution enhanced dispersion with enhanced mass transfer by ultrasound in supercritical fluid, SEDS-EM, is introduced by us.

In this paper, PEG is selected as a modal polymeric candidate, which can be used to

enhance the hydrophilicity of some poor water soluble drugs. However, PEG cannot form a fixed morphology in the supercritical CO2. Therefore, PLA is selected to be a frame material. PEG and PLA possess some good advantages for pharmaceutical and biomedical applications, such as excellent biodegradability, biocompatibility, non-systemic toxicity. The modified supercritical antisolvent technique, solution enhanced dispersion in supercritical CO_2 with enhanced mass transfer (SEDS-EM), is proposed for the production of PEG-PLA nanoparticles.

2. MATERIAL AND METHOD

1.1 Materials

PLA (Mw=20000) was obtained from Shandong Medicine Instrument Institute. (Shandong, China). PEG (Mw=10000) was obtained from Sinopharm Chemical Reagents Co., Ltd (Shanghai, China). Dichloromethane (DCM) with a purity of 99.5% was purchased from Ling Feng Chemical Reagent Co.,Ltd (China) as the solvent to prepare solution. Carbon dioxide (CO_2) with a purity of 99.95% was supplied by Rui Li Co.,Ltd (China).

1.2 Apparatus and procedure

The schematic diagram of SEDS-EM process for the production of particles is shown in Figure 1. The experiments were carried out in the semi-continuous mode. The major parts of the apparatus include a supercritical CO_2 supply system, a solution feeding system and a high pressure precipitation vessel (G) which consists of an ultrasound generation system and a coaxial nozzle (I). CO_2 from the cylinder (A) was liquefied by a chilling system (B) and delivered constantly by a piston pump (C) through the heat exchanger (D) into the high pressure vessel (G, volume=120 cm^3). Pressure was maintained in the vessel by a back pressure regulator (H) and temperature maintained by a heating tape with a thermocouple and an insulation layer. Once the pressure and temperature reached the desired values, the ultrasonic horn (J, made of Ti-6Al-4V, Φ_{tip}=15 mm) inside the vessel was turned on at the desired power supply (frequency=20 kHz), and the solution was injected inside the vessel through the capillary tube (inner part of the coaxial nozzle, Φ=50 μm). First, when the solution was contacted with the flowing CO_2 from the outer part of the coaxial nozzle, the solution jet mixed with CO_2 rapidly and was broken into small droplets immediately. Next, these small droplets were sprayed on the surface of the ultrasonic horn tip and were atomized into many smaller droplets. Particles precipitated swiftly from these droplets due to the removal of the solvent by supercritical CO_2. The diagram of the formation of droplets and nanoparticles in the SEDS-EM process is shown in Figure 2. After all the solution was injected, the ultrasonic processor was turned off and fresh CO_2 was continuously pumped into the vessel to flush the vessel to remove the residual organic solvent. The particles were collected by a filter placed at the CO_2 outlet of the vessel.

In this study, the operating pressure and temperature were kept at 8.8 MPa and 32 ℃ in order to prepare samples with supercritical CO_2. The flow rate of CO2 was 3.0 kg/h.

The concentration of PLA in the solution was kept at 20 mg/ml. The feed rate of solution was 1 ml/min.

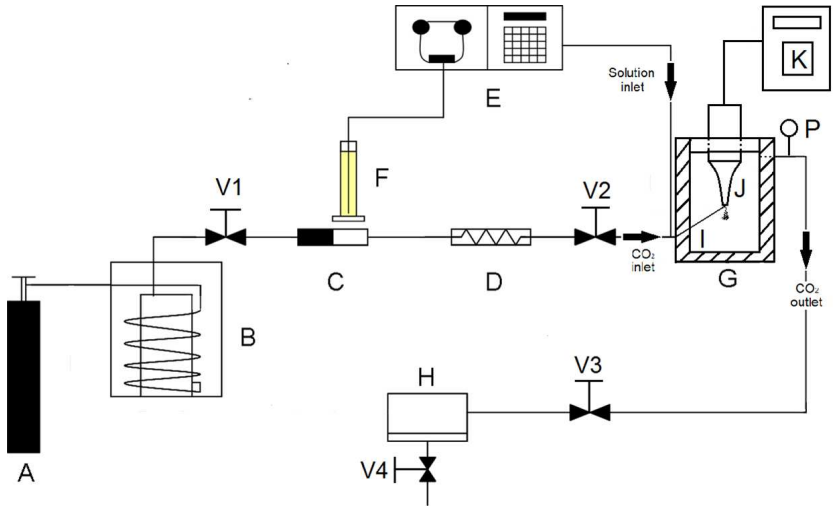


Figure 1 Schematic diagram of the SEDS-EM apparatus

A-CO_2 cylinder B-chilling system (refrigerator) C-piston pump D- heat exchanger E-HPLC pump F- polymer solution G-high pressure vessel (with a heating tape and an insulation layer) H-back pressure regulator (BPR) I- coaxial nozzle J- ultrasound horn (transducer) K-ultrasonic processor P-pressure gauge V1, V2, V3, V4-control valves

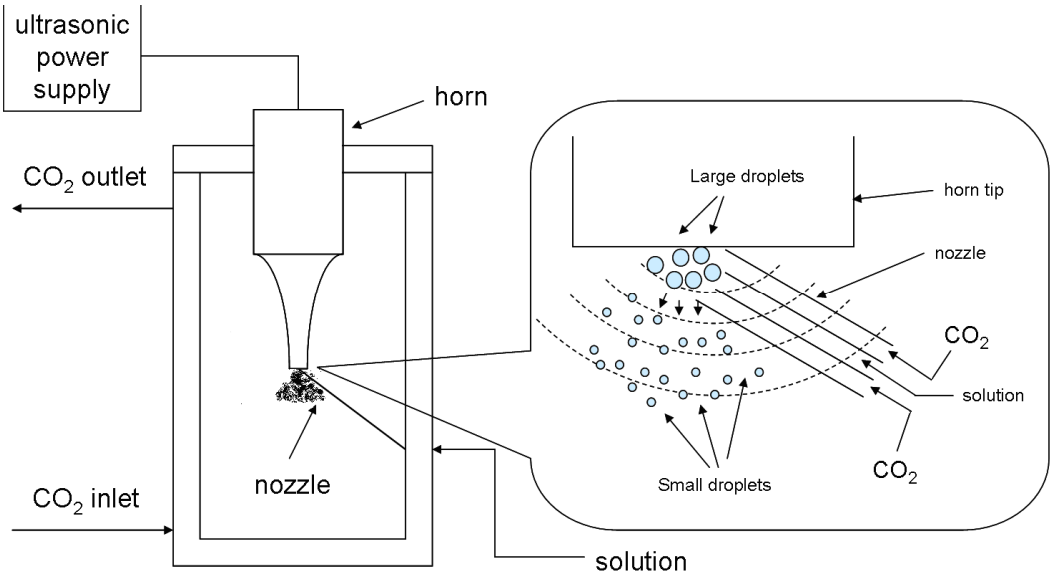


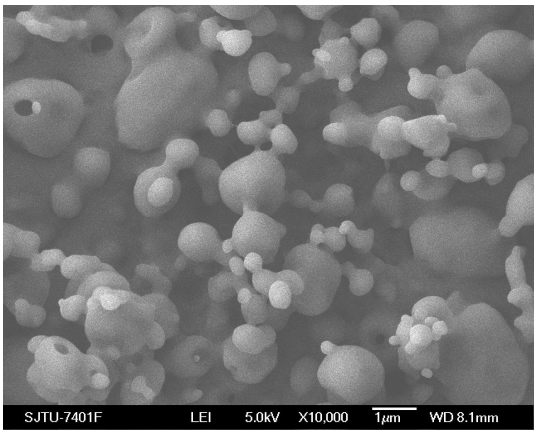
Figure 2 The diagram of the formation of droplets in the SEDS-EM process

1.3 Characterization (Morphology and size)

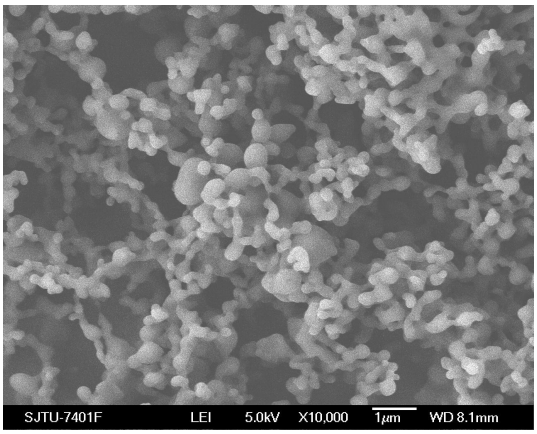
Morphological characterization of samples was observed by a scanning electron microscopy (SEM, JEM-7401F, JEOL, Ltd., Japan). A small amount of specimen is placed on one surface of a double-faced adhesive tape that sticks to the sample support and coated with gold under vacuum condition for about 20 s to enhance the

electrical conductivity of samples. The mean particle size and size distribution were measured with the Image-Pro software (version 6.0.0.260, Media Cybernetics, Inc.), using at least 500 particles for each experiment.

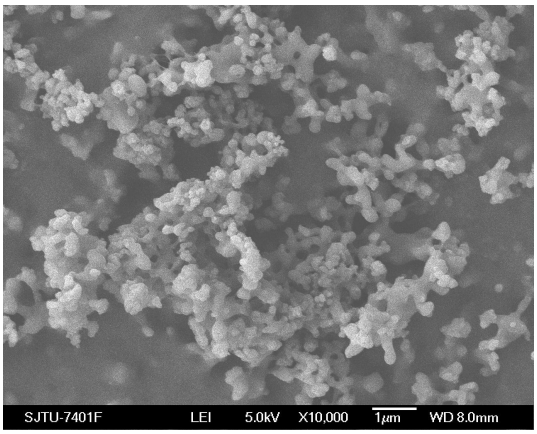
3. DISCUSSION AND RESULTS



A (0W)



B (180W)



C (360W)

Figure 3 The SEM images of PEG-PLA particles prepared with different ultrasound power

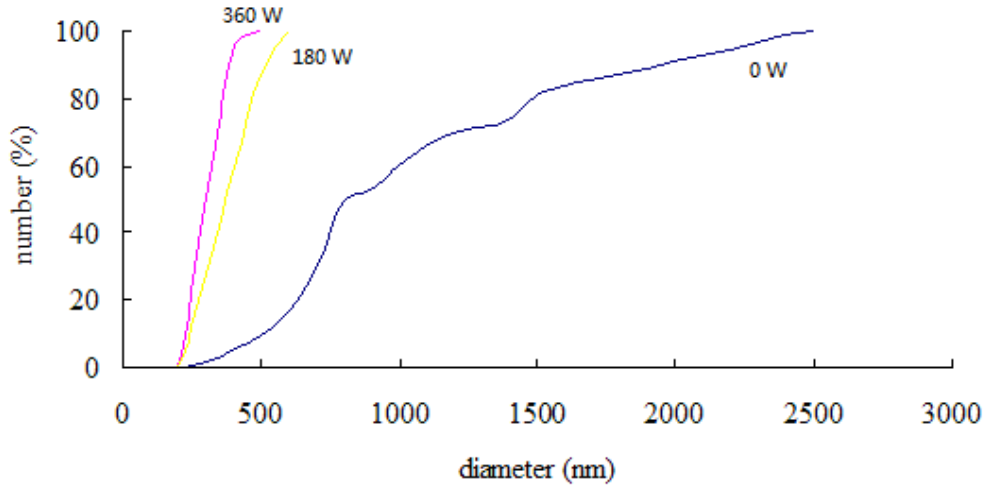
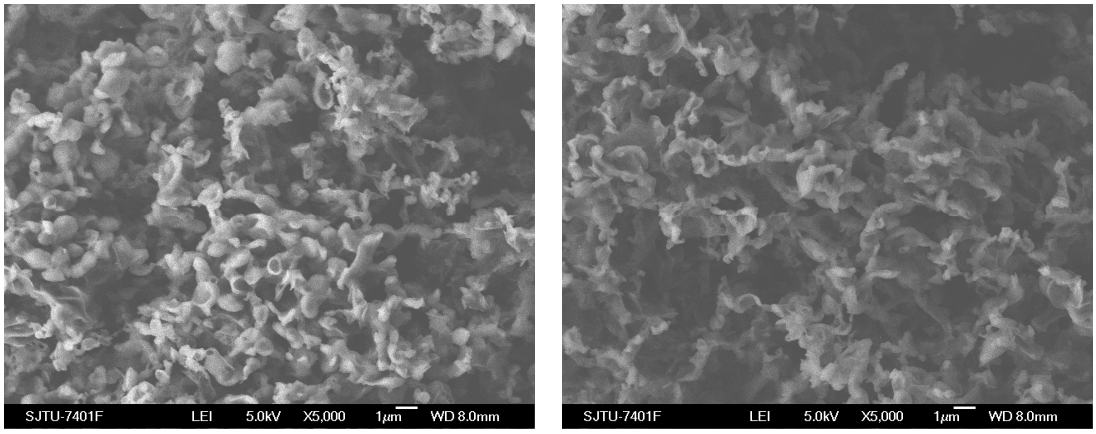


Figure 4 The particle size distribution of PEG-PLA particles prepared with different ultrasound power

The SEM images of the PEG-PLA particles produced with different ultrasound power supply (0W, 180W and 360 W) are shown in Figure 3. The concentration of PEG in the solution is 2.22 mg/ml (PEG wt%=10%). Compared to the samples prepared with ultrasound, the size of the particles prepared without ultrasound is larger. According to Figure 3A and the particle size distribution (PSD) of this sample in Figure 4, the particles are not uniform and the mean size of these particles is about 1000 nm. However, when ultrasound was applied in the production of PEG-PLA nanoparticles, the modification of the morphology and PSD of these particles are obvious. The particles appear more uniform with narrow PSD, and the mean particle size obviously decreased to 200-500 nm. In SEDS-EM technique, the application of a coaxial nozzle provides the jet breakup of the solution, but also the ultrasound field enhances suspension of the droplets and even more reduces the droplet size. [10] The combination of these two methods can obviously promote the quality of the particles produced by supercritical antisoulvent process. Furthermore, the particle size decreases with the increase of the power supply. In this study, the mean diameter of the PEG-PLA particles decreased from 400 nm to 300 nm when the power supply increased from 180 W to 360 W.

The amount of PEG in the solution also affects the morphology of the particles. When the concentration of PEG increased to 8.6 mg/ml and 20 mg/ml (PLA:PEG=30% and 50%), the morphology of the sample changed a lot, which is shown in Figure 5. The shape of the particle under such conditions is not spherical but hollow structure. That means if the operating condition is in the supercritical region, the amount of PEG in the solution should be considered, because the Tg (glass transition temperature) and the melting point of PEG is relatively low. Above the supercritical temperature of CO_2, PEG becomes “soft” and the morphology of PEG could maintain in a fixed morphology.



PEG 30% PEG 50%

Figure 5 The SEM images of PEG=PLA particles with different amount of PEG

4. CONCLUSIONS

A new SEDS-EM method was successfully developed to fabricate uniform PEG-PLA nanoparticles. Compared with SEDS (without ultrasound) techniques, SEDS-EM can provide smaller and more uniform particles. This modified technique may promote the administration of supercritical antisolvent process in pharmaceutical industry.

ACKNOWLEDGEMENT

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