Preparation of Cefuroxime Loaded PVP Particles by Supercritical Anti-Solvent Process

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ABSTRACT
Batch supercritical antisolvent precipitation (SAS) process was used to produce Cefuroxime Axetil amorphous (CFA, antibiotic) loaded Polyvinylpyrrolidone (PVP-K30) spherical particles with mean diameter of 2-5 μm. Solutions of (CFA + PVP-K30) in methanol with overall concentrations of 50-150 mg/ml and drug/polymer ratios of ¼ - ¼ were sprayed into the $scCO_2$ at 100-200 bar and 35-50 °C with flow rates of 0.85-2.5 ml/min. An increase almost in all process parameters caused an increase in the mean particle size and broadened the particle size distribution. The temperature and the drug/polymer ratio seemed to be the most important parameters affecting the particle morphology.

INTRODUCTION
Most controlled drug delivery systems focus on the production of drug loaded polymeric particles by incorporation or encapsulation of drug within a polymer. There are several techniques to produce drug loaded polymeric particles such as emulsion evaporation, phase separation, spray-drying, freeze-drying and interfacial polymerization. Excessive solvent use and disposal, thermal and chemical degradation of products, trace residues, and inter-batch particle size variability are the main drawbacks of these methods [1-3]. Supercritical fluid (SCF) technology presents a new and interesting route for particle formation, which avoids most of the drawbacks of the traditional methods. One such method, the supercritical supercritical antisolvent precipitation (SAS) process, seems to be a potential method to produce particles from various materials [4-8]. In this work SAS was used to produce drug loaded polymer particles in $scCO_2$.

MATERIALS AND METHODS
Materials
Methanol (Lab-Scan % 99.8) was used as the solvent to dissolve Cefuroxime Axetil and PVP. CO_2 (% 99.9), used as the supercritical antisolvent, was obtained from HABAS A.S. (Istanbul). Cefuroxime Axetil (CFA) and Polyvinylpyrrolidone (PVP-K30, $\overline{M}_V = 30000 - 50000$) were kindly supplied by Fako-Actavis (Istanbul) and Bilim Pharmaceuticals Co. (Istanbul), respectively.

Methods
The experimental setup (Fig.1) mainly consists of a syringe pump (Teledyne Isco 260D) to deliver CO_2, a dosing pump (Dosapro Milton Roy Milroyal) to deliver the solution, a capillary PEEK nozzle of 120 μm internal diameter to spray the solution into the high pressure cell of 761 ml internal volume containing a stainless steel collection basket and frit at the bottom. A cold trap located at the exit of the high pressure cell was used to recover the liquid solvent.

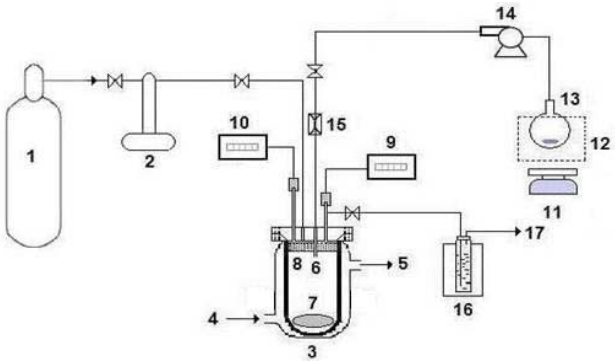


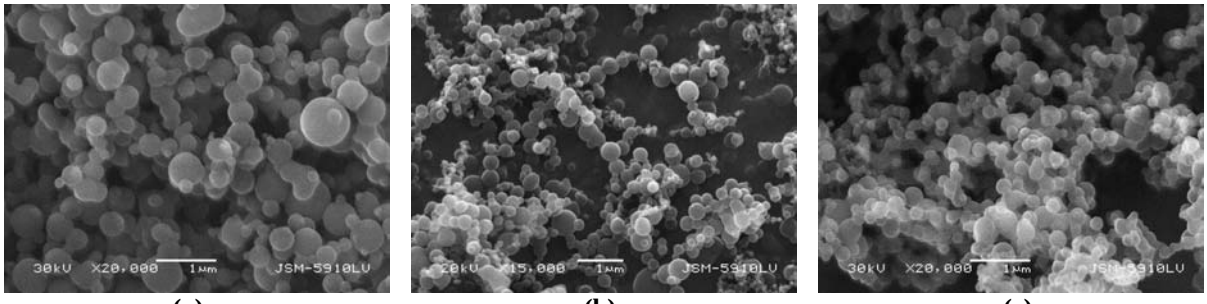
Figure 1. The SAS setup: 1) CO_2 cylinder, 2) Syringe pump, 3) High pressure cell, 4) Heating bath inlet stream, 5) Heating bath outlet stream, 6) Nozzle, 7) Stainless steel collection basket and frit, 8) Filter, 9) Digital pressure display, 10) Digital temperature display, 11) Magnetic stirrer, 12) Heating bath, 13) Solution reservoir, 14) Dosing pump, 15) Check valve, 16) Cold trap, 17) Vent [6].

Initially, the high pressure cell was filled with CO_2 until the desired pressure. Then the solution of drug and polymer was sprayed through the nozzle into the high pressure cell. As the solution was sprayed into the cell, precipitation occurred because of supersaturation of liquid droplets caused by the miscibility of $scCO_2$ and the organic solvent. After the spraying was stopped the high pressure cell was swept with CO_2 to prevent liquid recondensation.

Morphology of samples was analyzed by JEOL JSM-5910LV scanning electron microscope. The drug loaded particles were coated with gold/palladium mixture using a sputter coater (Quorum Technologies SC7620). Particle size and particle size distribution (PSD) were determined by Sympatec Helos particle size analyzer.

RESULTS

The effects of process parameters such as pressure, temperature, solution concentration, flow rate and drug/polymer ratio on the particle size and morphology were investigated in the production of CFA loaded PVP-K30 spherical particles with mean particle sizes 2-5 μm. As the pressure increased particle morphology was not affected significantly but a slight coalescence was observed at 200 bar (Fig. 2a-c).



(a) **(b)** **(c)**

Figure 2. SEM images of (CFA + PVP-K30) particles precipitated from methanol at 40 °C, 100 mg/ml, 0.85 ml/min, drug / polymer: 1/1; (a) 100 bar, (b) 150 bar, (c) 200 bar.

Fig. 3 shows that the mean particle size increases as the pressure increases. Since the particle size distribution is slightly narrowest at 150 bar, the rest of the experiments were performed at this pressure.

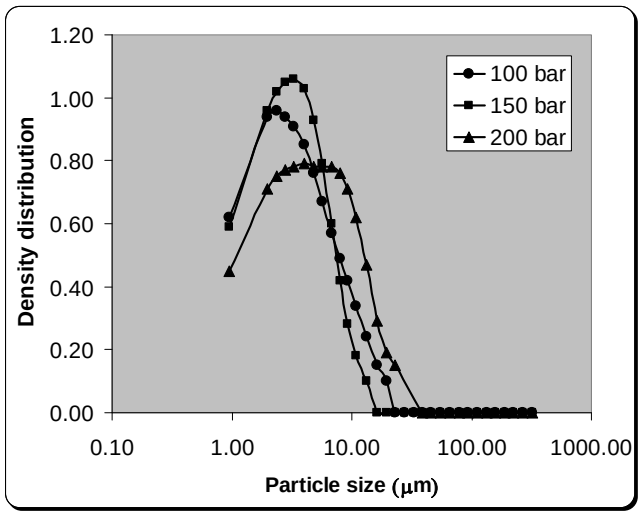


Figure 3. PSD of (CFA + PVP-K30) particles precipitated from methanol at 40 °C, 100 mg/ml, 0.85 ml/min, drug / polymer: 1/1; (●) 100 bar, (■) 150 bar, (▲) 200 bar.

The temperature was varied between 35-50 °C. The particles obtained at 35 and 40 °C were spherical and discrete (Fig. 4 a, b). Although the particles obtained at 45 and 50 °C were spherical, they coalesced (Fig. 4 c, d). Thus the particle morphology was considerably affected by temperature.

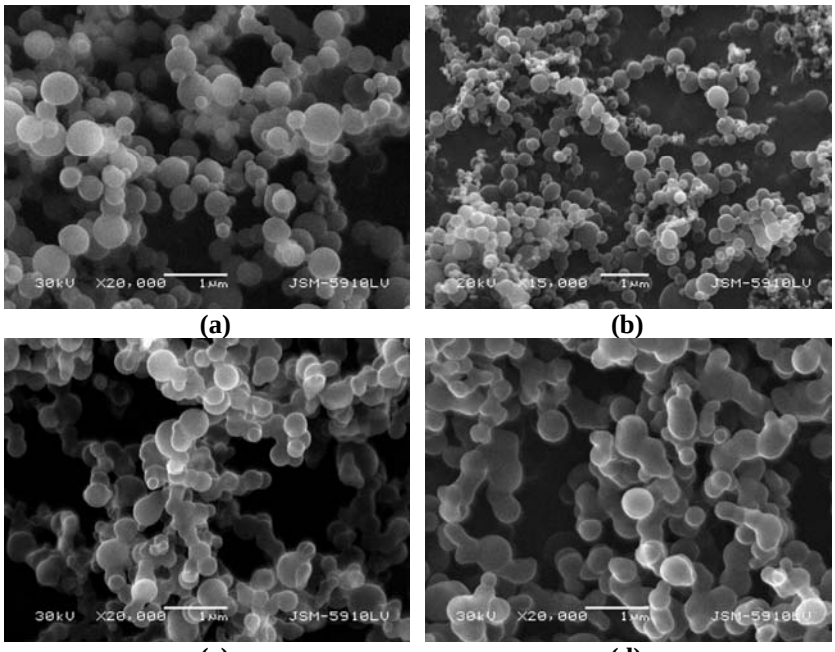


Figure 4. SEM images of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 100 mg/ml, 0.85 ml/min, drug / polymer: 1/1; (a) 35 °C, (b) 40 °C, (c) 45 °C, (d) 50 °C.

Increase of the temperature did not affect the mean particle size significantly. The mean particle sizes at 40, 45 and 50 °C, were almost the same, but it was slightly lower at 35 °C. However, it was observed that the particle size distribution changed with temperature (Fig. 5). Slightly narrower distributions were observed as the temperature increased.

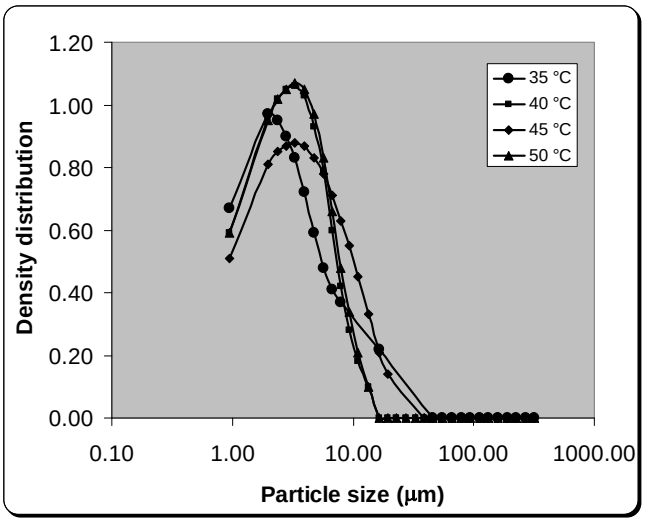
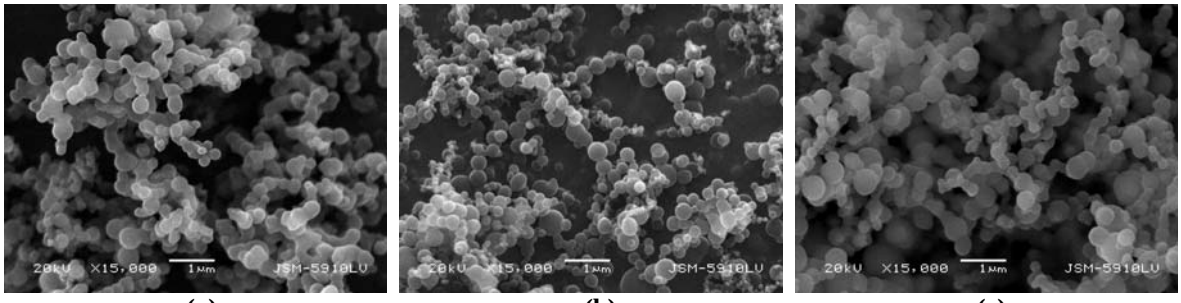


Figure 5. PSD of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 100 mg/ml, 0.85 ml/min, drug / polymer: 1/1; (●) 35 °C, (■) 40 °C, (◆) 45 °C, (▲) 50 °C.

Solutions having concentrations of 50-150 mg/ml were sprayed to high pressure cell. The solution concentration slightly changed the particle morphology. Coalescence was observed for 50 and 150 mg/ml (Fig. 6 a, c) solutions. Also, the mean particle size and the particle size distribution at these concentrations were very similar (Fig. 7). Spherical and discrete particles were obtained at 100 mg/ml (Fig. 6 b). However, at this concentration the mean particle size was larger and the particle size distribution was slightly broader.



(a) **(b)** **(c)**

Figure 6. SEM images of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 0.85 ml/min, drug / polymer: 1/1; (a) 50 mg/ml, (b) 100 mg/ml, (c) 150 mg/ml.

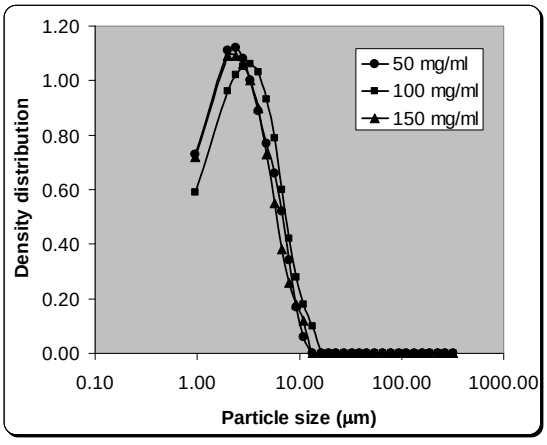
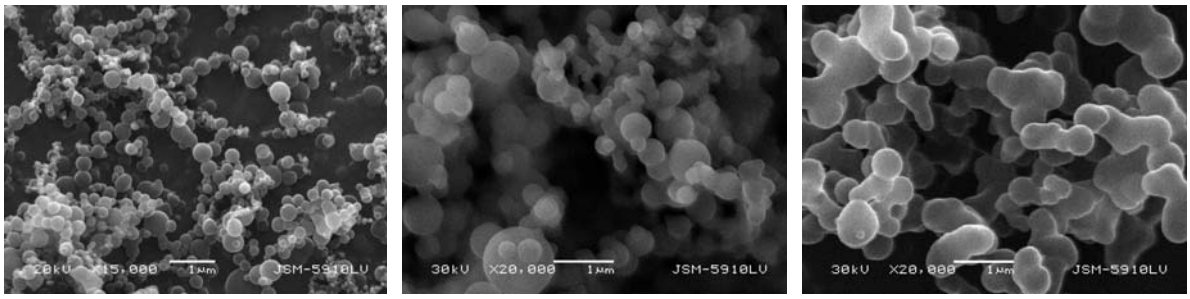


Figure 7. PSD of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 0.85 ml/min, drug / polymer: 1/1; (●) 50 mg/ml, (■) 100 mg/ml, (▲) 150 mg/ml.

The drug/polymer ratio of the solutions was varied between 1/1 - 1/4. As the polymer content of solution increased from 1/1 ratio, significant coalescence was observed in the SEM image for the ratios of 1/2 and 1/3 (Fig. 8). The product obtained using 1/4 ratio was not analyzed because it was not in powder form and adhered to the walls of the high pressure cell. However, as seen in Fig. 9, increase of the drug/polymer ratio slightly increased the mean particle size, and broadened the particle size distribution.



(a) **(b)** **(c)**

Figure 8. SEM images of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 100 mg/ml 0.85 ml/min, drug / polymer; (a) 1/1, (b) 1/2, (c) 1/3.

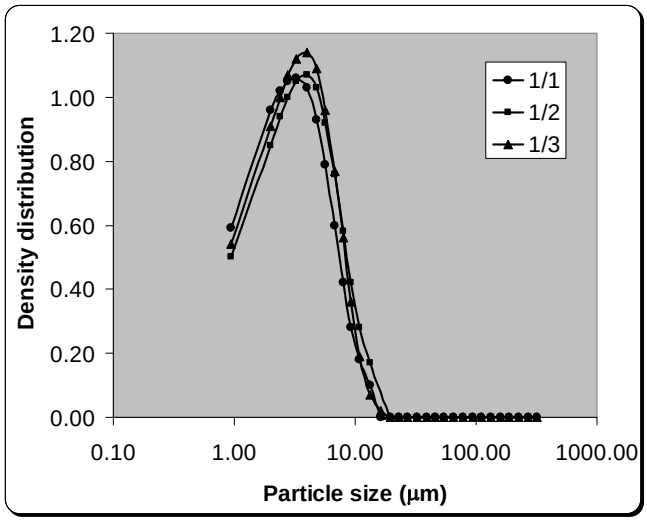
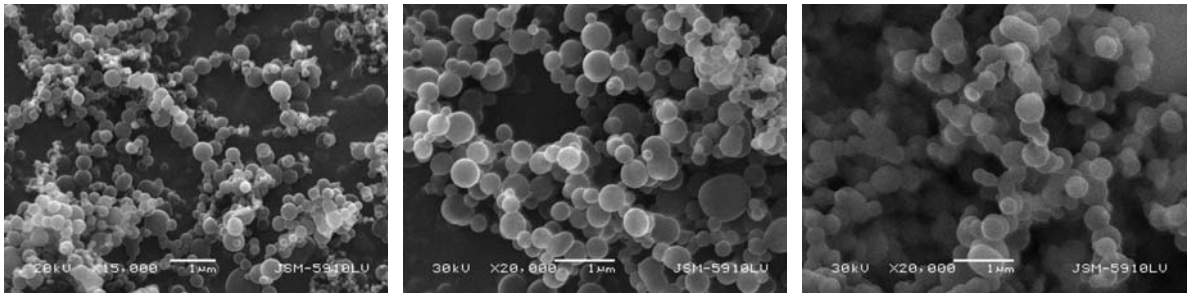


Figure 9. PSD of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 100 mg/ml 0.85 ml/min, drug / polymer; (●) 1/1, (■) 1/2, (▲) 1/3.

Solutions were also sprayed at three different flow rates in the range of 0.85-2.5 ml/min at the operating conditions given in Fig.10. The solution flow rate affected the particle morphology somewhat. 0.85 and 2 ml/min flow rates yielded spherical and discrete particles, whereas coalescence was observed at 2.5 ml/min. Although the mean particle size was not affected, the particle size distribution was affected significantly as seen in Fig. 11. Due to a problem in the particle size analyzer during the measurement of particles obtained at the flow rate of 2 ml/min, particle size analysis of this sample could not be reported here, but the SEM image (Fig. 10b) implies quite a variation in particle sizes.



(a) **(b)** **(c)**

Figure 10. SEM images of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 100 mg/ml, drug / polymer: 1/1; (a) 0.85 ml/min, (b) 2 ml/min, (c) 2.5 ml/min.

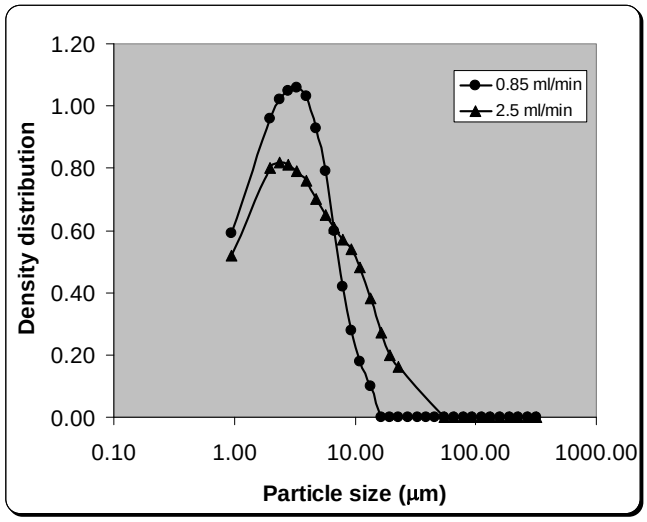


Figure 11. PSD of (CFA + PVP-K30) particles precipitated from methanol at 150 bar, 40 °C, 100 mg/ml, drug / polymer: 1/1; (●) 0.85 ml/min, (▲) 2.5 ml/min.

CONCLUSIONS

The production of CFA loaded PVP-K30 spherical particles with 2-5 μm mean particle sizes was achieved. Effects of process parameters such as pressure, temperature, solution concentration, flow rate and drug/polymer ratio on particle size and morphology were investigated. An increase almost in all process parameters caused an increase in the mean particle size, and broadened the particle size distribution. The temperature and the drug/polymer ratio seemed to be the most important parameters affecting the particle morphology.

ACKNOWLEDGEMENT

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