Effect of the Process Mode on the Properties of the Drug-Polymer Composite Particles Prepared by SAS Process

I. N. Uzun[1*], P. Alessi[2], I. Kikic[2], N. De Zordi[3], M. Moneghini[3], D. Solinas[2], S. Dinçer[1], O. Sipahigil[4].
[1]Yildiz Technical University, Department of Chemical Engineering, Istanbul, Turkey
[2] University of Trieste, Department of Chemical, Environmental and Raw Materials Engineering, Trieste, Italy
[3] University of Trieste, Department of Pharmaceutical Sciences, Trieste, Italy
[4]Marmara University, Department of Pharmaceutical Technology, Istanbul, Turkey
*e-mail: iparnimet@gmail.com, Tel: +902123834765, Fax: +902123834725

ABSTRACT
In this work, a study has been carried out to prepare drug-polymer composites of Cefuroxime Axetil amorphous (CFA, antibiotic) loaded Polyvinylpyrrolidone (PVP-K30) by batch and continuous supercritical antisolvent (SAS) process. Solutions of (CFA + PVP-K30) in methanol or dichloromethane with overall concentrations of 50-150 mg/ml and drug/polymer ratios of 1/1-1/4 were sprayed with flow rates of 0.85-6 ml/min into the $scCO_2$ at 100-150 bar and 35-50 °C. The effects of the process mode on the properties of the composite particles have been investigated. DSC, XRD and SEM analyses have been carried out to enlighten the particle formation mechanisms of two processes and to determine the relationship between the mechanism and product properties.

INTRODUCTION
Processing of pharmaceutical compounds using supercritical fluids has attracted great attention in recent years. Advantages such as high purity products, environmental protection, and greater experimental versatility make supercritical processing a promising alternative to conventional processing currently used in the pharmaceutical industry. The limitations of the conventional particle processing techniques have lead to particle formation processes based on the use of supercritical fluids as solvents or antisolvents, as effective methods for controlling particle formation. Furthermore, micro- and nano-particles of drug-polymer composites used in the preparation of controlled release formulations can be produced by supercritical fluid technology. SAS process is one of the supercritical particle processing techniques used in the production of drug-loaded polymeric systems [1-6]. In this work batch SAS process which is constructed in Yildiz Technical University and continuous one which is constructed in University of Trieste was used to produce drug loaded polymer particles in $scCO_2$ [7].

MATERIALS AND METHODS
Materials
Methanol (Lab-Scan % 99.8, Sigma-Aldrich % 99.8), acetone (Sigma-Aldrich % 99.8) and dichloromethane (Sigma-Aldrich % 99.8) were used as the solvents to dissolve Cefuroxime Axetil and PVP. CO_2 (% 99.9), used as the supercritical antisolvent, was supplied from HABAS A.S. (Istanbul, Turkey) and SIAD (Trieste, Italy). Cefuroxime Axetil (CFA) and Polyvinylpyrrolidone (PVP-K30,) were kindly supplied by Fako-Actavis (Istanbul, Turkey) and Bilim Pharmaceuticals Co. (Istanbul, Turkey), respectively.

Methods

The batch and continuous SAS experimental setups are shown in Fig.1. The batch setup (Fig. 1a) mainly consists of a syringe pump (Teledyne ISCO 260D) to deliver CO_2, a dosing pump (Dosapro Milton Roy Milroyal) to deliver the liquid solution, a capillary PEEK nozzle of 120 µm internal diameter to spray the solution into the stainless steel high pressure cell of 761 internal volume containing a stainless steel collection basket and frit at the bottom. A heating jacket is used to maintain the system temperature and a cold trap located at the exit of the high pressure cell is used to recover the liquid solvent.

a)

b)

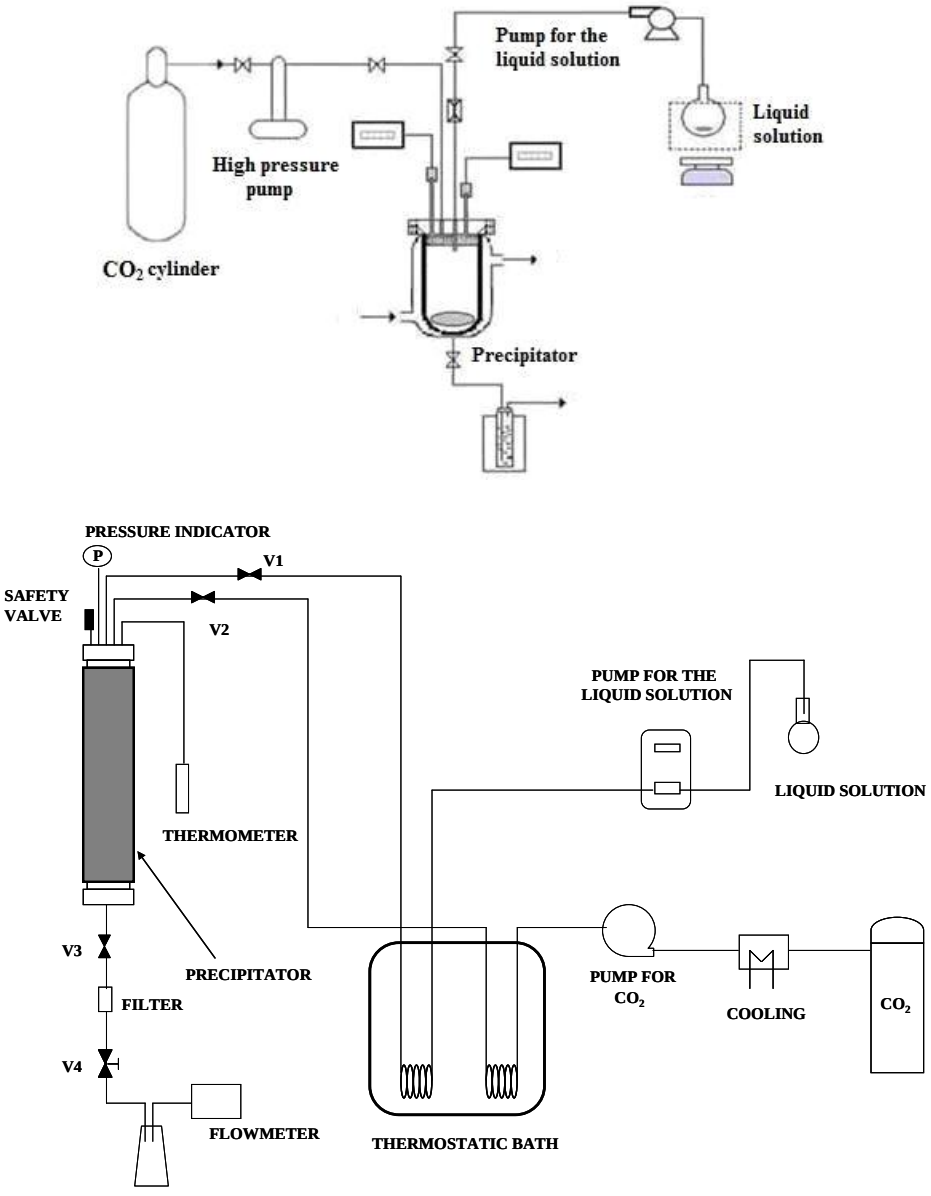
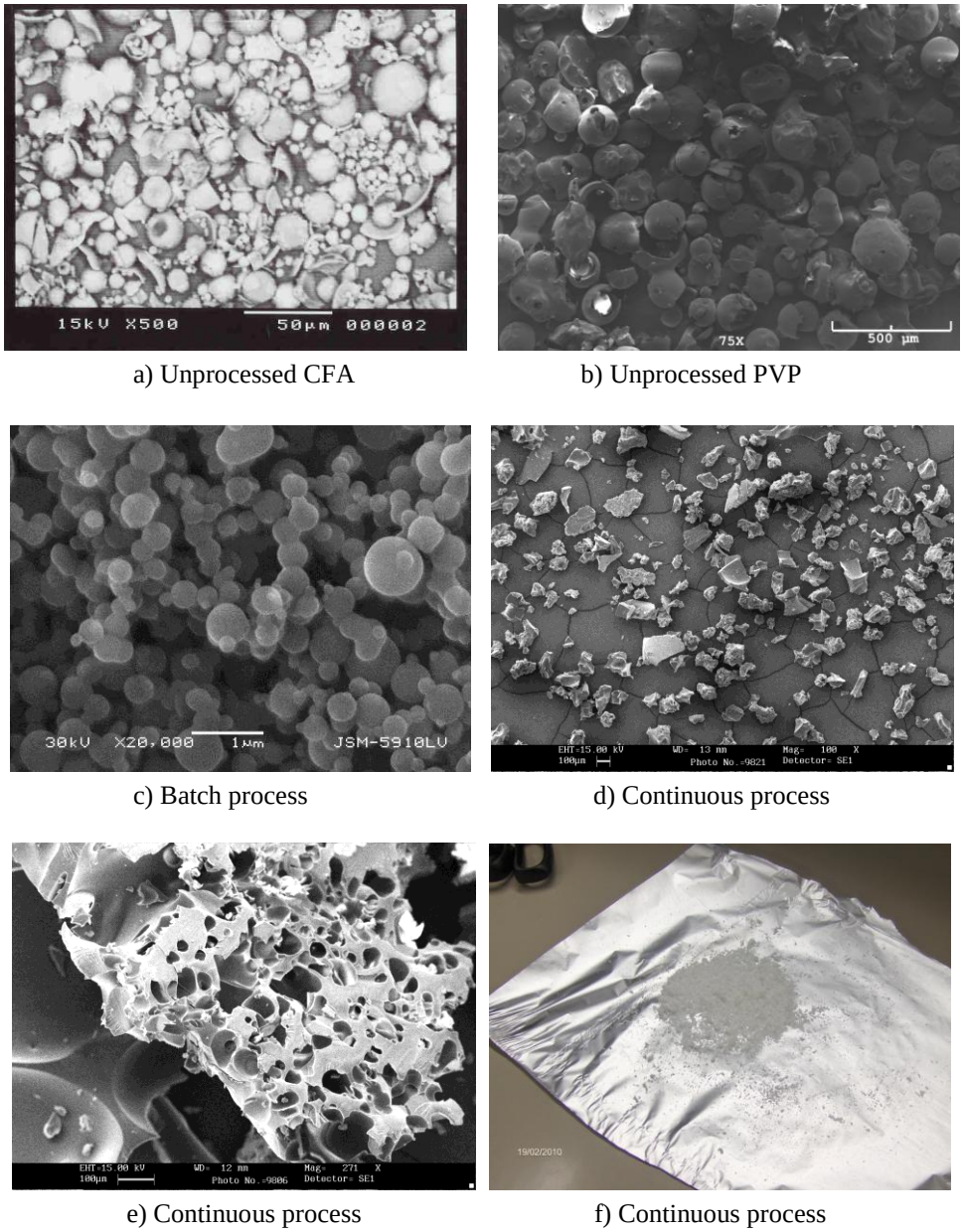


Figure 1. a) The batch SAS setup b) The continuous SAS setup

The precipitator (AISI-316 steel, internal diameter and volume of 50 mm and 400 cm^3 respectively) is jacketed ensuring temperature to be kept within ± 0.5 °C. Liquid CO_2 is fed from the top of the precipitator by a high pressure pump (Lewa EK-M-210V1). The liquid

solution, kept at the precipitator temperature by an electric heat plane, is pumped (ConstaMetric® 3200 P/F) to the top of the precipitator and then sprayed through a nozzle with a diameter of 100 µm (Lechler 212.004.17.AC). The outlet flow is then filtered (0.22 µm) to prevent precipitate losses and regulated by a heated metering valve (Whitey SS-21RS4). Temperature and pressure values in the precipitator are measured by a Delta OHM thermometer (HD 9214, ± 0.1 °C) and a DRUCK pressure transducer (DPI 260, ± 0.1 bar).



a) Unprocessed CFA b) Unprocessed PVP

c) Batch process d) Continuous process

e) Continuous process f) Continuous process

Figure 2. SEM images of a) Unprocessed CFA, b) Unprocessed PVP, CFA-PVP particles precipitated from c) methanol at 100 bar, 40 °C, 100 mg/ml, drug/polymer: 1/1 and 0.85 ml/min of solution flow rate, d) and e) methanol at 100 bar, 40 °C, 100 mg/ml, drug/polymer: 1/1, 0.5 ml/min of solution flow rate and 1.3 l/min CO_2 flow rate, f) dichloromethane at 120 bar, 40 °C, 100 mg/ml, drug/polymer: 1/1, 6 ml/min of solution flow rate and 1.3 l/min CO_2 flow rate.

The configurations of two processes are nearly the same but their operation procedures are different. In batch process the organic solution is sprayed into static $scCO_2$ while it is sprayed into flowing $scCO_2$ in the continuous one.

In batch process, the high pressure cell was filled with CO_2 from the top of the system until the desired pressure. CO_2 flow was cut after the system reached at precipitation conditions. Then the solution of drug and/or polymer was sprayed through the nozzle from the top of the high pressure cell into static CO_2. As the solution was sprayed into the cell, precipitation occurred because of supersaturation of solution 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. In continuous process, CO_2 always flowed through the system from the beginning of the experiment till the end and the solution of drug and/or polymer was sprayed co-currently into flowing CO_2.

Morphology of samples obtained in batch process 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). A scanning electron microscope (model 500, Philips, Eindhoven, The Netherlands) was used for the samples obtained in continuous process. Before SEM analysis the samples were sputter-coated with Au/Pd using a vacuum evaporator (Edwards, Milano, Italy). XRD (STOE D500 Siemens, Monaco, Germany) and DSC (Setaram CS 92) analyses were also performed to investigate the changes in crystallinity and morphology after processing.

RESULTS

In this work batch and continuous SAS process have been used to produce drug loaded polymeric particles. A comparison was held between two process modes. The effects of the process mode on the properties of the composite particles have been investigated. Particle formation mechanisms of two processes and relationship between the mechanism and product properties have been investigated.

Precipitate in powder form was obtained in batch process while hard and sticky precipitate was obtained in continuous one. The difference in the appearance of precipitates indicates that plasticization of the polymer occurred in continuous process. In continuous process CO_2 is flowing therefore diffusivity of CO_2 is expected to be higher than the batch process. As known, in SAS process two-way mass transfer occurs between solution phase and CO_2. The mass transfer of CO_2 into solution phase may also increase with increased diffusivity. Therefore in continuous process the mass transfer rate of CO_2 into solution phase may be higher than the rate of solvent into CO_2 phase. This may increase exposure of polymer to CO_2 inducing plasticization. This plasticization effect probably changed the precipitate morphology. Plasticization cause an increase in the entanglement of polymer chains which results in lower mass transfer rates of solvent, poor mixing, lower supersaturation and nucleation rates hence formation of films instead of powder. As seen in Fig 1c the precipitate obtained in continuous process consists of porous particles which have irregular shape and size. The pores in the precipitate may probably formed during the depressurization step by removal of dissolved CO_2 in polymer which also confirms that polymer was exposed to CO_2 intensively.

Because precipitate in powder form was not obtained with methanol some experiments has been carried out with dichloromethane. Production of precipitate in powder form was

succeeded with dichloromethane. It is less polar solvent than methanol and higher affinity with CO_2. Therefore when studied with dichloromethane higher mass transfer rates, better

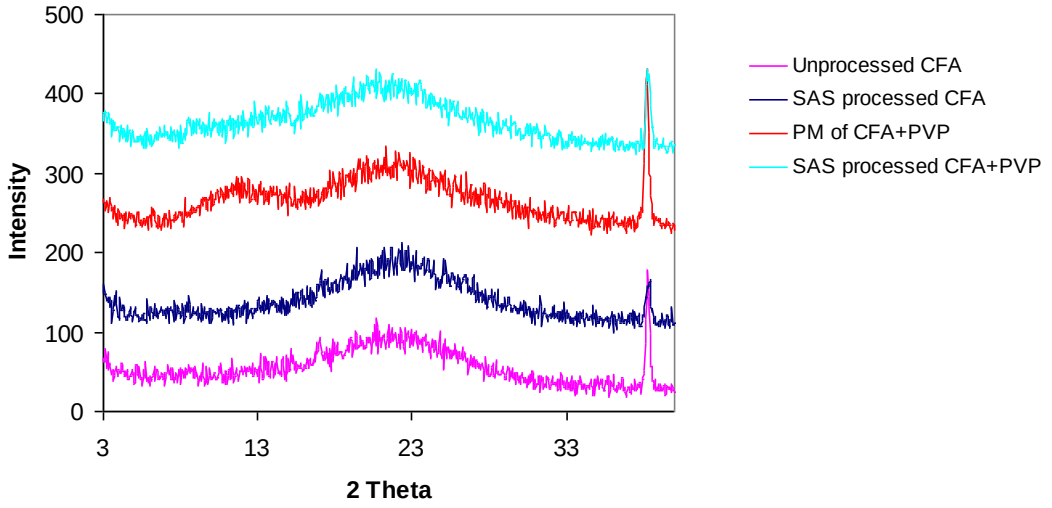


Figure 3. XRD patterns of raw materials and SAS processed samples in continuous mode

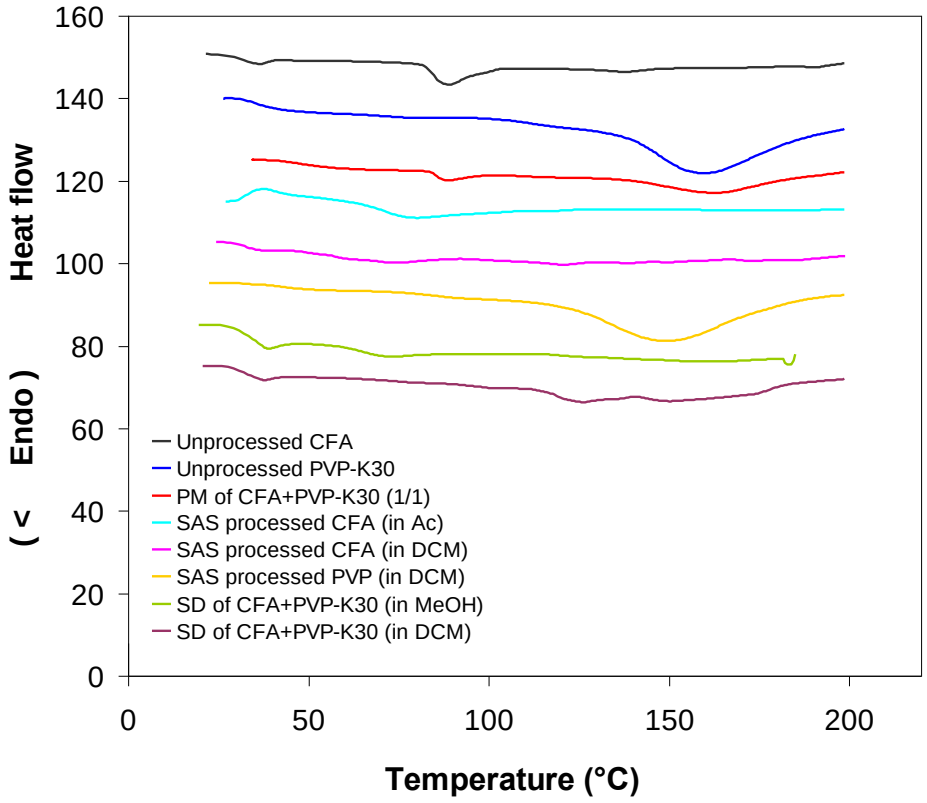


Figure 4. DSC curves of raw materials and SAS processed samples in continuous mode

mixing, higher supersaturation and nucleation rates were probably obtained resulting in powder precipitate. When drug or polymer was processed alone in continuous process precipitates in powder form were obtained. CFA exists in polymorphous form as crystalline or

amorphous structures. Crystal form of this type of drugs sometimes changes depending on the processing method and conditions. But as seen in Fig. 3 supercritical processing caused no polymorphic transition of CFA from amorphous form to crystalline one. SAS processing of materials changed their thermal behavior (Fig. 4). There was a noticeable melting peak of pure CFA around 90°C while this peak began to disappear and shifted to the right when it was processed. These changes may be caused by changing morphology with the processing. For the pure polymer there was a broad peak of glass transition around 160 °C. There was no change in the peak size but it shifted to the right after processing. This is expectable because as known $scCO_2$ has a plasticizing effect on polymers.

The thermal behavior of solid dispersions is also different from starting materials. DSC curve of physical mixture seems to be the sum of the two peaks of raw materials except the intensity. The characteristic peaks of raw materials began to disappear and their size also changed after producing solid dispersions by SAS.

CONCLUSIONS

It was succeeded to produce products in powder form of raw materials and their solid dispersions by both of the processes. But particles with different morphologies were obtained in each mode because of changing mass transfer characteristics depending on the process mode. Thermal behaviors of processed materials and solid dispersions were also different from the starting materials.

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