

Operating regimes and mechanism of particle formation during the precipitation of polymers using the PCA process

Y. Pérez de Diego^{a,*}, H.C. Pellikaan^b, F.E. Wubbolts^a, G.J. Witkamp^a, P.J. Jansens^a

^a *Laboratory for Process Equipment, Delft University of Technology, Leeghwaterstraat 44, 2628CA Delft, The Netherlands*

^b *Feyceon D&I B.V., Rijnkade 17A, 1382 GS, Weesp, The Netherlands*

Received 7 July 2004; received in revised form 13 December 2004; accepted 14 December 2004

Abstract

The vapour–liquid equilibrium phase behavior of a solvent and carbon dioxide provides two different regions of operation for the precipitation with a compressed antisolvent (PCA) process. Below the critical pressure of the mixture there is an interface between the liquid- and vapour-phase. Solution droplets are formed by atomisation in the nozzle. Above the critical- (or saturation-) pressure there is no phase boundary and contact between CO₂ and solution takes place by mixing. Additionally, in both operating regions, droplets of a polymer rich-phase are formed as result of a liquid–liquid phase split induced in the polymer solution when it gets in contact with the CO₂.

This article provides experimental evidence for the hypothesis that when processing polymer solutions there are two different mechanisms of droplet formation governing the final size of the precipitated polymer particles: hydraulic atomisation and liquid–liquid phase split. The system L-poly(lactic acid) (L-PLA)–dichloromethane (DCM)–CO₂ was used to demonstrate that particle size can be manipulated by modifying the operating conditions. Working at conditions below the mixture critical pressure of the solvent–CO₂ mixture it was possible to produce polymer particles in the range of 5–50 μm. At conditions where the two fluids are completely miscible, L-PLA particles ranging from 0.1 to 2 μm and microfibers were obtained. The possibility of co-precipitation of cholesterol and L-PLA was also addressed.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Polymer; Carbon dioxide; Particle formation mechanism; Antisolvent precipitation

1. Introduction

Microparticles consisting of an active compound embedded in a polymeric matrix are being studied extensively as controlled release systems for pharmaceuticals. Supercritical fluid antisolvent processes offer a great potential for processing these new pharmaceutical products because they are able to produce very small solvent-free particles with a narrow size distribution at mild operating conditions.

Considerable experimental work has been done in the last decade on the precipitation of biodegradable polymers using the precipitation with a compressed antisolvent (PCA) process [1]. However, the mechanism of particle formation is not very clear yet. One of the reasons for this lack of insight in the mechanism of particle formation is the complexity of the

process, in which phase behaviour, mass transfer, precipitation kinetics and hydrodynamics strongly interact with each other.

Regarding the phase behaviour of the system solvent–antisolvent, Wubbolts et al. [2] identified two different operating regions for the PCA process. They addressed the precipitation of ascorbic acid and acetaminophen and showed that particle size and morphology were different when working at conditions below or above the mixture critical pressure of the solvent–CO₂ system. Studying the precipitation of cholesterol from diethylether using CO₂ as antisolvent, Wubbolts [3] demonstrated that at conditions below the critical pressure of the mixture, cholesterol precipitation is confined to the droplets produced by atomisation of the solution at the nozzle. Above the critical pressure of the mixture, particle size is determined by the precipitation of the particles in a homogeneous mixture solvent–antisolvent. Similar results have been reported by Shekunov et al. [4] who also dealt

* Corresponding author. Tel.: +31 1527 86646; fax: +31 1527 86975.
E-mail address: y.perezdediego@wbmt.tudelft.nl (Y. Pérez de Diego).

with the crystallisation of acetaminophen and Reverchon et al. [5] who used these different operating regions to manipulate the size of yttrium acetate particles. To our knowledge, no work has been focused yet on studying the differences on the mechanism of particle formation of polymers when working in these two different operating regions.

Hydrodynamics, mass transfer and precipitation kinetics are very much dependent on the phase behaviour of the system solvent–CO₂.

Regarding the hydrodynamics of the PCA process, there is a general consensus that below the critical pressure of the mixture solvent–CO₂, the formation of solution droplets is due to atomisation in the nozzle. Above the mixture critical pressure formation of droplets is not expected, due to the inexistence of surface tension between the solvent and the CO₂. Some authors as Sarkari et al. [6] and Lengsfeld et al. [7] have examined the kinetics of the spray process at conditions of complete solvent–antisolvent miscibility and confirmed that turbulent mixing, and not droplet formation dominates the solvent–antisolvent contacting mechanism. A confusing fact when processing polymers is that spherical particles resembling droplets are formed when working above the mixture critical pressure of the system solvent–antisolvent. In this special case, one has to take into account that droplets are mostly formed by a liquid–liquid phase split induced in the polymer solution when it gets into contact with the antisolvent [8].

Concerning mass transfer, mixing of the fluids is faster than droplet formation at conditions above the mixture critical pressure. In this region, mass transfer takes place mainly by turbulent diffusion [9]. Below the critical pressure mass transfer occurs by molecular diffusion through the solvent droplet interface, by evaporation of the solvent and condensation of the CO₂ [3].

Phase behaviour influences nucleation rates through the different levels of supersaturation attained in both operating regions. In the miscible region, mass transfer is very fast and high supersaturation values are obtained. Small particles are produced due to the high nucleation rates achieved. When a solvent–CO₂ interface exists, mass transfer is limited to molecular diffusion through the interface and supersaturation reaches lower values.

Even though the phase behaviour solvent–antisolvent strongly influences fluid dynamics, mass transfer and precipitation kinetics, very often it is not taken into account [10]. That is the reason why after following a theoretical approach based on droplet formation in the miscibility region, Rantakylä et al. [11] found no correlation between the particle size predicted by their model and the experimental particle size of the polymer particles they processed.

The aim of this work is to show experimental evidence for the hypothesis that when processing polymer solutions there are two regions of operation (below and above the mixture critical pressure) and two different mechanisms of droplet formation governing the final size of the precipitated polymer particles (hydraulic atomisation and liquid–liquid phase

split). Either below or above the critical pressure of the mixture, carbon dioxide induces a liquid–liquid phase split in the polymer solution. In addition, below the mixture critical pressure of the mixture, hydraulic atomisation produces droplets of solution.

Poly(L-lactic acid) was chosen as model polymer because it is biodegradable and suitable for drug release applications. Experiments at different operating conditions were performed to study the particle formation mechanism when precipitating L-PLA below and above the mixture critical pressure of the system dichloromethane–CO₂. At the same time, the possibility of co-precipitating an active compound with these polymer particles was addressed. Cholesterol, model compound for biologically active steroids, was used as a second solute in most of the experiments described in this article.

Resulting from our experimental work, different operating windows are identified and a mechanism of particle formation for the precipitation of polymers using the PCA process is proposed.

2. Phase behaviour

2.1. Binary P,x phase diagrams organic solvent–CO₂

The phase behaviour of the solvent–CO₂ system determines the operating regime of the jet. The presence of solute has a minor influence on this phase behaviour.

Fig. 1 shows the P,x phase diagram of a typical solvent and carbon dioxide above its critical temperature. In that case, the liquid line of the phase envelope does not end at the saturation pressure of carbon dioxide but in a mixture critical point, which is the top of the phase envelope. The solvent and the supercritical carbon dioxide vapour are fully miscible above the mixture critical point. Below this point there is a vapour–liquid coexistence region for some mixture compositions.

What type of equilibrium situation is attained when pure solvent and carbon dioxide are contacted depends on the pressure of the system relative to the mixture critical pressure.

At conditions above the mixture critical pressure (Region 2, in Fig. 1) there is no interface between the solvent and the carbon dioxide. The CO₂ and solvent merge by mixing.

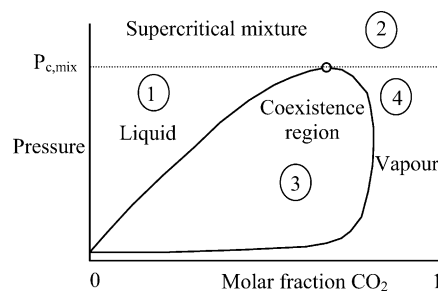


Fig. 1. Typical P,x phase diagram for a binary system of a common solvent and carbon dioxide, above the critical temperature of carbon dioxide (304 K).

Download English Version:

<https://daneshyari.com/en/article/9635781>

Download Persian Version:

<https://daneshyari.com/article/9635781>

[Daneshyari.com](https://daneshyari.com)