

PRODUCTION OF L-PLA MICROPARTICLES BELOW AND ABOVE THE MIXTURE CRITICAL PRESSURE OF THE SYSTEM DCM-CO₂

Y. Pérez ^{*(a)}, H. 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) Feyecon D&I B. V., Rijnkade 17A, 1382 GS, Weesp, The Netherlands

E-mail: Y.PerezDeDiego@wbmt.tudelft.nl

Fax: +31 15 2786975

The vapor-liquid equilibrium phase behavior of a solvent and carbon dioxide provides two different regions of operation for the PCA process. Below the critical pressure of the mixture there is an interface between the liquid- and vapor phase. Solution droplets are formed by atomization in the nozzle. Above the critical- (or saturation-) pressure there is no phase boundary and contact between CO₂ and solution takes place by mixing. In addition, either above or below the mixture critical pressure, droplets of polymer are formed as result of a liquid-liquid phase split induced in the polymer solution when it gets in contact with the CO₂.

The aim of this article is to show experimental evidence for the claim that when processing polymer solutions there are two different mechanisms of droplet formation governing the final size of the precipitated polymer particles: atomization and liquid-liquid phase split. The system PLA-DCM-CO₂ was used to demonstrate that particle size can be easily manipulated by modifying the operating conditions. Working at conditions below the mixture critical pressure of the solvent it was possible to produce polymer particles in the range 5-50 µm. At conditions where the two fluids are completely miscible in the whole composition range, a mixture of PLA particles ranging from 0.2-2 µm and fibers was obtained. The possibility of encapsulation of cholesterol in the PLA particles was also addressed and the most suitable conditions were defined.

INTRODUCTION

Microparticles consisting of an active compound embedded in a polymeric matrix are being studied extensively as controlled release systems for pharmaceutical drugs. 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.

A lot of experimental work has been done in the last years on the precipitation of biodegradable polymers using the Precipitation with a Compressed Antisolvent (PCA) process [1]. However, it is not very clear yet what the mechanism of particle formation is. One of the reasons for this lack of insight in the mechanism of particle formation is the complexity of the process, in which phase behavior, mass transfer, precipitation kinetics and hydrodynamics strongly interact with each other.

This work is focused on studying the role of phase behavior on controlling the mechanism responsible of particle formation.

The aim of this work is to show experimental evidence for the claim 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 (atomization and liquid-liquid phase split). Either below or above the critical pressure of the mixture, droplets of a polymer-rich phase are formed. In addition, below the mixture critical pressure of the mixture, droplets are formed due to atomization in the nozzle.

This work uses L-PLA (L- polylactic acid) as biodegradable matrix material due to its controlled drug release applications and cholesterol as drug to encapsulate since it is a suitable model compound for biologically active steroids. Experiments were performed at different operating conditions to study the mechanism responsible of particle formation when precipitating PLA below and above the mixture critical pressure of the system DCM-CO₂. Additional experiments were performed to try to encapsulate cholesterol in the polymer particles.

Binary P,x phase diagrams organic solvent-CO₂

Figure 1 shows a P,x phase diagram of a typical solvent and carbon dioxide at conditions above the critical temperature of CO₂. 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 vapor are fully miscible above the mixture critical point. Below this point there is a vapor-liquid coexistence region for some mixture compositions.

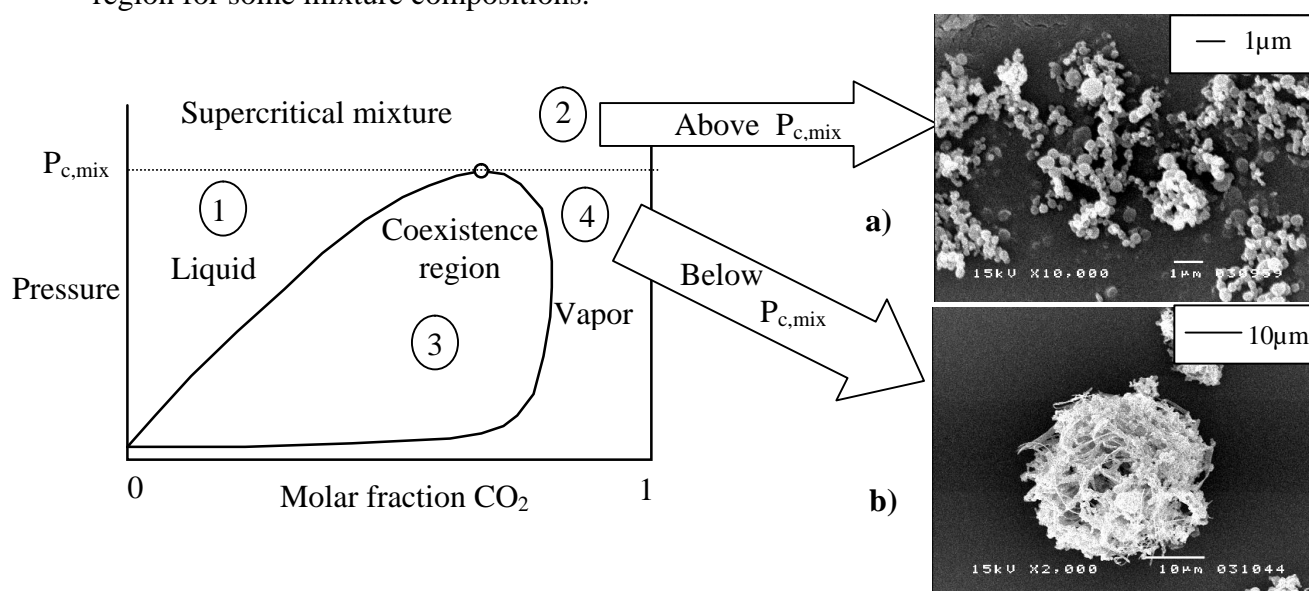


Figure 1. Typical P,x phase diagram for a binary system of a common solvent and carbon dioxide, above the critical temperature of carbon dioxide (31°C). Examples of the two different PLA morphologies obtained above or below the mixture critical pressure.

How the 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 pressures above the critical pressure of the mixture there is no interface between the solvent and the carbon dioxide (region 2 in Figure 1). The CO₂ and solvent merge by mixing instantaneously.

Below the mixture critical pressure there is an interface between the vapor- and liquid phases. Carbon dioxide now dissolves into the solvent (and vice versa) by mass transfer through the phase boundary. With an overall composition and pressure in region 1, all carbon dioxide vapor is absorbed by the solvent and when equilibrium is attained the mixture is in a liquid state. In region 3 both a vapor and a liquid with the equilibrium compositions are present, while in region 4 all solvent evaporates and only a vapor phase remains.

MATERIALS AND METHODS

Materials

Poly (L-lactic acid) with a mean molecular weight of 100.000 g/mol. was supplied by PURAC BioChem. Carbon dioxide (purity 99.97%) was supplied by Hoek Loos. Dichloromethane (DCM, purity 98.0%) was purchased from Fluka.

Particle characterization methods

Processed particles were analyzed by a JEOL JSM-5400 Electron Scanning Microscope. Cholesterol content of the PLA particles was analyzed using a colorimetric method [1].

Phase behavior of the studied systems

Most of the experiments described in this article were performed at constant temperature (35°C). The critical points for the system dichloromethane-CO₂ in the temperature range from 33 to 43 °C have been determined by Reaves et al. [3]. According to their data the mixture critical pressure for the system DCM-CO₂ at 35°C is 76.5 bar. The phase behavior of the system DCM-CO₂ at 38°C has been reported by Vega et al. [4].

The high pressure phase behavior of poly(L-lactic acid) in mixtures of CO₂ and dichloromethane have been measured by Lee et al.[5]. They described a LCST (Lower Critical Solution Temperature) behavior for this ternary system. The presence of CO₂ induces a liquid-liquid phase split in the PLA-DCM solution. When high concentrations of CO₂ are used this liquid-liquid phase split is displaced to lower temperatures.

Experimental setup

The polymer solution was sprayed into 1 liter vessel filled with CO₂ using a 67 µm capillary nozzle. Solution flow was modified between 0.5 and 5 ml/min. Carbon dioxide flow was around 180g/min. A detailed description of the setup has been given elsewhere [6]

RESULTS

Below mixture critical pressure

All the experiments in this region were performed at constant temperature (35°C). The influence of pressure and solution flow rate on droplets stability and particle morphology was studied. At low pressures (below 60 bar), the extraction of solvent out of the droplets was not fast enough and droplets reached the filter plate before being completely dried, hence, a film was obtained. When pressure is increased to 65 and 75 bar, spherical particles that resemble droplets are obtained (see Figure 2.a). The morphology of the produced PLA particles indicates that each final polymer particle emerged from a solution droplet originated by atomization in the nozzle. Each polymer droplet seemed to be formed by an interconnected network of smaller droplets. One also can see that precipitation of cholesterol needles has been confined to the solution droplets (Figure 1.b).

Moderate solution flow rates are needed to atomize the solution and to keep droplets' structure. Spraying at too low flow rates (below 0.5ml/min), no atomization of the solution is observed and an irregular product is found on the filter plate. Spraying at solution flow rates above 5ml/min, product obtained does not keep the spherical shape of the solution droplets produced by atomization in the nozzle (Pictures are not shown).

Above the mixture critical (-saturation) pressure

Working above the mixture critical pressure, particle size was not affected by moderate changes in pressure or solution flow rates. A mixture of 2-0.2 μm particles (Figure 1) and microfibers (Figure 2.b) was always obtained. Cholesterol was not detected in the final particles. It was extracted by the CO_2 during the process. To solve this limitation of the process, working temperature was decreased to 10°C to be able to spray in the miscibility region DCM- CO_2 at lower pressures (60-75 bar). Encapsulation of cholesterol was then successfully achieved. A mixture of 1-0.1 μm particles and microfibers was obtained.

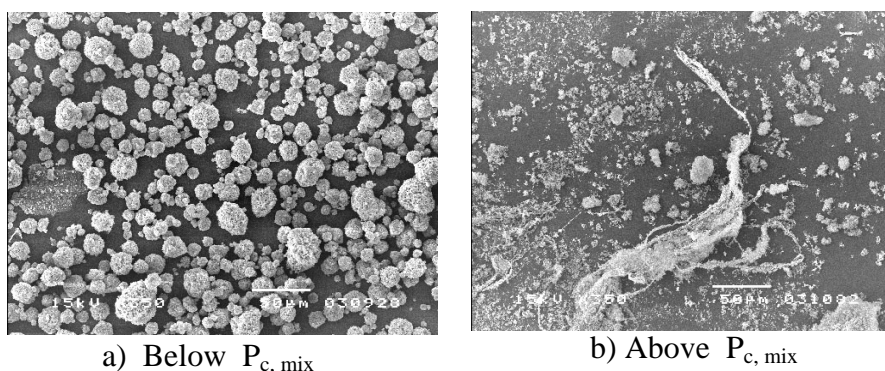


Figure 2. *L-PLA particles produced at conditions below and above the mixture critical pressure.*

DISCUSSION

The proposed mechanism of particle formation below the mixture critical point is shown in figure 3. First, solution droplets are formed as a result of atomization in the nozzle. Immediately after dispersion of the solution into the CO_2 , mass transfer through the droplet interface takes place and CO_2 starts to condensate in the droplets at the same time that DCM evaporates. The dissolution of CO_2 in the droplets induces a liquid-liquid phase split in the polymer solution. Polymer-rich phase droplets are formed inside each solution droplet. These polymer-rich phase droplets may agglomerate inside each solution droplet and form an interconnected network. As the DCM is extracted by the CO_2 , polymer solidifies. If the solution droplets are stable enough, polymer solidifies on the droplets' surface and the structure of the original solution droplets is maintained. If solution is sprayed at high solution flow rates (high Re numbers), turbulence further breaks the solution droplets and irregular structures are obtained instead of spherical polymer particles.

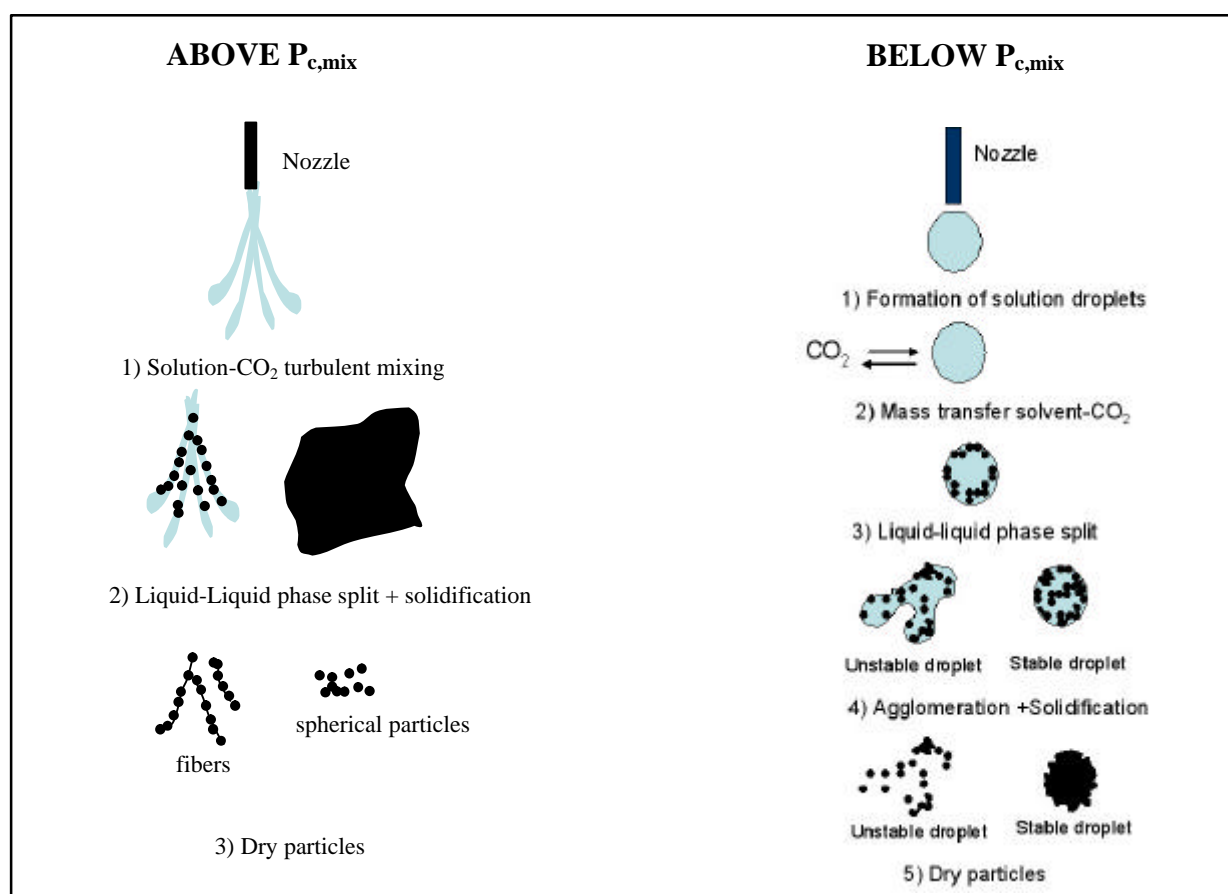


Figure 3. Proposed mechanism of particle formation below and above the mixture critical pressure

The shape and size of the PLA particles that were formed below the mixture-critical pressure strongly suggests that the precipitation process was spatially confined to the droplets that were produced by the nozzle. The initial size of those droplets would determine the size and shape of the produced particles. The size distribution of the solution droplets is responsible for the final particle size distribution of the polymer particles showed in figure 2.a. Droplets could not be stabilized at all the experimental conditions and spraying at high solution flow rates (high Re numbers) a product of irregular morphology was obtained. Pressures close to the

mixture critical pressure are needed in order to make mass transfer fast enough, so solvent is extracted before droplets reach the filter plate.

At conditions of complete miscibility between CO₂ and DCM, polymer precipitation is not confined to droplets. The mechanism of particle formation above the critical pressure of the mixture is also shown in Figure 3. As the CO₂ gets in contact with the polymer solution a liquid-liquid phase split is induced. Polymer-rich phase droplets form and as the DCM is being extracted, they solidify. Mixing, phase split and solidification processes occur simultaneously and different particle morphologies (fibers or individual particles) are produced.

CONCLUSIONS

Experimental evidence is provided on the important role of phase behavior on the mechanism of particle formation during the PCA process. The vapor-liquid equilibrium phase behavior of a solvent and carbon dioxide provides two different regions of operation for the PCA process. Below the critical pressure of the mixture there is an interface between the liquid- and vapor phase. When a solution is dispersed into the carbon dioxide this interface confines the precipitation process to the droplets. Above the critical- (or saturation-) pressure there is no phase boundary and precipitation occurs through the entire volume of the reactor.

A liquid-liquid phase split takes place when the polymer solution gets in contact with the CO₂. This phenomenon happens in the two studied operating regions. The liquid-liquid phase split is responsible of formation of droplets at conditions of complete miscibility between solvent and CO₂. Extraction of the solvent induces the solidification of these droplets.

PLA particle size can be easily manipulated by modifying the mechanism of particle formation (i.e. the operating region of the process). Working at conditions below the critical pressure of the mixture DCM-CO₂ it was possible to produce PLA particles in the range 5-50µm. The particle size depends mainly on the initial size of the droplets that are produced by the nozzle. At conditions where the two fluids are completely miscible in all the composition range, particles ranging from 0.2-2 microns and microfibers were obtained. Above the critical pressure of the DCM-CO₂ cholesterol encapsulation efficiency was very low because the solubility of the cholesterol in the surrounding CO₂ phase. Performing the process at lower temperatures, at conditions above the saturation pressure of the CO₂ improved this encapsulation efficiency.

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