Improved PCA Process for the Production of Nano- and Microparticles of Polymers

Y. Pérez, F. E. Wubbolts, G. J. Witkamp, and P. J. Jansens
Laboratory for Process Equipment, Delft University of Technology, Leeghwaterstraat 44, 2628 CA Delft, The Netherlands

Th.W. de Loos
Physical Chemistry and Molecular Thermodynamics, Delft University of Technology,
Julianalaan 136, 2628BL Delft, The Netherlands

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The system dextran-DMSO-CO_2 has been chosen as a model system to study the fundamentals of the precipitation of biodegradable polymers, using the precipitation with a compressed antisolvent (PCA) process. At conditions of completely miscibility between the organic solvent (DMSO) and CO_2, it is proposed that the formation of droplets in the system is not the consequence of atomization of the DMSO solution, but rather the result of the occurrence of a liquid-liquid phase split when the DMSO-solution and CO_2 are intimately mixed. Penetration of CO_2 into the droplets and stripping of DMSO induces the solidification of these droplets. A new device was designed to separate the three steps involved in the process: mixing of CO_2 and solution, liquid- liquid phase split, and stripping of the solvent. This new device eliminates agglomeration of particles, and yields reproducible results. The particle size can be easily manipulated over a size range from several nanometers to tenths of microns by changes in the operating conditions. The influence of these operating conditions (pressure, temperature, polymer concentration, and solution/CO_2 composition ratio) on particle morphology has been studied. © 2004 American Institute of Chemical Engineers *AIChE J,* 50: 2408–2417, 2004

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Introduction

Microencapsulation of pharmaceutical substances with polymers for controlled or sustained release is one of the main fields of interest for the pharmaceutical industry (Kumar, 2000; Kumar and Kumar, 2001).

Traditional techniques for the preparation of these microcapsules, such as coacervation, double emulsion/evaporation processes, freeze drying and spray drying, have limitations that include thermal and chemical degradation of the pharmaceuticals, large residual solvent concentrations and difficulties in controlling particle size and particle-size distribution during processing. To address the shortcomings of conventional techniques, new processes based in the use of supercritical fluids are being extensively studied (Benedetti et al., 1997; Jung and Perrut, 2001). The PCA process (precipitation with a compressed antisolvent) has a huge potential to produce small solvent-free particles with a narrow size distribution at mild operating conditions (Bodmeier et al., 1995; Fisher and Muller, 1991).

Although other supercritical fluids could be chosen for carrying out this process, CO_2 is by far the most extensively investigated when processing pharmaceutical compounds. The reason for this selection is that it is nontoxic, nonflammable, inert, and it is easily removed from the final product after the process. In addition, it is nonexpensive and it is the second most abundant solvent on earth.

Correspondence concerning this article should be addressed to Y. Perez de Diego at Y.PerezDeDiego@wbmt.tudelft.nl.

To determine the suitable operating conditions to attain the microencapsulation, a thorough study is required on the effect of process parameters on the precipitation of each of the components separately. Controlled precipitation of organic compounds using the PCA process has successfully been achieved in our group (Wubbolts et al., 1999; Wubbolts, 2000). This article deals with the precipitation of polymers.

The model system chosen for this research is the system dextran/DMSO/CO_2. Dextran is a biodegradable polymer that has been previously used as model polymer for studying these systems (Subra and Jestin, 2000; Reverchon et al., 2000). Dextrans are being actively investigated for sustained delivery of therapeutic and imaging agents, particularly for injectables and colon specific drug delivery systems (Mehavar, 2000). DMSO is a common solvent for processing pharmaceutical compounds. Furthermore, it has been shown (Winters et al., 1996) that protein drugs, potentially important pharmaceutical compounds to be formulated in these controlled release systems, retain their activity after supercritical processing using DMSO as a solvent.

Previous work in our group to precipitate dextran using the conventional PCA process, revealed a lack of reproducibility of the results, and to agglomeration of the particles (Pérez de Diego et al., 2001). This lack of control over the process arose from lack of insight in the interaction between phase equilibria, mass transfer, fluid dynamics, and precipitation kinetics. In order to be able to control and to manipulate the size and morphology of the produced particles, the different steps involved in the process needed to be separated.

Others have tried to obtain a better control over the PCA process influencing fluid dynamics and mass-transfer processes. Mawson et al. (1997) used a coaxial nozzle to reduce agglomeration. Chattopadhyay and Gupta (2002) proposed the use of ultrasonic nozzles in order to produce a narrow particle-size distribution of small droplets. Recently, Jarmer et al. (2003) have designed a new type of nozzle combining a swirl flow and a micromixing swirl chamber to optimize mixing between solvent and compressed antisolvent.

The aim of this work is to develop a modification of the PCA process that allows the control over the size, and the morphology of the precipitated particles in a reproducible manner. However, the new device that is presented in this article is not focused on controlling droplet formation and/or to enhance mixing of the fluids. The approach of this work is based on slowing down the kinetics of the precipitation process.

The mechanism of particle formation proposed in this article is based on the assumption that the process is dominated not by atomization of the polymer solution, but by turbulent mixing when the process is carried out at conditions of complete miscibility between the organic solvent, and the CO_2 (Lengsfeld et al., 2000; Sarkari et al., 2000). The formation of droplets is explained by a liquid-liquid phase split induced in the polymer solution when it is intimately mixed with the CO_2. The morphology of the sphere-like particles is explained by the formation of polymer-rich droplets in a continuous CO_2-DMSO medium. Penetration of CO_2 into the droplets and stripping of DMSO induces the solidification of these droplets. In this article, the term "stripping" refers to the separation process, wherein a liquid mixture is contacted with a gas (supercritical fluid) to selectively remove components by mass transfer from the liquid to the gas phase.

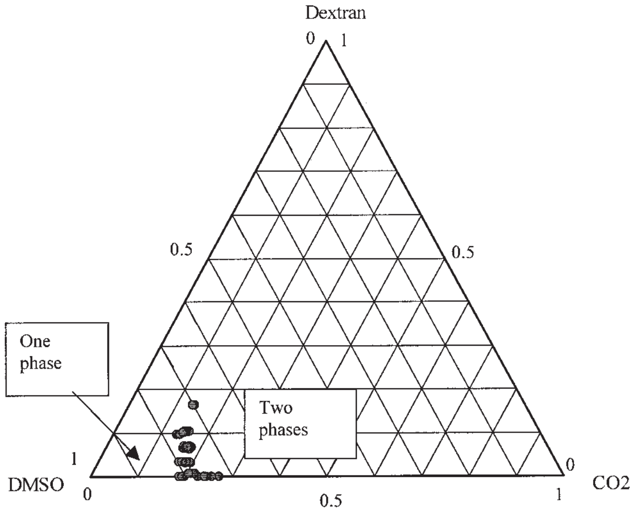

Figure 1. Measured ternary diagram of the system dextran/DMSO/CO_2 at 12 MPa and 40°C.

Percentages are in weight fraction.

On the basis of this hypothesis, a new device was designed (Pellikaan and Wubbolts, 2002) to separate the three main steps involved in the PCA process: mixing, phase split, and stripping of the solvent.

It will be shown that this modification of the PCA process eliminates agglomeration of particles and yields reproducible results. The particle size can be easily manipulated over a size range from several nanometers to tenths of microns by changes in the operating conditions. The influence of these operating conditions (pressure, temperature, polymer concentration, and solution/CO_2 ratio) on particle morphology has been studied.

Theory

Phase diagram dextran-DMSO-CO_2

At ambient conditions, the induction of a liquid-liquid phase split when a solution of amorphous polymer is brought into contact with a liquid antisolvent is a very well known phenomenon (Kimmerle and Strathmann, 1990; Yilmaz and McHugh, 1986; Witte, 1994). Dixon and Johnson (1993a), and Dixon et al. (1993b) have proposed that the same liquid-liquid phase split will take place at high-pressures, when supercritical CO_2 is used as antisolvent.

The phase behavior of the system dextran/DMSO/CO_2 was measured at high- pressures in order to find supporting evidence of the formation of this liquid-liquid phase split.

Two independent methods were used to determine the phase diagrams:

- At constant temperature and pressure by the vanishing point method developed by Wubbolts (2000). The measured ternary diagram at 12 MPa and 40°C is shown in Figure 1.
- At constant composition, using the well-known Cailletet tube described by De Loos et al. (1986).

These measurements prove that the presence of CO_2 induces a liquid-liquid phase split in the dextran-DMSO solution. Furthermore, it was observed that the position of the binodal was not significantly affected by changes in pressure or temperature (within the studied range 10–15 MPa and 20–60°C).

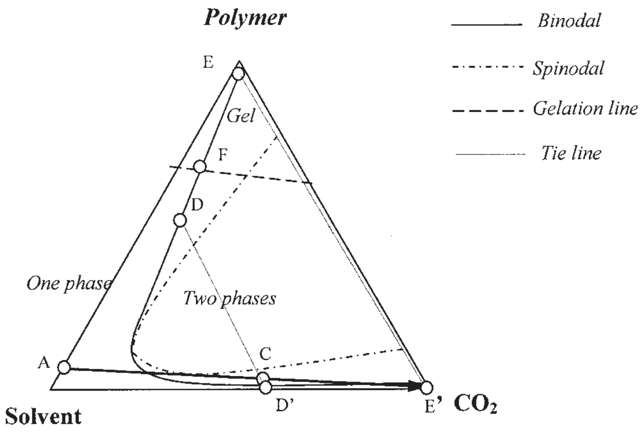

Figure 2. General phase diagram for the system dextran-DMSO-CO_2.

Proposed mechanism of particle formation.

Mechanism of droplet formation

All the experiments described in this article were carried out at conditions of complete miscibility between the organic solvent and the CO_2. Because of the lack of surface tension between the DMSO and CO_2 when working in the miscibility region, one would not expect droplet formation while spraying. Lengsfeld et al. (2000) have explored the time-scale of surface tension evolution in jets of miscible fluids injected into critical or near critical solvents, to determine whether the jet atomizes into droplets or simply evolves as gaseous plumes. They have found, for the system dichloromethane(DCM) -CO_2, that in the miscibility region, the distance for vanishing of the surface tension is shorter than the characteristic jet breakup length, so distinct droplets could not be formed. They also extrapolate this result to spraying dilute solutions of polymer. According to their studies microparticles result from precipitation within a homogeneous supercritical fluid rather than inside discrete droplets.

The formation of polymer nanoparticles could be explained by the precipitation mechanism represented in Figure 2 (Pérez de Diego et al., 2002). Point A is the composition of the initial polymer solution. When this solution is brought into contact with pure CO_2, the overall composition of the system will follow the pathway represented by the arrow in Figure 2. At a certain composition (represented by the point C), phase separation takes place by formation of a highly viscous polymer rich liquid phase (composition D) and a solvent rich phase (composition D'). Whether this phase split takes place by spinodal decomposition, or by nucleation and growth is subject for further study. Upon adding additional CO_2, the composition of the polymer rich phase will evolve from the point D to E, as the overall composition moves from C to the pure CO_2 vertex (for example, by the increase of the CO_2 concentration in the vessel). When the composition of the polymer rich phase reaches the gelation line point F, the morphology of the polymer phase is "frozen" (the high viscosity hinders the movement of the polymer chains).

Classical nucleation theory

Supersaturation (S) is the driving force for the formation of a new phase in a homogeneous solution. It is defined as the relation between solute concentration present in the system C, and the equilibrium solute concentration C_e, at a given pressure and temperature. It can be expressed by the following equation

$$S = \frac{C}{C_e}$$

At high supersaturations, which are typical for the antisolvent precipitation process described in this article, the most important mechanism predicting particle size is that of primary nucleation.

The classical nucleation theory (Kashchiev et al., 1992, 2003) predicts that the number of nuclei formed per unit time per unit volume (J) is expressed in the form

$$J = A \cdot S \cdot \exp\left[-\frac{16\pi\gamma^3 v^2}{3k^3T^3(\ln S)^2}\right]$$

A is the pre-exponential kinetic parameter, and has units of $m^{-3}s^{-1}$, k is the Boltzmann constant (1.3805×10^{-23} $J.K^{-1}$), T is the temperature in Kelvin v is the molecular volume, γ is the interfacial tension, and S is the supersaturation.

The minimum stable nucleus size, critical nuclei size (r_c), is calculated using the following expression

$$r_c = \frac{2\gamma v}{kT \ln S}$$

The three main variables to govern the rate of nucleation and nucleus size are temperature, degree of supersaturation, and interfacial tension.

New device for controlling PCA process

According to the proposed mechanism of particle formation, the three main steps involved in the PCA process are: mixing of the solutions, phase split, and stripping of the solvent from the polymer rich droplets.

The main reason for the poor reproducibility of the results when using the conventional PCA setup (Figure 3a) is most likely related to the fact that these three steps were taking place at similar time-scales. At the operating conditions of the convectional PCA process, high concentration of CO_2 present in the vessel, and high supersaturation levels are attained. When the supersaturation is high, the kinetics of the phase split is very fast, and phase split may take place at the same time-scale as the mixing of the fluids. Because phase split occurs at nonhomogeneous mixing conditions, the results are poorly reproducible.

The new device presented in this article aims to control the PCA process by separating the time-scales of mixing, phase split, and stripping of the solvent. This device, represented in Figure 3b, is divided in three parts:

- *T-mixer*. Polymer solution is sprayed in the small volume T-mixer, using a nozzle in order to achieve a fast mixing between CO_2 and solution. To delay the phase split, the polymer solution is mixed with a relatively small amount of CO_2. By reducing the amount of CO_2 in the mixture, the supersaturation decreases, and the kinetics of the phase split becomes

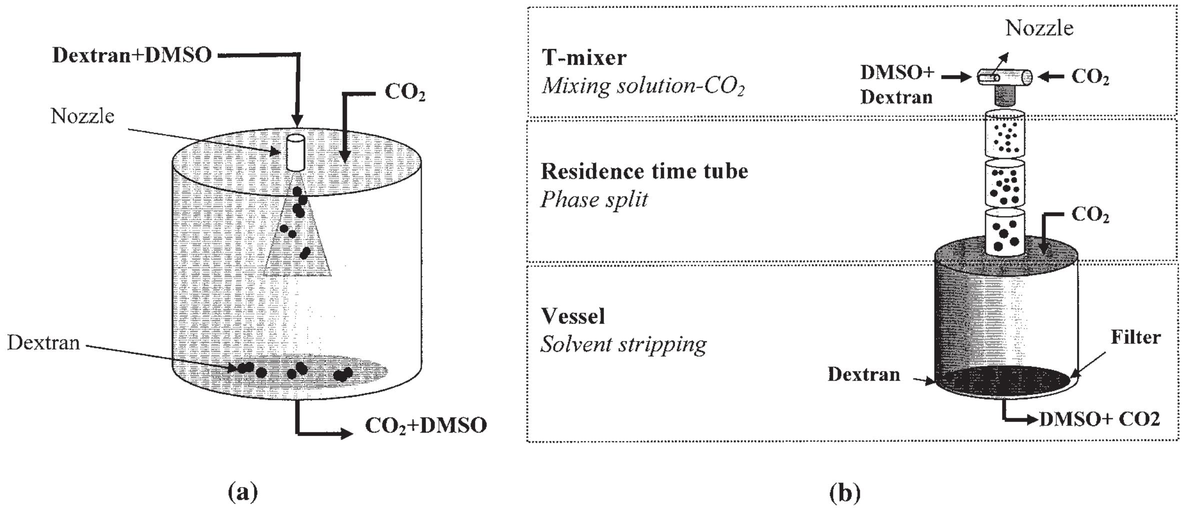

Figure 3. (a)Conventional PCA process. (b) Improved device for PCA.

slower and phase split occurs at conditions of homogeneous mixing. The composition in this T-mixer is represented by point C in Figure 2.This composition can be easily changed by modifying the flow rates of solution and CO$_2$.

- *Residence time tube*. A tube of variable length is used for giving the system time to complete the phase split and to attain the equilibrium conditions (D, D'). Coalescence of the formed polymer-rich droplets may also take place in this tube.
- *Vessel*. The mixture dextran-DMSO-CO$_2$ enters the vessel and mixes with a high flow of CO$_2$. At this point, DMSO is extracted from the polymer rich phase droplets until they reach the final composition (E).

Experimental methods

Materials

Dextran (product number D4751) was obtained from Sigma-Aldrich. The reported average molecular weight was 64,000–76,000. Carbon dioxide (99.97%) was supplied by Hoek Loos. DMSO (99.7%) was purchased from Acros Organics.

Particle characterization methods

Processed dextran was analyzed by a JEOL JSM-5400 Electron Scanning Microscope. Particle-size distributions were calculated by counting more than 100 particles from the SEM pictures. X-ray diffraction studies of the raw material and processed dextran were performed.

Apparatus

The experimental setup is represented in Figure 4. The carbon dioxide is taken from the storage tank (1), and is cooled to 5°C in the heat exchanger (2) to prevent cavitation in the positive displacement pump (3). After the pump, a buffer vessel (4) dampens the fluctuations in flow. In the buffer vessel the CO$_2$ is heated, and its pressure is limited by a control-loop (5) that acts on the pump. From the buffer vessel the CO$_2$ is heated to the experiment temperature (6), and it is supplied to a one L autoclave (7). A water jacket is used to maintain a constant temperature inside the vessel during the experiment. The pressure in the system is regulated automatically using a

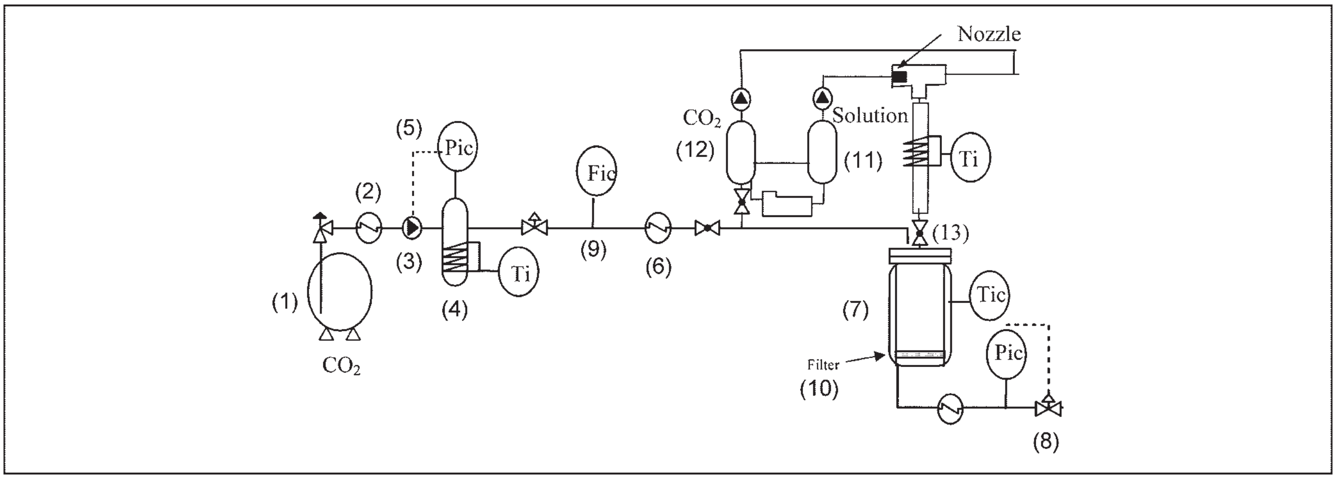

Figure 4. Experimental setup.

Table 1. Overview Experimental Conditions Studied

Thermodynamic variables		Hydrodynamic variables	
Temperature	10°C–60°C	Nozzle diameter	100, 120, 200 μm
Pressure	10–20 MPa	Solution flow rate	2–18 cm^3/min
Dextran concentration	0.5–5% wt		
Molar CO_2/DMSO rate in T-mixer	0.15–0.9		
Residence time	1–175 seconds		

back pressure valve (8). There is a flow meter (9) for the CO_2, and a Pt 100 sensor for measuring the temperature in the autoclave. A 0.2 μm porous size membrane filter (10) supported on a metallic filter (3 μm porous size) is used to collect the precipitated polymer particles.

Two ISCO 260 Syringe pumps (11, 12) are used to pump CO_2 and the solution inside the T-mixer. A water jacket is used to maintain the pumps at the experiment temperature.

CO_2 enters the T-mixer through a 0.32 cm outside diameter line. Polymer solution is sprayed in the T-mixer, using a nozzle of variable diameter (100, 120, or 200 μm). These nozzles are designed to be used in waterjet cutting systems, and were supplied by Resato and Comadur S.A.

The T-mixer that is being used in the experiments is a 0.63 cm outside diameter union tee piece. The residence tube used is a tube of 1.27 cm outside diameter, and variable length (28.7, 17.8, 13.2, 6.7, and 0 cm). Electrical heating is used to keep constant the temperature in the T-mixer and residence tube.

Operational procedure. CO_2 is fed with the pump (3) at a constant flow rate of 180g/min to the autoclave (7). When the autoclave (7) reaches the desired value of pressure, polymer solution (11) and CO_2 (12) are simultaneously pumped in the T-mixer at a constant flow rate. The mixture goes through the residence time tube, and finally it enters the vessel where it is mixed with the continuous flow of CO_2 pumped by pump 3. Polymer particles formed are collected on the filter plate (10), and the mixture DMSO-CO_2 continuously leaves the vessel.

Once all the polymer solution have been injected, the flow of CO_2 through the residence tube is maintained for 10 min in order to carry all the particles and solvent present in the residence tube to the vessel. Then, the pump (12) is stopped and the valve (13) is closed. CO_2 pumped by the positive displacement pump (3), continues to flow into the vessel to wash out the supercritical solution formed by the CO_2, and the solvent. This washing operation is carried out for 30 min to avoid the condensation of the solvent inside the vessel during depressurization.

Experimental conditions

A detailed description of the experimental conditions can be found in Table 1. Table 2 shows the process conditions of all the experiments showed in this article.

Results and discussion

X-Ray diffraction studies showed that both commercial and processed dextran particles were amorphous.

Effect of fluid dynamic variables

The hypothesis of mixing not interfering with particle formation was considered, and the fluid dynamic variables were manipulated (changing nozzle diameter or solution flow rate).

If the DMSO-solution was sprayed below 2 cm^3/min, mixing with the CO_2 was not good, and the product precipitated as a viscous gel inside the T-mixer. Spraying the solution at flow rates above 6 cm^3/min, the mixing between the fluids was good enough, and further increase of the flow rate had no effect on the final particle morphology.

Figure 5 shows the SEM pictures of the particles produced at 12 MPa and 40°C at two different solution flow rates when the concentration of CO_2 in the residence time tube is 74% mol. The particles obtained at the same conditions and 50% mol CO_2 present in the residence time tube are shown in Figure 6. Residence time tubes of different length were used to study the influence of the solution flow rate in order to keep the residence

Table 2. Detail of the Conditions of the Experiments Described in this Article

Experiment	Photo	Pressure (MPa)	Temperature (°C)	CO_2 flow (cm^3/min)	Solution flow (cm^3/min)	% wt dextran in DMSO	% mol CO_2	Volume residence tube (cm^3)	Residence time (s)	Nozzle diameter (μm)
1	Not shown	10	40	7.31	2.66	1	74	25.9	156	100
2	Not shown	12	40	13.5	6	5	75	16	49	100
3	Not shown	12	40	14.46	6	2	74	25.9	76	100
4	Not shown	12	40	14.46	6	0.6	74	25.9	76	100
5	5.a, 9.d	12	40	14.46	6	1	74	25.9	76	100
6	5.b	12	40	28.92	12	1	74	25.9	38	100
7	6.a	12	40	10.4	12	1	50	25.9	69	120
8	6.b	12	40	5.2	6	1	50	10.2	59	120
9	7	12	40	21.7	9	1	50	5.8	13	100
10	8.a	12	40	5.2	6	1	50	5.8	35	120
11	8.b	12	40	5.2	6	1	50	25.9	139	120
12	9.a	12	40	1.28	6	1	20	25.9	213	100
13	9.b	12	40	4.9	12	1	32	25.9	92	100
14	9.c	12	40	5.2	6	1	50	25.9	139	100
15	11.a	20	40	12.5	6	1	74	23	75	120
16	11.b	10	40	16.5	6	1	74	25.9	69	120
17	12.a	12	20	12.5	6	1	74	25.9	84	120
18	12.b	12	40	14.46	6	1	74	16	76	100
19	12.c	20	60	14.5	6	1	74	23	67	120

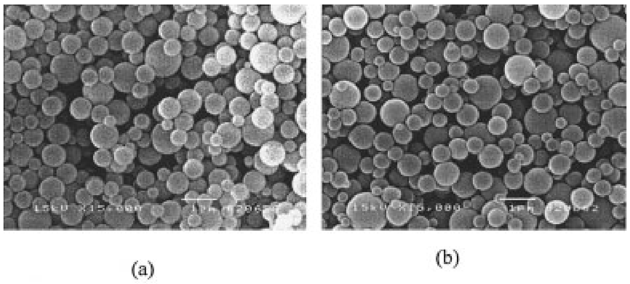

Figure 5. Effect of increasing solution flow rate on particle morphology.

Experiments carried out at 12 MPa and 40°C, with a molar ratio of CO_2 in the residence tube of 74%. Residence time in the residence time tube was larger than 30 s. Solution flow rate was 6 mL/min (a), and 12 mL/min (b).

time in the device constant. Results indicate that there are no significant differences in particle size when the solution flow through the nozzle is changed. In the same way, changes in the nozzle diameter from 100 to 200 μm did not seem to affect the size of the produced particles.

Results suggest that the use of a nozzle is only important for attaining a fast mixing between the polymer solution and the CO_2. No experimental evidence of atomization influencing droplet formation was found.

Effect of residence time in the T-mixer

The residence time in the residence-time tube (see Figure 3) before entering the vessel was found to be an important parameter in obtaining spherical polymer particles.

Experiments at different residence times in the residence-time tube were carried out using 74% mol CO_2 in the T-mixer at 12 MPa and 40°C. Figure 7 shows particles at a residence time of around 13 s. At such short residence times, very small irregular particles are obtained, their appearance is similar to that from convectional arrangement of the PCA process. The morphology of the droplets is frozen just when they were starting to form. Figures 5a and 5b show the particles obtained at longer residence time in the tube (38 and 76 s). It can be seen that increasing the residence time in the tube beyond 38 s does not affect particle size or morphology in the experiments carried out at 75% mol CO_2.

When using 50% mol CO_2 in the residence tube, at 40° C and 12 MPa, it was found that small particles are produced at residence times in the tube of around 35 s (Figure 8a). Increasing the residence time in the device above 1 min, particle size reaches a constant value (Figure 8b and Figure 6b). These results suggest that a certain time is required for the phase split to be completed.

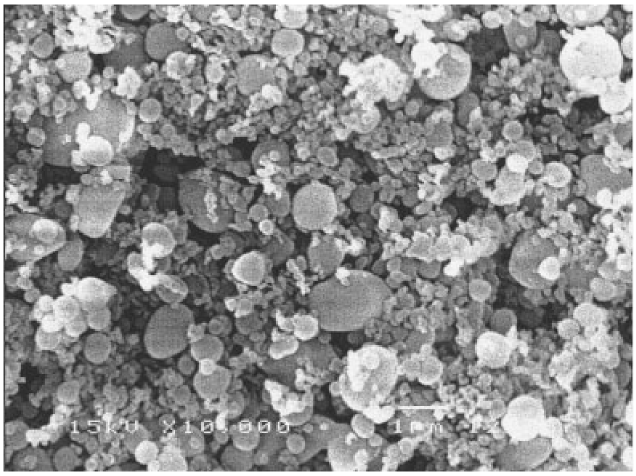

Figure 7. Dextran particles obtained at short residence times in the residence-time tube.

Experiment carried out at 12 MPa and 40°C, with a molar ratio of CO_2 in the residence tube of 74%. Estimated residence time was 13 s.

Effect of concentration of dextran in the DMSO.

The properties of the particles were similar in the lower concentration range of 0.5–2 wt. %. For more concentrated polymer solutions (5 wt. % dextran) a gel-phase in the T-mixer was obtained. As the concentration of dextran increases, the viscosity of the solution rises sharply, which hampers proper mixing with CO_2 in the T-mixer. The process is, therefore, not operable at polymer concentrations above approximately 3 wt. %. Apparently, the effect of increasing polymer concentration in the studied concentration range does not affect much the value of supersaturation.

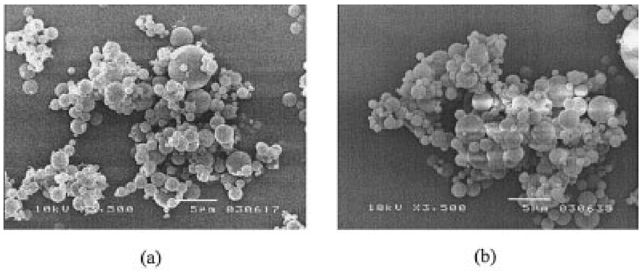

Figure 6. Effect of increasing solution flow rate on particle morphology.

Experiments carried out at 12 MPa and 40°C, with a molar ratio of CO_2 in the residence tube of 50%. Residence time in the residence time tube was around 70 s. Solution flow rate was 12 mL/min (Figure 6a), and 6 mL/min (Figure 6b).

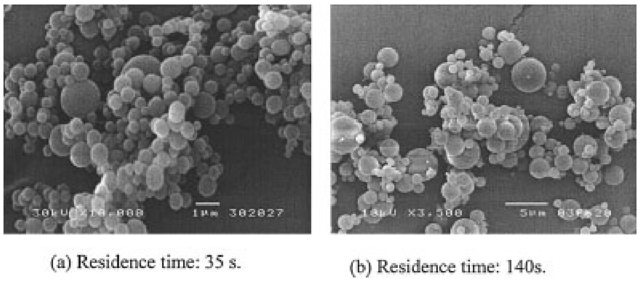

Figure 8. Influence of residence time on morphology.

Experiments carried out at 12 MPa and 40°C, with a molar ratio of CO_2 in the residence tube of 50%. A120 micron nozzle was used and the solution flow rate was 6 mL/min. The residence time was 35 s in Figure 8a and 140 s in Figure 8b. Figure 7b shows dextran obtained with a residence time of 70 s.

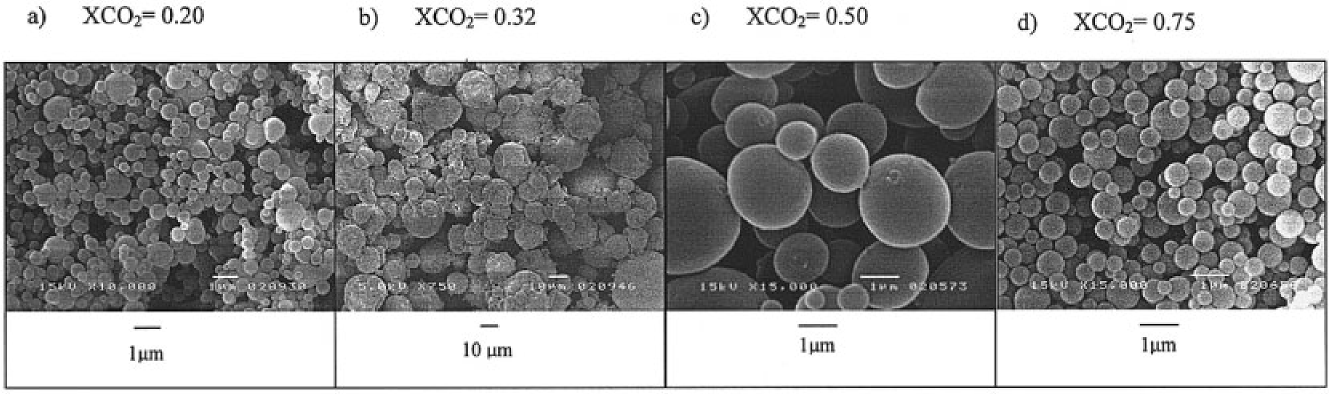

Figure 9. Influence of CO_2 concentration on particle size and particle-size distribution at 40°C and 12 MPa.

Notice that scale is not the same in all the pictures.

Concentration of CO_2 in the residence tube

The operating condition with the most pronounced effect on particle size was found to be the concentration of CO_2 in the residence-time tube. SEM pictures of dextran particles produced at 40 °C and 12 MPa at different CO_2 concentration are shown in Figure 9. The particle-size distribution of these particles is shown in Figure 10. A decrease of the CO_2 concentration in the T-mixer produces an increase in the particle size, whereas the particle-size distribution becomes broader. This trend was observed in every series of experiments at different operating conditions.

Classical nucleation theories applied to the formation of liquid droplets dictates that at a higher supersaturation smaller droplets are produced. As it was expected, a higher supersaturation (that is, higher concentration of CO_2 in the mixture) yielded a smaller particle size. Coalescence of droplets cannot be discarded as a mechanism influencing the size of the particles. The ratio polymer-rich phase to polymer-lean phase decreases when the amount of CO_2 increases. An increase in the amount of CO_2 is likely to reduce coalescence of droplets due to dilution.

The trend (lower CO_2 concentration, larger particles) is broken when very small amounts of CO_2 are used. (See Figure 9, 20% mol CO_2). This behavior can be understood by studying the phase diagram of the system dextran/DMSO/CO_2. It has been found that for compositions below 30% mol CO_2, only one phase is present in the system at 12 MPa and 40°C. Concentrations of CO_2 below 30% mol at this pressure and temperature will not induce a liquid-liquid phase split. So, when CO_2 and the polymer solution are mixed at such conditions no phase split happens during the

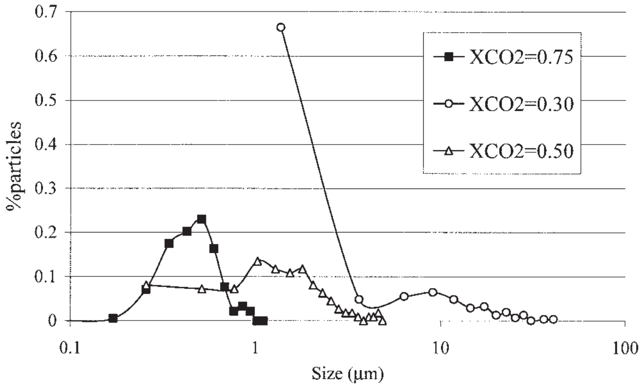

Figure 10. Influence of CO_2 concentration on particle size and particle- size distribution at 40°C and 12 MPa.

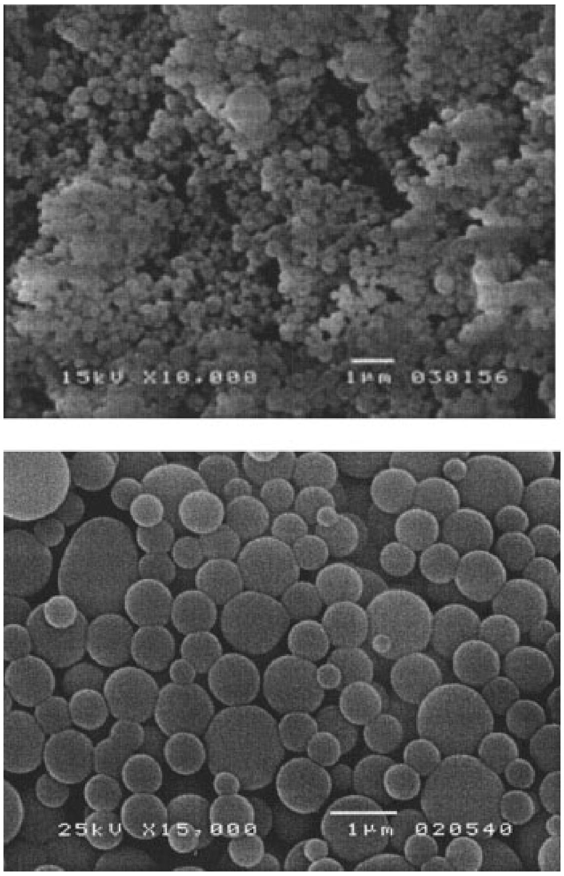

Figure 11. Influence of density on particle morphology.

Experiments carried out at 40°C, with a molar ratio of CO_2 in the residence tube of 74%. Top: 20 MPa, 840kg/m^3. Bottom: 10 MPa, 628 kg/m^3. Figure 9d shows the results of the experiment carried out at 12 MPa and 717 kg/m^3

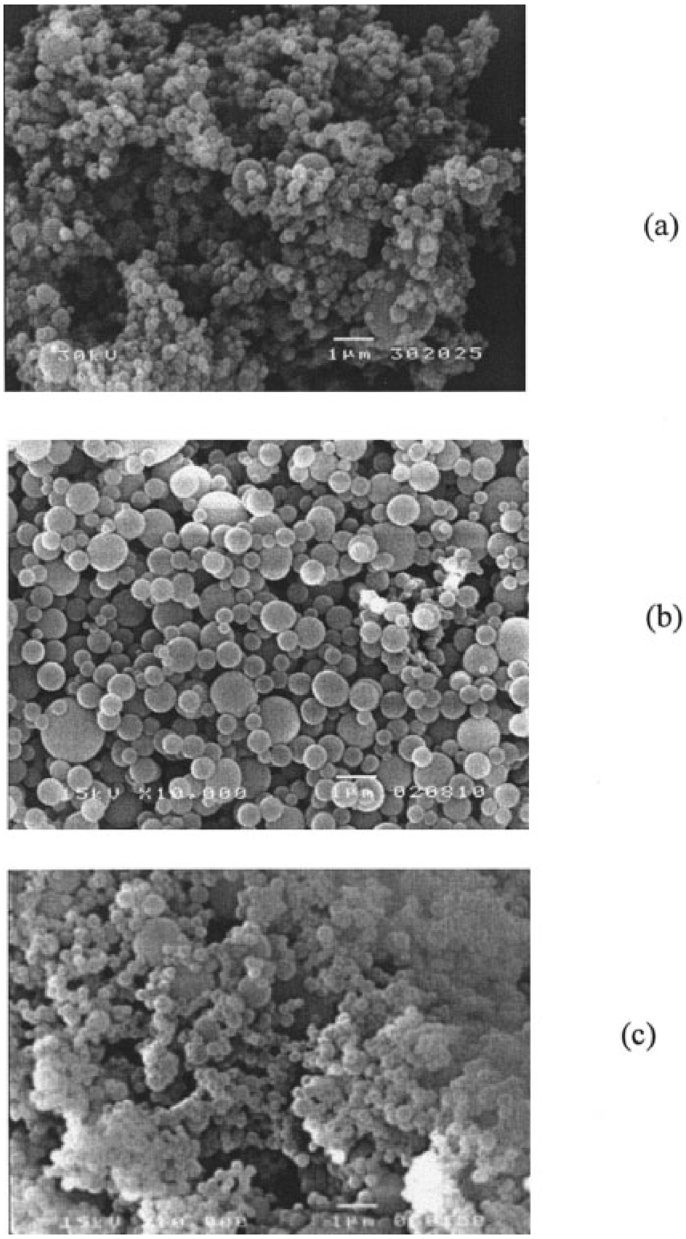

Figure 12. SEM picture of dextran produced at 74% mol CO_2 in the resident time tube at different temperatures, pressures and CO_2 densities.

(a) 12 MPa, 20°C, 878 kg/m^3; (b) 12 MPa, 40°C, 717 kg/m^3, (c) 20 MPa, 60°C, 723 kg/m^3. Scale is the same in all the pictures.

time the mixture stays in the residence time device. However, once the mixture goes inside the vessel, the concentration of CO_2 increases to around 95% mol and phase split is induced. The particles are small because they are produced at high concentrations of CO_2.

The bimodality observed in Figure 10, for a composition of 30% mol CO_2, could be due to the fact that supersaturation was not completely consumed during in the residence time tube, and a new burst of nucleation takes place when the solution gets in contact with the CO_2 in the vessel. There is no evidence of this phenomenon under different operating conditions.

Influence of density of the CO_2

The density of the CO_2 was varied at constant temperature by changes in the operating pressure (10 MPa-20 MPa). The mean particle size was found to decrease with an increase in density from 628 kg/m^3 to 840 kg/m^3 (Figure 11).

The same effect was observed when the density of the CO_2 was varied at constant pressure by changes in the operating temperature. Experiments performed at 12 MPa and 20°C showed a decrease on particle size with respect to those carried out at 12 MPa and 40°C (Figure 12a. and 12b).

At higher densities (higher pressures and/or lower temperatures), the interfacial tension between the two liquid phases decreases and, according to the classical nucleation theory, nucleation rate is enhanced.

The increase in the viscosity of the polymer solution at lower temperatures could also contribute to the small particle size observed in experiments carried out at 20°C. At low-temperatures, gelation of the polymer rich phase happens very fast and coalescence of droplets would be hindered.

Influence of temperature

The influence of changing the temperature at constant density conditions was studied. At 12 MPa and 40 °C and at 20 MPa and 60°C the CO_2 density is very similar (717 kg/m^3 and 723 kg/$m^{3,}$ respectively). Results showed that at equal density conditions, the particles obtained at higher temperatures are smaller (Figures 12b and 12c). This behavior can also be explained by means of the classical nucleation theory. At higher-temperatures more nuclei are formed, and the final particle size will be smaller.

Conclusions

At conditions of complete miscibility between organic solvent and CO_2, it is proposed that the formation of droplets in the system is not the consequence of atomisation of the DMSO solution, but rather the result of the formation of a liquid-liquid phase split when the DMSO-solution and CO_2 are intimately mixed. The morphology of the sphere-like particles is explained by the formation of polymer-rich droplets in a continuous CO_2-DMSO medium. Penetration of CO_2 into the droplets and stripping of DMSO induces the solidification of these droplets. Experimental results support the proposed mechanism of particle formation. Indeed, results seem to indicate that the use of a nozzle is only important for attaining a fast mixing between the polymer solution and the CO_2. No experimental evidence of atomization influencing droplet formation was found.

On the basis of this mechanism of droplet formation, a modification of the PCA process has been designed to separate the three main steps involved in the PCA process when processing polymers at conditions of complete miscibility of solvent and CO_2: mixing, droplet formation and stripping of the solvent.

The newly invented spraying device (T-mixer plus residence time tube) effectively solves the agglomeration and reproducibility problems found when some biodegradable polymers, such as dextran, are processed using the conventional PCA process, where a solution is injected into a bulk of CO_2.

It has been shown that a minimum residence time in the residence time tube is necessary to attain an equilibrium droplet size. This minimum time depends on the supersaturation induced in the system. Further increasing of the residence time does not change the product's appearance.

By varying pressure, temperature, and solution/CO_2 molar ratio the particle size can be easily manipulated from several nanometers to some micrometers. The influence of these variables on particle size can be explained according to the classical nucleation theory. An increase in temperature, in CO_2 density or in antisolvent concentration (CO_2 concentration) causes higher supersaturation levels and smaller particles are obtained. Coalescence of droplets should not be discarded as an important process contributing to increase the size of the particles.

Because the behavior of many other polymers is similar to the behavior of dextran, one would expect that this improved PCA process can be applied to many other systems.

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