An improved PCA process for the production of nano- and microparticles of biodegradable polymers

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Despite numerous experimental and theoretical studies the fundamentals of the Precipitation with a Compressed Antisolvent (PCA) process are not sufficiently understood. To elucidate the mechanism of particle formation, the phase behaviour of the system dextran/DMSO/CO_2 at high pressures was investigated. The solubility measurements showed that the presence of CO_2 induces a liquid–liquid phase split in the DMSO-dextran solution. These solubility measurements support the idea that 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 new polymer-rich-liquid phase 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.

Based on this mechanism of droplet formation, a new device was designed and implemented in the PCA equipment. 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, solution/CO_2 flow rate) on particle morphology has been studied.

1. INTRODUCTION

Supercritical fluid antisolvent processes have a huge potential for producing very small solvent-free particles with a narrow size distribution at mild operating conditions. The aim of this research is to investigate and develop CO_2 based supercritical antisolvent processes to prepare nano- and microparticles of drugs dispersed in biodegradable polymers (the so-called controlled drug release systems).

Problems related with reproducibility of the results and agglomeration were found when processing some biodegradable polymers, such as dextran, using the conventional PCA setup ([1], [2]). The system dextran/DMSO(dimethylsulphoxide)/CO_2 has been chosen as the model system for studying the PCA process of polymers. The phase behaviour of this system at high pressures was measured to understand the mechanism of particle formation. As a result of a better understanding of the process, an improved PCA process was developed [3]. This new design allows good reproducibility and the manipulation of the particle size with the operating conditions.

Once the formation of polymer particles has been understood and can be controlled, the encapsulation of pharmaceutical compounds will be addressed. Because the behaviour of many other polymers is similar to the behaviour of dextran, one would expect that this improved PCA process can be applied also to many other polymer systems.

2. THEORY

2.1 Mechanism of particle formation

All the experiments described in this paper were carried out at conditions of completely 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. [4] 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 atomises 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 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 1 [5]. Point A is the concentration of the initial polymer solution and point B is the final concentration of the system after mixing with all the CO_2 in the vessel. At point C (overall composition in the T-mixer) phase separation takes place by formation of a highly viscous polymer rich liquid phase (composition D) and a solvent rich phase (composition D'). The composition of the polymer rich phase will evolve from the point D to E as the overall composition moves from C to B (e.g. 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).

Figure 1. Proposed mechanism of particle formation

2.2 New T-mixer for controlling PCA process

The main reason for the poor reproducibility of the results when using the conventional PCA set-up was found to be related to the fact that this liquid-liquid phase split takes place before complete mixing of the dextran solution with the CO_2 is achieved. A new device was designed to separate the three processes: mixing, phase split and stripping of the DMSO from the polymer- rich droplets. This device is represented in figure 2.
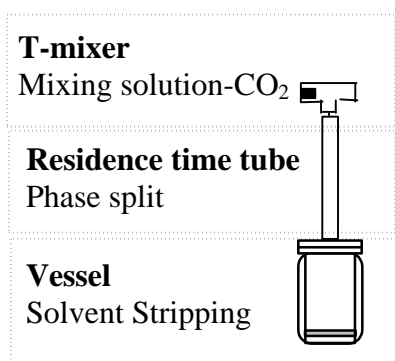

Figure 2. Detail of the improved device for PCA

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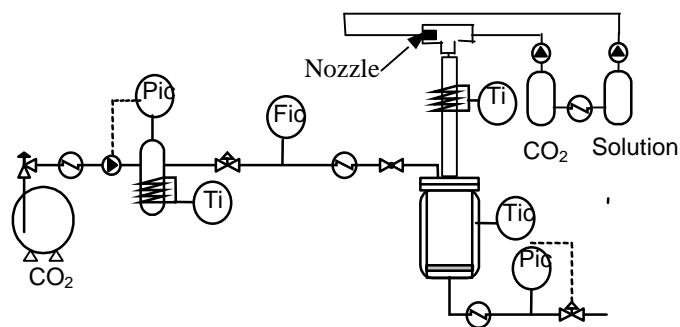
Figure 3. Improved PCA process set-up

By reducing the amount of CO_2 in the mixture, the kinetics of the phase split becomes slower and it is possible that the phase split starts at conditions of homogeneous mixing.

The first part of the device is a T-mixer. In this part, the dextran solution is pre-mixed with a relatively small amount of CO_2. The composition in this T-mixer is represented by the general point C in figure 1. Then, a tube of variable length (residence time tube) is used for giving the system enough residence time to complete the phase split and to attain the equilibrium conditions (D, D'). Finally, 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).

3. MATERIALS AND METHODS

Dextran (product number D4751) was obtained from Sigma-Aldrich and it has an average molecular weight of 64000-76000. Carbon dioxide (99.97%) was supplied by Hoekloos. DMSO (99.7%) was purchased from Acros Organics.
Processed dextran was analysed by a JEOL JSM-5400 Electron Scanning Microscope.

4. EXPERIMENTS AND RESULTS

4.1 Phase behaviour

In order to find supporting evidence for the proposed mechanism of particle formation, the phase behaviour of the system dextran/DMSO/CO2 was measured at high pressures.

Two independent methods were used to determine the phase diagrams:

- at constant temperature and pressure by the vanishing point used by Wubbolts[6]. Results were reported in [4].
- at constant composition, using the Cailletet tube described in [7]. One of the measured PT diagrams is shown in Figure 2. All the measured cloud point lines have a positive slope, indicating LCST (Lower Critical Solution Temperature) behaviour.

These measurements show that the presence of CO_2 induce a liquid-liquid phase split in the dextran-DMSO solution. Work is in progress on measuring these phase diagrams more extensively and in modelling the results using the Sanchez-Lacombe Equation of State.
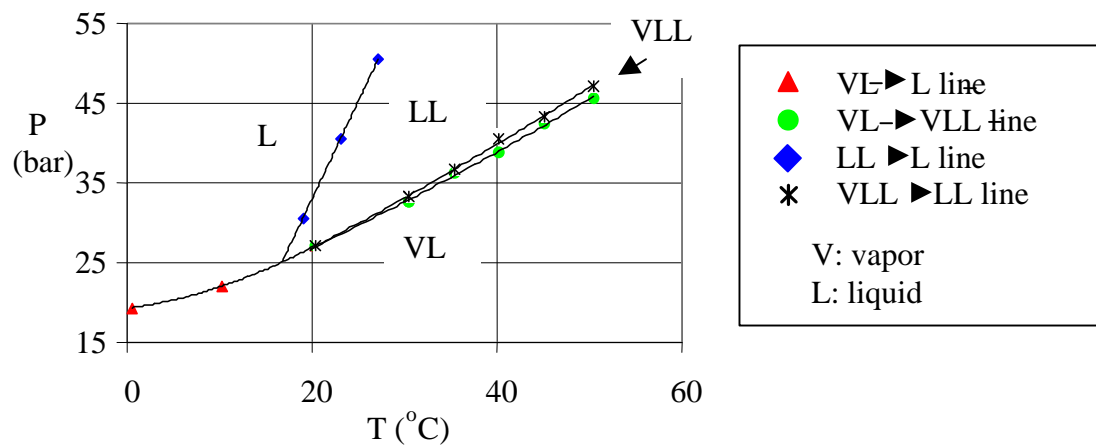
Figure 4. Measured PT diagram for 0.5%wt dextran in DMSO with 20%wt CO_2 using the Cailletet tube described in [7]

4.2 Experiments using T-mixer

Experiments where carried out using the experimental set up represented in Figure 3. The range of studied experimental conditions was:

Thermodynamic variables		Hydrodynamic variables	
Temperature	10°C- 60°C	Nozzle diameter	100, 200 micron
Pressure	100- 200 bar	T-mixer angle	0°, 90°.
Dextran concentration	0.5-5% wt		
Solution flow rate	2-18 ml/min		
Molar CO_2/DMSO rate in T-mixer	0.2 –0.9		
Residence time	1-175 seconds		

All the experiments where done at conditions of completely miscibility between the DMSO-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.

First, the hypothesis of mixing not interfering with particle formation was considered and the hydrodynamic variables were manipulated (changing nozzle diameter, T-mixer configuration or solution flow rate). It was found that the solution flow rate had a dominant effect and above 6ml/min, the other hydrodynamic variables had no effect on the final particle morphology. If the DMSO-solution was sprayed below 2ml/min, mixing with the CO_2 is not good and the product precipitates as a viscous gel in the T-mixer.

The residence time in the residence-time tube (See Fig.3) before entering the vessel was found to be an important parameter in obtaining spherical polymer particles. A minimum time is needed for the phase split to be completed. Prolonging the residence time in the tube beyond that minimum does not affect particle size or morphology. The nature of this phase split (by spinodal decomposition or nucleation and growth) is not clear yet.

The properties of the particles were not affected when using diluted dextran solutions (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 leading which hampers proper mixing with CO2 in the T-mixer.

The operating condition with the most pronounced effect on particle size was found to be the concentration of CO_2 in the T-mixer (Fig 5 and 6). The particle size distributions of particles produced at 40 ºC and 120 bar are shown in Fig 7. A decrease of the amount of CO_2 in the mixture produces an increase in the particle size while the particle size distribution becomes broader. This tendency was observed in every series of experiments at different operating conditions.
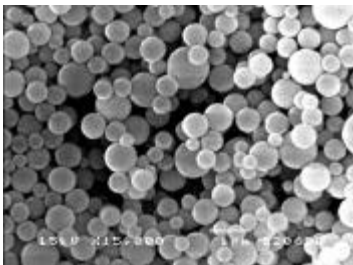

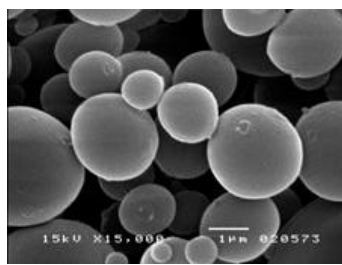**Figure 5**. 1%wt dextran solution processed at 120 bar and 40ºC. Molar fraction CO_2 =0.74

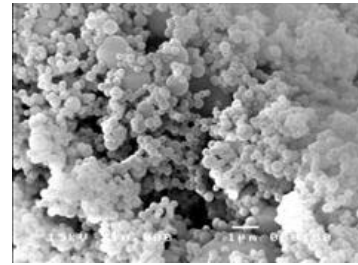**Figure 6**. 1%wt dextran solution processed at 120 bar and 40ºC. Molar fraction CO_2 =0.50

Figure 7. 1%wt dextran solution processed at 200 bar and 40ºC. Molar fraction CO_2 =0.74
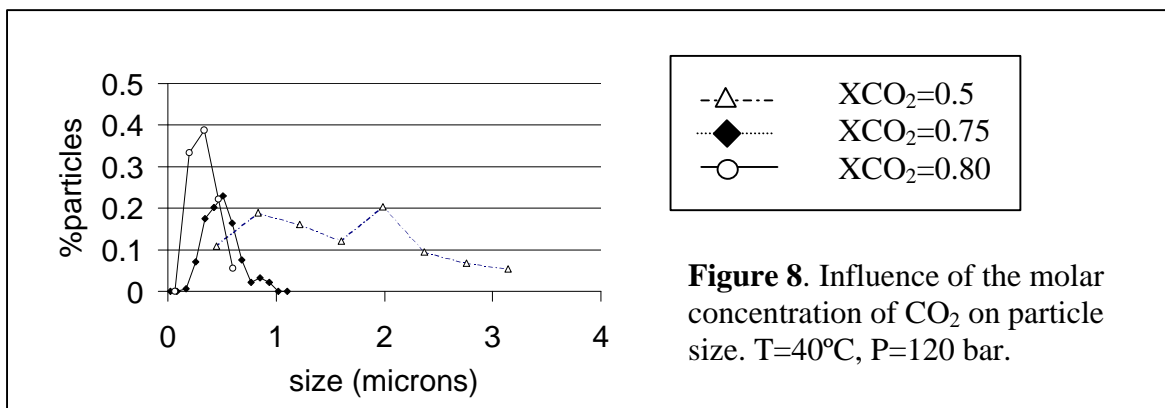

Figure 8. Influence of the molar concentration of CO_2 on particle size. T=40ºC, P=120 bar.

Finally the mean particle size was found to decrease with an increasing upstream pressure in the range of 120 bar to 200 bar (Fig. 5 and Fig. 7).
Changes in temperature from 40°C-60°C, however, do not seem to affect particle size. This suggests that temperature has a relatively weak influence on the phase behaviour and the relevant physical properties (density, interfacial tension and viscosity). This is subject to further study.

5. CONCLUSIONS

The measured phase diagrams show that the introduction of CO_2 in a DMSO-dextran solution induces a liquid–liquid phase split in the DMSO-dextran solution. This supports the idea that formation of droplets in the system is not due to atomisation of the DMSO solution but rather to the formation of a new polymer-rich-liquid phase when solution and CO_2 get in contact. The sphere-like morphology of the 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 evaporation of DMSO induces the solidification (gelation) of these droplets. The droplet size distribution resulting from the liquid-liquid phase split probably can be considered as the "template" for the eventual particle size distribution.

The new combined 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. By varying pressure, temperature, polymer concentration and solution/CO_2 flow rate with the new device, the particle size can be easily manipulated from several nanometers to tenths of microns. CO_2 concentration at the moment that the liquid-liquid phase split takes place was found to be the most powerful operating variable to influence particle size.

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

6. REFERENCES

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