PRECIPITATION OF A POLYMER BLEND USING SUPERCRITICAL CARBON DIOXIDE

A. Vega-González*, P. Subra

Laboratoire d'Ingénierie des Matériaux et des Hautes Pressions, CNRS, Institut Galilée, Université Paris XIII,

99 Avenue Jean Baptiste Clément, 93430, Villetaneuse, France

vega@limhp.univ-paris13.fr   fax : (33) 1 49 40 34 14

Biodegradable polymers and their copolymers have become recently an important area of research in medicine and pharmacy as delivery materials. Environmental issues have highlighted the need for alternative industrial particle formation processes, in order to: reduce the amount of organic solvents used, lead to solvent-free final products and, have the ability to control desired particle properties. Different micronization techniques based on the use of supercritical fluids (SF) are currently under development, precipitation from supercritical solutions and precipitation using SF as non-solvents.

In this work we consider the precipitation of a PMMA/PCL blend from dichloromethane using the supercritical antisolvent process. Carbon dioxide was contacted with 0.23 – 1 wt % polymer solutions, and with polymer + cholesterol solutions, in a semi-continuous mode of operation. Temperature was kept constant for all the experiments, 314 K; and 2 different pressures were used, 11 and 8.5 MPa.

INTRODUCTION

Biodegradable polymers and their copolymers and blends have recently become an important area of research as they can be used as drug or protein delivery materials. Polymethylmetacrylate (PMMA) is an acrylic hydrophobic biostable polymer that has been used as bone cement in orthopaedic surgery and dental applications. It has also been used for preparing PMMA nanoparticles containing enalaprilat, a typical angiotensin-converting inhibitor very poorly absorbed from the gastrointestinal tract [1]. Poly (ε-caprolactone) (PCL) has been spotlighted as biodegradable polyester because of its morphologic and physical properties and its miscibility with some important engineering plastics; therefore much work has been devoted to preparing linear and well-defined linear block copolymers [2]. This polyester was also used to prepare oily core microcapsules using bovine serum albumin as a model protein, and it was found that insignificant degradation of the protein occurred during in vitro release from PCL microcapsules [3].

A polymer blend is a mixture of two or more different kinds of polymer chains, which are not covalently bonded together [4]. Biodegradable polymer composites usually show improved characteristics compared to their separate components. Thus, different new composite materials have been synthesized as, starch based blends with acrylic polymers such PMMA and poly (acrylic acid) [5]; blends of biodegradable poly-L-lactic acid (PLLA) and poly-DL-lactic acid (PDLLA) or PCL [6]; and P (MMA-co-HEMA) hydrogel matrices [7].

Advances in drug delivery systems over the last years have highlighted the need for alternative particle-formation processes in the pharmaceutical industry, in order to use smaller quantities of organic solvents and to obtain solvent-free final products. Supercritical processing of pharmaceuticals provides an attractive alternative to these environmental issues. Different particle-formation processes based on supercritical fluids (SF) are available,

precipitation from supercritical solutions and precipitation using SF as non-solvents. As many polymers and pharmaceuticals are almost insoluble in supercritical carbon dioxide, the antisolvent method shown great potential for processing these materials.

This work reports the use of the supercritical antisolvent process for the precipitation of a PMMA/PCL blend from dichloromethane solutions.

I- MATERIALS AND METHODS

I.1 Materials

Poly (methylmethacrylate) – polycaprolactone (PMMA/PCL) microheterogeneous beads were provided by the CSIC (Departamento de Química Macromolecular), Madrid, Spain. It was synthesized according to a previously published procedure [8]. Methylene chloride (HPLC grade) was obtained from Prolabo (France) and use without additional purification. CO_2 (99%, industrial grade) was purchased from Air Liquide (FRANCE).

I.2 Method

The apparatus used for the experiments was operated in a semi-continuous mode. It is shown schematically in Figure 1. SC CO_2 was fed from the top to the spray chamber (1), this chamber consists of a high-pressure vessel (Autoclave Engineers) with sapphire windows allowing a visual observation of both the spray and the precipitation. The CO_2 was discharged from the bottom of the vessel, where the precipitated polymer is collected onto a membrane filter placed on top of a stainless steel filter. The pressure inside the vessel was controlled downstream with a micrometering valve, and the temperature was controlled by heating jackets (Watlow). Methylene chloride solutions of the polymer blend were sprayed into the vessel using a dual-piston minipump (Milton Roy LDC).

Once the temperature of the vessel has attained the desired value, the CO_2 was pumped to the vessel until the desired pressure was reached. Then, the system was allowed to equilibrate maintaining the CO_2 flow at a fixed value. The polymer solution was then introduced at the top of the precipitation chamber through a conical spray type nozzle; once the desired volume of solution was sprayed, CO_2 flow was maintained in order to dry the precipitated particles. After purging with pure CO_2, the vessel was slowly depressurized, at the experimental temperature.

I.3 Characterization

The morphology of polymer samples was analyzed and imaged by scanning electron microscopy (SEM, Leica 5440) after sputter coated with gold-palladium to a thickness of approximately 90 Å. Particle size was estimated manually from SEM photographs.

II- RESULTS AND DISCUSSION

II.1. Polymer in DCM solutions

Results are presented in Table 1, for the experiments carried out at 11 MPa and 314 K. Pure PMMA and PCL, and two different compositions of PCL in the PMMA/PCL blend were used, and two different nozzle diameters were tested.

These results showed that whatever the experimental conditions, the polymer always precipitated as fibres.

We have studied the effect of varying the polymer solution concentration from 0.23 wt% to 1%. In this range, the precipitated fibres are composed of many subfibres, which in

turn seemed to be composed of small particles or microspheres that are flocculated or fused end-to-end, as can be seen in figure 1. According to literature, fibres formation result from several factors as, hydrodynamics of the liquid jet breakup [9]; dilute to semi-dilute transition concentration of the polymer solution [10]; severe agglomeration leading to primary particles that are no longer discernible, as PMMA particles when they are exposed to CO_2 [11]; or phase equilibria.

Table 1. Polymer morphology obtained by spraying a polymer in DCM solution into flowing CO_2. T = 315 K, P = 11 MPa.

Polymer	Yield wt %	Solution flow rate (mL/min)	Liquid CO_2 flow rate (mL/min)	Microstructure	Macrostructure
100 μm conical spray nozzle					
PMMA-15%PCL					
0,96	81	1	102	Microspheres flocculated	Fibres
0.23	68	1	6,6	Microspheres flocculated	Fibres
0.23	79	0.3	6,7	Microspheres flocculated	Fibres
0.23	55	2.9	6,8	Microspheres flocculated	Fibres
PMMA-30%PCL					
0,98	57	1	102	Microspheres flocculated	Fibres
PMMA					
0,92	70	1	102	Microspheres flocculated	Fibres
PCL					
0.78	8.4	0.7	102	blocks	Film
200 μm conical spray nozzle					
PMMA-15%PCL					
0.23	30	0.3	6.8	Microspheres flocculated	Fibres

Figure 1. SEM photograph of PMMA/PCL fibres obtained by spraying a polymer in DCM solution into flowing CO_2 a 11 MPa and 314 K. 100 μm nozzle.
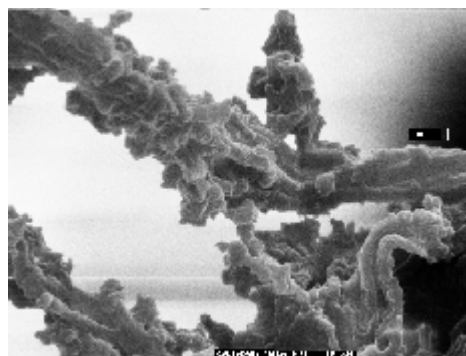
Precipitation of pure polymer solutions were also realised in order to determine if the fibres formation could be linked to one or both of the polymers contained in the blend. It was found that only pure PMMA precipitates as fibres, whereas pure PCL only formed a film that coated the internal walls of the vessel, no free particles were collected in this case.

The influence of the PCL content upon the precipitates morphology was also investigated. An increase in the content of PCL in the blend from 15 to 30% lead to similar micro and macrostructures.

RMN analysis shown that the proportion of the 2 polymers in the precipitate was the same than in the original product, so no fractionation took place during the precipitation process.

II.2. Polymer + cholesterol in DCM solutions

Cholesterol, a model steroid, has been chosen to study its encapsulation on the polymer blend. Similar experimental conditions than for the blend solutions were used. Results are presented in Table 2.

Table 2. Polymer morphology obtained by spraying a polymer + cholesterol solution in DCM into flowing CO_2. T = 315 K, P = 11 MPa.100 µm nozzle.

wt. % CO_2 free Polymer/Cholesterol	Yield wt % [*]	Solution flow rate (mL/min)	Liquid CO_2 flow rate (mL/min)	Microstructure	Macrostructure
PMMA-15%PCL + cholesterol					
0,3 / 0,2	70*	5,7	102,33	Microspheres flocculated	Fibrous network
0,7 / 0,4	61*	0,9	102,31	Microspheres flocculated	Fibrous network
0,94 / 0,6	96*	1	102,31	Microspheres flocculated	Fibres
PMMA-30%PCL + cholesterol					
0,95 / 0,6	80*	1	102,35	Microspheres flocculated	Fibrous network

*: the recovery yield is calculated on the basis of the introduced amount of polymer as all the cholesterol is lost during the drying step.

Experimental yields are of the same order of those obtained with the pure blend solutions. Experiments carried out with pure cholesterol had shown that under similar conditions, and due to cholesterol solubilization by pure CO_2 and CO_2+DCM mixtures, most of the cholesterol was lost during the spraying and drying steps.

The morphology of the precipitate obtained in this case is very similar to the previous one, as can be seen from figure 2.

Figure 2. SEM photograph of the precipitate obtained by spraying a polymer + cholesterol in DCM solution, into flowing CO_2 a 11 MPa and 314 K. 100 µm nozzle.
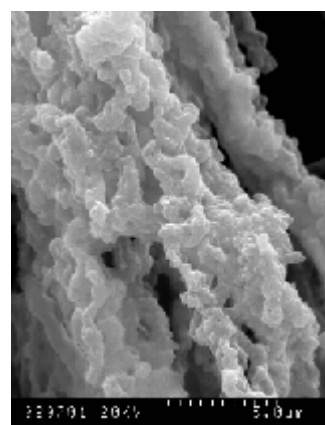
For these polymer + cholesterol solutions, we have tested a different pressure, in order to determine if in that case the morphology was different. The result is presented in Table 3.

Table 3. Polymer morphology obtained by spraying a polymer + cholesterol solution in DCM into flowing CO_2. T = 315 K, P = 8.5 MPa.100 µm nozzle.

wt. % CO_2 free Polymer/Cholesterol	Yield wt %	Solution flow rate (mL/min)	Liquid CO_2 flow rate (mL/min)	Microstructure	Macrostructure
PMMA-15%PCL + cholesterol					
3.4 / 7.7	91	2.5	67	Small needles and rods	Cotton like powder

In this run the drying time had been reduced in order to avoid the cholesterol loss. The precipitate obtained in this case had a different morphology, which is closer to the characteristic morphology of pure cholesterol, as can be seen in figure 3. Nevertheless, RMN analysis showed that the precipitate is composed of both solutes, the polymer blend and cholesterol.
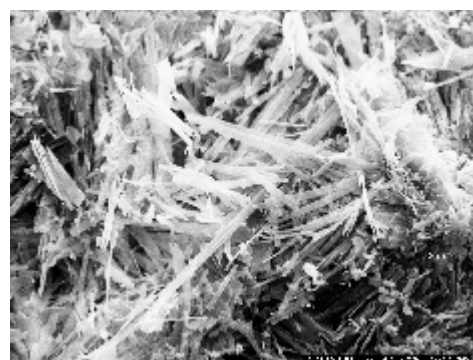

Figure 3. SEM photograph of the precipitate obtained by spraying a polymer + cholesterol in DCM solution, into flowing CO_2 a 8.5 MPa and 314 K. 100 µm nozzle.

CONCLUSION

The precipitation of a polymer blend, PMMA/PCL, in DCM solutions, and of the polymer blend + cholesterol solutions, by the antisolvent process were studied. The results indicated that at 11 MPa and 314 K, the polymer blend precipitates as fibres whatever the other experimental conditions, liquid solution flow, CO_2 flow or concentration, were.

Reducing the pressure to 8.5 MPa lead to a different morphology, closer to the cholesterol morphology, but in fact the precipitate contained both solutes. This may be explained by a coating of the cholesterol needles by the polymer.

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REFERENCES

[1] AHLIN, P., KRISTL J., KRISTL, A., VRECER, F., Int. J. Pharm., Vol. 239, **2002**, p.113.

[2] EROGLU, M. S., HAZER, B., BAYTAL, B. M., J. Appl. Polym. Sci., Vol. 68, **1998**, p.1149.

[3] YOUAN, B. B. C., JACKSON, T. L., DICKENS, L., HERNANDEZ, C., OWUSU-ABABIO, G., J. Control. Release, Vol. 76, **2001**, p. 313.

[4] HUBBELL, D. S., COOPER, S. L., J. Appl. Polym. Sci., Vol. 21, **1977**, p. 3035.

[5] ESPIGARES, I., ELVIRA, C., MANO, J. F., VÁZQUEZ, B., SAN ROMÁN, J., REIS, R. L., Biomaterials, Vol. 23, **2002**, p. 1883.

[6] CHEN, C-C, CHUEH, J-Y, TSENG, H., HUANG, H-M., LEE, S-Y., Biomaterials, Vol. 24, **2003**, p. 1167.

[7] HOFFMAN, A. S., Adv. Drug Deliv. Rev., Vol. 43, **2002**, p. 3.

[8] ABRAHAM, G. A., GALLARDO, A., MOTTA, A., MIGLIARESI, C., SAN ROMÁN, J., Macromol. Mater. Eng., Vol. 282, **2000**, p. 44.

[9] DIXON, D. J., JOHNSTON, K. P., J. Appl. Polym. Sci., Vol. 50, **1993**, p. 1929.

[10] MAWSON, S., KANAKIA, S., JOHNSTON, K. P., Polymer, Vol. 38, **1997**, p. 2957.

[11] MAWSON, JOHNSTON, K. P., BETTS, D. E., McCLAIN, J. B., DeSIMONE, J. M., Macromolecules, Vol. 30, **1997**, p. 71.