Precipitation of PMMA/PCL Blends Using Supercritical Carbon Dioxide

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ABSTRACT: Solutions of a poly(methyl methacrylate)–poly(ε-Caprolactone) (PMMA/PCL) polymer blend in dichloromethane (DCM) and mixtures of the same polymer blend and cholesterol in DCM were sprayed into supercritical carbon dioxide. Carbon dioxide was contacted with 0.23–1 wt % polymer solutions and with 0.3–1 wt % polymer plus 0.1–0.6 wt % cholesterol solutions in a continuous mode of operation. Pressure and temperature were constant for almost all of the experiments, 11 MPa and 314 K, respectively. Fibrous networks composed of many smaller microfibrils were obtained by spraying the different solutions through a conical nozzle into concurrently flowing supercritical carbon dioxide. This morphology suggests such an important degree of agglomeration that primary particles are no longer discernible. Processing the polymers with CO_2 leads to the removal of contaminants as the precipitate was free of monomer and initiator. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 2422–2426, 2004

Key words: antisolvent; amorphous PMMA; PMMA/PCL blend; drug delivery systems; fibers; nucleation

INTRODUCTION

Due to increasing awareness of environmental problems, demand for the synthesis of biodegradable polymers and their copolymers and blends has been growing,[1] not only to substitute large quantities of engineering plastics that are used every day, but also because recently they have become an important area of research and as drug or protein delivery materials. Poly(methyl methacrylate) (PMMA) is an acrylic hydrophobic biostable polymer that has been used as bone cement in orthopedics and traumatology. Poly(ε-caprolactone) (PCL) is a soft and hard tissue-compatible material that has been used as a bioresorbable matrix. It has also been used to prepare oily core microcapsules containing bovine serum albumin for the controlled delivery of protein vaccines,[2] and as a matrix material for tissue engineering.[3]

In the search for new compounds, it is necessary to develop improved formulations to solve the drawbacks of the original products. The introduction of changes in the copolymers or polymer blend formulations can improve or at least maintain their mechanical properties, diminish their toxicity, and control drug release. Thus, many new composite materials have been synthesized as PCL-*b*-PMMA crosslinked block copolymer[1], P(MMA-*co*-HEMA) hydrogel matrices[4], PLGA/PMMA nanoparticles[5], biodegradable and stable composite foams of porous apatite cement infiltrated with ε-caprolactone or methylmethacrylate[6], calcium phosphates and polymethylmethacrylate composites[7], glass/PMMA composites[8], and PMMA/PCL heterogeneous blends.[9]

Environmental issues have highlighted the need for alternative particle-formation processes in the pharmaceutical industry, processes that should operate with small quantities of organic solvents, lead to solvent-free final products, and have the ability to control desired particle properties.[10]

Different micronization techniques based on the use of supercritical fluids (SF) are currently under development, precipitation from supercritical solutions, and precipitation using SF as nonsolvents. In the first case, the technique involves dissolution of the solute in the SF; this process has been called rapid expansion of supercritical solutions (RESS). The second method is used for the crystallization of solutes that are insoluble in SFs from liquid solutions; this process is generally called gaseous antisolvent (GAS).

As many polymers and pharmaceuticals are almost insoluble in supercritical carbon dioxide, the supercritical antisolvent method has shown great potential

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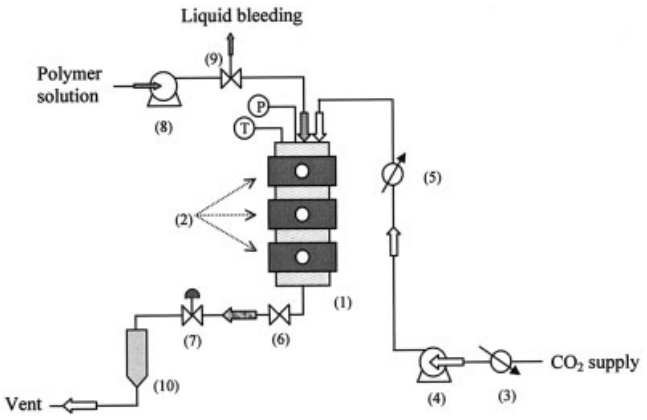

Figure 1 Experimental apparatus: (1) high-pressure vessel; (2) sapphire windows; (3) CO_2 cooling bath; (4) CO_2 pump; (5) CO_2 heating bath; (6) valve; (7) micrometering valve; (8) liquid solution pump; (9) three-ways valve; (10) separator.

for processing these materials,[11,12] and for obtaining different morphologies such as microspheres for drug delivery systems,[13] sponges for medical tissue engineering,[11] or fibers and threads that could be used for suture purposes or as medical tissue.[11]

In this work, we consider the precipitation of a PMMA/PCL blend and of mixtures of the blend + cholesterol from dichloromethane.

EXPERIMENTAL

Materials

PMMA/PCL microheterogeneous beads were provided by the Departamento de Química Macromolecular, Instituto de Ciencia y Tecnología de Polímeros (CSIC, Madrid, Spain). The polymer was synthesized by using a suspension polymerization method, according to a previously published procedure.[9] Methylene chloride (DCM, HPLC grade) was purchased from Prolabo (France) and was used without additional purification. CO_2 (99.5%, industrial grade) was obtained from Air Liquide (France).

Apparatus and procedure

The experiments were conducted in the apparatus shown schematically in Figure 1, operated in a semicontinuous mode, where supercritical CO_2 was fed from the top and discharged from the bottom of the thermostated precipitation vessel. The spray chamber (1) consisted of a high-pressure vessel (Autoclave Engineers), 5 cm i.d. $\times$ 25 cm long, rated to 320 bar at 150°C, with sapphire windows at three different levels (2) allowing a visual observation of both the spray and the precipitation. At the bottom of the vessel, the precipitated polymer is collected onto a membrane filter placed on top of a stainless steel filter of 2-μm porosity. The CO_2 was cooled by flowing through a cold water + ethanol bath (3) and then was pumped at constant flow by using a reciprocating LEWA (EK3) pump (4). Prior to entering the precipitation chamber, it flowed through a second water bath (5) to be preheated at the vessel temperature. The pressure inside the vessel was controlled downstream with an Autoclave Engineers micrometering valve (7), and the temperature was controlled by heating jackets (Watlow). Methylene chloride solutions of PMMA/PCL were sprayed into the precipitation chamber by using a reciprocating dual-piston minipump (Milton Roy LDC).

Once the temperature of the vessel had attained the desired value, the CO_2 was pumped to the high-pressure vessel via a ⅛ in tube, keeping the valve (6) closed, until the desired pressure was reached. Then, the valve (6) was opened and the system was allowed to equilibrate, maintaining the CO_2 flow at a fixed value. The polymer solution was cocurrently introduced into the precipitation chamber through a conical spray-type nozzle (Lechler). After leaving the precipitator, the CO_2/DCM solution was depressurized across the metering valve and separated in a homemade cyclonic separator (10). Once the polymer solution was sprayed, CO_2 flow was maintained, to dry the precipitated polymer. After approximately 40 min of purging with CO_2, the vessel was slowly depressurized, at the experimental temperature. Tubing and valves after the vessel were heated to prevent freezing due to CO_2 expansion, and they were flushed with DCM between each experiment. Pressure and temperature were constant for almost all of the experiments, 11 MPa and 314 K, respectively.

Characterization

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

Purity and composition of processed solid samples were determined by proton nuclear magnetic resonance (^{1}H-NMR) analysis. ^{1}H-NMR spectra were recorded in a Varian XLR-300 NMR spectrometer operating at room temperature and 300 MHz, from deuterated chloroform solutions (0.05 wt/v).

RESULTS AND DISCUSSION

As this work is the first step in the study of pharmaceutical compounds encapsulation, we tested the precipitation of polymer and polymer + cholesterol solutions in DCM. Cholesterol, a model steroid, has been chosen in this case to study its encapsulation on a PMMA/PCL polymer.

TABLE I
Observed Polymer Morphology Produced by Spraying a Polymer in DCM Solution into Flowing CO_2

Polymer wt % CO_2 free	Recovery yield wt %	Solution flow rate (mL/min)	Liquid CO_2 flow rate (mL/min)	Microstructure	Macrostructure
			PMMA-15%PCL		
0.96	81	1	102	5–15 μm o.d. subfibers	Fibrous network
0.227	68	1	6,6	7–10 μm o.d. subfibers	Fibrous network
0.227	79	0.3	6,7	1–5 μm o.d. subfibers	Fibrous network
0.228	55	2.9	6,8	1–2 μm o.d. subfibers	Fibers
			PMMA-30%PCL		
0.98	57	1	102	5–15 μm o.d. subfibers	Fibrous network
			PMMA		
0.92	70	1	102	0.6–3 μm o.d. subfibers	Fibers
			PCL		
0.78	8.4	0.7	102		Blocks

T = 315 K, P = 11 MPa, conical spray nozzle.

Polymer in DCM solutions

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

It can be seen that, whatever the experimental conditions and/or the blend compositions, the polymer always precipitated as a fibrous network. An example of fiber microstructure is given in Figure 2. It appears that fibers are composed of many smaller fibers that seemed to result from small particles that are fused end-to-end. Dixon and Johnston[14] have observed a similar behavior when using the PCA process for the precipitation of polystyrene solutions in toluene. In their case, for a concentration of 3.5 wt % the structure of the precipitate appears to be composed of very small subfibers, more connected than expected merely by flocculation of microspheres, where the primary fibers are composed of 100- to 200-nm spheres that are fused to form short fibers. They explain this by the fact that at this concentration the solution is in the semidilute region; chain entanglements increase the solution vis-

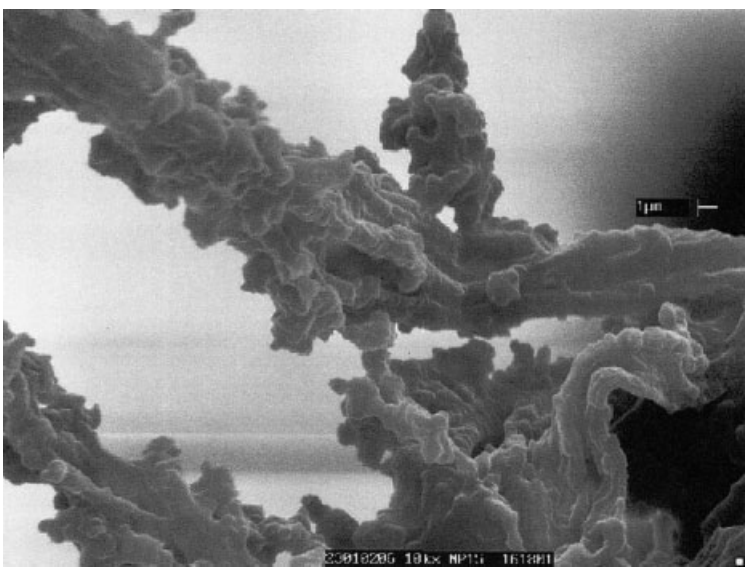

Figure 2 SEM photograph of PMMA/PCL fibers formed by spraying a polymer in DCM solution, through a 100-μm nozzle into CO_2 at 11 MPa and 314 K.

TABLE II
Observed Polymer Morphology Produced by Spraying a Polymer + Cholesterol Solution in DCM into Flowing CO_2

wt. % CO_2 free polymer/cholesterol	Recovery yield wt %[a]	Solution flow rate (mL/min)	Liquid CO_2 flow rate (mL/min)	Microstructure	Macrostructure
		PMMA-15%PCL + cholesterol			
0.295/0.196	70[a]	5.67	102.33	0.25–1.5 μm o.d. subfibers	Fibrous network
0.3/0.211	50[a]	0.91	102.31	0.5–1.5 μm o.d. subfibers	Fibrous network
0.69/0.43	61[a]	0.9	102.31	0.9–2 μm o.d. subfibers	Fibrous network
0.64/0.384	44[a]	1.2	102.31	5–10 μm o.d. subfibers	Fibrous network
0.94/0.63	96[a]	1.01	102.31	0.5–2 μm o.d. subfibers	Fibers + film
		PMMA-30%PCL + cholesterol			
0.95/0.62	80[a]	0.98	102.35	0.4–1.7 μm o.d. subfibers	Fibrous network

[a] The recovery yield is calculated on the basis of the introduced amount of polymer as all the cholesterol is lost during the drying step.
T = 315 K, P = 11 MPa, conical spray nozzle.

cosity and cause kinetic limitations for the formation of discrete polymer microspheres.

We have examined the effect of varying the polymer solution concentration from 0.96 to 0.23 wt % and of reducing the liquid CO_2 flow rate from 102 to 6.64 mL/min. Neither the network nor the microstructure were affected. The morphology of the precipitate was always the same. According to literature, fiber formation results from several factors: hydrodynamics of the liquid jet breakup[14]; polymer in DCM dilutes to semi-dilute transition concentration[15]; severe agglomeration leading to primary particles that are no longer discernible, as is the case for PMMA particles when they are exposed to CO_2[16]; or phase equilibria. Further measurements concerning solutions viscosity and phase behavior of the polymer–CO_2 system are needed to explain these observations.

We also investigated the influence of the PCL content upon the morphology. An increase in the PCL content of the polymer blend led to similar micro- and macrostructures. The main difference resides in the recovery yield, which decreases from 81 to 57% when the content of PCL in the blend increases from 15 to 30%. This result may be due to the PCL solubilization in CO_2 resulting from its low molecular weight.

The precipitation of pure PMMA in DCM solutions results also in fibers formation, but in this case they are of a smaller diameter.

Polymer + cholesterol in DCM solutions

Similar experimental conditions for the pure polymer solutions were used. Results are presented in Table II.

The experiment yields are of the same order of those obtained with pure polymer solutions.

From the SEM picture presented in Figure 3 we can see that the precipitate morphology is very similar to that of the precipitate obtained from the pure polymer solutions. Further experiments were carried out with pure cholesterol in DCM. Under similar conditions, and due to cholesterol solubilization in pure CO_2 and in CO_2+DCM mixtures, most of the cholesterol was lost during the spraying and drying steps.

RMN analysis

Fiber RMN analysis showed that there are no traces of cholesterol when coprecipitated with the polymer blend. Neither are there any monomer present in the precipitates. Processing with CO_2 led to the removal of contaminants in the same time as the precipitation

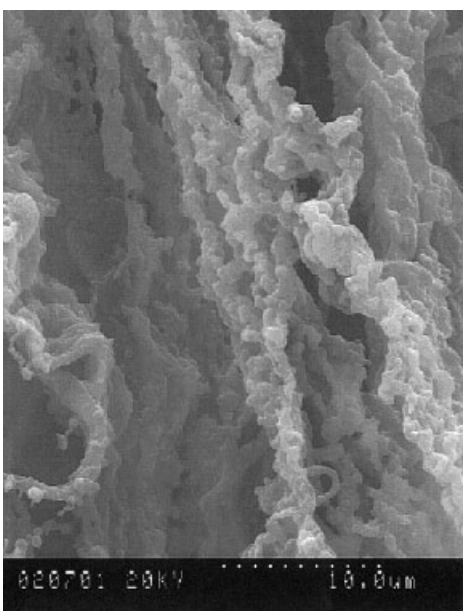

Figure 3 SEM photograph of PMMA/PCL fibers formed by spraying a polymer + cholesterol mixture in DCM, through a 100-μm nozzle into CO_2 at 11 MPa and 314 K.

occurred. Likewise, the ratio of PCL to PMMA of the precipitated polymer was the same as the raw materials' ratio, meaning that no fractionation took place during the precipitation and drying steps.

CONCLUSIONS

Fibrous networks and fibers of PMMA/PCL blends were produced by using supercritical CO_2 as an antisolvent in a semicontinuous SAS process. This macrostructure was the result of severe agglomeration of primary spherical particles, which fused end-to-end to form small subfibers, closely interconnected, leading to longer fibers formation. Polymer blend fibers are an important class of synthetic biomaterials that are widely used in temporary therapeutic applications such as wound closure, tissue regeneration, and sutures, and the supercritical technique proposed in this work allowed us to obtain such fibers free of contaminants. What is more, experimental runs yielded between 44 and 96 wt % in polymer, pointing out the interest of this technique from the material recovery point of view.

Cholesterol encapsulation was not successful. One of the principal reasons was its solubility in pure CO_2 and in the CO_2 + DCM mixture. Decreasing the drying time and the antisolvent density may be a useful way to reduce cholesterol loss and to favor its encapsulation.

The small amounts of organic solvent required, in addition to the mild temperatures used, make this antisolvent process an interesting option.

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