Behavior of Poly(methyl methacrylate)–Based Systems in Supercritical CO_2 and CO_2 Plus Cosolvent: Solubility Measurements and Process Assessment

C. Domingo,[1] A. Vega,[2] M. A. Fanovich,[1] C. Elvira,[3] P. Subra[2]

[1]*Instituto de Ciencia de Materiales de Barcelona, CSIC, Campus de la UAB, 08193 Bellaterra, Spain*
[2]*Laboratoire d'Ingenierie des Matériaux et des Hautes Pressions, C.N.R.S., Institut Galilée, Université Paris Nord, 19 Avenue Jean Baptiste Clément, 93430 Villetaneuse, France*
[3]*Instituto de Cienca y Tecnología de Polímeros, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain*

Received 15 March 2002; accepted 14 May 2003

ABSTRACT: Microspheres based on synthetic polymers such as poly(methyl methacrylate) (PMMA) and PMMA blends are known for their medical and optical applications. The development of methods for processing polymeric microspheres using a nontoxic solvent, like supercritical carbon dioxide ($SCCO_2$), is desirable. This work investigates the solubility and behavior of polymers (PMMA and PMMA/polycaprolactone blend) and solutes (cholesterol and albumin) in $SCCO_2$ and $SCCO_2$ + cosolvent (acetone, ethanol, and methylene chloride). The knowledge of solubility behavior of materials in $SCCO_2$ aids in the selection and/or design of the most appropriate technique for materials processing. Processing PMMA-based polymers with pure $SCCO_2$ leads to polymer swelling. The lack of polymer solubility in pure CO_2 precludes their micronization by the RESS (rapid expansion of supercritical solutions) process, but on the other hand allows their impregnation. Polymer plasticization caused by CO_2 can be exploited in the PGSS (particles from gas-saturated solutions) process. Addition of a liquid cosolvent to CO_2 enhances the dissolution of solutes and polymers. Precipitation of the studied polymers by antisolvent techniques seems feasible only by use of CO_2 + methylene chloride. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 90: 3652–3659, 2003

Key words: amorphous PMMA; PMMA/PCL blends; supercritical CO_2; swelling; solubility

INTRODUCTION

Many researchers have studied the use of poly(methyl methacrylate) (PMMA) microspheres in a wide variety of applications ranging from medical or biological[1,2] to optical.[3] One of the most important uses of the nondegradable PMMA is as a bone cement,[2] although it has the disadvantage of preventing the bone from growing into the space where the cement is placed, which leads to weakened bones.[4] To prevent this problem, some attention have been devoted to the use of biodegradable polymers,[5,6] for example, poly-ϵ-caprolactone (PCL), which is nontoxic and relatively cheap.[7] The main drawbacks of this compound are its slow degradation rate attributed to a high degree of crystallinity and hydrophobicity and poor mechanical properties. It has been shown that by blending PCL with other polymers the rate of biodegradation is generally enhanced.[8] Blending this polymer with PMMA allows tailoring the hydrophilicity of the matrix without significantly affecting the mechanical integrity.[9]

In this work, the polymers chosen for analysis were pure PMMA and a blend consisting of PMMA and PCL. The blend was a mixture of microdomains of PCL in a matrix of PMMA. The *in vivo* biodegradation process of PCL is expected to lead to the formation of a kind of PMMA foam, resulting in hollow microenvironments that could promote cell proliferation and implant integration.[10] Recent experiments performed in our laboratory have indicated that the PMMA/PCL microcomposites are eroded by either basic or acid treatment up to degrees that produce the disintegration of the particles in small fragments that could be easily cleared from the body. Besides, PMMA is the most widely used implant carrier for local sustained delivery of antibiotics, antifungal and antiinflammatory drugs, or even cancer chemotherapeutic agents (e.g., gentamicin, fluconazole, or cisplatin).[11–13] Finally, PMMA-based microspheres are considered as a good alternative to the traditional extrudable ethylene vinyl acetate (EVA) copolymer used for the localized sustained release of bioactive proteins and osteoinductive agents (e.g., human growth hormone or bone morphogenetic protein) used to enhance the regenerative ability of bone and other tissues.[14] In other fields

Correspondence to: C. Domingo (conchi@icmab.es).
Contract grant sponsor: EC Project Suprohar; contract grant number: G1RD-CT-2000-00164.

TABLE I
Source and Purity of Materials Employed

Chemical	Supplier	Purity (wt %)
Carbon dioxide	Airgaz	>99.9
Acetone	Prolabo	>99
Ethanol anhydrous	Carlo Erba	99.9
Methylene chloride	Carlo Erba	99.5
Cholesterol	Sigma	>99
Ovalbumine	Sigma	Grade II
PMMA	Lab-synthesized	95_{PMMA}, 4_{MMA}, 1_{BPO}
PMMA/PCL	Lab-synthesized	83_{PMMA}, 12_{PCL}, 4_{MMA}, 1_{BPO}

of applications, PMMA is used in the production of advanced optical components.[3] PMMA doped with some chromophores (e.g., azodyes) exhibits nonlinear optical properties that are important in the communications industry.

The presence of impurities, residual monomer, water, and so forth in PMMA polymer can greatly affect the performance in the mentioned applications. Moreover, most of the cited additives added to the polymer (either drugs or dyes) are thermally labile. Therefore, the development of efficient and clean methods for polymer processing at a low temperature is required. New ways to prepare microcomposite polymer/solute systems are also needed, to diminish the large amount of organic solvent used in conventional processes. Supercritical fluid (SCF) technology has already proven its applicability in the area of polymer processing.[15,16] The most commonly used SC solvent is carbon dioxide (CO_2), with a convenient critical point of 304 K and 7.4 MPa. Polymers have only very limited solubility in supercritical carbon dioxide ($SCCO_2$) because CO_2 has a much lower cohesive energy density than that of the polymers. The key issue in most of the successful applications of $SCCO_2$ in polymer processing is the sorption and swelling behavior of polymers at high pressure. In particular, polymeric systems containing PMMA can dissolve a relatively large amount of CO_2, leading to a large glass-temperature depression and thus low temperature and advantageous manufacturing processes at supercritical conditions.[17] Although there has been interest in exploiting pure $SCCO_2$ as a solvent to process polymers, fewer studies have concentrated on the behavior of the polymeric phase in contact with $SCCO_2$ plus an organic liquid or a cosolvent. A liquid cosolvent can greatly enhance polymer solubility in $SCCO_2$ if it has an intermolecular potential that matches closely with that of a polymer repeat unit.

In SCF technology, $SCCO_2$ can be used as a solvent [rapid expansion of supercritical solutions (RESS) process[18–21]], as an antisolvent [gas antisolvent (GAS) process and related processes[22–25]], or as a suspension medium [particles from gas-saturated solutions (PGSS) process[26]]. Monolithic systems, where the solute is dispersed at a molecular level in a polymer body, can be prepared by using an impregnation process in which the transfer of the solute into the matrix is aided by the SCF.[27–29] Materials solubility (both polymer and solute or additive) in CO_2 + cosolvent must be considered before selecting the most appropriate process. In this work, materials solubility was studied as a first step, before defining micronization or encapsulation processes. The chosen organic solutes, to be studied as model compounds, are (respectively) a CO_2-soluble compound, cholesterol (water-insoluble), and a nonsoluble one, albumin (a water-soluble globular protein widely used by researchers as a model protein). Finally, the influence of three liquid solvents [acetone, ethanol, and methylene chloride (CH_2Cl_2)] on polymer behavior was investigated. Acetone and CH_2Cl_2 are known to be good solvents for the studied polymers, whereas ethanol is not.

EXPERIMENTAL

Materials

Sources and purity of materials are listed in Table I. Acetone, ethanol, and CH_2Cl_2 were used as cosolvents for CO_2. Cholesterol and albumin were chosen as the organic solutes. Finally, PMMA and a blend with PCL were selected as polymeric matrices. Polymers were synthesized in our laboratory following a published procedure,[9] based on a suspension polymerization method. The resulting polymers showed a number-average molecular weight of 540,000 and 42,000 for PMMA and PCL, respectively.

Apparatus and procedure

The behavior of organic compounds and polymers upon contact with either $SCCO_2$ or $SCCO_2$ + liquid solvent was studied in a high-pressure analytical-scale equipment (Sample Preparation Accessory, LDC Analytical, ThermoQuest Division, San Jose, CA) (Fig. 1). A one-pass flow technique, in conjunction with a gravimetric determination, was used for solubility measurements. The reliability of equipment and pro-

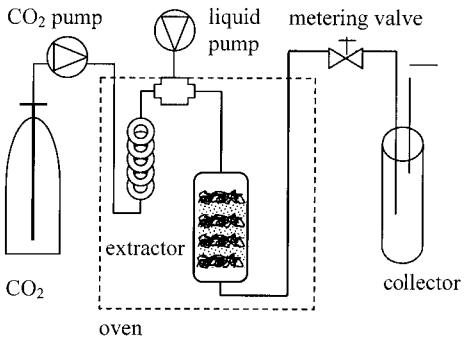

Figure 1 Experimental setup.

cedure was previously verified.[30] Liquid CO_2 was compressed to the operating pressure with a high-pressure pump. The dissolution cell (held in a controlled-temperature oven, with accuracy of 1 K) consisted of a tubular extractor of 10 mL, charged with about 0.4 g of either a pure solute or a binary mechanical mixture of organic compound plus polymer (50 wt %). System pressure was controlled (accuracy 0.1 MPa) by means of a metering valve. The extracted solute was recovered from the depressurized fluid by bubbling through a collector filled with a liquid solvent. To recover parts of solute that could have precipitated in the expansion device, the metering valve was flushed with a few milliliters of a liquid solvent.[31,32] The liquid solvent was further evaporated before weighing of the mass of extracted solid solute (Balance B5 C1000, accurate to within $\pm$0.01 mg; Mettler, Greifensee, Switzerland). This technique allowed the analysis of both the extracted solute and the material that remained in the extractor (the residue) after processing. Either pure CO_2 or CO_2 + cosolvent was used as a solvent, the procedure being slightly different in the two cases.

In experiments carried out with pure CO_2, the extractor was charged with the solute mixed with glass-wool fibers as bed packing. CO_2 was allowed to flow through the extractor for 60 min. Consumption of CO_2 was measured by a gas flow meter (Kobold MAS-4009, Hofheim, Germany). The flow rate was maintained at about 0.7 mL min^{-1}. Series of similar experiments were performed at various flow rates ranging from 0.54 to 1.40 mL min^{-1}. Variation of the flow rate within this range was found to have no effect on the measured solubility, thereby confirming that equilibrium was attained.

A typical experiment with CO_2 + cosolvent involved charging the extractor with the solute packed with glass beads to avoid solid compaction. A second pump (CM 3200; LDC Analytical) was connected to the setup, before the entrance of the extractor (Fig. 1), for liquid solvent addition. Various compositions of CO_2 + cosolvent were obtained by adjusting both flow rates, with a total flow rate < 1.5 mL min^{-1}. In each experiment the cosolvent/CO_2 ratio was increased in four consecutive steps. Each step lasted 30 min, at the end of which a collection procedure was performed before continuing the experiment with an increased amount of cosolvent.

Sample characterization

Purity and composition of the processed solid samples were determined by ^{1}H-NMR analysis. ^{1}H-NMR spectra were recorded in a Varian XLR-300 NMR spectrometer (Varian Associates, Palo Alto, CA) operating at room temperature and 300 MHz, from deuterated chloroform solutions (0.05 wt/vol). Scanning electron micrographs of polymer beads were obtained by use of a scanning electron microscope (SEM, JEOL JSM-840, Peabody, MA).

RESULTS AND DISCUSSION

Behavior of materials in pure $SCCO_2$

Experiments were carried out at a pressure of 20 MPa and temperatures of 312 and 333 K. Single- and two-solute systems were studied. Solubility values are reported in Table II.

For cholesterol, measured solubility values were in agreement with literature data.[33–35] Albumin solubility in $SCCO_2$ was negligible upon working conditions. For the studied polymers, a measurable amount of material was extracted, but because of the multicomponent nature of polymeric samples, the quantified mass could not be directly related to solubility. The composition of the extracted material was first analyzed using ^{1}H-NMR spectroscopy. Figure 2(a) shows the ^{1}H-NMR spectra of raw PMMA as well as the extracted and residual portions, after SC processing. Raw PMMA showed the main signals assigned to the polymeric chain (–O—CH_3 at 3.5 ppm and α-CH_3 at 0.8–1.2 ppm) together with those allocated to the residual monomer MMA (–C═CH_2 at 5.5–6.2 ppm) and benzoyl peroxide (BPO; –C_6H_5 at 7.2–8.1 ppm). The extracted material mainly consisted of MMA monomer and BPO initiator. The residue displayed only the PMMA signals. A similar result was obtained for the PMMA/PCL system [Fig. 2(b)]. Signals of PMMA, PCL (–O—CH_2 – at 4.0 ppm and –CO—CH_2 – at 2.5 ppm), MMA, and BPO were observed in the raw material added to the extractor. After processing with compressed CO_2, the residue was purified of contaminants that were found in the extract. Using the data obtained from the ^{1}H-NMR analysis, the mass of contaminants was removed from the polymer solubility calculation.

SEM micrographs were used to examine changes in the external appearance of PMMA and blend residue as a result of $SCCO_2$ treatment. For PMMA, some of

TABLE II
Solubility Data in Pure $SCCO_2$, Expressed as Percentile Weight of Extracted Amount per Unit Mass of CO_2[a]

Solute 1	Solute 2	T (K)	$Solubility_{solute\ 1}$ (wt %)
Cholesterol	—	312	0.050
		333	0.053
Albumin	—	312, 333	—
PMMA	—	312, 333	<0.001
PMMA/PCL	—	312	0.001 ($65\%_{PMMA}$, $35\%_{PCL}$)
		333	0.001 ($80\%_{PMMA}$, $20\%_{PCL}$)
Cholesterol	PMMA	312	0.016
		333	0.017
	PMMA/PCL	312	0.018
		333	0.019
Albumin	PMMA	312, 333	—
	PMMA/PCL	312, 333	—

[a] P = 20 MPa.

the beads lost sphericity after processing with CO_2 [Fig. 3(a), (b)], evidencing a glassy to rubbery transition. CO_2 causes a large depression (60 K or more) in the glass-transition temperature of PMMA at relatively low pressure (4–6 MPa).[17,36] In this work, experimental conditions of pressure and temperature were high enough to induce plasticization in the polymer, and thus morphologic changes in the beads. For the PMMA/PCL residue, bead deformation was less evident [Fig. 3(c), (d)]. The blend is a microheterogeneous system, where semicrystalline PCL domains are immersed in a matrix of amorphous PMMA. Plasticization is a process that has been described to last for several hours,[37] whereas the extent of our experiments was only 1 h. $SCCO_2$ diffusion rates in the glassy PMMA are expected to be higher than those in the blend also involving the nonswellable PCL.[38,39]

Series of experiments were also conducted on mixed beds, composed of an organic (solute 1: either cholesterol or albumin) and a polymer (solute 2: either PMMA or PMMA/PCL). ^{1}H-NMR analysis was used to determine the composition of the extracted materials. In most cases, the ^{1}H-NMR signals assigned to solute 1 hinder the integration of the signals corresponding to the small fraction of polymer (solute 2) that could be extracted. Therefore, solubility of solute 2 could not be accurately calculated and is not shown in Table II. The first unexpected result was obtained for systems involving cholesterol. The presence of polymer in the extraction bed significantly lowered the solubility of this material with respect to that in the cholesterol/CO_2 binary system. In these experiments, the extractor was filled with a multicomponent system, consisting mainly of an organic and polymer, but also by an initiator and residual monomer. This behavior of negative cosolute effect induced by the multicomponent system may result from intermolecular interactions between components that preclude cholesterol dissolution.[40,41]

Behavior of materials in $SCCO_2$ + cosolvent

Experiments were performed at 313 K and 18 MPa. For acetone, ethanol, and CH_2Cl_2, within the composition range investigated in this study, the binary mixtures were a single phase.[42–44]

Solubility data of solids, upon addition of cosolvent to CO_2, are given in Table III. Cholesterol solubility was markedly increased by the addition of any of the three cosolvents. Albumin solubility was now observable, the higher cosolvency effect of which was with CH_2Cl_2. The solubility of PMMA and PMMA/PCL in

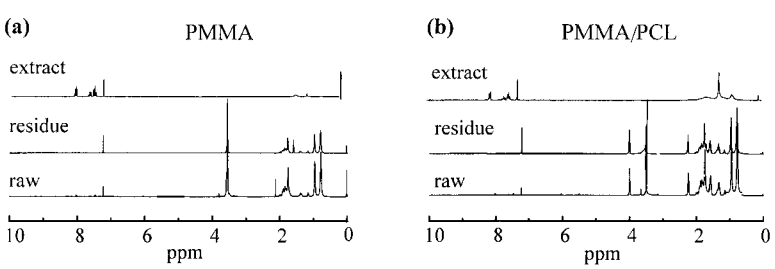

Figure 2 ^{1}H-NMR spectra of raw, residual, and extracted polymers: (a) PMMA and (b) PMMA/PCL. Samples were processed at 20 MPa and 313 K.

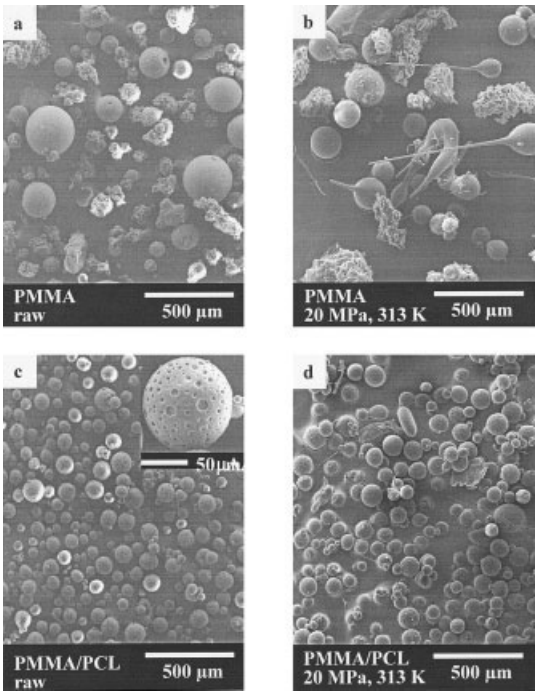

Figure 3 SEM micrographs of raw and 60-min SC-processed polymers (residue) at 20 MPa and 313 K.

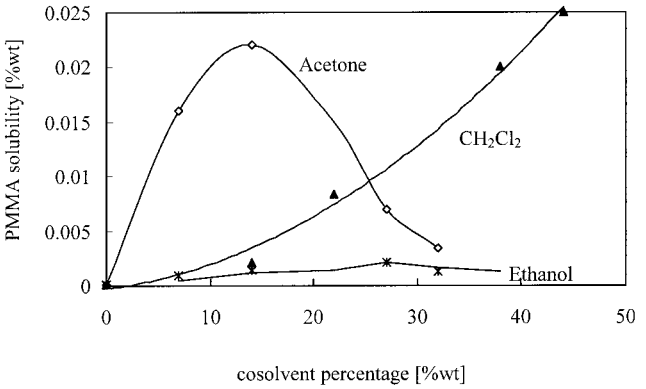

Figure 4 Solubility behavior of PMMA with respect to the amount of cosolvent added to $SCCO_2$. Experiments were performed at 18 MPa and 313 K.

pure acetone, ethanol, and CH_2Cl_2 was estimated by shaking 0.1 g of polymer in 10 mL of solvent at 313 K for 60 min. Acetone and CH_2Cl_2 were good solvents for the studied polymers, whereas ethanol was not. By mixing $SCCO_2$ with any of the three studied cosolvents, the solubility of PMMA increased with respect to the solubility in pure CO_2 (compare data in Tables II and III). However, trends on solubility level, with respect to the amount of cosolvent added to CO_2, were different for each liquid solvent (Fig. 4). For CO_2 + ethanol, the solubility was low and practically not affected by the increase in cosolvent percentage. For CO_2 + CH_2Cl_2, the solubility increased continuously by raising the cosolvent percentage. For CO_2 + acetone, the polymer solubility, as a function of solvent percentage (between ~ 7.0 and 32 wt %), exhibited a maximum at about 15 wt % of cosolvent. The decrease on solubility at high cosolvent ratios may come from the particular procedure used, given that data were obtained by sequential increments of cosolvent percentage on a single polymer batch. On the other hand, the decrease may also be attributable to the rejection of polymer out of the CO_2 + acetone mixture when

TABLE III
Solubility of Solids in $SCCO_2$ Plus Different Extends of Cosolvent, Expressed as Percentile Weight of Extracted Amount per Unit Mass of Fluid[a]

	Acetone		Ethanol		CH_2Cl_2	
Solute	wt % of cosolvent	Solubility (wt %)	wt % of cosolvent	Solubility (wt %)	wt % of cosolvent	Solubility (wt %)
Cholesterol	9.4	0.085	9.3	0.130	12.4	0.097
	14.5	0.130	14.3	0.180	22.0	0.174
Albumin	7.0	0.005	7.0	0.003	11.0	0.004
	14.5	0.003	15.0	0.001	20.0	0.006
	25.9	0.002	24.4	<0.001	38.3	0.008
	28.5	0.002	31.5	0.001	43.6	0.005
PMMA	7.0	0.016	7.7	0.001	15.8	0.002
	14.5	0.022	13.0	0.001	22.0	0.008
	26.6	0.007	26.9	0.002	38.3	0.020
	31.8	0.003	31.5	0.001	43.6	0.025
	100	very high	100	very low	100	total
PMMA/PCL	7.0	0.025 (88%$_{PMMA}$, 12%$_{PCL}$)	7.7	0.001 (51%$_{PMMA}$, 49%$_{PCL}$)		
	14.5	0.003 (31%$_{PMMA}$, 69%$_{PCL}$)	14.3	0.001 (24%$_{PMMA}$, 76%$_{PCL}$)	12.0	0.005 (88%$_{PMMA}$, 12%$_{PCL}$)
	26.6	0.004 (22%$_{PMMA}$, 78%$_{PCL}$)	24.4	0.003 (18%$_{PMMA}$, 82%$_{PCL}$)	21.4	0.010 (91%$_{PMMA}$, 9%$_{PCL}$)
	31.8	0.039 (74%$_{PMMA}$, 26%$_{PCL}$)	31.5	0.003 (86%$_{PMMA}$, 14%$_{PCL}$)	36.8	0.014 (73%$_{PMMA}$, 27%$_{PCL}$)
	100	very high	100	very low	100	total

[a] Experiments were performed at 18 MPa and 313 K.

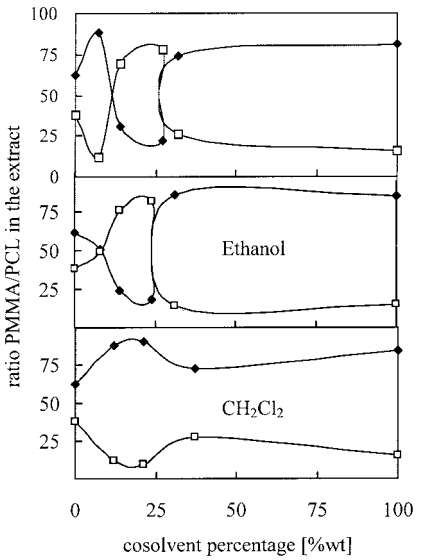

Figure 5 Variation of the PMMA/PCL ratio in the recovered extracts obtained by adding different amounts of cosolvent to $SCCO_2$. Experiments were performed at 18 MPa and 313 K. ◆, PMMA; □, PCL.

solvent–solvent interactions outweighed solvent–polymer interactions.[35]

Within the range of pressure, temperature, and solvent composition investigated, solubility trends for PMMA in the blend were different from those found for the individual polymer. First, for the three studied cosolvents, the amount of PMMA extracted from the blend was much lower than the amount extracted from the individual polymer. Second, for acetone and ethanol solvents, the solubility increased significantly at high cosolvent percentages. The most remarkable finding, accessible from the blend behavior in solvent mixtures, was related to variations of the PMMA/PCL ratio in the various recovered extracts (Fig. 5). For ethanol and acetone, the amount of PCL extracted with respect to PMMA increased when the cosolvent content was increased from about 7.0 to 30 wt %. For cosolvent proportions $>$ 30 wt %, the amount of extracted PCL drastically diminished with respect to PMMA. Thus at high cosolvent proportions, the solubility behavior of polymer blend in CO_2 + cosolvent mixtures was similar to that in pure liquid solvents. For CH_2Cl_2 the ratio PMMA/PCL in the extracted samples was always similar to that in the original polymer; that is, the fraction of PMMA was considerably higher than that of PCL.

SEM micrographs were used to examine changes in appearance of PMMA and PMMA/PCL residues as a result of liquid solvent or $SCCO_2$ + cosolvent treatment (Fig. 6). For PMMA polymer, only samples contacted with CO_2 + ethanol maintained the spherical shape of the particles [Fig. 6(b)], although beads were slightly deformed and compacted around the glass beads' packing material. Alternatively, PMMA beads contacted with CO_2 plus either acetone [Fig. 6(a)] or CH_2Cl_2 [Fig. 6(c)] completely lost the original shape. For PMMA/PCL beads, similar pictures where obtained regardless of the cosolvent used [Fig. 6(d)–(f)]. Beads were still visible, although distorted, providing further evidence of the extreme difficulty of plasticization of PMMA/PCL with respect to PMMA.

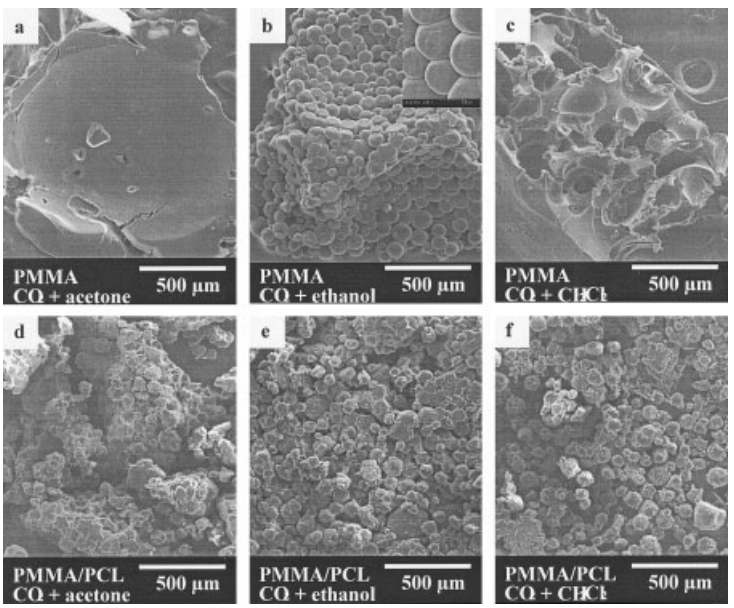

Figure 6 SEM micrographs of polymers (residue) after 120-min treatment with mixtures of $SCCO_2$ + cosolvent at 18 MPa and 313 K.

Relevance in the preparation of microparticles

The ultimate goal of this work was to provide fundamental knowledge for selecting the most adequate SC process for micronization or encapsulation of solutes. Process selection must be carried out in connection with materials behavior and solubility in $SCCO_2$ and fluid mixtures. Results from the materials solubility survey in pure and mixed $SCCO_2$ (Tables II and III) give the first indication of which SC-processing technique seems to be a better choice. Cholesterol, with values in the 0.05 wt % solubility range, is considered as a soluble compound in compressed CO_2 and can be micronized using the RESS process, with or without the addition of a cosolvent. In contrast, albumin showed a negligible solubility in pure $SCCO_2$, under working conditions, and a very low solubility in fluid mixtures. Therefore, this material would be better processed using antisolvent techniques. The low solubility of PMMA and PMMA/PCL also preclude their micronization by RESS.

Although most polymers are not soluble in $SCCO_2$, the solubility of compressed CO_2 in many amorphous polymers is as high as that of typical liquid swelling agents.[45,46] CO_2 has the advantage of being a nonpermanent swelling agent and solvent-free end products are easily obtained. Polymers themselves are rarely pure materials because they are contaminated with polymerization agents and residual monomers and solvents. For biomedical applications, in the final polymer-based drug system, the contaminants may produce side effects detrimental to a patient's health, which limit their use in human therapy. Polymer purification is thus very valuable. It was shown that CO_2 removed toxic residual monomers and initiator of polymerization from PMMA and PMMA/PCL (Fig. 2). This effect is based on polymer swelling induced by CO_2, which facilitates diffusion of impurities out of the polymer. The same effect can be used for polymer impregnation by diffusion of a solute from the carrier SCF to the swelled polymeric matrix. The final additive/polymer content ratio will be a function of the relative solubility of the solute in the fluid and polymer phases. Thus the low solubility of polymers in $SCCO_2$ is, in contrast, an interesting feature for producing monolithic loaded microspheres free of residual monomer or solvent. However, for compounds of low solubility in $SCCO_2$, the impregnation process would be economically acceptable only if the solute shows a high affinity for the polymeric matrix. In purification or impregnation processes, the morphology of the polymer beads should not be significantly altered. Of the two investigated polymers, PMMA was the most vulnerable to morphological distortive effects caused by treatment with CO_2 (Figs. 3 and 6). PMMA/PCL showed little or no gross deformation.

The addition of a cosolvent modifies solids solubility in $SCCO_2$. To date, most of the performed experiments have been carried out to study the increase of solubility of organic solids by the addition of low amounts (2–5 wt %) of liquid cosolvent to CO_2. With respect to encapsulation, it is necessary to investigate the solubility of organics and polymers in mixtures of $SCCO_2$ and relatively large amounts of different cosolvents. In this work, an increase in solubility by the addition of cosolvent to CO_2 was observed for all studied solids (Table III). Frequently, a good solvent at normal conditions can be located as an adequate cosolvent at SC conditions. However, the behavior of polymers has been found to be different with respect to that of small organic molecules. First, both the fluid and cosolvent are generally soluble in the polymer. Second, a large amount of cosolvent is needed to detect an increase in solubility. Finally, the choice of cosolvent can be motivated by either a good dissolution level at normal conditions or a synergic effect.[19] Indeed, a nonsolvent at atmospheric conditions may become an effective cosolvent for polymers when mixed with CO_2.

The behavior of studied polymers in CO_2 + cosolvent allows us to propose several ways for the micronization of these materials using the RESS process. For pure PMMA (Fig. 4), enhancement of the extracted amount by addition of ethanol to CO_2 occurs, but a RESS process based on this mixture may be economically questionable. In contrast, CH_2Cl_2 significantly enhanced the dissolved amount of PMMA. Acetone also increased polymer solubility, but only when it was added in percentages lower than about 15 wt %. Similarly, acetone and methylene chloride are potential cosolvents for RESS of PMMA/PCL, but the amount of cosolvent added influenced the composition of the extracted material (Fig. 5).

Precipitation of polymers by antisolvent techniques, although feasible, is related to the differences of polymer solubility in pure liquid solvent and that in CO_2 + liquid solvent. The choice of the liquid solvent to initially dissolve the polymer is crucial for inducing supersaturation by CO_2 addition, and as a consequence will determine the final particle size and yield. Pure ethanol dissolved polymers only slightly; thus, unless the ethanol content is very low in the CO_2 + ethanol mixture, precipitation may not occur, given that the solubility in pure ethanol was in the same range of order as the solubility in the mixture. The solubility ratio was more favorable with CH_2Cl_2, especially at a content of 15 wt % of liquid solvent. CH_2Cl_2 dissolved the polymers to a considerable extent, so small size could be expected. For acetone, solubility of the polymers was not a continuous function of the liquid solvent percentage in the fluid mixture, and thus nucleation and growth of particles are difficult to control.

CONCLUSIONS

Regarding potential SC techniques for the manipulation of the studied materials, generalizations are summarized in the following remarks, based on the observed solubility behavior. They are not claimed to be exhaustive or even of the most appropriate engineering design, given that liquid solvents other than acetone, ethanol, or CH_2Cl_2 can facilitate micronizing or encapsulating compounds.

- Processing of PMMA-based polymers with $SCCO_2$ leads to polymer swelling, which facilitates the removal of toxic contaminants and the impregnation with additives.
- The low solubility of polymers in pure CO_2 precludes their micronization by RESS.
- The studied liquid solvents are potential cosolvents for RESS processing of polymers. Increasing the amount of cosolvent is not a guarantee of increasing solute solubility, as was shown for the system CO_2–acetone–PMMA. On the other hand, only at high cosolvent ratios were the components of the PMMA/PCL blend dissolved homogeneously.
- Precipitation of the investigated polymers by antisolvent techniques seems feasible using only CH_2Cl_2 as a liquid solvent. For ethanol, polymers are not soluble enough in the pure liquid solvent. For acetone, the behavior appears too complex such that nucleation and growth of particles, and thus particle size, are difficult to control effectively.

The authors acknowledge European Community Project Suprophar (G1RD-CT-2000-00164) for financial support and thank B. DeGioannis for help with solubility measurements and G. Abraham for preparation of polymers.

References

1. Robinson, J. R.; Lee, V. H. L. Controlled Drug Delivery: Fundamentals and Applications; Marcel Dekker: New York, 1987.
2. Burkoth, A. K.; Anseth, K. S. Biomaterials 2000, 21, 2389.
3. West, B. L.; Kazarian, S. G.; Vincent, M. F.; Brantley, N. H.; Eckert, C. A. J Appl Polym Sci 1998, 69, 911.
4. Tams, J.; Joziasse, C. A. P.; Bos, R. R. M.; Rozema, F. R.; Grijpma, D. W.; Pennings, A. J. Biomaterials 1995, 16, 1049.
5. Middleton, J. C. Biomaterials 2000, 21, 2335.
6. Du, J.; Jasti, B.; Vasavada, R. C. J Controlled Release 1997, 43, 223.
7. Lin, W.-J.; Lu, C.-H. J Membr Sci 2002, 198 109.
8. Hubbell, D. S.; Cooper, S. L. J Appl Polym Sci 1977, 21, 3035.
9. Abraham, G. A.; Gallardo, A.; Motta, A.; Migliaresi, C.; San Román, J. Macromol Mater Eng 2000, 282, 44.
10. Siripurapu, S.; Gay, Y. J.; Royer, J. R.; DeSimone, J. M.; Khan, S. A.; Spontak, R. J. Mater Res Soc Symp 2000, 629, FF991.
11. Domb, A. J., Ed. Polymeric Site Specific Pharmacotherapy; Wiley: New York, 1994.
12. Siakumar, M.; Panduranga Rao, K. React Funct Polym 2000, 46, 29.
13. Walenkamp, G. H. I. Biomaterials in Surgery; Thieme-Verlag Medical Publishers: Stuttgart, Germany, 1998.
14. Kim, H. D.; Valentini, R. F. Biomaterials 1997, 18, 1175.
15. McHugh, M.; Krukonis, V. Supercritical Fluid Extraction; Butterworth–Heineman: Stoneham, MA, 1994.
16. Cooper, A. I. J Mater Chem 2000, 10, 207.
17. Condo, P. D.; Johnston, K. P. J Polym Sci Part B: Polym Phys 1994, 325, 23.
18. Debenedetti, P. G.; Tom, J. W.; Yeo, S.-D.; Lim, G.-B. J Controlled Release 1993, 24, 27.
19. Mishima, K.; Matsuyama, K.; Tanabe, D.; Yamauchi, S.; Young, T. J.; Johnston, K. P. AIChE J 2000, 46, 857.
20. Ksibi, H.; Subra, P. Adv Powder Technol 1996, 7, 21.
21. Domingo, C.; Berends, E.; Van Rosmalen, G. M. J Supercrit Fluids 1997, 10, 39.
22. Reverchon, E.; Della Porta, G.; de Rosa, I.; Subra, P.; Letourneur, D. J Supercrit Fluids 2000, 18, 239.
23. Ghaderi, R.; Artursson, P.; Carlfors, J. Pharm Res 1999, 16, 676.
24. Engwicht, A.; Girreser, U.; Muller, B. M. Biomaterials 2000, 21, 1587.
25. Thiering, R.; Dehghani, F.; Dillow, A. J Chem Technol Biotechnol 2000, 75, 42.
26. Shine, A.; Gelb, J. World Pat. WO 98/15348, 1997.
27. Magnan, C.; Bazan, C.; Charbit, F.; Joachim, J.; Charbit, G. High Pressure Chem Eng 1996, 509.
28. Alessi, P.; Cortesi, A.; Kikic, I.; Colombo, I. In: Proceedings of the 5th Meeting on Supercritical Fluids, Nice, France, 1998.
29. Domingo, C.; García-Carmona, J.; Fanovich, A.; Llibre, J.; Rodríguez-Clemente, R. J Supercrit Fluids 2001, 21, 147.
30. Subra, P.; Castellani, S.; Ksibi, H.; Garrabos, Y. Fluid Phase Equilib 1997, 131, 269.
31. Castellani, S. Ph.D. Thesis, University of Paris XIII, 1996.
32. Subra, P.; Castellani, S.; Jestin, P.; Aoufi, A. J Supercrit Fluids 1998, 12, 261.
33. Wong, J. M.; Johnston, K. P. Biotechnol Prog 1986, 2, 29.
34. Yun, S.; Lion, K.; Guardial, G.; Foster, N. Ind Eng Chem Res 1991, 30, 2476.
35. Kosal, E. J Supercrit Fluids 1992, 5, 169.
36. Wissinger, R. G.; Paulatis, M. E. J Polym Sci Part B: Polym Phys 1987, 25, 2497.
37. Vincent, M. F.; Kazarian, S. G.; Eckert, C. A. AIChE J 1997, 43, 1838.
38. Shieh, Y.-T.; Su, J.-H.; Manivannan, G.; Lee, P. H. C.; Sawan, S. P.; Sapll, W. D. J Appl Polym Sci 1996, 59, 695.
39. Shieh, Y.-T.; Su, J.-H.; Manivannan, G.; Lee, P. H. C.; Sawan, S. P.; Sapll, W. D. J Appl Polym Sci 1996, 59, 707.
40. Liu, G.-T.; Nagahama, K. J Supercrit Fluids 1996, 9, 152.
41. Lucien, F. P.; Foster, N. R. J Supercrit Fluids 2000, 17, 111.
42. Suzuki, K.; Sue, H.; Itou, M.; Smith, L.; Inomata, H.; Arai, K.; Saito, S. J Chem Eng Data 1990, 35, 63.
43. Chang, C.; Day, C.; Ko, C.; Chiu, K. Fluid Phase Equilib 1997, 131, 243.
44. Vega-González, A.; Tufeau, R.; Subra, P. J Chem Eng, to appear.
45. Lee, S.; MacHugh, M. Polymer 1997, 38, 1317.
46. Berens, A. R.; Huvard, G. S.; Korsmeyer, R. W.; Kunig, F. W. J Appl Polym Sci 1992, 46, 231.