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A one-pot method to enhance dissolution rate of low solubility drug molecules using dispersion polymerization in supercritical carbon dioxide

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ABSTRACT

The surfactant assisted polymerization of 1-vinyl-2-pyrrolidone in supercritical carbon dioxide in the presence of Piroxicam, selected as a model of a low aqueous solubility drug, was studied in order to prepare in a single step a polymeric composite to enhance the rate of dissolution of the pharmaceutical compound. Reactive entrapping was carried out at 65 °C in the *P* range 21–38 MPa. Under proper operative conditions we obtained the composite under the form of sub-micron spherical particles with relatively narrow particle size distribution. Drug loadings higher than 12% (w/w) were obtained and XRD and Raman spectroscopy suggest that the anti-inflammatory agent is dispersed in the matrix with a non-crystalline structure. The dissolution rate of the drug from the composites was significantly faster both than that of the pure compound and of its physical mixture with the polymer. Collected results suggest that the proposed one-pot process can be used to prepare polymer based composites to increase bioavailability of low solubility drugs without utilization of toxic solvents and under mild temperature conditions.

1. Introduction

The oral route is considered the best way of administration of drug molecules. To make possible its utilization, the bioactive compound must exhibit high enough permeability and dissolution rate that is dependent on its water solubility. There are many well known drugs such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol, whose oral administration has been challenged by poor water solubility, that have required the development of suitable formulations. More recently, the availability of high throughput screening of potential therapeutic agents led to a significant enhancement of the number of poorly soluble drug candidates. Indeed about 40% of new active compounds are characterized by a small water solubility resulting in poor oral bioavailability due to insufficient dissolution throughout the gastrointestinal tract (Prentis et al., 1988). This drawback risks to prevent their practical utilization (Lipper, 1999) and the development of new formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

The modified Noyes–Whitney (Noyes and Whitney, 1897) equation offers a rationale base to define some simple strategies to improve the dissolution rate of low solubility pure drugs:

$$\frac{dm}{dt} = AD\frac{C_s - C}{h}$$

where C is the instantaneous concentration of drug in the medium, A is the surface area available for dissolution, D is the diffusion coefficient of the molecule, C_s is its solubility in the dissolution medium and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

From this simple mass balance equation one can infer that to enhance the dissolution rate dm/dt it is possible to increase the total drug surface area A by micronization and/or by optimizing its wetting characteristics, to promote perfect sink conditions ($C \to 0$), to reduce the thickness of the boundary layer or by increasing the apparent drug solubility C_s. Among them, change in the fluodynamic regime to modify the value of h does not seem practical in vivo while the attainment of sink conditions depends on the permeability of the drug across the gastrointestinal mucosa as well as on the composition and volume of the lumenal fluids. For these reasons the easiest methods to enhance drug dissolution rate seem to be formulation approaches that can be classified as physical or chemical modifications (Leuner and Dressman, 2000). Among the former it can be mentioned particle size reduction by micronization or nanosuspension, modifications of the crystal habit, polymorphs, pseudopolymorphs (including solvates), complexation/solubilisation, use of surfactants or of cyclodextrines, drug dispersion in carriers, eutectic mixtures, solid dispersions both non-molecular and at the level of solid solutions.

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In principle the simplest route to reduce average size of a particulate drug is milling of the bioactive compound. Anyway the increase of the surface area amplifies the tendency of the polymer particle to agglomerate so that the final effect can be significantly decreased if coalescence of the particle is not prevented. In this context the utilization of solid dispersion, particularly those obtained at molecular level (solid solutions), allows one to have the drug with the highest surface area possible and embedded in a carrier matrix that prevents recrystallization of the drug molecules.

For these reasons solid dispersion, a concept firstly introduced by Sekiguchi and Obi (1961), has attracted considerable interest as a means of improving the dissolution rate and oral bioavailability of poorly water-soluble drugs. There are mainly two methods to prepare solid dispersions, i.e. the melting method and the solvent method.

The former involves mixing of the drugs and carriers in their melt state and subsequent cooling and congealing at low temperatures to obtain solid dispersion slabs (Chen et al., 2004; Law et al., 2003). In the case of high-melting-point carriers like poly(vinylpyrrolidones) (PVP), coprecipitation of drugs and carriers is achieved by the alternative solvent method which involves the solubilisation of drugs together with carriers in a suitable solvent followed by the evaporation of the solvent under a reduced pressure to obtain coprecipitates (Chiou and Riegelman, 1969; Sethia and Squillante, 2004).

Both these approaches are characterized by manufacturing difficulties and stability problems that complicate their applicative utilization. These could be the thermal degradation of the bioactive compound, the lack of miscibility at the melt state or the difficulty of decreasing residual concentration of solvents, often toxic, to acceptable levels due to the mass transfer resistances induced by the gradual increase in the local viscosity of the coprecipitated coagulum.

Supercritical carbon dioxide ($scCO_2$) is a non-conventional compressible solvent whose chemico-physical properties can be changed by adjusting the density. This property, that is typical of all sc fluids, is coupled with CO_2 specific technical–economical features such as a low-cost, a large availability, excellent biocompatibility and mild critical parameters that make possible its utilization in the supercritical region with thermo labile compounds.

Quite interestingly $scCO_2$, exhibiting an intense plasticizing effect towards amorphous polymers, have been used by several researchers as a solvent and swelling agent to prepare solid dispersion of drugs in polymer matrixes by impregnation (Kikic and Vecchione, 2003; Kazarian and Martirosyan, 2002; Manna et al., 2007).

In all aforementioned strategies the preparation of the controlled release dosage form must be carried out in a two step process: first the polymer must be synthesized and then the drug must be dispersed in the matrix by hot melt or solvent method (in liquid or supercritical phase).

On the other hand, $scCO_2$ has proven to be an interesting alternative to conventional solvents as polymerization medium (Kendall et al., 1999; Cooper, 2000; Wood et al., 2004) and it has been successfully used as dispersing medium in the synthesis of poly(vinylpyrrolidone) (Berger et al., 2000; Carson et al., 2000; Galia et al., 2004) that is a polymer already described in a series of pharmacopoeias (e.g., in the U.S.) and then accepted for several pharmaceutical applications as solubilizer, crystallization retarder, for detoxification, for reducing the irritant action and toxicity of certain substances, as a tablet binding and coating agent, as a suspension stabilizer, and as a dispersant for pigments in tablet-coating suspensions (Hallensleben, 2004). When administered orally it is regarded as not being toxic, presumably because it has a too high molecular weight to be adsorbed from the gastrointestinal mucosa.

We have recently found that a solid polymer–ibuprofen composite can be prepared with a single pot process by performing the surfactant assisted polymerization of 1-vinyl-2-pyrrolidone (VP) in $scCO_2$ in the presence of the drug (Galia et al., 2008) where we obtained high PVP yields under the form of spherical particles with sub-micron diameter and narrow particle size distribution. Drug dissolution from such composites resulted decreased with respect to the pure compound particularly when the hydrophilic monomer was copolymerized with methyl methacrylate.

In this study we have tested the possibility of using a similar approach to enhance the rate of dissolution of Piroxicam that was selected as a model of low water solubility drug.

2. Materials and methods

2.1. Materials

VP from Aldrich (99+%) deinhibited by distillation under vacuum at about 80 °C or by passage through an activated basic alumina column was used. The initiator, 2,2′-azobis(isobutyronitrile) (AIBN, Fluka) and CO_2 (Rivoira 99.998 pure) were used as received. The reactive macromonomer poly(dimethylsiloxane) surfactant Sb1784, with double methacrylic chain-ends, was kindly donated by Degussa and used as received. Its structure can be described by the formula:

$$CH_2{=}CH{-}O(CO){-}R{-}[Si(CH_3)_2O]_n{-}Si(CH_3)_2{-}R{-}O(CO){-}CH{=}CH_2$$

where R is an alkyl group, $n = 260$ and $M_n = 20{,}000$ g/mol.

Piroxicam was purchased from Aldrich (assay higher than 98%). Cyclohexane was Riedel de Han HPLC grade. NaCl, Na_2HPO_4 and KH_2PO_4 were Aldrich ACS grade. All of them were used as received. Bidistilled water was used to prepare buffer solutions.

2.2. Phase behaviour investigation apparatus

The visual investigation of the phase behaviour of the CO_2/VP/Piroxicam mixture was performed in a fixed volume view cell from Thar Technologies, stirred by a magnetic stir bar. The temperature control of the system was ensured by immersion of the cell in a water bath whose temperature was controlled by a PID controlled with an accuracy of ±0.2 °C, while the pressure was recorded by means of a pressure transducer (Barksdale UPA 3).

The drug was loaded in the view cell dissolved in the liquid monomer. After purging of the air with a controlled flow rate of gaseous CO_2 the vessel was sealed and loaded with liquid CO_2 at room temperature by using an ISCO syringe pump, up to reach a desired density. The total amount of solvent introduced was measured weighing the vessel with an electronic scale (Mettler PM34 max 30 kg, precision 0.1 g). Then the cell was heated to 65 °C according to a procedure elsewhere described (Galia et al., 2003).

2.3. Polymerization apparatus

Polymerizations were carried out in a stainless steel constant volume (27 mL) batch autoclave, stirred by a magnetic bar and inserted in an automated control system of the temperature elsewhere described (Galia et al., 2003). The proper amounts of each condensed component of the polymerization mixture (monomer, initiator, surfactant, and drug) were charged in the reactor, the vessel was then deoxygenated by a controlled flow rate of gaseous CO_2 maintained for 10 min. After sealing the reactor, liquid CO_2 was added at room temperature by using an ISCO syringe pump, the total amount of solvent introduced was measured weighing the vessel with an electronic scale (Mettler PM34 max 30 kg, precision 0.1 g) up to reach the desired value of density of the polymerization mix-

ture. The reactor was then inserted in the control system and heated at the reaction temperature while the acquisition of the temperature T_r and pressure P of the polymerization mixture was started. Also the temperature of the heating water bath T_w was recorded by a Pt 100 sensor. The completion of the polymerization process was determined from the observation of the pressure and temperature profiles recorded by the control system, its end considered corresponding to the stabilization of the pressure P.

At the end of the polymerization the reactor was cooled down to room temperature and depressurized by bubbling the gas in cyclohexane to trap solid polymer entrained by the fluid stream. The reactor was opened and the collected polymer was washed with cyclohexane to remove the unreacted monomer and the solute superficially present, the polymer product was recovered through centrifugation and dried in a vacuum oven at 50 °C for 5 h and stored in a dry atmosphere for further characterization.

2.4. Polymer characterization

Polymer yields were determined gravimetrically.

Particle morphologies were analyzed and imaged with a Philips scanning electron microscope (SEM). Samples were sputter-coated with gold to a thickness of 200 Å. The particle size distributions were evaluated by measuring the diameters (D_i) of at least 100 individual particles through a software for image analysis of micrographs, then the number average particle size (D_n) and particle size distribution (PSD $= D_w/D_n$) were determined according to equations reported elsewhere (Galia et al., 2004).

Raman studies were performed using a Renishaw Labram micro-Raman spectrometer equipped with a 532 nm He/Ne laser source, 1800 L/nm grating, and a Leica microscope system.

Spectra collection was performed at room temperature under the following conditions: 50× microscope objective, 50 μm pinhole size, 300 μm slit width, and 5 s exposure time. Each spectrum represents the average of two measurements. Sample profiling (2D mapping) was performed under the same conditions taken randomly at least 5 points in the x and y plane to verify that collected spectra can be considered representative of the sample as a whole. The samples were spread flat on a glass microscope slide.

X-ray powder diffractograms were obtained by Philips PW 1130 diffractometer ($\theta/2\theta$ geometry) using Cu $K\alpha$ radiation produced by an X-ray sealed tube powered by 40 kV × 30 mA.

Infrared spectra were recorded on a Perkin-Elmer Spectrum 2000 Explorer FTIR with an averaging of 16 scans at a resolution of 1 cm^{-1} using a near-IR fast recovery deuterated tryglicine sulphate detector. Analyses were performed on the polymer powder mixed with anhydrous KBr and then compressed to produce solid pellet.

The Piroxicam release kinetics were studied in vitro at 37 ± 0.2 °C dispersing 50 mg of polymer in 60 mL of an aqueous buffer solution at pH 6.8 prepared mixing suitable amounts of sodium chloride, sodium phosphate bibasic and potassium phosphate monobasic in water. The solution was stirred by a magnetic stir bar and the drug release was monitored using a PC controlled Avantes fiber optic UV–vis spectrophotometer equipped with a DH2000 light source and a reflection dip probe (optical path 1 cm) that was immersed in the aqueous phase. All connections between components and optical fibers were made with SMA 905 connectors. The signal from each spectrometer was recorded as transmitted intensity and converted in absorbance spectra by the spectrometer manufacturer's software (AVA-Soft version 5, Avantes) running on the PC, using a previously recorded blank spectrum of the buffer solution at the typical operating conditions. Piroxicam concentration was estimated, after calibration with solutions of known concentration, by integrating the absorbance in the range of λ from 354 to 359 nm where is located the maximum absorbance of the drug.

Drug loading of polymers was estimated by dissolving about 10 mg of the composite in 40 g of methanol. A sample of the solution was analyzed by UV–vis spectroscopy. Also in this case a calibration with samples of known concentration was performed. Reported values are the average of three determinations with an uncertainty estimated whithin ±7% and are expressed as weight concentration with respect to the amount of synthesized polymer.

3. Results and discussion

3.1. Conceptual analysis of the proposed methodology

The idea of preparing a drug–polymer solid dispersion by polymerization of VP in the presence of the pharmaceutical compound was prompted by some considerations on what it is known about the synthesis of PVP in dense carbon dioxide. The polymerization of VP in $scCO_2$ is an heterogeneous process since the monomer is soluble in the compressible solvent while the polymer is not. Even if in a previous study of this polymerization system (Galia et al., 2004) we have observed some features that could be compatible with a microemulsion process, the most probable technique is the dispersion one. In this case the polymerization starts in a homogeneous mixture and a short time interval is postulated where pure homogeneous polymerization kinetics is operative, leading to the formation of oligomers whose solubility depends on their size. As soon as a critical chain length is reached, oligomeric free radicals undergo homogeneous nucleation to eventually form precursor particles. They grow through homocoagulation and propagation, the former being the main mechanism as they imbibe a relatively low amount of monomer as a consequence of the high curvature of their surface. This coagulation of primary particles continues until the interfacial surface is covered by the minimum amount of steric stabilizer that imparts colloidal stability to the particles. From this point on (critical point) the particle count is fixed and they growth by heterocoagulation and/or propagation. According to such a theory a crucial factor for the successful performance of the polymerization is the availability of a surfactant effective in the stabilization of the growing polymer particles preventing their coalescence and allowing the progression of the process up to high yields. Under these conditions, all the component of the polymerization system are partitioned between the continuous and the dispersed phase. The main locus of polymerization gradually shifts from the continuous medium to the dispersed one since radicals generated in the continuous medium are trapped by the polymer particles before they are terminated owing to their high specific area. If this event occurs, high molecular weight polymer is obtained because macroradicals growth in an environment with high local viscosity where termination is slower.

In this conceptual scenario it seems reasonable to think that, if drug molecules have a good affinity towards the monomer and the polymer matrix, they could accumulate inside the polymer particles with high concentration and they could be found dispersed at the end of the process under nanocrystalline or even molecular form. The latter possibility should be more probable if the drug is soluble in the monomer and the vinyl compound is preferentially partitioned in the polymer particles. In this case the drug molecularly dissolved in the monomer swollen polymer particles could precipitate under non-structured form while the monomer concentration is depleted.

Sekikawa et al. (1979) observed that PVP might impede the crystallization of drug molecules when they are coprecipitated with the polymer from supersaturated solution and this effect was attributed to the presence of specific interactions between the two component that suppress or retard the crystallization of the low molecular weight compound. Solid dispersions of Piroxicam with PVP, prepared by means of solvent method, were studied using FT-

Table 1
Composition of the ternary systems studied in the view cell.

ρ (g/mL)	VP, % (w/w)	Drug, % (w/w)[a]
0.93	20	5
0.93	20	10
0.95	20	15

[a] Based on the monomer.

IR spectroscopy (Tantishaiyakul et al., 1999). It was observed a shift towards lower wavenumber of N–H or O–H stretching vibration that was attributed to a solid-state hydrogen bonding interaction between the polymer and the drug.

When chemical processes are carried out in supercritical fluids, the solubility behaviour of involved species can significantly affect the performances of the process. For the process under consideration, in principle, the success of the methodology does not require a complete miscibility of the drug with the polymerization mixture. To obtain high drug loading in the polymer, it should be in fact enough, a high solubility of the pharmaceutical compound in the dispersed phase, since the good transport properties of the supercritical continuous medium allows a fast transport rate of the drug inside the particles. In this case, if part of the drug is present as a solid dispersion, it would act as a reservoir phase.

3.2. Phase behaviour of the VP/CO_2/Piroxicam system

The phase behaviour of the ternary system constituted by the monomer, the drug and the compressible solvent was studied by visual observation in a fixed volume view cell.

The experiments were performed with a total density ≥0.93 g/mL, using a concentration of VP fixed at 20% (w/w) and changing the concentration of the drug (Table 1).

All systems were initially characterized by the coexistence of two fluid phases: an heavy one richer in VP and yellow coloured, reasonably because the drug was mainly dissolved in it, and a light one transparent and richer in CO_2. While the temperature was increased, the volume of the monomer rich phase gradually decreased and in the temperature interval 45–50 °C we observed the disappearance of the meniscus between the two phases accompanied by the precipitation of the drug under the form of a solid powder.

This behaviour was attributed to the solubilisation of VP in $scCO_2$ accompanied by precipitation of the drug that must have a limited solubility in the polymerization medium also in the presence of the monomer that, increasing the polarity of the fluid phase, should act as a cosolvent. In the case of the lowest investigated concentration of Piroxicam the powder dissolved at about 62 °C when the pressure inside the view cell reached a value of about 26 MPa and the system appeared to be constituted by a single phase to the visual observation. When the concentration of the drug was augmented the system never became homogeneous and was always constituted by a solid dispersion of part of the drug in a fluid phase constituted by CO_2 and VP.

3.3. Preparation of PVP–Piroxicam composite by dispersion polymerization of VP in the presence of the drug in $scCO_2$

To test the validity of the previously discussed one-pot route in the preparation of drug–polymer composites to enhance the rate of dissolution of low solubility drugs, we performed polymerizations of VP in $scCO_2$, at 0.93–0.94 g/mL density values, in the presence of different initial concentrations of Piroxicam. The results are summarized in Table 2 (entries 2–4) together with data obtained in a control test performed in the absence of any drug (entry 1). In all the experiments monomer converted almost quantitatively (yield equal or higher than 90%) in a free flowing powder substantially constituted by sub-micron spherical particles (Fig. 1a–d). The product collected from the drug free run was white while, when the anti-inflammatory was present, the powder was yellow coloured and characterized by particles with broader particle size distribution.

The reaction time was decided according to the evolution of the pressure profile inside the reactor. In all the experiments the P gradually increased during the process of about 3–4 MPa above P^0 up to reach a stable value. The attainment of this value was much faster when no drug was added to the polymerization mixture.

The variation of the pressure during the synthesis of macromolecules in $scCO_2$ was studied by Lepilleur and Beckman (1997) in the case of the dispersion polymerization of methyl methacrylate. These authors have shown that the instantaneous pressure drop can be related to the polymerization rate, the degree of compressibility of the polymerization mixture, the difference between molar volumes of the polymer and the monomer and the variation of the volume changes upon mixing terms for each phase. This means that, provided that temperature, pressure and initial monomer concentration are similar, one can use the change in pressure with time to compare the rate of polymerization at different drug concentrations. According to these considerations one can conclude that the presence of the pharmaceutical compound decreased the rate of the polymerization.

When we estimated drug loadings (Table 2 entries 2–4) we found that, under adopted conditions, the higher the amount of Piroxicam initially loaded in the reactor the higher its concentration entrapped in the polymer matrix. The XRD patterns of pure Piroxicam and PVP, of PVP/Piroxicam composites prepared with 10 and 15% (w/w) initial concentration of the anti-inflammatory agent with respect to the monomer and of selected physical mixtures of the polymer and the drug at different compositions are depicted in Fig. 2. The polymer product is an amorphous powder having no crystalline structure (Fig. 2f). X-ray powder diffraction data for Piroxicam (Fig. 2a) correspond to those published for cubic β form of the drug (Reck et al., 1988; Reck and Laban, 1990; Vrečer et al., 2003).

Table 2
Polymerization of VP in the presence of Piroxicam: effect of the initial drug concentration and of the density of the polymerization medium.

Entry	ρ (g/mL)	Drug, % (w/w)[a]	P^0 (MPa)	Yield (%)	Drug loading, % (w/w)	Product	D_n (μm)	PSD
1	0.94	0	35	90	–	Powder	0.23	1.09
2	0.93	5	34	95	4.5	Powder	0.26	1.33
3	0.93	10	33	98	9.3	Powder	0.21	1.29
4	0.94	15	38	95	12.3	Powder	0.24	1.30
5	0.90	5	24	82	4.6	Powder	0.25	1.16
6	0.88	5	21	84	4.0	Powder	0.31	1.50

VP 20% (w/w); AIBN and Sb1784 concentration respectively 0.33% and 5% both (w/w) based on the monomer; T = 65 °C; CO_2 added in such amount to reach the desired density. Reaction time 320–430 min but in drug free experiment that was stopped after 90 min. P^0: initial pressure. D_n: number average diameter; PSD = D_w/D_n: particle size distribution, D_w: weight average diameter.

[a] Based on the monomer.

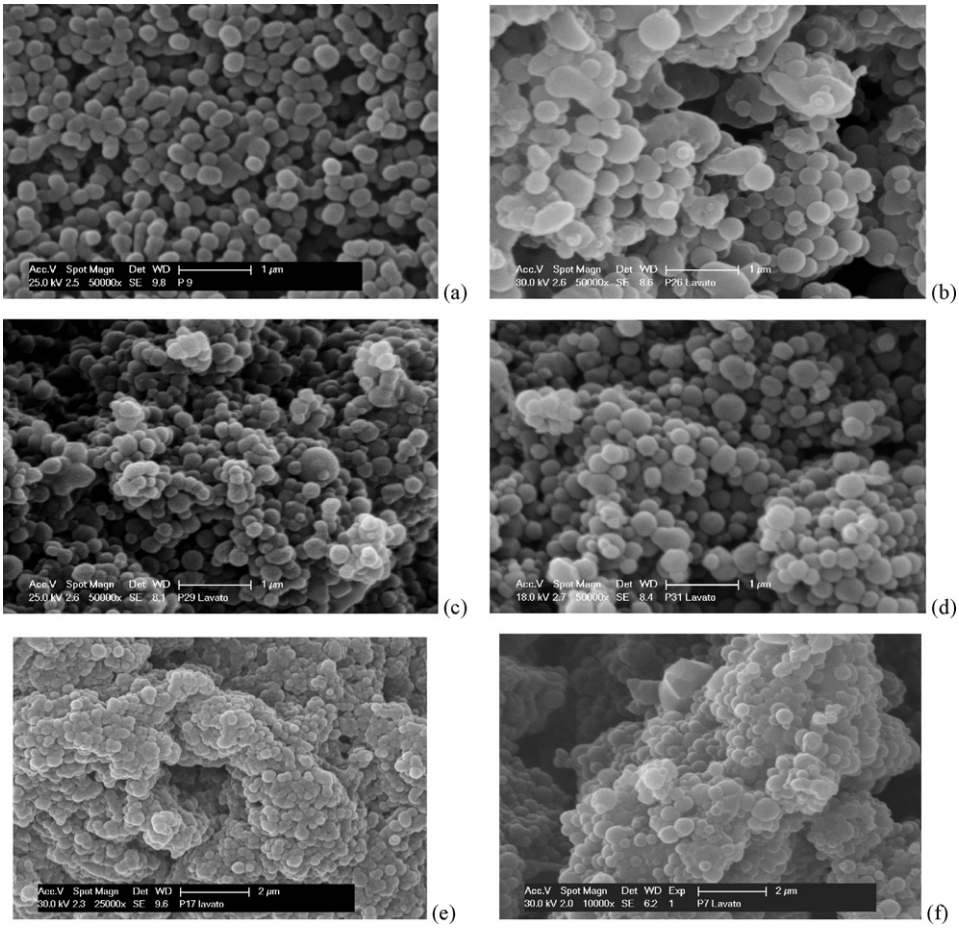

Fig. 1. PVP particles synthesized in $scCO_2$ in the presence of different Piroxicam concentrations and density of the polymerization medium. Initial drug concentration (%, w/w with respect to the monomer) and density (g/mL) respectively are: 0 and 0.94 (a), 5 and 0.93 (b), 10 and 0.93 (c), 15 and 0.94 (d), 5 and 0.90 (e), and 5 and 0.88 (f). All other experimental conditions are reported in Table 2.

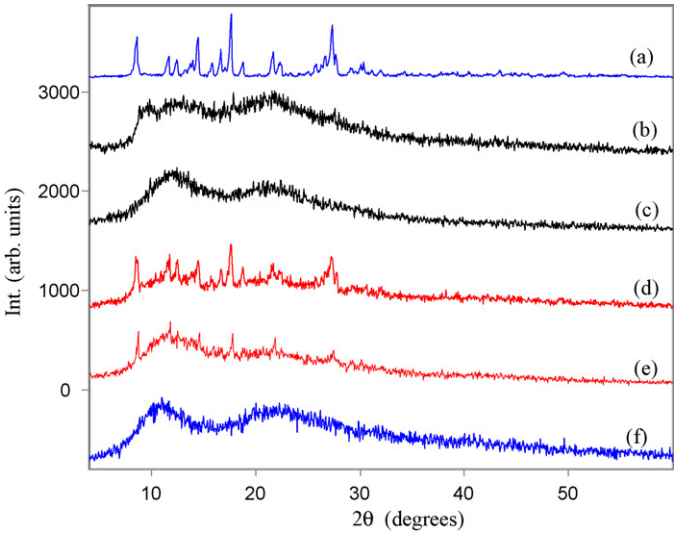

Fig. 2. XRD patterns of pure Piroxicam (a); PVP sample synthesized in $scCO_2$ in the absence of the drug (entry 1 Table 2) (f); physical mixtures prepared mixing PVP and Piroxicam at different drug concentrations: 15% (w/w) (e) and 25% (w/w) (d); drug–PVP composites prepared in $scCO_2$ with different initial drug loadings in the polymerization mixture: 10% (w/w) (entry 3, Table 2) (c); 15% (w/w) (entry 4, Table 2) (b).

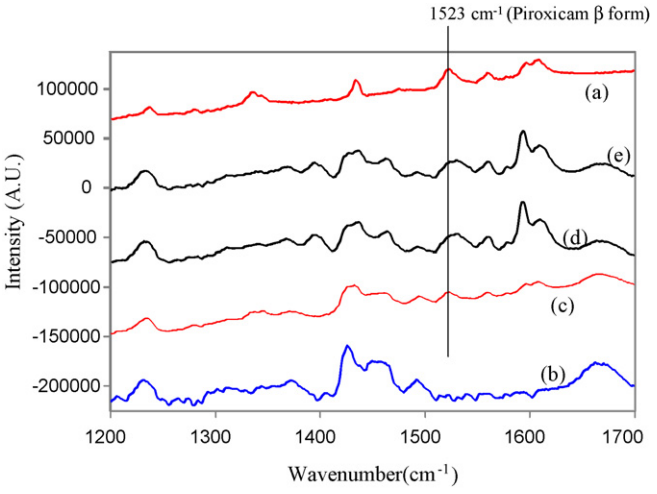

Fig. 3. Raman spectra of pure Piroxicam (a); PVP sample synthesized in $scCO_2$ in the absence of the drug (entry 1, Table 2) (b); physical mixtures prepared mixing PVP and Piroxicam at 5% (w/w) drug concentration (c); drug–PVP composite prepared in $scCO_2$ with different initial drug loadings in the polymerization mixture: 5% (w/w) (entry 2, Table 2) (d); 10% (w/w) (entry 3 Table 2) (e).

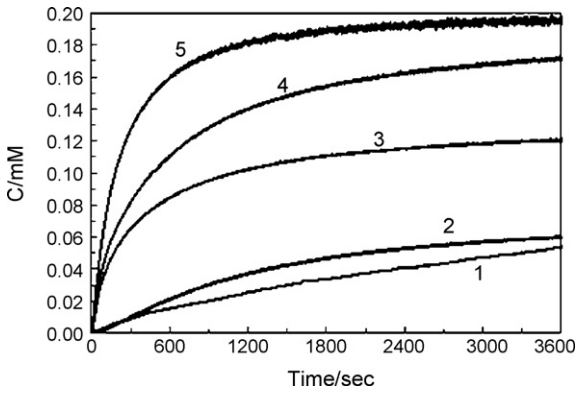

Fig. 4. Release profiles of Piroxicam from composites prepared in experiments of Table 2. Initial drug concentration % (w/w) with respect to the monomer: (curve 3) 5 (curve 4), 10 (curve 5) 15. The dissolution profiles of 2.5 mg of the pure drug (curve 1) and of a physical mixture PVP–Piroxicam (PM 5%) at 5% (w/w) drug concentration (curve 2) are added for comparison.

The XRD peaks of crystalline Piroxicam in all physical mixtures (Fig. 2d and e) were similar to those in the pure drug, indicating no modification in the crystallinity of the pharmaceutical compound. In the case of the diffraction pattern of the composites prepared by polymerization in $scCO_2$ no peak was displayed (Fig. 2b and c) thus suggesting that an amorphous dispersion was obtained.

Drugs in amorphous dispersions may be present in two forms (Kanaze et al., 2006): molecularly dispersed, a condition ensuring the highest dissolution rates, or nanodispersed with particle sizes that in our study must be smaller than the average diameter of the polymer particles (about 250 nm).

To further investigate the state of the drug in the polymer composite we used micro-Raman spectroscopy. When FT-Raman spectra of the pure drug were collected (Fig. 3a) we observed the presence of a band at 1523 cm^{-1} that was reported to be characteristic of the β form (Bertoluzza et al., 1999; Redenti et al., 1999). This result is coherent with that of the XRD spectroscopy (Fig. 2a). No relevant peak was detected in the spectrum of the polymer synthesized in $scCO_2$ in the region 1510–1590 cm^{-1} (Fig. 3b). When physical mixture was analyzed, the peak at 1523 cm^{-1} could be detected with a shape quite similar to that of the pure drug (Fig. 3c).

On the other hand, in the case of the composites the peak shifted to 1529 cm^{-1} and broadened (Fig. 3d and e). This can be considered a further indication that the crystalline structure of the pharmaceutical compound was altered presumably as a consequence of the interactions between the drug molecules and the macromolecular network.

The dissolution profiles of Piroxicam from the composites prepared in $scCO_2$ are reported in Fig. 4 where is also shown the dissolution of 2.5 mg of the pure compound dispersed in the same volume of buffer solution used for the dissolution tests. We can clearly see that the release of the drug from the composites is considerably faster than the dissolution of the pure pharmaceutical compound. Moreover the higher the initial amount of the drug loaded in the reactor the faster its dissolution rate. This effect can be highlighted by comparing the values of time necessary to dissolve 20% of the total amount of drug released (Table 3). We observed a 65% reduction of this parameter when mixing the drug with the polymer. Quite interestingly it was further reduced of almost one order of magnitude when the pharmaceutical compound dissolved from the composites.

In the case of polymeric controlled drug delivery systems it was proposed to classify the release mechanisms of the pharmaceutical compound using three main typologies of system differentiated on the basis of the chemico-physical characteristics of the macromolecular matrix.

According to this classification one can distinguish: (a) drug diffusion from non-degraded polymer (diffusion-controlled system); (b) enhanced drug diffusion due to polymer swelling (swelling-controlled system); (c) drug release due to polymer degradation and erosion (erosion-controlled system). Water is a good solvent of PVP. In spite of this, in a previous investigation we observed that the polymer synthesized in $scCO_2$ with a monofunctional polysiloxane macromonomer surfactant was characterized by a significant gel fraction (Galia et al., 2004, 2008).

This result was attributed to the formation of a polymer with a very high molecular weight and to the presence of an hydrophobic shell constituted by the CO_2-philic tails of the stabilizer that is grafted or even crosslinked (when a bifunctional stabilizer like that adopted in this study is used) with the polymer chains. To support this hyphothesis, when VP was polymerized in $scCO_2$ in the presence of an effective stabilizer, DeSimone and co-workers estimated an $M_w = 3.06 \times 10^6$ g/mol using static light scattering techniques (Carson et al., 2000). During all dissolution tests performed in this study part of the composite added to the buffer solution was collect undissolved at the end of the experiment so that the drug dissolution is only partially accompanied by the dissolution of the polymer matrix. According to aforementioned considerations it seems reasonable that the release of Piroxicam from the composites should be mainly regulated by a mechanism of the type b.

The release kinetics of a drug from a swelling-controlled polymer matrix depends on several factors such as the rate of molecular transport of the drug molecules inside the polymer matrix, the specific surface area of the composite, the concentration and the microstructure of the drug encapsulated in the polymer particles. The matrix is penetrated by water molecules that induce swelling of the material decreasing polymer chain concentration and changing the level of their disentanglement (Lee and Peppas, 1987). This process results in the transformation of part of the polymer from the glassy to the rubbery state with consequent increase of its volume and leads to the generation of a rubbery region (also termed gel layer) in which the drug mobility increases. The polymer will also dissolve at the polymer–solvent interface, that moves owing to the swelling of the matrix, because at this site concentration of chains is very low and their entanglement is weak. In this system a deviation from Fickian model is observed when the drug release is controlled

Table 3
Time necessary to the dissolution of 20% of the drug, values of n exponent and corresponding correlation coefficients R^2 obtained from the fitting of experimental release profiles for systems studied in Fig. 5.

Profile	System	Drug loading, % (w/w)	$t_{20\%}$ (s)	n (t < 45 s) R^2	n (t > 60 s) R^2
1	Piroxicam	100	1190	–	–
2	PM 5%	5	430	–	–
3	Composite 5%	4.8	56	1.40 0.98	0.53 0.99
4	Composite 10%	9.3	65	1.23 0.99	0.52 0.99
5	Composite 15%	12.3	51	1.40 0.99	0.68 0.99

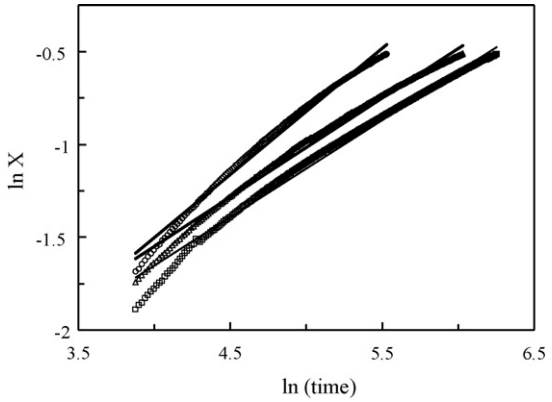

Fig. 5. Logarithmic plot of M_t/M_∞ vs. release time computed at $t > 60$ s for composites prepared in $scCO_2$ with different initial drug concentrations (Table 2): (△) entry 2 (□) entry 3 (○) entry 4.

not only by the diffusion of the drug inside the matrix, but also by the polymer disentanglement and dissolution process. In fact, when the matrix is contacted with water, the drug dissolves owing to a concentration difference at the glassy–rubbery front and diffuses out through the rubbery-solvent front under the driving force of the concentration gradient established between the two interfaces. If water penetration can be neglected no polymer relaxation occurs and the drug dissolution is controlled by Fickian diffusion (Case I) inside the glassy polymer matrix. Differently if the water mobility is relevant, the rate of the solute release is controlled by the kinetics of the structural modifications induced by the solvent uptake and we are in the case of a relaxation controlled release generally identified by the expression "non-Fickian Case II-transport". Between these limiting situations an "anomalous transport" can be operative if both diffusion and relaxation contemporary occurs in a quite undistinguishable manner.

A rigorous mathematical modelling of the release profiles for swellable polymeric systems is rather complex. The problem is a special case of moving-boundary diffusion problems and requires the utilization of highly non-linear constitutive equations that must be solved using numerical methods. Anyway a simple semi-empirical equation based on a power-law expression was proposed by Korsmeyer et al. (1986a,b) to describe the drug release from swelling-controlled systems:

$$\frac{M_t}{M_\infty} = X = kt^n$$

where k is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism and $X = M_t/M_\infty$ is the fractional release of drug. In the case of drug release from monodisperse spheres $n = 0.43$ and $n = 0.83$ for Fickian and Case II-transport respectively while intermediate values are indicative of anomalous transport.

Values of $\ln X = \ln(M_t/M_\infty)$ vs. ln(time) for Piroxicam dissolution were plotted at low release time ($t < 45$ s) and for time higher than 60 s keeping $X \leq 0.60$ (Fig. 5). We observed that both these set of data can be fitted linearly with a good agreement ($R^2 \geq 0.98$) and much higher value of the exponent n were obtained in the initial part of the release process (Table 3). This behaviour was already reported by other researchers and defined as super Case II release kinetics (Brazel and Peppas, 1999). After this initial period n reach values typical of an anomalous transport in which the role of polymer relaxation and drug diffusion cannot be easily decoupled.

Since the preparation of the drug–polymer composites was performed using $scCO_2$ as a dispersing medium an operative parameter that we decided to investigate was the density of the polymerization mixture. To this purpose we performed a set of polymerizations at fixed composition of the reaction system but changing the total amount of components loaded in the reactor. These experiments were performed at 20% (w/w) VP concentration (a value that was kept unaltered for the whole investigation) with 5% (w/w) Piroxicam and 0.33% (w/w) AIBN concentrations with respect to the vinyl monomer (entries 5 and 6, Table 2).

In these experiments the composite was obtained with yields slightly higher than 80% under the form of a powder constituted by substantially spherical particles with D_n in the range 0.25–0.31 μm. PVP particles generated at lower density (Fig. 1e and f) resulted more agglomerated than those obtained at higher density at the same drug concentration (Fig. 1b).

The amount of Piroxicam entrapped inside the matrixes does not seem significantly affected by the medium density, drug loadings ranging in the interval 4.0–4.6% (w/w) for all investigated samples (Table 2, entries 2, 5 and 6). Also the drug dissolution rate, always much faster than that of the pure anti-inflammatory agent, was found substantially not affected by the density of the polymerization medium. When composites were analyzed by Raman spectroscopy we observed the same broadening and shift of the characteristic peak at 1529 cm^{-1} previously commented in the discussion of the effect of the initial drug concentration. This result suggests that, at all investigated densities, the crystalline structure of the drug is altered during the polymerization process. We wish to underline that in these experiments we can be sure that the drug was completely dissolved in the polymerization mixture only when its density was 0.93 g/mL. Anyway, also in lower density systems, the drug was significantly loaded under non-crystalline form inside the polymer thus giving a further element supporting the hypothesis that, owing to a favourable partitioning equilibrium of the drug inside PVP, the undissolved bioactive compound can act as a reservoir phase supplying the drug to the growing polymer particles thanks to the intermediation of the continuous fluid phase. This aspect increases the generality of the method since it is not a priori necessary to start with an homogeneous reaction system that is a condition markedly dependent on the nature of the considered drug.

3.4. Homopolymerization of VP in the presence of Piroxicam: effect of the concentration of the initiator and of the stabilizer

As previously reported, the release kinetics of a swelling-controlled DDS can be markedly affected by the rate of molecular transport of the water molecules inside the polymer matrix, its relaxation kinetics and the osmotic pressure occurring during the swelling process (Brazel and Peppas, 1999). These phenomena should be modified changing the molecular weight distribution of the polymer support and to investigate such possibility we performed the polymerization of VP in the presence of Piroxicam, at two different density levels (0.90–0.92 g/mL and 0.93–0.94 g/mL) modifying the initial concentration of AIBN (Table 4, entries 1–6). Higher values of this parameter accelerate the rate of free radical generation making easier the formation of shorter dead chains. In all experiments the composites were obtained with yields higher than 80% under the form of spherical particles with $D_n = 0.2$–0.3 μm (Fig. 6a–f) and drug loadings between 3.7 and 4.8% (w/w). Also for these materials, Raman spectroscopy indicated that, under adopted conditions, the drug is dispersed in the polymer matrix under non-crystalline form independently on the investigated initial concentration of AIBN.

As previously reported, the density seemed to have no effect on the dissolution kinetics of the drug when its role was studied at the lowest initiator concentration adopted in this study. On the other hand, when we recorded the release profiles from composites obtained at different AIBN loadings, we observed

Table 4
Polymerization of VP in the presence of Piroxicam. Effect of the initial concentration of the initiator and of the stabilizer.

Entry	ρ (g/mL)	P^0 (MPa)	AIBN, % (w/w)[a]	Sb1784, % (w/w)[a]	Yield (%)	Drug loading, % (w/w)	Time (min)	D_n (μm)	PSD
1	0.90	24	0.33	5	82	4.6	430	0.25	1.16
2	0.92	30	1.00	5	88	3.8	290	0.28	1.09
3	0.91	25	2.99	5	98	4.0	150	0.18	1.47
4	0.93	33	0.33	5	95	4.8	350	0.26	1.33
5	0.94	36	1.00	5	97	4.4	260	0.28	1.13
6	0.94	34	2.98	5	93	3.7	180	0.29	1.09
7	0.93	32	0.33	10	96	4.5	310	0.19	1.19
8	0.92	31	2.96	10	99	3.7	150	0.17	1.23

VP 20% (w/w); $T = 65\,^{\circ}C$; CO_2 added in such amount to reach the desired density; Piroxicam 5% (w/w) with respect to the monomer. P^0: initial pressure. D_n: number average diameter; PSD $= D_w/D_n$: particle size distribution, D_w: weight average diameter.
[a] Based on the monomer.

different behaviours at the two different levels of densities adopted.

Composites prepared in reaction media with density equal or lower than 0.92 g/mL gave a dissolution kinetics of the drug that does not significantly change with the initiator concentration used to synthesize the polymer matrix.

When we studied the dissolution rate of Piroxicam from composites prepared in systems with initial density of 0.93–0.94 g/mL,

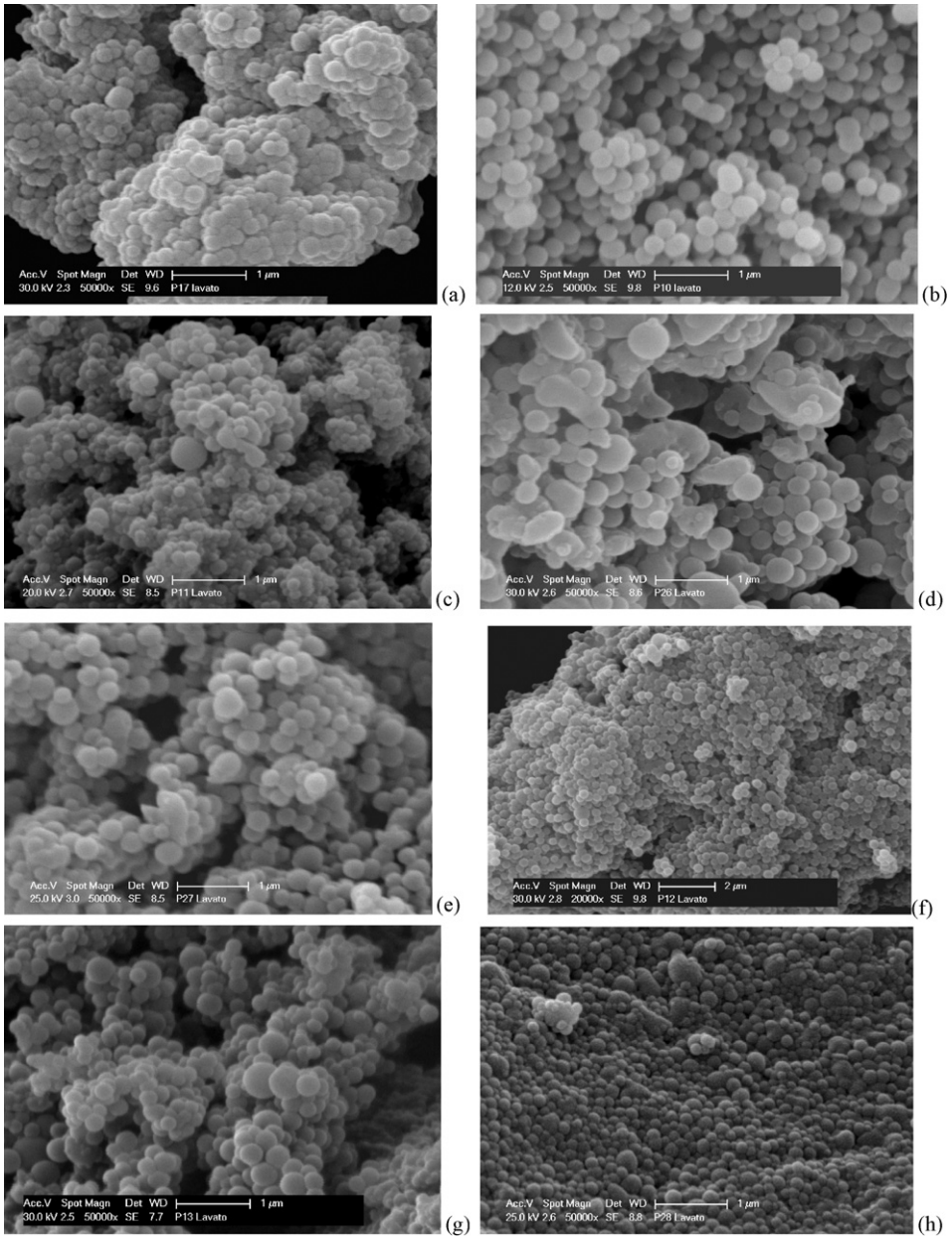

Fig. 6. PVP–Piroxicam composites synthesized in $scCO_2$ at different initial concentrations of initiator and stabilizer (%, w/w with respect to the monomer). Experimental conditions are reported in Table 4. Entries: 1 (a), 2 (b), 3 (c), 4 (d), 5 (e), 6 (f), 7 (g), and 8 (h).

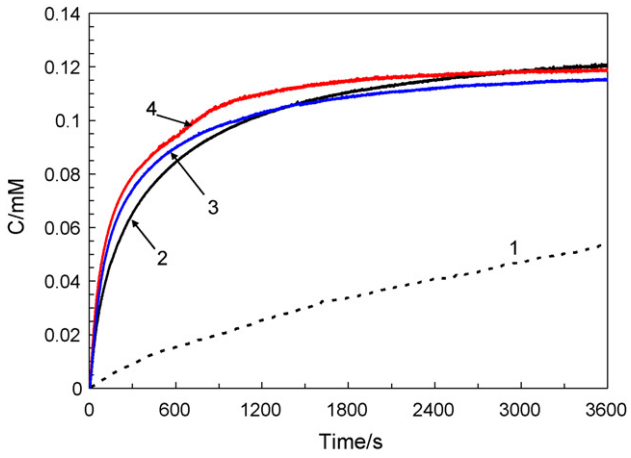

Fig. 7. Release profiles of Piroxicam from composites prepared in experiments of Table 4 (entries 4–6). AIBN 0.33% (w/w) (curve 2) AIBN 1.00% (w/w) (curve 3) AIBN 2.99% (w/w) (curve 4). The dissolution of 2.5 mg of the pure drug (curve 1) is added for comparison.

we observed a slight acceleration of the release rate when the initiator concentration was increased (Fig. 7).

Such different behaviour brought us to reconsider the effect of the density on the solvent power of the continuous medium. In the investigated system, the polymerization occurs heterogeneously and after polymer nucleation two phases are present inside the reactor. Given the presence of the surfactant, that leads to the formation of a dispersed phase with high interfacial area, it seems reasonable to assume that low molecular weight species are equilibrium partitioned between the two phases. The initiator dissolved in the highly local viscous polymer phase should give a limited contribution to the rate of generation of free radicals in the reactor owing to a small efficiency factor in the decomposition step arising from the significant cage effect. Then free radicals should be substantially generated in the supercritical phase whose solvent power increases with the density thus biasing the equilibrium partitioning of the initiator towards the continuous medium. When high concentrations of initiator are used, this solvent effect can increase the rate of generation of the radicals to such a level that the modification of the average molecular weight of the polymer becomes so relevant to affect the dissolution rate of the entrapped Piroxicam. These considerations could explain why the acceleration of the dissolution of the drug with an enhancement of the initiator concentration was observed only at the highest investigated values of density.

Another important parameter that can change the rate of dissolution of a low water solubility compound dispersed in a polymer matrix is the interfacial area of the composite. The higher is its value the faster should be the rate of accumulation of the bioactive molecule in the release medium. On the basis of this consideration we studied the effect of such parameter in the dissolution of Piroxicam from composites prepared in $scCO_2$. In a previous research on the polymerization of VP in $scCO_2$ in the presence of siloxane reactive surfactants we observed that the interfacial area of the polymer matrix can be increased by increasing the concentration of the stabilizer (Galia et al., 2004) [18]. To check if this behaviour can be reproduced also in the presence of the drug we performed additional experiments at high densities of the polymerization mixture (0.92–0.93 g/mL) changing the AIBN loading while the stabilizer concentration was augmented to 10% (w/w) (Table 4, entries 7 and 8).

At both initiator concentrations, when the surfactant concentration was augmented from 5 to 10% (w/w) the average diameter of the polymer particles decreased (Table 4 entries 4–7 and 6–8 and Fig. 6d–g and f–h) thus leading to a polymer dispersion with higher interfacial area as already occurred in the case of drug free polymerization of VP. In all cases we found that more than 70% of the drug initially loaded in the reactor was entrapped inside the polymer particles and spectroscopic analyses confirmed once more a modification of its crystalline structure with respect to that of the pure compound.

In spite of this similarity of behaviours, when we recorded the dissolution profiles, we observed different effects of the stabilizer concentration depending on the AIBN concentration. When its initial concentration was 0.33% (w/w), the higher interfacial area of the macromolecular matrix was coupled with an acceleration of the dissolution rate of the drug (curves 1 and 2 Fig. 8).

Differently when the Sb1784 concentration was augmented at initial AIBN loading of about 3% (w/w) we observed that the reduction of the average diameters of the particles was accompanied by a decrease in the dissolution rate of the drug (curves 3 and 4 Fig. 8) that, in any cases, was significantly higher than that of the pure Piroxicam (curve 5 Fig. 8). The lower dissolution rate from composites prepared at the highest adopted concentrations of initiator and stabilizer was first tentative attributed to differences in the surface concentration of adsorbed silicone surfactant that a previous investigation has shown not eliminable by washing with liquid cyclohexane (Galia et al., 2008). Given its hydrophobic nature, an increase in the surface density of such compound should decrease the wettability of the matrix thus adversely affecting the rate of dissolution of the drug. To verify this hypothesis we estimated the surfactant content of the synthesized polymers by FT-IR spectroscopy. In the spectra it can be detected a band at 1660 cm^{-1} corresponding to the stretching of the carbonyl of the VP repeat union and two absorption bands at about 1000–1100 cm^{-1} (Si–O–Si bonds) and 810 cm^{-1} (Si–CH_3 bonds) related to the PDMS present in the polymer. In this estimation it was neglected any contribution of the amide I resonance band of Piroxicam (located at 1640–1630 cm^{-1} depending on its crystalline form) (Taddei et al., 2001) to the carbonyl peak of PVP given the low drug concentration adopted in this set of experiments and the marked difference in the response factors of the two different functionalities.

When we compared the ratios of the absorbance of the Si bands to that of the band at 1660 cm^{-1} normalized with respect to the average diameter of the particles, we did not find significant differences in the surface concentration of surfactant among the different composites. From a purely speculative point of view, it could be considered that the surfactant adopted in this study is a bifunc-

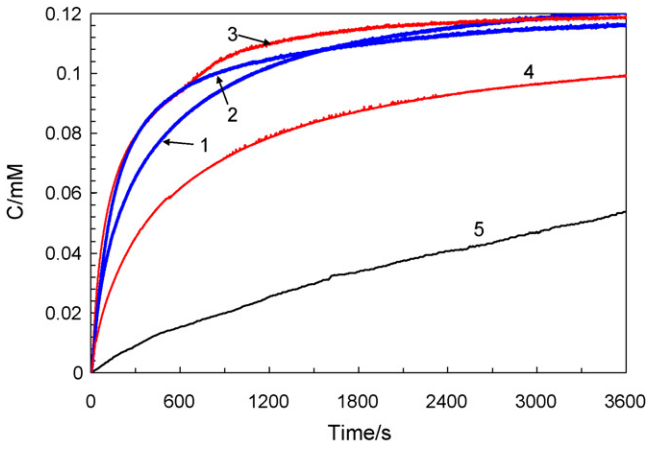

Fig. 8. Release profiles of Piroxicam from composites prepared with different Sb1784 concentrations. Entry 4 Table 4 (curve 1), entry 7 Table 4 (curve 2), entry 6 Table 4 (curve 3), entry 8 Table 4 (curve 4). The dissolution of 2.5 mg of the pure drug (curve 5) is added for comparison.

tional reactive stabilizer, characterized by an high solubility in the polymerization mixture, that must generate in situ the real surface active agent by graft copolymerization with the monomer in the continuous medium. If the rate of generation of the graft copolymers becomes too high in comparison of the rate of growth of the interfacial area, the amount in excess with respect to that necessary to cover particle surfaces can be buried inside them during their growth making possible the generation of crosslinks in the matrix. This event, whose probability should increase with the concentration of initiator and reactive surfactant, should decrease the swelling of the matrix thus limiting the diffusion rate of the drug.

4. Conclusions

Polymeric composites constituted by PVP and Piroxicam, selected as a model of drug with low water solubility, were prepared in a one-pot process performing the dispersion polymerization of 1-vinyl-2-pyrrolidone in supercritical carbon dioxide in the presence of the bioactive compound. The composite was obtained with monomer yields higher than 80% under the form of spherical submicron particles characterized by high interfacial area. More than 70% of the pharmaceutical compound was charged inside the particles also when its initial concentration in the polymerization medium was significantly higher than its solubility. XRD and Raman spectroscopy suggest that Piroxicam is dispersed in the polymer matrix under non-crystalline morphology at all investigated operative conditions. Dissolution rates of the anti-inflammatory agent from composites prepared in $scCO_2$ were significantly faster than those obtained both with the pure drug and from its physical mixtures with the polymer. The release kinetics were observed to increase with the drug loading of the polymer particles and with the initial concentration of the initiator provided that high enough density of the polymerization mixture is adopted. More controversial was the effect of an increase of the surfactant concentration. Even if an increase of this parameter was always accompanied by an enhancement of the interfacial area of the composite, only with the lowest investigated AIBN concentration (0.33%, w/w) this effect was associated to an acceleration of the dissolution rate. The opposite happened when the same experiments were repeated at about 3% (w/w) initiator concentration. These results were tentatively attributed to the reactive nature of the adopted stabilizer.

Acknowledgements

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