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: we have tested the possibility of preparing a drug-polymer composite by a single pot process performing the surfactant assisted polymerization of 1-vinyl-2-pyrrolidone in supercritical carbon dioxide in the presence of a drug in order to synthesize and impregnate the polymer in a single step. Under adopted conditions we have obtained the composite under the form of spherical particles with sub-micron diameter and narrow particle size distribution. Piroxicam was selected as a model for a low water solubility drug and its dissolution profiles from the impregnated matrixes were characterized by a significant enhancement of the dissolution rate in comparison with that of the pure drug.

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 in turn dependent on its water solubility. 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 [1]. This drawback risks to prevent their practical utilization [2] and the development of new formulations of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenge to formulation scientists in the pharmaceutical industry.
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 dispersions, 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 prevent recrystallization of the drug molecules.
There are mainly two methods to prepare solid dispersions, i.e. the melting 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 [3, 4]. In the case of high-melting-point carriers like polyvinylpyrrolidones (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 [5, 6].
Both these approaches are characterized by manufacturing difficulties and stability problems that make difficult their applicative utilization such as the possibility of thermal degradation of the bioactive compound, lack of miscibility at the melt state or the difficulty of reaching in the formulations, low residual amount of solvents, that are often toxic.

Supercritical carbon dioxide ($scCO_2$) is a not-conventional compressible solvent whose chemico-physical properties can be changed by adjusting the density. This property, that is typical of all supercritical 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 [7-9].
In all aforementioned strategies the preparation of the controlled release dosage form must be implicitly 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 [10-12] and it has been successfully used as dispersing medium in the synthesis of poly(vinylpyrrolidone) [13-15] that is a polymer already described in a series of pharmacopoeias (e.g., in the U.S.) and then accepted for several pharmaceutical applications [16]. 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 [17] where we obtained high PVP yields under the form of spherical particles with sub-micron diameters and narrow particle size distribution. Drug dissolution from such composites resulted decreased with respect to the pure compound.
In this study we want to investigate the possibility of using the same approach to enhance the rate of dissolution of low solubility drugs to increase their bioavalaibility.

MATERIALS AND METHODS

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–[$Si(CH_3)_2$O]n–$Si(CH_3)_2$–R–O(CO)–CH=CH_2
where R is an alkyl group, n = 260 and Mn = 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.
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 [18]. The proper amounts of each condensed component of the polymerization mixture (monomer, initiator, surfactant, 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 mixture. 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 hours and stored in a dry atmosphere for further 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 [15].
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 40kV x 30 mA.
The Piroxicam release kinetics was 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. 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.

RESULTS

To test the possibility of using a one-pot route in the preparation of drug-polymer composites to accelerate the 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 concentration of Piroxicam. The results are summarized in Table 1 (entry 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 in a free flowing powder substantially constituted by submicron spherical particles (Fig. 1a).

Table 1. Polymerization of VP in the presence of different concentrations of Piroxicam.

Entry	Drug, % w/w[a]	P^0, MPa	Yield, %	Drug Loading, % w/w	Product	D_n, μm	PSD
1	0	35	90	---	powder	0.23	1.09
2	5	33	95	4.8	powder	0.26	1.33
3	10	33	98	9.3	powder	0.21	1.29
4	15	38	95	12.3	powder	0.24	1.30

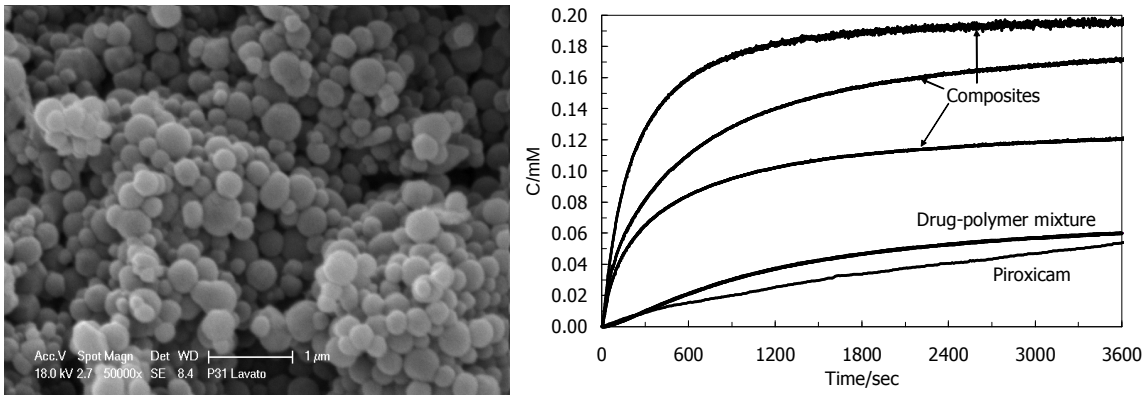
[a] based on the monomer.

VP 20 % w/w; AIBN concentration 0.33% w/w based on the monomer; T=65°C; CO_2 added in such amount to reach the density of 0.93-0.94 g/mL; Sb1784 5 % w/w with respect to the monomer. Reaction time 350-410 min but in drug free experiments 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.

When we estimated drug loadings (Tab. 1 entry 2-4) we found that 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 a PVP/Piroxicam composite prepared with 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 have been compared. The polymer product is an amorphous powder having no crystalline structure while diffraction data for piroxicam correspond to those published for cubic β form of the drug [19].

The XRD peaks of crystalline Piroxicam in all physical mixtures were similar to those in the pure drug, indicating no modification in the crystallinity of the pharmaceutically compound. In the case of the diffraction pattern of the composite prepared by polymerization in $scCO_2$ no peak was displayed thus suggesting that an amorphous dispersion was obtained.



(a) (b)

Figure 1. (a) PVP particles synthesized in $scCO_2$ in the presence of 15% w/w Piroxicam concentration. (b) Release profiles of Piroxicam in buffer solution (pH 6.8) at 37°C from PVP-Piroxicam composites prepared in experiments of Table 1. The dissolution profiles of 2.5 mg of the pure drug (Piroxicam) and of a physical mixture PVP-Piroxicam at 5% w/w drug concentration are added for comparison.

The dissolution profiles of Piroxicam from the composites prepared in $scCO_2$ are reported in Fig. 1(b) where it 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.

CONCLUSION

Polymeric composites constituted by PVP and Piroxicam were prepared performing the dispersion polymerization of 1-vinyl-2-pyrrolidone in supercritical carbon dioxide in the presence of the drug. The composites were obtained with monomer yields higher than 90% under the form of spherical sub-micron particles characterized by high interfacial area. More than 70% of the pharmaceutical compound was entrapped inside the particles.
XRD analyses suggest that Piroxicam is dispersed in the polymer matrix under non-crystalline morphology.
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.

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