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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-