IMPREGNATION OF PVP MICROPARTICLES WITH PIROXICAM THROUGH A SUPERCRITICAL SOLVENT

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The aim of the work is to enhance the oral bioavailability of piroxicam, a non-steroidal anti-inflammatory drug, by inserting it into a poly(vynilpyrrolidone) (PVP) biocompatible matrix using supercritical CO_2 as an impregnating solvent. Supercritical CO_2 is a valid alternative to conventional methods since it is a clean non-toxic solvent able to plasticize amorphous polymers.
The impregnated powders have been analysed via X-ray diffraction and FTIR spectroscopy to determine the physical state of the drug in the polymer and their molecular interactions. In vitro release tests were also performed and compared with those of the physical mixtures with the same drug content. The experimental results demonstrated that supercritical CO_2 can be used to obtain the impregnation of PVP with piroxicam. When the impregnation was performed at 300 bar and 100°C, no drug crystals were detected in the impregnated samples with a piroxicam content below 13%. The in vitro release tests showed a huge increase in the kinetics of release due to the absence of drug crystals.

INTRODUCTION

According to the Biopharmaceutical Classification System, “class II” crystalline drugs have very high permeability in the gastrointestinal tract but very low solubility and dissolution rate in aqueous solutions, which results in a low oral bioavailability [1]. The dissolution rate of a “class II” drug can be enhanced by dispersing it in a water-soluble biocompatible polymer, such as poly(vinylpyrrolidone) (PVP), polyethylene glycol, hydroxy propyl methylcellulose, etc., which inhibit the crystallization of the drug [2]. This can be obtained with many conventional techniques [2, 3], such as melt extrusion, under-vacuum solvent evaporation or spray-drying. Unfortunately, all these techniques have some drawbacks: for example, melt extrusion cannot be carried out for thermo-sensible drugs, while traces of a potentially toxic organic solvent are trapped into the polymer matrix when a solvent evaporation or spray-drying technique is used. For these reasons, supercritical processes have been considered for the preparation of drug dispersions [4]. Supercritical CO_2 ($scCO_2$) can be employed thanks to its good solvent properties and its ability to plasticize and swell many polymers. Its use is advantageous since it is non-toxic and easy to remove from the final product at the end of the process.
Among the different approaches, polymer powder impregnation techniques with $scCO_2$ have been recently used in literature to achieve the impregnation of PVP with some crystalline drugs (i.e. carbamazepine, ibuprofen, ketoprofen) [5-7]. In these processes, the crystalline drug is dissolved by $scCO_2$ and thus conveyed through the swollen polymeric matrix until the partition equilibrium takes place between the phases. PVP is often used in pharmaceutical formulations due to its ability to interact with weak carboxylic acids via hydrogen bonding. When the interaction occurs, amorphous solid dispersions of the drug in the polymer can be obtained, which exhibit higher release rates with respect to the simple physical mixtures of the components. The investigation of the physical state of the components in the pharmaceutical formulations is, then, important in order to correlate the nature of the solid dispersion with the release kinetics. A number of techniques have been used in literature [2] for this purpose such as thermoanalytical methods, calorimetric analysis, X-ray diffraction, spectroscopic and microscopic methods.

Experiments have been performed in this study to enhance the oral bioavailability of piroxicam, a typical “class II” drug, by inserting it into a PVP-K15 matrix using $scCO_2$ as the impregnating solvent. The impregnated powders were analysed via X-ray diffraction and FTIR spectroscopy to investigate the physical state of the drug in the polymer. The samples were, then, compressed into tablets and the in vitro release profiles were determined in an aqueous solution simulating the gastric liquid. The release curves of the impregnated polymer tablets were compared with those of the physical mixtures with the same drug content.

I - MATERIALS AND METHODS

Pure CO_2 (99.998%) was purchased from SIAD S.p.A. while piroxicam (>98%) and poly(vinylpyrrolidone)-K15 (MW~10000) were supplied by Sigma-Aldrich. The chemical structures of piroxicam and PVP are shown in Fig.1.

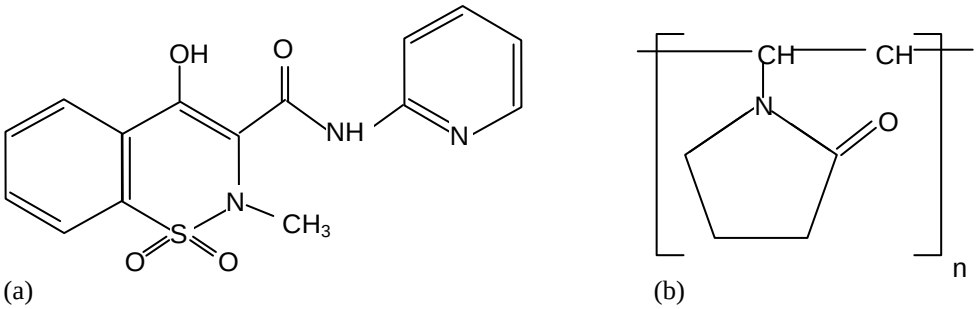

Fig. 1. (a) Piroxicam chemical structure. (b) Poly-vinyl-pyrrolidone repeating unit.

The supercritical impregnation process was carried out in the apparatus shown in Fig. 2. Physical mixtures of the drug and the polymer, with different drug contents, were prepared by manually mixing the proper components in a mortar; the mixture was, then, introduced in cylinders of filter paper, which were set inside an impregnation vessel. The vessel was positioned inside an oven that maintained all the system at constant temperature. At the beginning of the test, the vessel was by-passed, the on-off valve was opened and the apparatus was run in a continuous mode until the selected working conditions were reached. The vessel was then filled in with the supercritical solvent and the on-off valve was closed. The physical mixtures were contacted with the supercritical medium at constant temperature and pressure for a period of time sufficient to reach the thermodynamic equilibrium of the system. At the end of the test the apparatus was discharged through the heated restrictor valve equipped with a solvent trap.

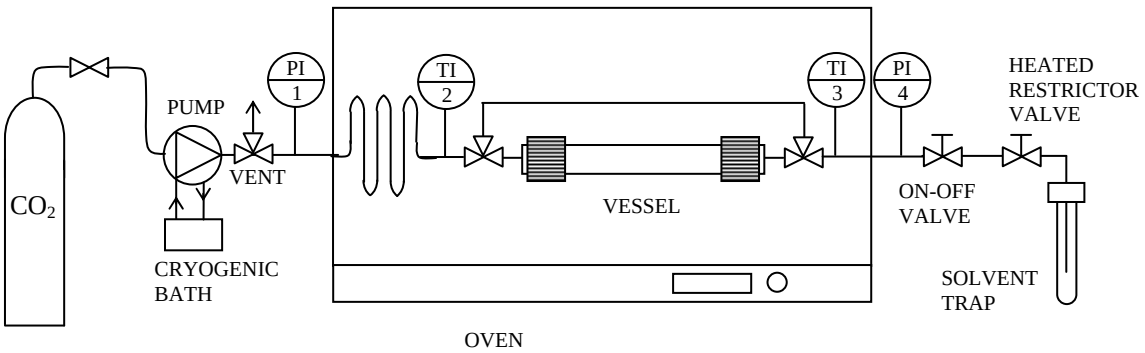

Fig. 2. Experimental apparatus.

At the end of the impregnation run, the impregnated polymer was extracted from the vessel and subjected to different tests and analyses.

The first series of tests was conducted to determine the exact piroxicam amount after the impregnation run. A 2-3% decrease in the piroxicam percentage always occurred with respect to the initial amount in the physical mixture before the supercritical treatment. That was a consequence of the drug dissolution in the $scCO_2$ atmosphere surrounding the physical mixture during the impregnation process and the final discharge step. A weighted sample (about 100 mg) was dissolved in a known methanol volume and then diluted (1:10) in a 0.01 M HCl aqueous solution. The use of methanol was necessary to guarantee a fast and complete dissolution of the piroxicam, while the subsequent dilution in the HCl solution was able to fix the drug absorbance peak at 343 nm. The piroxicam concentration in the polymer was obtained from the spectroscopic analysis of the solution in the UV range (UNICAM UV2-300 spectrophotometer).

X-ray diffraction and FTIR spectroscopic analyses were then carried out to determine the physical state of the drug in the impregnated polymer and their molecular interactions. X-ray analyses were performed in a Philips X'Pert-MPD diffractometer (Cu Kα radiation; 2θ range 4÷50°; Δ2θ step: 0.02°; step time 1 s). A Thermo-Nicolet 5700 spectrophotometer was used for the FTIR analyses (potassium bromide glass pellet method with 256 scans and a 1 cm^{-1} resolution step).

In vitro release tests were finally performed and compared with those of the physical mixtures with the same drug content. All samples were compressed into 10-mm wide cylindrical tablets using a manual press. The compression pressure was set at 1 tonne and the amount of each sample was 100 mg. Release tests were carried out in a USPII apparatus provided with a paddle stirrer rotating at 50 rpm and an on-line UV spectrophotometer. The vessel contained a 750-ml solution (HCl in distilled water, pH 2) at 37 °C, simulating the gastric liquid. The drug release profiles were measured detecting the absorbance at 343 nm.

II – RESULTS AND DISCUSSION

Impregnation results

Preliminary impregnation experiments conducted at low temperature (40-50 °C) revealed that the crystalline drug in the physical mixture poorly interacted with the polymer to produce an amorphous solid dispersion. This confirmed some literature impregnation experiments, which were performed with a continuous mode technique and resulted in a low piroxicam uptake in the PVP (<4%) at 40°C and 160 bar [8].

Further tests demonstrated that a temperature higher than 80°C was necessary to achieve a significant impregnation. Successful results were, then, obtained fixing the working conditions at 100 °C and 300 bar. Different impregnated samples were produced with a piroxicam amount included in the 5-30% range: the X-ray and FTIR analyses pointed out that no drug crystals were present in the samples with a piroxicam content below 13%.

In Fig. 3 the X-ray spectrum of pure piroxicam is compared with those of some impregnated polymers at different drug percentage. The figure shows that a completely amorphous material is obtained when the piroxicam amount in the polymer is equal to 12.8%; some crystals are, instead, detected at the higher drug percentages.

The same results were confirmed by FTIR analyses. Fig. 4 reports the FTIR spectra of the pure components as well as those of some physical mixtures and impregnated samples. According to Tantishaiyakul et al. [9], who produced solid dispersions of piroxicam in PVP with the conventional solvent method, the most interesting region of the spectra is that from 4000 to 3000 cm^{-1}. In that region, PVP K15 displays a large peak while an absorption band at 3338 cm^{-1} can be observed for piroxicam (Fig.4.a), representing the stretching vibration of the NH group of the drug in its crystalline cubic form [10]. According to Fig. 4.b the FTIR spectra of the physical mixtures (PM) seem to be only the sum of the piroxicam and PVP spectra; the same can be observed for the impregnated sample (IP 18.2%) where drug crystals were detected by the X-ray analyses. The NH stretching vibration band was not detected in the amorphous impregnated sample (IP 12.8%): this was explained by the hydrogen bonds occurring in the

solid dispersions between the NH group of the drug and the >N or C=O functions of the PVP. Such hydrogen bonds might be strong enough to weaken the NH stretching resulting in a weak and broad peak that is completely covered by the bond stretches of the PVP. Therefore, the amorphousness might be predicted by the disappearance of this NH peak [9].

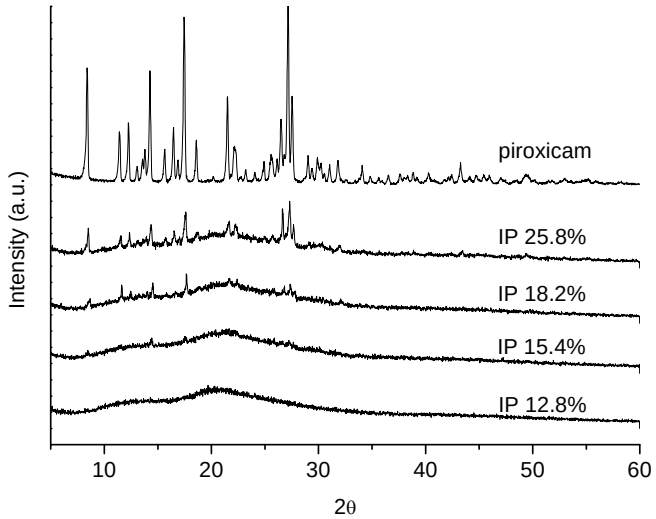

Fig. 3. X-ray patterns of piroxicam and the impregnated polymers (IP) at different drug content.

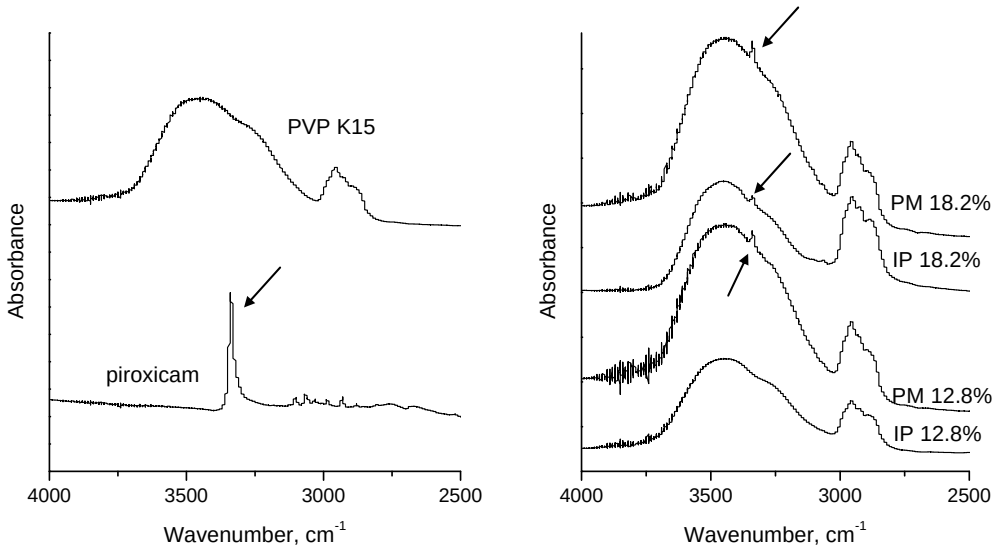

Fig. 4. FTIR spectra of: (a) piroxicam and PVP;
(b) impregnated polymers (IP) and physical mixtures (PM) at different drug content.

Other experiments were, then, performed to investigate the role of the operating conditions of the impregnating solvents on the physical state of the drug in the final product. No significant changes in the results occurred when pressure was varied between 200 and 300 bar. The role of temperature was, on the other hand, much more important. Below 80°C the amount of non-crystalline drug was lower than 13% while at 120 °C a degradation of piroxicam occurred.

Drug release tests

The drug release tests were conducted on the samples obtained at 300 bar and 100 °C. The experiments were performed both on the impregnated polymers (IP) and the corresponding physical mixtures (PM) at the same drug content.

Fig.5 shows some release profiles of the impregnated polymers at different drug contents (11.3-12.8-18.2-25%). The figure also reports the release curve for pure piroxicam tablets (dotted line) and those for two physical mixtures (dashed lines) respectively at the minimum (11.3%) and maximum (25%) piroxicam content. Unevenness in some parts of the curves corresponds to a rupture or a position change of the tablet in the aqueous solution during the dissolution tests.

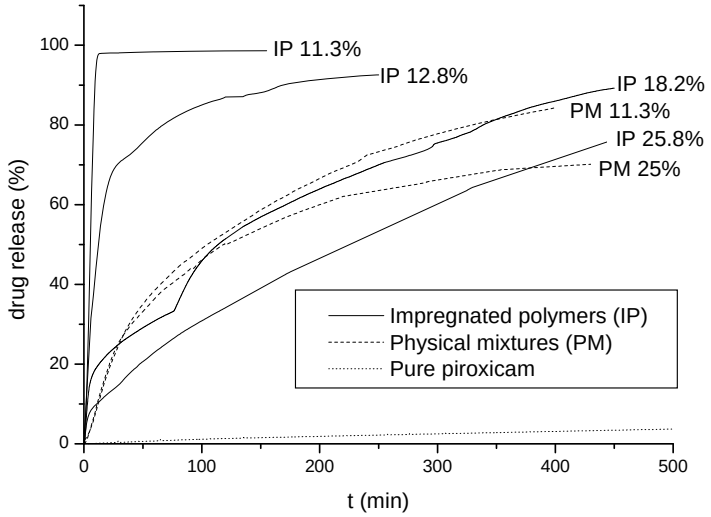

Fig. 5. Percent drug release profiles of pure piroxicam, impregnated polymers and physical mixtures at different piroxicam content. Impregnation performed at 300 bar and 100°C.

The impregnated samples with piroxicam content below 13% showed a huge increase in the kinetics of release with respect to the physical mixtures due to the total absence of drug crystals. On the other hand, the impregnated samples where drug crystals were still present exhibited only an initial drug dissolution rate as fast as the completely amorphous tablets while, afterwards, the slope of the curves slowed down. The final percentage of drug release for all the impregnated samples was higher than that of the corresponding physical mixtures. The higher presence of the crystalline phase in the physical mixture tablets explains, in fact, the lower dissolution of the piroxicam at the end of an experiment due to the higher amount of poorly soluble residue.

Table 1. Indices to compare the release of physical mixtures (PM) and impregnated polymers (IP). Impregnation performed at 300 bar and 100°C.

Piroxicam content (%)		$\%_{10}$	t_{50} (min)	t_{75} (min)
7.51%	IP	87.8%	6	9
	PM	9.3%	108	228
11.3%	IP	94.7%	6	8
	PM	7.8%	105	267
12.8%	IP	48.6%	11	48
	PM	5.5%	139	335
18.2%	IP	18.9%	114	297
	PM	5.0%	171	405
25.8%	IP	9.9%	215	447
	PM	6.3%	190	475

The above considerations are summarized in Table 1 where the indices $\%_{10}$, t_{50} and t_{75} are reported. $\%_{10}$ is the percentage of piroxicam released from the tablet after 10 min, while t_{50} and

t_{75} are the times corresponding, respectively, to 50% and 75% of the release. The table points out the huge increase in the dissolution rate for the impregnated samples with a piroxicam content below 13%, which is maintained during all the release process. The impregnated samples with higher drug content show a slightly faster rate only in the first 10 min of the release while the values of t_{50} and t_{75} have the same order of magnitude as those of the physical mixtures.

CONCLUSION

Experiments have been successfully performed to achieve the impregnation of PVP-K15 with piroxicam through a supercritical solvent. The research was mainly focused on the results obtained at 100°C and 300 bar. The X-ray and FTIR analyses pointed out that no drug crystals were present in the impregnated samples with a piroxicam content below 13%, which also exhibited a huge increase in the kinetics of release with respect to the corresponding physical mixtures at the same drug content. The best result was obtained for the impregnated sample containing a piroxicam amount equal to 11.3%, which released the 94.7% of the drug after 10 min, with respect to the 7.8% released by the corresponding physical mixture after the same period of time.
An investigation of the role of the working conditions of the supercritical solvent showed a scarce influence of pressure on the results while temperature had to be higher than 80 °C and lower than 120°C to guarantee the same quality of the impregnated products.

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