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ORIGINAL ARTICLE

Role of hydroxypropylmethylcellulose (HPMC 4000) in the protection of the polymorphs of Piroxicam extended release tablets

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Piroxicam;
Polymorphism;
Hydroxypropylmethylcellulose 4000;
Crystallization;
Extended release

Abstract The present study deals with the influence of hydroxypropylmethylcellulose 4000 in the protection of Piroxicam polymorphs which could appear during the processes of formulation of extended release tablets.

The physico-chemical tests and the dissolution profiles of polymorphs and tablets showed that the metolose incorporated in the tablets at a rate equivalent to 5% could possibly act doubly; initially by protecting the piroxicam polymorphism transition (form II) during compression, then modulating its in vitro release (extended release).

1. Introduction

The polymorphism of the Piroxicam was largely studied in the 30 last years. Indeed, the first report on the polymorphism of the Piroxicam was published in 1982 (Mihalic et al., 1982). It proves that two polymorphic modifications assigned as cubic and needle and a monohydrate form, obtained by crystallization in various solvents, were known at that time.

In fact, former researches showed that the crystallization of the Piroxicam melted in a thermal cell of analysis DTA led to three modifications indicated by I, II and III (Kuhnert-Brandstätter and Völlenklee, 1985). Some studies showed that only modification I (cubic) is physically stable in a solid state to the thermal and mechanical stress (Vrêcer et al., 1991; Ghan and Lalla, 1992). Moreover, a study carried out in 1997 (Shakhtshneider, 1997) showed that the influence of a mechanical stress can generate the amorphization of the Piroxicam.

Many other studies have been reported dealing with the characterization of physicochemical properties of Piroxicam (Ivashchenko et al., 2003; Sheth et al., 2004; Suarez-Kurtz,

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Table 1 Polymorphic forms of the Piroxicam.

Form	Solvent	Crystallization kinetics
I	Benzylic alcohol	Slow
II	Ethanol	Slow
III	Ethanol	Rapid
IV	Ethanol	Slow (release)

Table 2 Tablet formula.

Raw materials	Conventional tablet (%)	Extended tablet (%)
Piroxicam	04	04
CMC viva pure 101	13	13
HPC	06	–
HPMC 4000	–	**05**
Monohydrate lactose	77	78

2005; Tantishaiyakul et al., 2008, 2009; Pieszczek and Jachowicz, 2010).

Aiming to study the role of the hydroxypropylmethylcellulose 4000 in the protection of polymorphs of the Piroxicam extended release tablets, we proceeded as follows:

1. Initially, we prepared different Piroxicam polymorphs by varying the nature of solvent and the kinetics of crystallization, then we characterized the polymorphs obtained by various analysis techniques namely: differential calorimetric analysis (ACD), diffraction of X-rays (DRX), infrared spectroscopy (IR), and the solubility test and finally we studied the profile of dissolution of Piroxicam polymorphs
2. Secondly and in order to test the effect of compression on Piroxicam polymorphism, we formulated, with different polymorphs of the selected active principle, the conventional tablets which were characterized by the DRX and studied considering the dissolution kinetics.
3. Finally, we formulated, with different Piroxicam polymorphs, tablets with extended release using the hydroxypropylmethylcellulose 4000, and then we followed the dissolution kinetics of the Piroxicam based on these forms after characterization with the DRX. The hydroxypropylmethylcellulose can act doubly: initially by protecting the transition of Piroxicam polymorphism when it undergoes the compression stress, then by modulating the in vitro release of the active principle.

2. Materials and methods

2.1. Materials

- Piroxicam: active principle; raw material Pfizer, (batch 0414890001).
- Pure microcrystalline cellulose viva: type 101, hydroxypropylcellulose FG-CAS Aldrich.
- Lactose monohydrate Merck and Magnesium Stearate: compression additives.

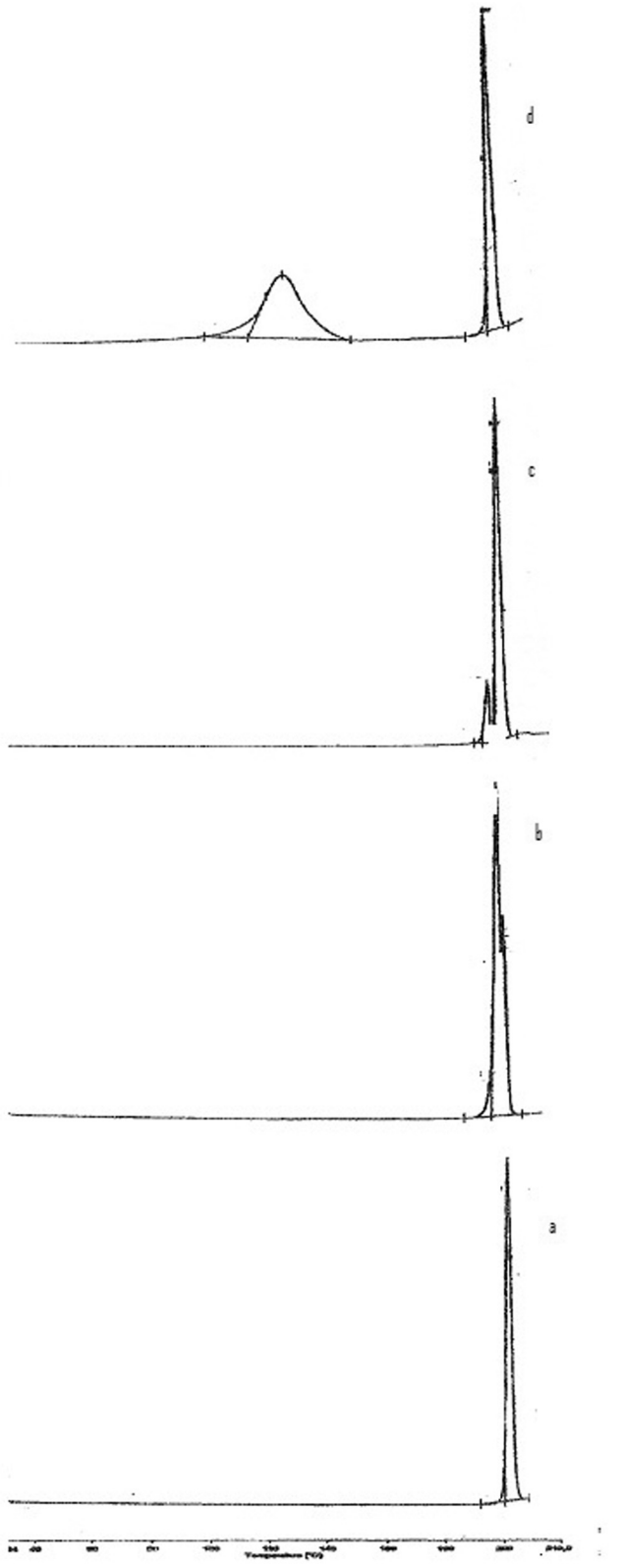

Figure 1 DSC curves representing the four Piroxicam polymorphic forms. (a: form 1, b: form 2, c: form 3, d: monohydrate form.)

- Hydroxypropylmethylcellulose HPMC 4000; Metolose 90 HS 4000 SR: Additive of the extended forms.

2.2. Preparation of polymorphs

It should be remembered that Piroxicam exists in several polymorphic forms:

- Form I, most stable
- Forms II and III, unstable
- Finally in the monohydrate form of yellow color.

For the realization of this work we carried out our tests using a sample of active principle equivalent to 500 mg and we prepared different polymorphs by varying the nature of employed solvent and the kinetics of crystallization as illustrated in Table 1.

In fact, the polymorphic forms are obtained according to the following method:

- Form I (cubic) by crystallization at ambient temperature of a saturated solution in benzylic alcohol,
- Form II (needle) by crystallization at ambient temperature of a saturated solution in ethanol,
- Form III by cooling with dry ice a saturated solution in ethanol,
- Hydrate form by release of a saturated solution in ethanol.

2.3. Preparation of the tablets

In the present study, we prepared tablets with conventional release and tablets with extended release containing Piroxicam (weight of the tablet: 400 mg). The Piroxicam is incorporated at a rate of 4% (16 mg). This amount was selected for solubility and linearity reasons of the calibration curve (16 mg/l). The selected formulas are mentioned in Table 2.

We prepared, for each polymorph, three compressed conventional tablets and three with extended release by means of a manual hydraulic press (press of standard workshop PRMB, power 8 tons) with a compressive force of 20 kN, then we studied the dissolution profile of the Piroxicam from the prepared tablets.

2.4. Characterization of the polymorphs

2.4.1. Differential calorimetric analysis

The differential calorimetric analysis (DSC) is carried out by means of an apparatus of differential thermal analysis DSC6 Perkin Elmer calibrated with an indium/zinc standard and controlled by the Pyris software.

For each polymorph, the test sample was approximately 3 mg. The sample is placed in an aluminum capsule then exposed to a heating kinetics of 30–250 °C, at a speed of 10 °C/min.

2.4.2. X-ray diffraction

For the analysis of the crystalline structure of different Piroxicam polymorphs, we operated as follows: The sample to be analyzed is crushed delicately in a mortar, then spread out over a sample holder blade of glass then placed in the diffractometer and exposed to X-rays.

The diffractometer used for the analysis is Philips type [monochromatic irradiation Cuα (0.15405 nm), the diffraction angle 2θ = (4–36°), the voltage is 20 kV and the current intensity is 40 mA].

The recording was carried out on 20 acquisitions and the results were treated using the software of processing data GONIO.

2.4.3. Infra-red spectroscopy

The analysis of the powders of different polymorphs by infrared spectroscopy is carried out according to the following protocol:

First the pellets are prepared by mixing approximately 3 mg of polymorph to be analyzed with potassium bromide, and then they are compressed under vacuum using a pellet press

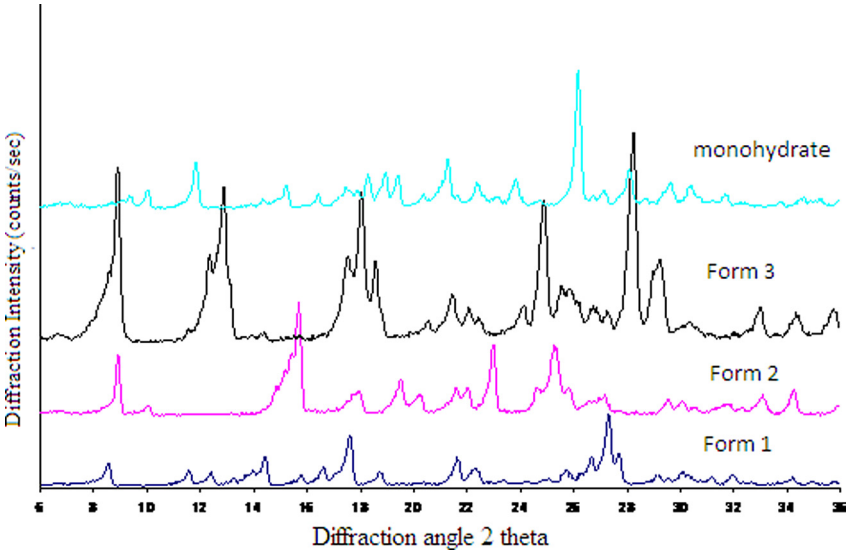

Figure 2 X-ray diffractogram of Piroxicam polymorphs.

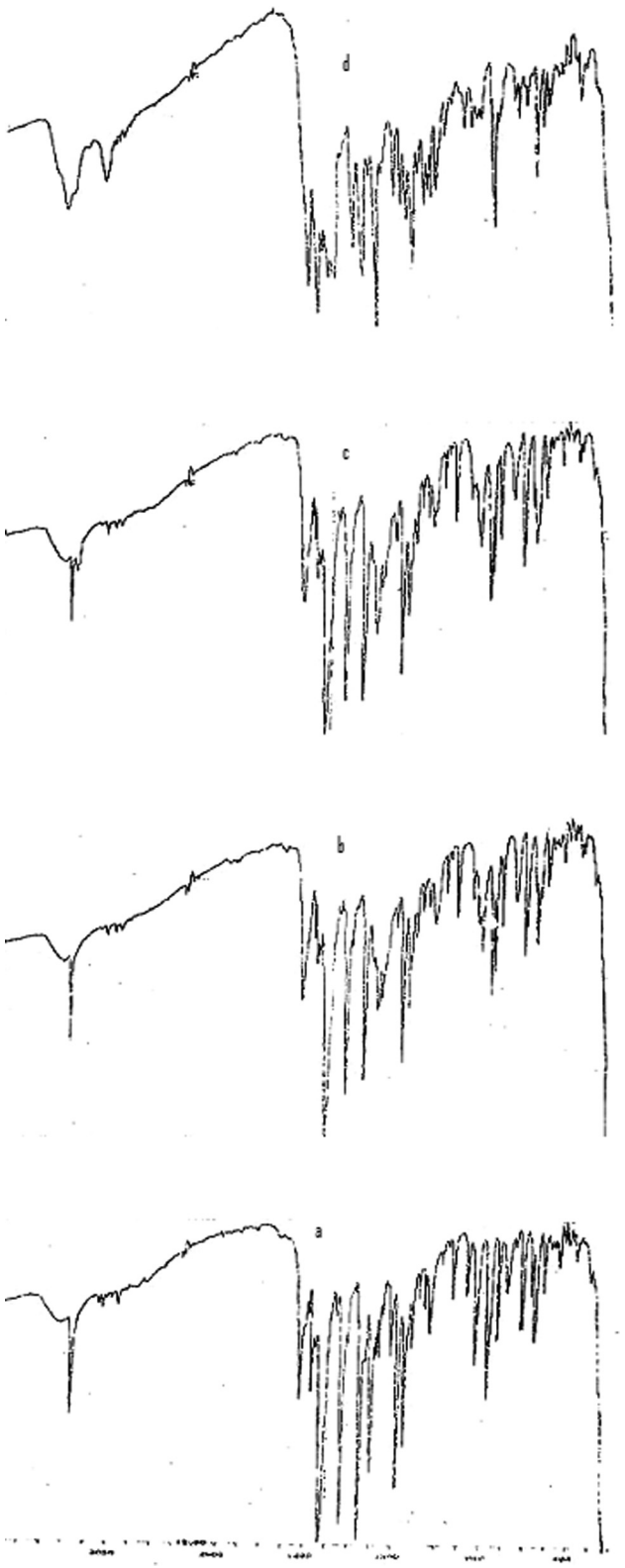

Figure 3 Infra-red spectra of the four Piroxicam polymorphic forms. (a: form 1, b: form 2, c: form 3, d: monohydrate form.)

with a force of 10 tons. Once the pellet is made, it is introduced into a Perkin Elmer standard 983G Infra-red spectrophotometer.

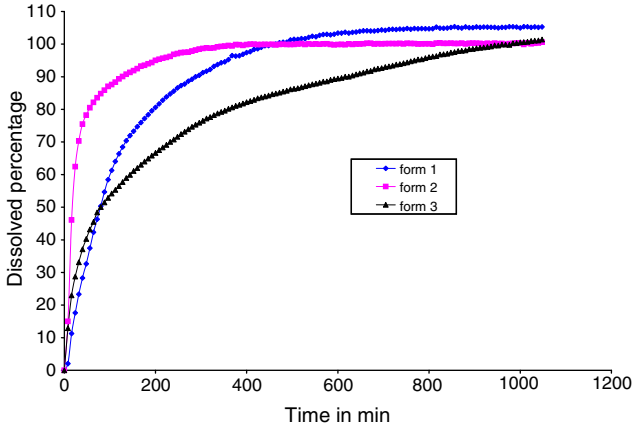

Figure 4 Dissolution profiles of forms 1, 2 and 3.

2.4.4. Solubility

The solubility test is carried out according to the method in USP 30-nf 25 with revolving pallet under the following operating conditions:

- Test sample: 200 mg
- Test medium: 900 ml (pH = 1.2)
- Test temperature: 25 °C and 37 °C
- Stirring speed: 50 tours/min

It is worth noting that, the tests were carried out at 25 °C and 37 °C in order to study the effect of the temperature increase on the solubility of the polymorphs. The expressed result is the average of three tests.

At last, the optical densities were read on a UV–VISIBLE Shimadzu UV-1601 spectrophotometer at the wavelength λ = 335 Nm.

It should be noted that the concentrations obtained after the test of solubility were taken as solubility of forms 1, 2 and 3.

2.4.5. Dissolution kinetics

The dissolution kinetics is carried out according to the method described in the USP 30 NF25.

The test is automated and controlled by a microcomputer using WINASPECT software. The results are expressed as a percentage of dissolved active principle.

Initially the dissolution tests of the three polymorphs of the Piroxicam (forms 1, 2 and 3) are realized, according to following operating conditions:

- Test sample 16 mg
- Test medium: 900 ml (pH = 1.2)
- Test temperature: 37 °C
- Stirring speed: 50 tours/min

2.5. Control of tablets

2.5.1. X-rays diffraction of the tablets

We operated under to the same operating conditions as the polymorphs. In fact, the tablets formulated with the different polymorphs are initially crushed in a mortar, then spread

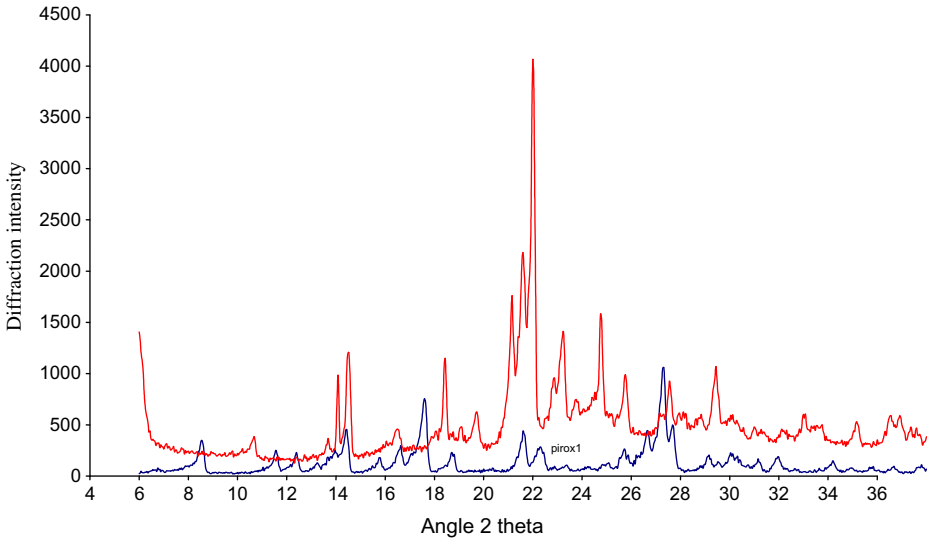

Figure 5 Diagram of X-ray diffraction of conventional tablets (form 1 of Piroxicam).

Table 3 Solubility of Piroxicam polymorphs at the temperatures 25 °C and 37 °C.

Polymorphs	Solubility at 25 °C (mg/l)	Solubility at 37 °C (mg/l)
Form 1	176.75	185.71
Form 2	**184.67**	**189.49**
Form 3	158.50	158.84

out over a glass blade sample holder then placed in the diffractometer.

2.5.2. *In-vitro dissolution*

We studied the dissolution profiles of tablets under the same operating conditions as the polymorphs (according to the method described in USP 30 NF25).

3. Results and discussion

3.1. *Polymorphs*

3.1.1. *Differential calorimetric analysis*

The differential calorimetric analysis shows for the four Piroxicam polymorphs: forms 1, 2, 3 and the monohydrate form, the respective melting points: 202.40 °C, 199.37 °C, unstable and 203.40 °C.

These results reveal that form 2 presents the lowest melting point and appears on curve DSC as a shoulder point just after its melting point. This could be due to the presence of two crystalline species in the sample which show a slight difference in melting point.

In addition, the monohydrate form displays a dehydration peak around 131.61 °C.

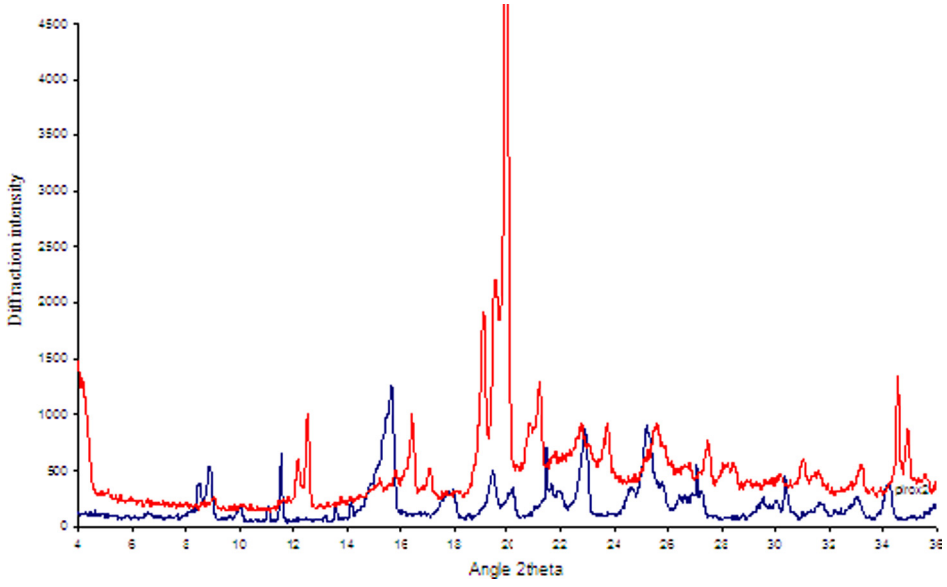

Figure 6 Diagram of X-ray diffraction of conventional tablets (form 2 of Piroxicam).

It is significant to note that the form 3 is unstable and is converted before its fusion, which is clearly illustrated on curve DSC by the appearance of a small endothermic peak around 195.59 °C (Fig. 1).

3.1.2. X-ray diffraction

The results of the diffractogram display the following angles for the four polymorphic forms of the Piroxicam.

Form 1: 8.56; 11.64; 12.44; 14.44; 17.64; 21.64; 26.72; 27.32; 27.72.

Form2: 8.92; 14.96; 15.28; 15.52; 15.68; 17; 96; 19.56; 23.20; 25.32.

Form 3: 8.64; 8.92; 12.36; 12.88; 17.56; 18.16; 18.60; 25.04; 28.24; 29.24.

Monohydrate form: 11.84; 15.28; 18.32; 18.96; 19.44; 21.32; 26.16; 28.12.

These results highlight the similarity between the diffraction diagrams of the four crystalline forms of the Piroxicam and those reported by Rasetti-Escargueil and Grangé (2005). (see Fig. 2).

3.1.3. Infra-red spectroscopy

The infra-red spectroscopy seems to be very useful for the characterization of the polymorphism of the Piroxicam. The infra-red spectra of forms 1 and 2 (Fig. 3) are practically identical to those published by Mihalíc et al. (1982) and Vrêcer et al. (1991).

It is worth to note that the principal differences in the infra-red spectra of Piroxicam polymorphs are observed between 3300 cm^{-1} and 3400 cm^{-1}, corresponding to the vibrations of the amide function N–H–C═O.

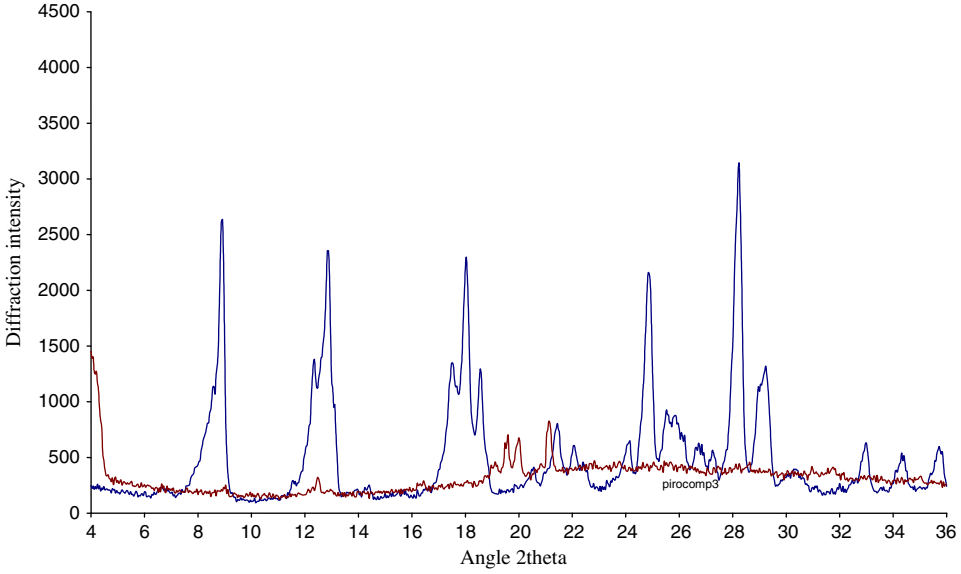

Figure 7 Diagram of X-ray diffraction of conventional tablets (form 3 of Piroxicam).

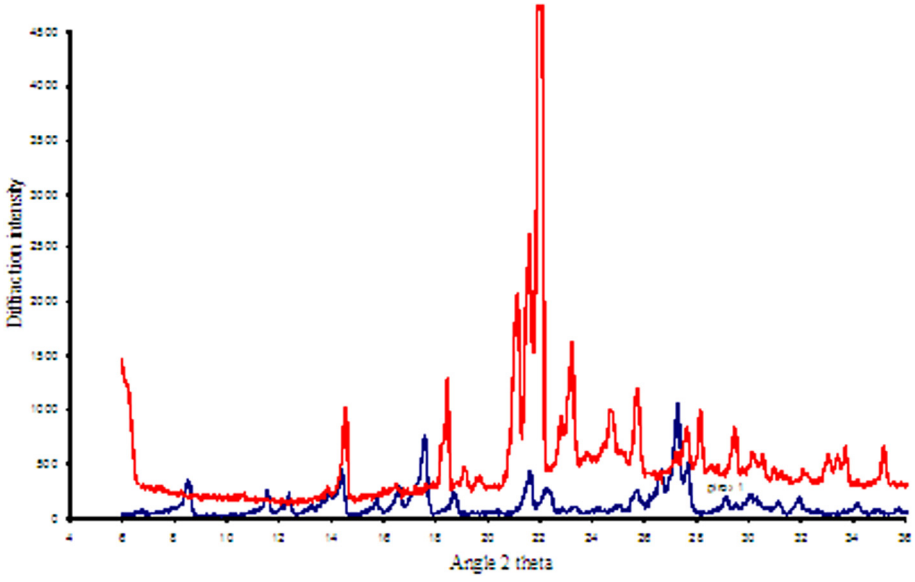

Figure 8 X-rays diffraction diagram of extended release tablets (form 1 of the Piroxicam).

The infra-red spectra show the absorption peaks of the amide function at 3337 cm^{-1} and 3392 cm^{-1} for forms 1 and 2, respectively.

The infra-red spectrum of form 3 shows a double peak for the amide function located at 3341 cm^{-1} and 3392 cm^{-1}.

The infra-red spectrum of the monohydrate form presents notable differences compared to the other Piroxicam polymorphic forms. Indeed the peaks corresponding to the amide function are located at 3099 cm^{-1} and 3452 cm^{-1}.

3.1.4. Solubility

The results mentioned in Table 3 show an increase in the solubility of the three crystalline forms of Piroxicam with increasing temperature.

These results are in contrast with those published by Kozjek et al. (1985), which showed a reduction in the solubility of form 2 with increasing temperature.

Indeed, our results show that form 2 shows a great solubility compared to the other forms. This is explained by the fact that it has the minimum melting point. Once in contact with the dissolution medium it dissolves easily. These results are comparable with those reported in the literature (Vrêcer et al., 2003).

3.1.5. Dissolution profiles

The dissolution profiles of Piroxicam polymorphs (Fig. 4), show that the most soluble form (form 2), displays a fast dissolution kinetics compared to the other two forms. In addition,

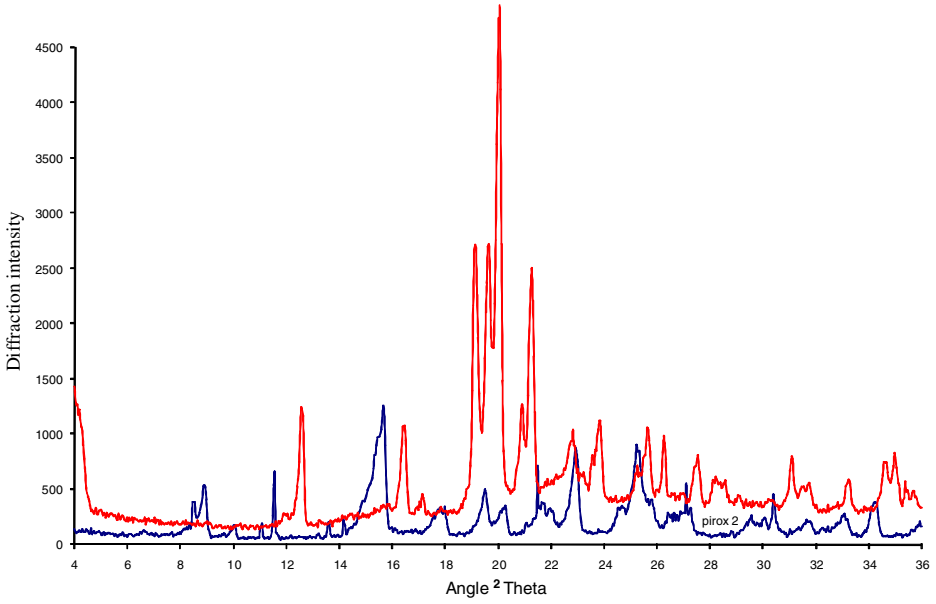

Figure 9 X-rays diffraction diagram of extended release tablets (form 2 of the Piroxicam).

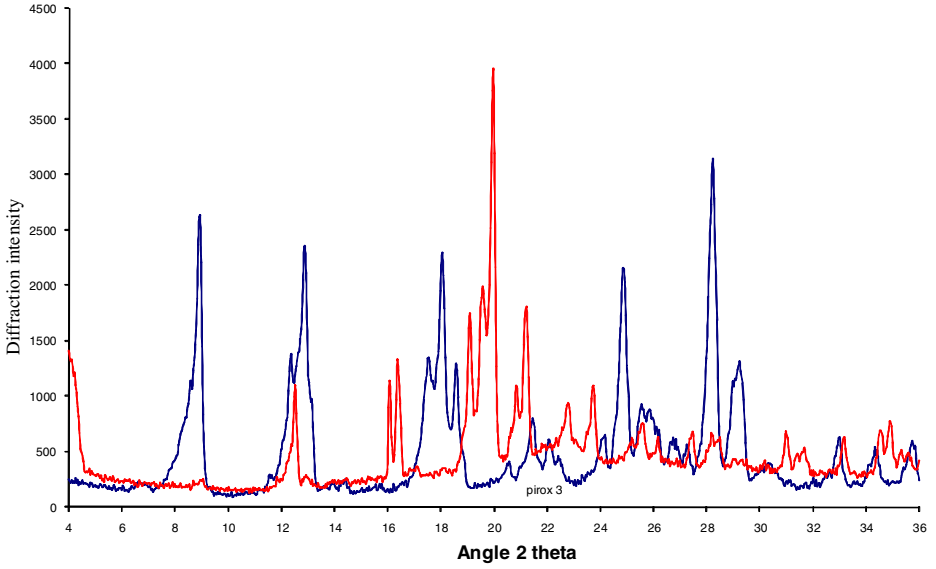

Figure 10 X-rays diffraction diagram of extended release tablets (form 3 of the Piroxicam).

it should be noted that 75% of Piroxicam forms 1, 2 and 3 are dissolved in 168 min, 40 min and 288 min, respectively.

These results are in agreement with those published in Cavallari et al. (2002) and Vrêcer et al. (2003) and confirm the results of the solubility study.

3.2. Tablets

3.2.1. X-ray diffraction of tablets with conventional release

The X-ray diffraction diagrams of the conventional tablets formulated with the different Piroxicam polymorphs (Figs. 5–7) show that after compression, the diffraction peaks are preserved for the tablets formulated with polymorphs 1 and 2 (Figs. 5 and 6), on the other hand for the tablets formulated with polymorphs 3 (Fig. 7), we note the disappearance of the peaks characterizing form 3. This could be possibly explained by an amorphization of form 3. This phenomenon is reported by Shakhtshneider (1997).

Also, it should be specified that to better visualize the polymorphic transformations with X-ray diffraction, the Piroxicam was introduced at 10%.

3.2.2. X-ray diffraction of tablets with extended release

The X-ray diffraction diagrams of tablets with extended release formulated with the different Piroxicam polymorphs (Figs. 8–10) show that after compression the diffraction peaks are preserved for all the tablets.

These results could be in agreement with those found by Andrea et al. (2004), which clearly mention the role of the HPMC in the protection of the recrystallization of the amorphous indometacin and the dehydration of monohydrate theophylline during compression.

3.2.3. Dissolution profiles of tablets with conventional release

Dissolution profiles of tablets with conventional release (forms 1, 2 and 3) (Fig. 11) show that 75% of Piroxicam with forms 1, 2 and 3 are dissolved in 120 min, 208 min and 88 min, respectively.

According to these results and compared to the dissolution profiles of pure polymorphs where the dissolution kinetics follows the order; accelerated for form 2, then form 1 then form 3 (Fig. 4), we note that after Piroxicam compression (forms 1, 2 and 3), the dissolution results are reversed. Indeed, the tablets (form 2) show the slowest kinetics and it is rather the tablets formulated with polymorph 3 which express the fastest dissolution kinetics.

These observations can be explained by the fact that during compression, the unstable form 3 is transformed into a more soluble form, which is observed with the X-ray diffraction by an amorphization of form 3 resulting in the absence of its diffraction peaks on the diffractogram (Fig. 7).

This hypothesis was also assumed by T.P Shakhtshneider in his work dealing with the stabilization of metastable phases of molecular crystals of Piroxicam and sulfathiazole under the effect of mechanical treatment (Shakhtshneider, 1997).

3.2.4. Dissolution profiles of tablets with extended release

The dissolution profiles of Piroxicam tablets (forms 1, 2 and 3) containing 5% of metolose and represented in Fig. 12 show a extended release of the active principle.

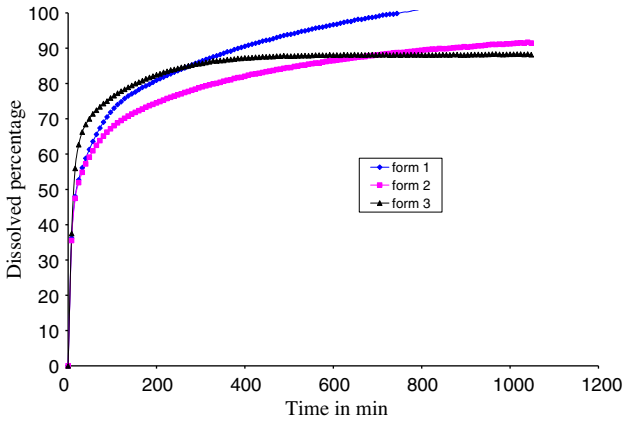

Figure 11 Dissolution profiles of tablets with conventional release (forms 1, 2 and 3).

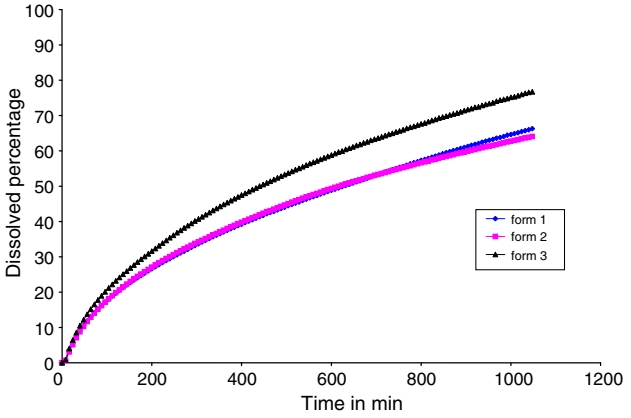

Figure 12 Dissolution profiles of tablets with extended release (forms 1, 2 and 3).

As well, it is noted that according to these results and compared to the dissolution profiles of pure polymorphs, the dissolution kinetics are in the following order: less extended for form 3, then those of forms 2 and 1.

Indeed, the tablets formulated from polymorphs (forms 1 and 2) show, in addition to the extended release of the Piroxicam, similar dissolution profiles.

This is explained by the influence of metolose which, incorporated in the tablets at a rate of 5%, could possibly act twice.

- First protecting the polymorphic transition of the form 2 during compression; which is due to its elastic behavior.
- Then by modulating the release of the active principle (sustained release).

3.2.5. Infra-red curves

In order to show the effect of hydroxypropylmethylcellulose protection on Piroxicam polymorphic transition (form II) during compression, we have completed our study by an infrared analysis as described below:

In addition to conventional tablets and extended-release tablets, formulated according to the previously mentioned compositions (Table 2), we have reformulated extended-release

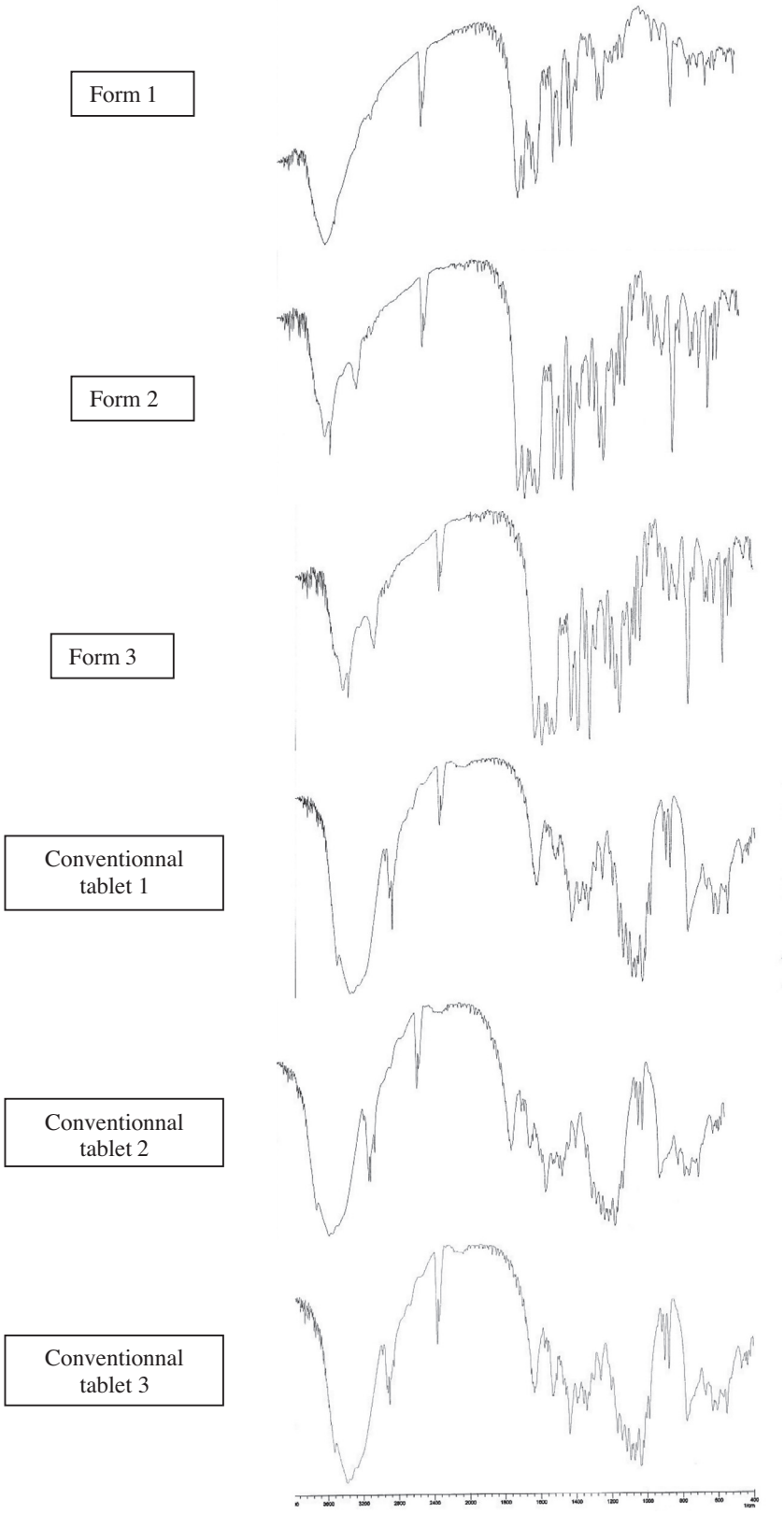

Figure 13 IR spectra of Piroxicam polymorphs and their conventional forms.

tablets by incorporating only the matrix excipient HPMC 4000 (5%) to the active ingredient present in the formula at a rate equivalent to 4%, and completed with a filler lactose monohydrate.

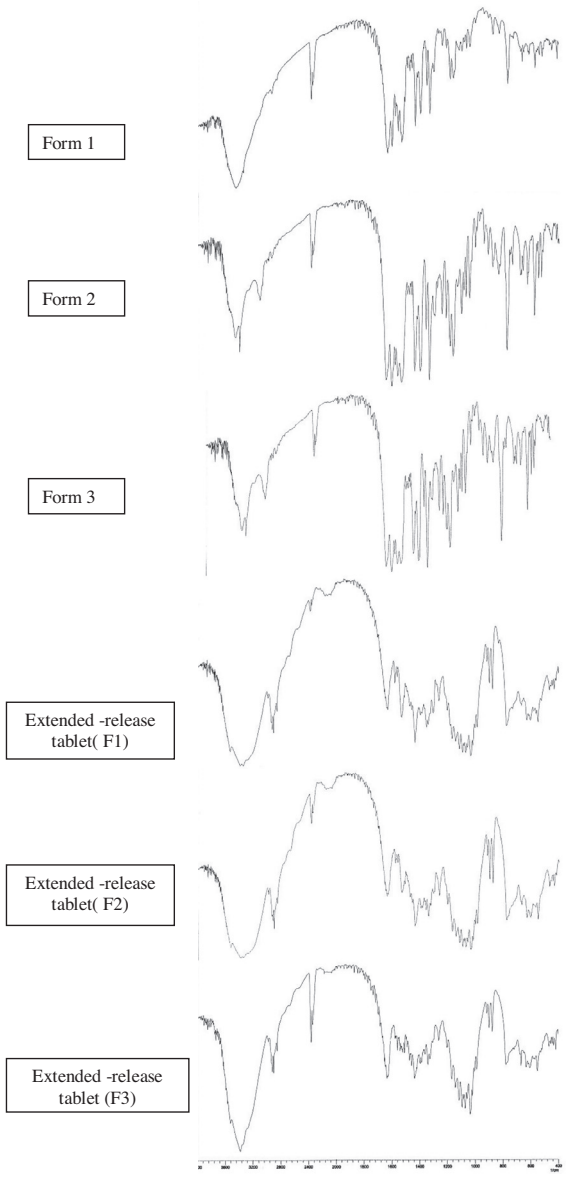

Figure 14 IR spectra of Piroxicam polymorphs and their extended forms.

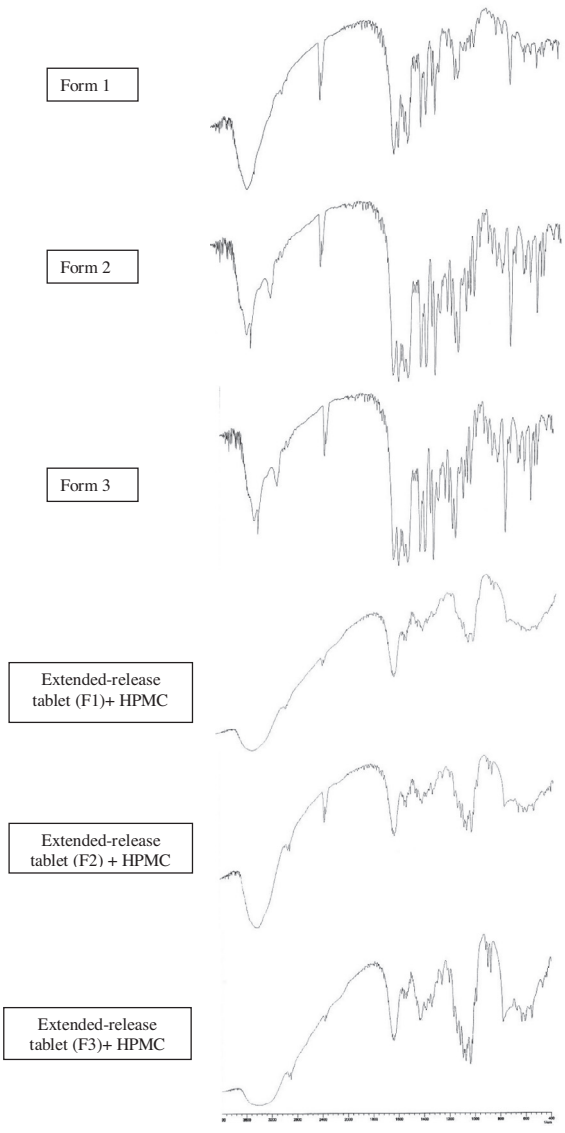

Figure 15 IR spectra of Piroxicam polymorphs and their extended forms with HPMC.

The IR spectra (Fig. 13) representing the infra-red polymorph profiles and the conventional forms show well the change in the vibration bands corresponding to N–H function located between 3337 cm^{-1} and 3392 cm^{-1}.

The IR spectra (Fig. 14) representing the infra-red polymorph profiles and the extended forms show the widening of the vibration band corresponding to the N–H function. Indeed this widening appears well after having formulated extended tablets of the different polymorphs with only HPMC 4000 at a rate of 5% and having completed with monohydrated lactose (Fig. 15).

The use of the infrared spectroscopy was, for a long time, a means to show and explain the possible interactions between active principle and excipient. In fact in our case the IR curves, show well these interactions which appear as a peak at 3340 cm^{-1} with a broad vibration band of N–H function of Piroxicam which is quite visible with the use of the formulas containing the HPMC 4000 as a single excipient of an extention effect.

4. Conclusion

The physico-chemical characterization of Piroxicam polymorphs (DRX), the follow-up of their evolution throughout the formulation process of the extended release tablets with the hydroxypropylmethylcellulose 4000 and the control of the in vitro release of the active principle made it possible to highlight the role of hydroxypropylmethylecellulose (HPMC 4000) in the protection of Piroxicam polymorphs.

In fact, the results revealed that hydroxypropylmethylcellulose 4000 incorporated in a rate equivalent to 5% in the Piroxicam tablets, in addition to the extention effect; allows the stabilization of form II during compression. This phenomenon was clearly illustrated by the dissolution profiles.

It will be thus possible to choose and suggest polymorph II, in order to formulate a extended release tablet based on hydroxypropylmethylcellulose (HPMC 4000): a matrix excipient known for its elastic behavior during compression.

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