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Research paper

Nanocrystals as tool to improve piroxicam dissolution rate in novel orally disintegrating tablets

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ABSTRACT

In this paper, orally disintegrating tablets (ODT) were prepared using nanocrystal formulations in order to optimise dissolution properties of lipophilic, poorly soluble drug piroxicam (PRX). Different nanocrystal formulations were prepared using a high pressure homogenisation technique and poloxamer 188 as stabiliser. Characterisation of PRX nanocrystal ODT was carried out by infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), differential scanning calorimetry and photon correlation spectroscopy. Dissolution study of PRX ODT was performed in distilled water (pH 5.5) and was compared to that of PRX coarse suspension ODT, PRX/poloxamer 188 physical mixture and bulk PRX samples. The XRPD and FTIR studies demonstrated that the homogenisation process led to a polymorphic transition from form I (bulk commercial PRX) to form III and monohydrate form of the nanocrystals. All ODT formulations prepared using PRX nanosuspensions showed a higher PRX dissolution rate compared with the ODT prepared with the coarse PRX. Since the solubility of the different PRX polymorphic forms increased only slightly from bulk PRX (form I) to monohydrate, form II and form III, we can conclude that the improvement in PRX dissolution rate is mainly caused by the increased surface-to-volume ratio due to the submicron dimension of the drug particles.

1. Introduction

Fast dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within few minutes when placed in the mouth without the any need for water. Direct absorption through the oral mucosa allows drugs to achieve the systemic circulation bypassing the gastrointestinal tract and the first-pass metabolism of the liver. To allow fast dissolving of dosage forms in the mouth, these delivering systems are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force. In the manufacture of orally fast disintegrating tablets, various technologies can be applied, including freeze-drying or lyophilisation, which results in preparations with high porosity and, consequently, rapid dispersion or dissolution [1,2].

Piroxicam (PRX) is a non-steroidal anti-inflammatory drug widely used in rheumatic disease because, due to its long half-life, it offers the convenience of a once-daily administration [3,4]. Due to adverse side effects associated with oral administration, such as gastric irritation, there is a considerable interest in developing new formulations to improve oral mucosa drug absorption. Oral piroxicam administration is characterised by slow absorption because this drug is poorly water soluble. A new technological approach for enhancing water solubility of drugs is the production of nanometer-sized drug particles with a large surface area, which increases the dissolution rate.

In the last few years nanosuspensions, dispersions of nanoparticles (nanocrystals), which are stabilised with the help of polymers or surfactants, have emerged as one of the most promising dosage forms for poorly water-soluble drugs [5,6]. In this work, the production of nanocrystals intended for oral use of PRX, using a high pressure homogenisation technique (HPH), is reported. The aim of this investigation was to increase the dissolution and buccal adsorption of PRX. To this purpose, poloxamer 188 stabilised PRX nanocrystals were used for the preparations of orally disintegrating tablets (ODT).

Characterisation of PRX nanocrystal ODT was carried out by different techniques: infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), differential scanning calorimetry (DSC), photon correlation spectroscopy (PCS), drug release profiles, in comparison with those of the starting materials: bulk drug, physical mixture and coarse suspension.

Dissolution study of PRX ODT was performed in distilled water (pH 5.5) and was compared to that of PRX coarse suspensions ODT, PRX/poloxamer 188 physical mixture and bulk PRX samples.

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2. Materials and methods

2.1. Materials

Pluronic F68 (poloxamer 188) was a gift from BASF AG (Ludwigshafen, Germany), and maltodextrin (DE 39) having a Dextrose Equivalent (DE) equal to 39 was kindly supplied by Roquette (France). Piroxicam (PRX), poly(ethylenglycol) 4000 (PEG 4000), xanthan gum (XG) molecular weight approximately 3×10^5 g/mol and high-performance liquid chromatography (HPLC)-grade methanol were purchased from Sigma–Aldrich (Milan, Italy). All the other compounds were of analytical grade and used as received from Sigma–Aldrich (Milan, Italy).

2.2. Methods

2.2.1. PRX polymorphic form preparation

All the crystalline forms of piroxicam were prepared following literature methods [4,5]. Commercial piroxicam agrees with form I (prismatic). Form II (needle) was crystallised from commercial piroxicam (250 mg) hot saturated absolute ethanol solution (18 ml). Form III was obtained by spray drying the hot saturated absolute ethanol solution (PRX 250 mg/ethanol 18 ml) in a Spray Dryer ForMate 4M8 using the following parameters: air flow rate: 10 ml/min, inlet temperature: 90 °C and outlet air: 50–60 °C. The monohydrate form was obtained by dissolving commercial piroxicam (250 mg) in acetone (15 ml) and by slowly adding distilled water (10 ml) till the appearing of a yellow precipitate which was filtrated and dried.

Table 1
Composition of PRX ODT.

Components % (w/w)	Formulations		
	1	2	3
Piroxicam	2.5	2.5	2.5
Poloxamer 188	0.5	1	1.5
PEG 4000	1	1	1
DE 39	20	20	20
Xanthan	0.25	0.25	0.25
H_2O	75.75	75.25	74.75

2.2.2. PRX polymorphic form solubility

The solubility of the different PRX polymorphic forms was determined in pure water, water with different concentrations of poloxamer 188 (Table 6), and in a maltodextrin, PEG4000 and xanthan gum water solution at the same PRX/additives ratios in the ODT formulation (Table 1). An excess of drug was added to the medium in screw capped tubes (10 ml) and stirred at 25 °C for 48 h. Each sample was centrifuged, and 0.2 ml of the clear supernatant was diluted with methanol and analysed by UV.

2.2.3. PRX/poloxamer 188 physical mixture preparation

Physical mixtures were prepared by blending PRX and poloxamer 188 in an agata mortar until a homogeneous mixture was obtained, using the same drug/surfactant ratio (w/w) of corresponding ODT formulations (Table 1).

2.2.4. Coarse suspension preparation

Drug coarse suspensions were prepared dispersing PRX in a poloxamer 188 bidistilled water solution using an Ultra Turrax T25 basic (IKA, Werke) for 1 min at 8000 rpm. Coarse suspensions were prepared using the same drug/surfactant ratio (w/w) of the corresponding ODT formulations (Table 1).

2.2.5. Nanosuspension preparation

Bulk PRX was dispersed in a poloxamer 188 bidistilled water solution using an Ultra Turrax T25 basic for 1 min at 8000 rpm. The obtained coarse suspension was sonicated for 1 h and then homogenised at high pressure (three cycles at 500 bar and 30 cycles at 1500 bar) using an Emulsiflex C5 apparatus (Avestin, Ottawa, Canada). Nanosuspensions were prepared using the same drug/surfactant ratio (w/w) of corresponding ODT formulations (Table 1).

2.2.6. ODT preparation

Xanthan gum, PEG4000 and maltodextrins were dissolved into the previously prepared nanosuspensions or coarse suspensions (Table 1). An amount of this suspension containing 20 mg of PRX was placed in a PVC blister, frozen at −20 °C and then freeze-dried for 24 h at −70 °C and 60 mm Hg, using a freeze-dryer apparatus (Criotecnica, Rome, Italy).

Table 2
Comparison of the 2θ degree value between each polymorph form, physical mixture, nanosuspension and ODT, (∗) = relative to form I, (^) = relative to form III, (#) = relative to monohydrate form.

I	II	III	Monohydrate	Physical mixture 2.5:1.5	Lyophilised nanosuspension	ODT
8.58	8.94	8.70	9.94	8.58(∗)	8.90(^)	–
11.62				11.58(∗)		
12.48				12.38(∗)		
13.24	10.06	–	11.76	13.22(∗)	11.90(#)	12.06(#)
13.96				13.96(∗)		
14.42				14.44(∗)		
–	–	12.66	–	–	12.88(^)	–
			13.78			–
			14.30			
17.66	–	17.80		17.60(∗)	14.36(#), 14.94(#), 16.40(#)	
			14.82			
			16.34			
–	19.66, 19.90, 20.28	18.40	–	–	–	–
–	22.98	24.62	21.20	–	24.88(^)	21.48(#)
26.72				26.60(∗)		
27.36	–	–	26.08	27.18(∗)	26.22(#)	26.34(#)
27.70				27.60(∗)		
			27.98	–	28.20(^)	28.06(^)
–	–	28.00	29.52			
		28.96	30.28		29.34(^)	28.32(^)
–	38.22	–	–	–	–	–

Table 3
Comparison of FTIR bands between each polymorph form, physical mixture, nanosuspension and ODT.

	Form I	Form II	Form III	Monohydrate	Nanosuspension	ODT
ν NH		3393	3343	3377	3344	Overlapped with ν OH
	3338		3323			
ν C=O	1630	1642	1634	1642	1636	1643
ν C=N	1530	1530	1531	Overlapped with δ OH	1534	1531
ν SO_2 as.	1351	1354	1354	1331	1331	1332
					1354	
					1185	1152
ν SO_2 s.	1181	1180	1184	1160		
					1150	
δ OH	–	–	–	1599	1602	1602

Table 4
PCS average diameter (Z-AVE), polydispersity index (PI) and zeta potential (ZP) of nanocrystals 1–3 before and after lyophilisation.

Formulations	Z-AVE (nm) before lyoph.	Z-AVE (nm) after lyoph.	PI before lyoph.	PI after lyoph.	ZP (mV) before lyoph.	ZP (mV) after lyoph.
1	432.3 ± 11.8	723.7 ± 14.5	0.36 ± 0.04	0.42 ± 0.04	−26.1 ± 0.8	−29.3 ± 0.7
2	553.1 ± 9.8	684.5 ± 18.3	0.49 ± 0.05	0.44 ± 0.04	−15.9 ± 0.1	−16.5 ± 0.6
3	414.3 ± 21.1	501.7 ± 21.1	0.40 ± 0.02	0.43 ± 0.04	−18.1 ± 0.4	−16.9 ± 0.6

Table 5
Percentage of released PRX after 60 min.

	% release from bulk PRX	% release from PRX nanosuspension ODT	% release from coarse PRX ODT	% release from physical mixture
Bulk PRX	10.81 ± 0.48			
Formulation 1		36.74 ± 0.76	15.24 ± 0.61	11.83 ± 0.36
Formulation 2		38.25 ± 1.47	13.73 ± 1.25	11.67 ± 0.48
Formulation 3		65.07 ± 5.10	17.82 ± 2.31	11.84 ± 0.54

Table 6
PRX solubility in water at different PRX:poloxamer 188 ratio (w/w).

PRX/poloxamer 188 ratio (w/w)	Solubility (mg/l)
Bulk PRX	14.33 ± 0.60
2.5:0.5 (formulation 1)	15.39 ± 1.25
2.5:1.0 (formulation 2)	15.03 ± 1.05
2.5:1.5 (formulation 3)	15.72 ± 1.14

2.2.7. Analytical characterisation

FTIR spectra were collected using a Perkin Elmer (MA, USA) FTIR Spectrometer "Spectrum One" in a spectral region between 4000 and 450 cm^{-1}. Samples were mixed in a mortar with KBr (1:100) and pressed in a hydraulic press (9 tons) to small tablets, which were then analysed by transmittance technique with 32 scansions and 4 cm^{-1} resolution.

The powder X-ray diffraction patterns were recorded with a Rigaku Miniflex diffractometer with a Ni-filtered CuKα radiation detector (λ = 1.5405 Å) operating at a voltage of 30 kV and a current of 15 mA. The samples were analysed in the 2θ range from 3° to 60° with a scan angular speed of 2°/min and a scan step time of 2.00 s.

The DSC curves of the different samples were recorded on a Perkin Elmer DSC 6 differential scanning calorimeter calibrated with indium at the heating rates of 10 °C/min. The thermal behaviour was studied by heating 2 mg samples in aluminium crimped pans under nitrogen gas flow within the temperature range 50–350 °C.

The SEM analyses were recorded on a Jeol JSM-5500LV at 20KV low vacuum.

2.2.8. In vitro dissolution studies

In vitro dissolution studies were performed according to the United States Pharmacopeia (USP) using the rotating basket method (Erweka apparatus). The dissolution media was 1000 ml of distilled water kept at 37 ± 0.1 °C and a rotation speed of 100 ± 2 rpm. At preselected time intervals, 1 ml samples was withdrawn (replaced with 1 ml of pre-thermostated fresh dissolution medium), filtered through polycarbonate membranes (0.45 μm, Millipore) diluted with ethanol (1:5) and analysed by UV for PRX content. Dissolution tests were performed in triplicate.

2.2.9. UV analysis

Quantitative determination of PRX was performed by UV spectroscopy. The stock standard solution of PRX (1 mg/ml) was prepared by dissolving the drug in ethanol and storing at 4 °C. A standard calibration curve (peak area of PRX vs. known drug concentration) was built up using standard solutions (0.5–100 μg/ml) prepared by dilution of the stock standard solution with ethanol. Calibration graphs were plotted according to the linear regression analysis, which gave a correlation coefficient value (R) of 0.999. Sample preparation and analyses were performed at room temperature.

2.2.10. Particle size measurement

The average diameter and polydispersity index (PI) of the nanocrystals were determined by photon correlation spectroscopy (PCS) using a Zetasizer nano (Malvern Instrument, UK). Samples were backscattered by a helium–neon laser (633 nm) at an angle of 173° and a constant temperature of 25 °C. The instrument systematically and automatically adapts to the sample by adjusting the intensity of the laser and the attenuator of the photomultiplier, thus ensuring reproducibility of the experimental measurement conditions. The PI was used as a measure of the width of the size distribution.

Zeta potential was estimated using the Zetasizer nano by means of the M3-PALS (Phase Analysis Light Scattering) technique, which

measures the particle electrophoretic mobility in a thermostated cell. All the samples were analysed 24 h after their preparation.

2.3. Statistical analysis of data

Data analysis was carried out with the software package R, version 2.10.1. Results are expressed as the mean ± standard deviation. Multiple comparisons of means (Tukey test) were used to substantiate statistical differences between groups, while Student's *t*-test was used for comparison between two samples. Significance was tested at the 0.05 level of probability (p).

3. Results and discussion

3.1. Bulk PRX characterisation

In literature, three polymorphs (I, II, III) and a monohydrate form of piroxicam are reported [7–9]. In order to better characterise the formulations, all the crystalline piroxicam forms were prepared following literature methods.

The powder diffractograms allow a clear identification of the PRX polymorphs, mainly in the range between 3° and 40° 2θ. In particular, form I shows intense diffraction peaks at 8.58°, 17.66° and 27.36° (2θ); form II at 8.94° and 38.22° (2θ); form III at 8.70° and 12.66° (2θ), while only the monohydrate form exhibits a peak at 26.08° (2θ). XRPD measurement comparison leads to the conclusion that bulk (commercial) piroxicam presents a crystalline form, which agrees with form I (Table 2).

FTIR spectra confirm this evidence. As reported in literature, piroxicam polymorphs and monohydrate exhibit many differences from 3400 to 3300 cm^{-1} in FTIR spectra where bands for OH and NH stretchings can be found. Other differences are evident for the bands in the 1700–1100 cm^{-1} range that can be assigned to the C=O, C=N, SO_2 (as. and s.) stretchings (Table 3).

DSC analysis of form I shows a melting point at 203 °C. The thermal behaviour of form II is influenced by scan rate; in fact, heating at 10 °C/min an endothermic peak at 201 °C with a shoulder at 202 °C is evident, while heating at 2 °C/min two endothermic peaks (198, 200 °C) occur. The form III melting point is 202 °C; the monohydrate form shows an endothermic peak at 131 °C, corresponding to water evaporation, followed by another peak at 202 °C.

In agreement with literature data [7], SEM analysis of the form I shows prismatic crystals, the form II needles; the monohydrate form exhibits irregular shape morphology, and the form III a spherical modification due to spray-drying process.

3.2. Nanosuspension and ODT preparation and particle size measurement

Different formulations of PRX nanosuspensions (water suspension of PRX nanocrystals) were produced by HPH using bulk PRX and different amounts of poloxamer 188 as stabiliser (Table 1). Preliminary tests were carried out in order to determine the appropriate operative conditions (homogenisation pressure and number of homogenisation cycles) for HPH (data not shown). Selected operational conditions for all the nanosuspension formulations were 30 homogenisation cycles at 1500 bar, which were preceded by 3 cycles at 500 bar as a kind of pre-milling. One thousand and five hundred bar was selected as homogenisation pressure, considering that working at 1000 bar led to average particle size larger than 1.5 μm independently of the number of cycles (less than 50 cycles). The number of homogenisation cycles was 30 because no significant reduction in the average particle size and/or the polydispersity index of the PRX nanocrystals was observed increasing the number of homogenisation cycles up to 50 at 1500 bar.

PCS diameter (Z-AVE), polydispersity index (PI) and Z potential of PRX nanocrystals were determined just 24 h after the last homogenisation cycle (Table 4). All formulations have a particle size below 600 nm and a PI lower than 0.5. Nanosuspension prepared using 1.5% of poloxamer 188 (calculated as % in the final ODT formulation) shows the lowest PCS average diameter, which is 414 nm (0.40 PI). However, in the formulations with a lower poloxamer 188 concentration, PCS average diameter slightly increases. In the tested range, hence, no direct relation between surfactant concentration and particle diameter was found.

As solid dosage forms are the election forms for oral administration, the liquid nanosuspension should be transformed into a dry powder suitable to generate tablets, capsules, pellets, etc.

This transformation can be achieved using different methods, including lyophilisation, spray drying, granulation and pelletisation [10]. In order to maintain the advantages of the liquid nanosuspension, the process used to obtain the powder should be well designed with the aim to avoid particle aggregation after rehydration of the obtained solid form. Indeed, the major advantages of nanocrystal in oral administration are increased dissolution rate (increased specific surface area, increased solubility, transformation in an amorphous or more soluble polymorphic form) and then bioavailability (for class 2 drug substance of Biopharmaceutics Classification System), reduction in gastric irritation and reduction in variation in bioavailability, resulting from the fed vs. fasted state [5].

In this study, prepared nanosuspensions were used to generate different orally disintegrating tablets (ODT) by means of the lyophilisation method (see Section 2). These formulations are dried products of a water-soluble mixture with drug, which is placed in blister pockets and freeze-dried to remove the water by sublimation.

Usually, in a lyophilisation process, cryoprotectants are added to the nanosuspensions to protect them from freezing damage, due to ice formation, and to minimise the particle size growth during lyophilisation. For this reason, different cryoprotectants, typically water-soluble sugars, have been generally added to the nanosuspension prior to lyophilisation [10]. However, the presence of the stabiliser itself, used in the nanosuspension preparation, can reduce particle aggregation after rehydration [11,12]. Indeed, we also demonstrated in a previous article that aggregation of diclofenac acid nanoparticles, after rehydration of the lyophilised powder, has been reduced using high concentrations of poloxamer 188 [11]. On the other hand, we must underline that also maltodextrins, used here to form the ODT matrix, might have act as cryoprotectant.

The ODT obtained by lyophilisation were then characterised. PCS diameter (Z-AVE), polydispersity index (PI) and Z potential of PRX particles were determined just after their disaggregation in water (few seconds). As it can be seen in Table 4, the lyophilisation process little influences the PRX particle size. In particular, the formulation with the highest poloxamer 188 concentration shows the smaller increase in PCS diameter.

3.3. Analytical characterisation

The characterisation studies were carried out on lyophilised nanocrystals of PRX dispersed in poloxamer 188, to avoid the analytical contribute of the ODT formulation components; subsequently, each ODT, corresponding lyophilised coarse suspensions and physical mixtures were analysed using XRPD, FTIR and DSC techniques.

As shown in Fig. 1, the diffraction pattern of poloxamer 188 shows two characteristic peaks at 19.26° and 23.40° (2θ), while the physical mixture pattern is approximately the superposition

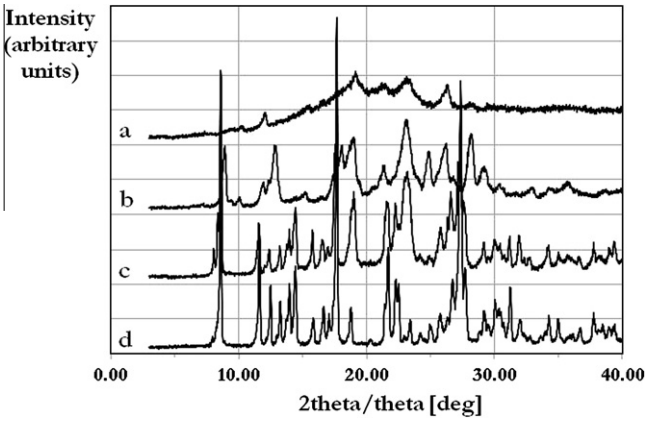

Fig. 1. Diffraction patterns of ODT formulation 3 (a), reference nanosuspension (b), physical mixture (c) and bulk piroxicam (d). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

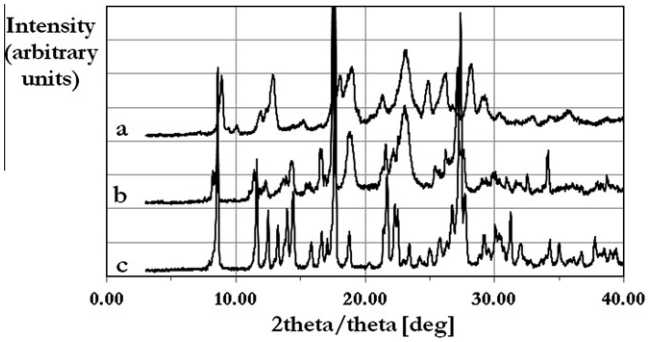

Fig. 3. Diffraction patterns of reference nanosuspension (a), coarse suspension (b), bulk PRX (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the raw materials (bulk PRX and poloxamer 188). In the nanosuspension, XRPD data demonstrate a crystalline structure but piroxicam exhibits diffraction peaks at a different 2θ degree value compared with those of bulk, suggesting a possible polymorphic transition. Due to the presence of amorphous DE39, the pattern of each ODT formulation is not crystalline whatever the poloxamer 188 peaks at 19.26° and 23.40° are evident.

The FTIR investigation gave results similar to that of the XRPD study. The spectrum of poloxamer 188 shows absorption bands due to OH (3600–3400 cm^{-1}) and C—O stretchings (1112 cm^{-1}); these absorption bands are also evident in the spectrum of the corresponding physical mixture.

In the nanosuspension spectrum, the N—H stretching can be found at 3344 cm^{-1}, the C=O stretching at 1636 cm^{-1}, the OH bending at 1602 cm^{-1}, the C=N stretching at 1530 cm^{-1}, the SO_2 asymmetric stretching at 1331 and 1354 cm^{-1} and the SO_2 symmetric stretching at 1184 cm^{-1}.

The FTIR analysis of ODT formulations shows absorption bands at 3390 cm^{-1} for OH stretching, 3000–2800 cm^{-1} for C—H sp^3 and 1151–1027 cm^{-1} for C—O stretching due to the presence of the excipients. However, as shown in the 1700–1100 cm^{-1} and 4000–2800 cm^{-1} regions reported in Fig. 2A–B, peaks of piroxicam in a different crystalline form compared to the bulk material are clearly visible.

Thermal behaviour of bulk piroxicam shows an onset temperature of 202 °C and a melting peak at 203 °C, while poloxamer 188 onset temperature is at 51 °C and the melting peak at 55 °C; the physical mixture shows the endothermic peaks of the raw components. Also, DSC termogram of the nanosuspension shows two endothermic peaks at 48 °C and 186 °C due to the fusion of the components, whereas all the ODT formulations, due to their amorphous state, do not exhibit significant thermal events.

Analytical results clearly demonstrate that PRX in nanosuspensions and in ODT does not agree with form I.

In XRPD, the comparison of the 2θ value between each PRX polymorph form, physical mixture, nanosuspension and ODT (Table 2) allowed us to ascertain that in these formulations PRX is present in a mixture of form III and monohydrate form.

The FTIR study (Table 3) confirmed the presence of monohydrate form and form III mixture in the nanosuspension and prepared ODT.

Furthermore, the comparison between XRPD and FTIR results of the coarse suspensions and the corresponding ODT allowed us to establish that the polymorphic transition took place during the high pressure homogenisation. To avoid the interference of the amorphous excipient, the study was carried out on nanosuspension; in Fig. 3, the XRPD pattern of the coarse suspension and bulk PRX are similar while that of the nanosuspension showed different diffraction peaks.

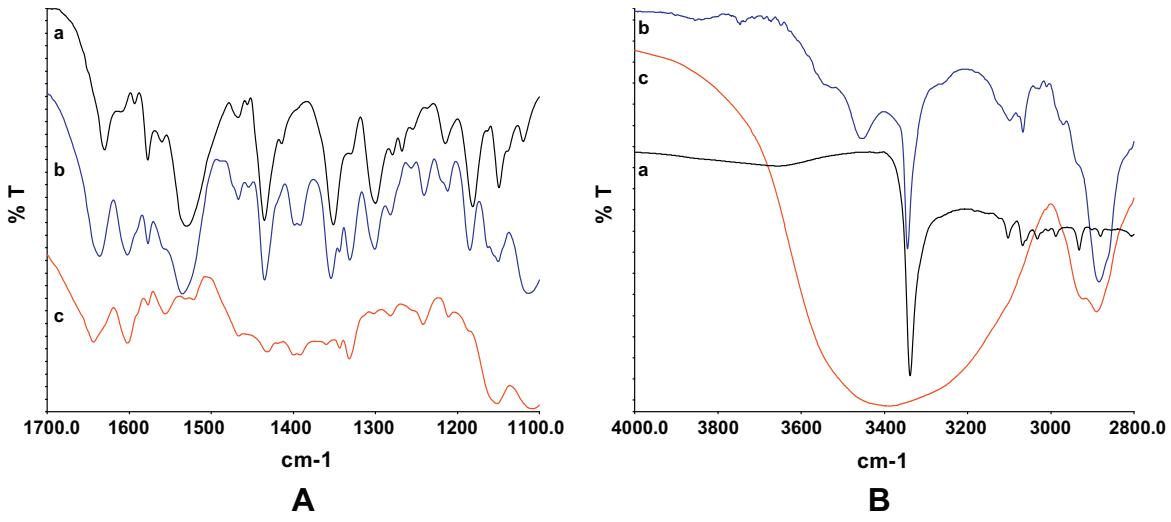

Fig. 2. FTIR spectra in the 1700–1100 cm^{-1} (A) and 4000–2800 cm^{-1} (B) range: piroxicam bulk (a), reference nanosuspension (b) and ODT formulation 3 (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The FTIR analysis, as shown in Fig. 4, confirmed the results of XRPD. While the NH stretching in bulk PRX and in coarse suspension is at 3338 cm^{-1}, in the nanosuspension is at 3344 cm^{-1} as in PRX form III, the C=O stretching shifted from 1630 to 1636 cm^{-1} and a new band at 1602 cm^{-1} characteristic of the monohydrate form is present.

Due to the homogenisation at high pressure, SEM analysis of nanosuspensions shows homogeneous crystal dimension, while

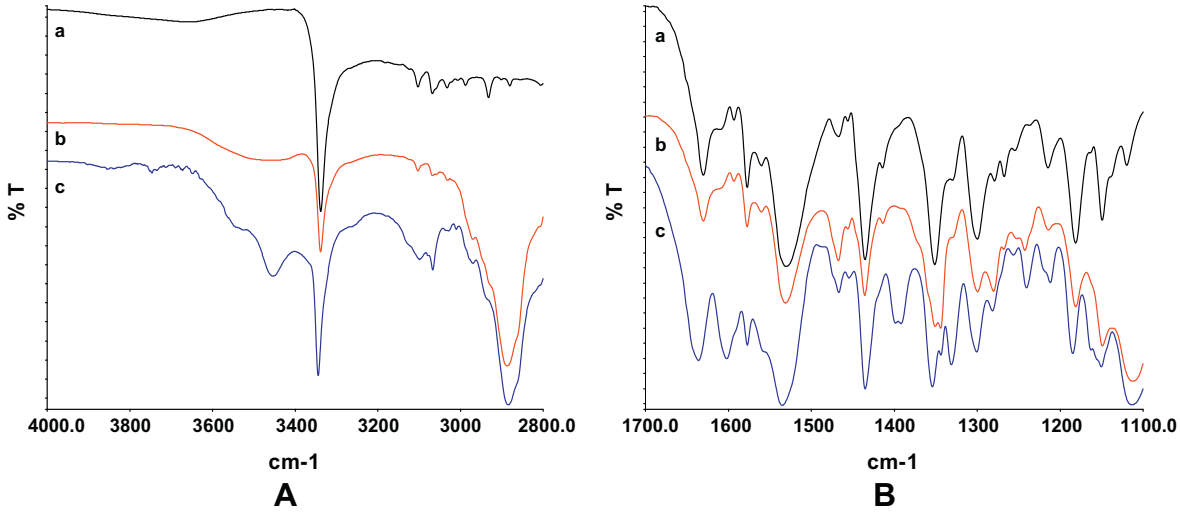

Fig. 4. FTIR spectra in the 4000–2800 cm^{-1} (A) and 1700–1100 cm^{-1} (B) range: piroxicam bulk (a) coarse suspension (b), reference suspension (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

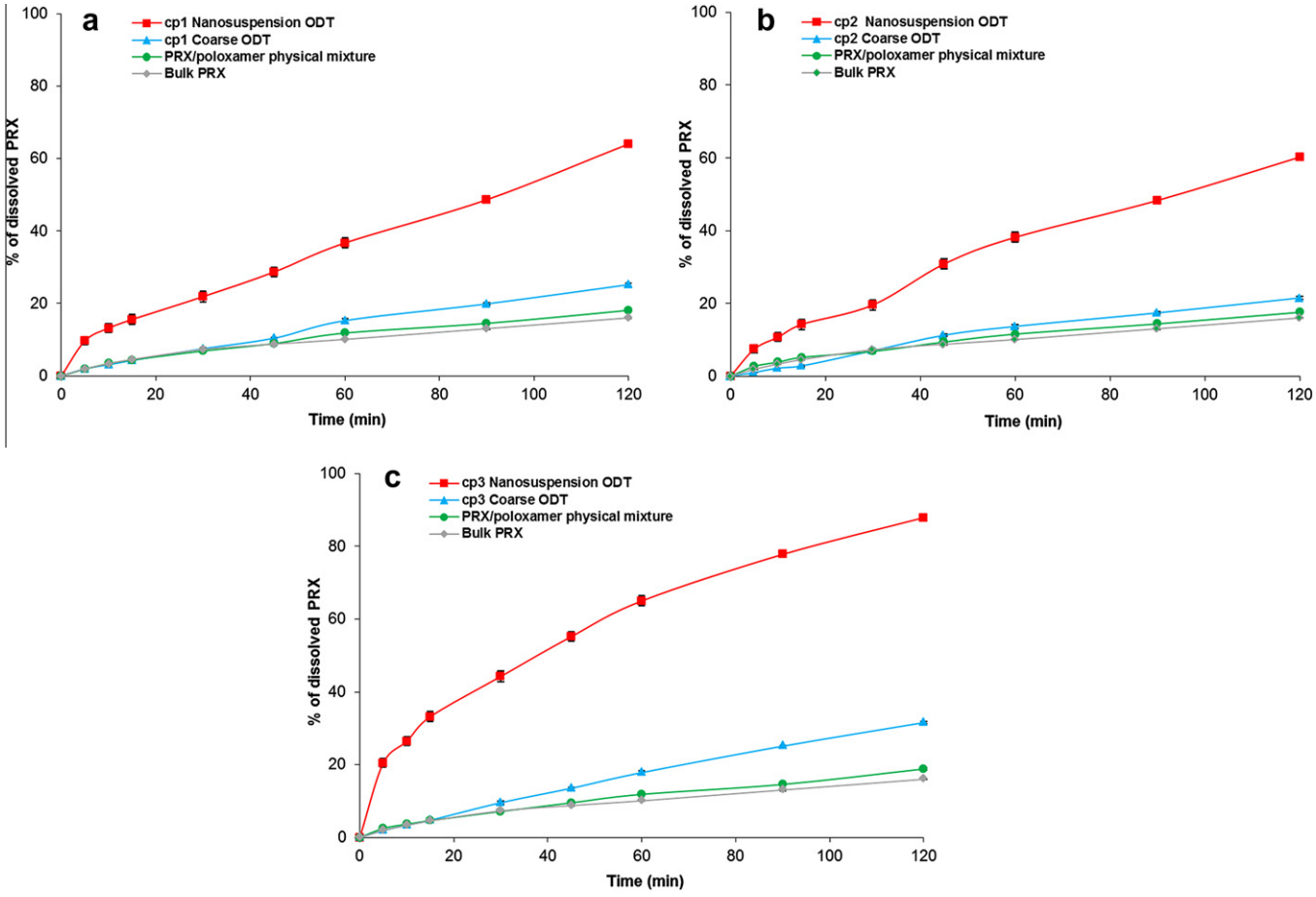

Fig. 5. (a–c) Dissolution profiles of ODT formulation 1 (a), formulation 2 (b), formulation 3 (c) prepared using PRX coarse and PRX nanocrystals compared to those of bulk PRX, PRX/poloxamer 188 physical mixture.

Table 7
PRX polymorphic form solubility in water.

PRX polymorphic form	Solubility (mg/l)
Form I (bulk PRX)	14.33 ± 0.60
Form II	16.72 ± 1.50
Form III	16.98 ± 2.09
Monohydrate form	16.52 ± 1.25

in the physical mixture prismatic crystals of piroxicam form I are clearly visible (data not shown).

3.4. In vitro dissolution studies

For class II drugs like PRX (poor solubility, high permeability), dissolution rate very often controls the rate of oral absorption. PRX dissolution test [13,14] was performed in distilled water according to the United States Pharmacopeia (USP). Bulk PRX dissolution rate was compared with those of ODT formulations prepared using coarse and nanocrystal PRX, and physical mixture of coarse PRX and poloxamer 188, in the same ratio of the corresponding ODT formulation. All samples contained 20 mg of PRX, since ODT with this drug dosage are currently marketed for the treatment of acute pain.

Dissolution profiles of the physical mixtures were very similar for the three different formulations and bulk PRX (Fig. 5a–c and Table 5). PRX water solubility studies (at the same PRX/poloxamer 188 ratio than the ODT formulations) showed that the presence of the surfactant did not increase the solubility of the drug (Table 5). For this reason, very similar dissolution profiles of bulk and physical mixtures were obtained.

All ODT formulations prepared using coarse PRX showed a faster release than bulk PRX and physical mixture of PRX/poloxamer 188 at different ratios.

In order to elucidate this behaviour, a study of the variation of the PRX solubility using the same PRX/excipient ratio as in the ODT formulation was carried out. No significant variation of the PRX solubility was found by adding PEG4000, xanthan gum or poloxamer 188 (as previously shown). By contrast, the addition of maltodextrin determined an increase in the PRX solubility (17.02 ± 0.45 mg/l) responsible for the increase in the coarse ODT dissolution rate.

All ODT formulations prepared using PRX nanocrystal showed a higher drug dissolution rate than ODT prepared using coarse PRX (Fig. 5a–c and Table 5). As previously demonstrated by XRPD and FTIR studies, the homogenisation process led to a polymorphic transition from the form I (bulk commercial PRX) to the form III and monohydrate form nanocrystals. Indeed, during homogenisation, cavitation forces as well as collision and shear forces determine break down of the drug particles down to the nanometer range. These high energetic forces can also induce a change in crystal structure and/or partial or total amorphisation of the sample, which could further enhances the solubility [15]. However, in our study, the solubility of the different PRX polymorphic forms increased only slightly from bulk PRX (form I) to monohydrate, to form II and to form III (Table 7). Therefore, the variation of the PRX polymorphic form is not the factor responsible for the higher dissolution rate of ODT nanocrystals or, at least, it is not the most important factor. We can conclude that, as predicted in the Noyes–Whitney [16] dissolution model, the improvement in piroxicam dissolution rate is mainly caused by the increased surface-to-volume ratio due to the submicron dimension of the drug particles [11,17,18].

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