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Formulation strategy and evaluation of nanocrystal piroxicam orally disintegrating tablets manufacturing by freeze-drying

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ABSTRACT

Piroxicam (PRX) is a non-steroidal anti-inflammatory drug characterized by a poor water solubility and consequently by a low oral bioavailability. In this work, different nanocrystal orally disintegrating tablets (ODT) were prepared to enhance piroxicam dissolution rate and saturation solubility. PRX nanocrystals were prepared by means of high pressure homogenization technique using poloxamer 188 as stabilizer. Three different ODTs were prepared with the same nanosuspension using different excipients in order to study their effect on the PRX dissolution properties. PRX nanocrystal size and zeta potential were determined by photon correlation spectroscopy. Additional characterization of PRX nanocrystal ODT was carried out by infrared spectroscopy, X-ray powder diffractometry, differential scanning calorimetry. Dissolution study was performed in distilled water (pH 5.5) and compared with PRX coarse suspension ODT, PRX/poloxamer 188 physical mixture, bulk PRX samples and a PRX commercial ODT. All PRX nanocrystal ODT formulations showed a higher drug dissolution rate than coarse PRX ODT. PRX nanocrystal ODT prepared using gelatin or croscarmellose as excipient showed a higher PRX dissolution rate compared with the commercial formulation and ODT prepared using xanthan gum. Overall results confirmed that improved PRX dissolution rate is due to the increased surface-to-volume ratio due to the nanosized drug particle but also revealed the important role of different excipients used.

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1. Introduction

The dissolution rate of many poorly water-soluble drugs limits their bioavailability via absorption into the oral and gastrointestinal tract. Nanosuspensions, dispersions of nanoparticles (nanocrystals), stabilized with the help of polymers or surfactants, have recently emerged as one of the most promising dosage forms for poorly water-soluble drugs. Indeed, the key characteristic of drug nanocrystals is their ability to enhance drug dissolution rate because of the increased interfacial surface area and saturation solubility (Keck and Müller, 2006; Merisko-Liversidge et al., 2003). Furthermore, the use of nanosuspension has the advantage of increasing photostability of the drug susceptible to degradation by light (Lai et al., 2013).

Piroxicam (PRX) is a non-steroidal anti-inflammatory drug characterized by slow absorption after oral administration because of its poor water solubility (Amidon et al., 1995; Graf, 1985). Due to adverse side effects associated with its oral administration, such as gastric irritation, there is a considerable interest in developing new formulations to improve oral mucosa drug absorption. During the last few years, our research group has been studying nanocrystals as a tool to improve drug dissolution rate and, thus, bioavailability of poorly soluble drugs. In particular, it demonstrated an improved dissolution rate for PRX nanosuspension incorporated in orally disintegrating tablets (ODT) in comparison with the corresponding coarse formulation (Lai et al., 2011).

In this work, we carried out a study on a new formulation strategy aimed to obtain nanocrystal orally disintegrating tablets

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Table 1
Composition of PRX–ODT.

Components %(w/w)	Formulations		
	ODT-xanthan	ODT-gelatin	ODT-croscaramellose
PRX	2.5	2.5	2.5
Poloxamer 188	1.5	1.5	1.5
PEG 4000	1	1	1
DE 39	20	20	20
Xanthan	2	–	–
Gelatin	–	2	–
Croscarmellose	–	–	2
H_2O	73.0	73.0	73.0

(ODT) of piroxicam with a drug dissolution profile faster than those of the ODTs currently available on the market.

For this purpose, we focused our attention on the influence of ODT excipients, on the enhancement of the PRX dissolution rate and, therefore, on its direct absorption through the oral mucosa. The absorption in this site allows the drug to reach the systemic circulation bypassing the gastrointestinal tract, thus avoiding the first-pass metabolism of the liver. In particular, starting from the same PRX nanosuspension formulation, we prepared and studied ODT by using three different excipients: xanthan gum, gelatin, and croscarmellose.

The amounts of xanthan gum, gelatin and croscarmellose employed in the preparation of the ODT are safe for administration in the oral mucosa as demonstrated by their use as pharmaceutical and food additives.

Xanthan gum, a polysaccharide secreted by the bacterium *Xanthomonas campestris* and gelatin, a derivation of collagen obtained from various animal by-products, are commonly used in food, pharmaceuticals, and cosmetic products as additive, gelling agent, rheology modifier, stabilizer, and binding agents. Croscarmellose sodium, or sodium CMC, is a cross-linked polymer of carboxymethylcellulose sodium. It is a white, fibrous, free-flowing powder, FDA-approved disgregant, commonly used in pharmaceutical formulations to facilitate the breakup of a tablet in the gastro intestinal tract after oral administration.

PRX nanocrystals were prepared using a high pressure homogenization technique (HPH) (Keck and Müller, 2006) and poloxamer 188 was used as a stabilizer. PRX nanosuspension ODT were prepared using a freeze-drying technology (Corveleyn and Remon, 1998; Owen et al., 2000; Sugimoto et al., 2006). Characterization 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). Dissolution study of PRX nanosuspension ODT was performed in distilled water (pH 5.5) and was compared to that of PRX coarse suspension ODT, PRX/poloxamer 188 physical mixture, bulk PRX samples and a PRX commercial ODT (Feldene Fast®).

2. Materials and methods

2.1. Materials

Pluronic F68 (poloxamer 188) was a gift from BASF AG (Ludwigshafen, Germany). 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, gelatin, croscarmellose, citric acid, aspartame, mannitol 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).

Table 2
PCS average diameter (Z-AVE), polydispersity index (PI) and zeta potential (ZP) of starting PRX nanocrystals and PRX nanocrystals after ODT disaggregation in water.

	Z-AVE (nm)	P.I.	ZP (mV)
PRX nanocrystals	414.3 ± 21.1	0.40 ± 0.02	−18.1 ± 0.4
ODT xanthan	509.3 ± 20.3	0.42 ± 0.07	−17.4 ± 0.7
ODT gelatin	532.5 ± 25.6	0.44 ± 0.07	−19.8 ± 0.5
ODT crosscaramellose	524.3 ± 19.7	0.43 ± 0.09	−21.8 ± 0.3

2.2. Methods

2.2.1. PRX polymorphic form preparation

All the crystalline forms of piroxicam were prepared following literature methods as previously reported (Vrečer et al., 1991, 2003). Commercial piroxicam agrees with form I (white prismatic crystals). Briefly, form II (white needle) was crystallized from commercial piroxicam hot saturated absolute ethanol solution. Form III (white powder) was obtained by spray drying. The monohydrate form (yellow powder) was obtained by dissolving commercial piroxicam in acetone and by slowly adding distilled water until the appearance of a yellow precipitate, which was filtrated and dried.

2.2.2. PRX polymorphic form solubility

The solubility of the different PRX polymorphic forms was determined in different media: pure water, water with different concentrations of poloxamer 188 (Table 6), maltodextrin, PEG4000 and xanthan gum (or gelatin or croscarmellose) water solution at the same PRX/additives ratios of the ODT formulation. PRX solubility was also determined in citric acid and/or aspartame and/or mannitol water solutions. 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, then 0.2 ml of the clear supernatant was diluted with ethanol and analyzed by UV.

2.2.3. PRX/poloxamer 188 physical mixture preparation

Physical mixture was 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 (Table 1).

2.2.5. Nanosuspension preparation

Nanosuspension was prepared using bulk PRX. 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 homogenized 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 with the same drug/surfactant ratio (w/w) of corresponding ODT formulations (Table 1).

2.2.6. ODT preparation

PEG4000, maltodextrins and xanthan gum or gelatin or croscarmellose, were dissolved into the previously prepared

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