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Research paper

Evaluation of β-lactose, PVP K12 and PVP K90 as excipients to prepare piroxicam granules using two wet granulation techniques

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Abstract

The present investigation aimed at evaluating the use of different excipients, β-lactose and polyvinylpyrrolidone of two molecular weights (PVP K12 and PVP K90), in the production of improved release piroxicam granules, by wet granulation using both water and steam as granulation liquid. The formulations examined were: piroxicam (Px)/β-lactose; Px/PVP K12 and Px/PVP K90, each one at a 1:9 weight ratio. The most significant difference between β-lactose and PVP is that, using the first excipient, both steam and water granules were produced while, when PVP were employed, only steam granules were obtained.

Image analysis revealed that β-lactose steam granules had a larger surface area with respect to water granules, whereas lower values of this parameter were observed in PVP-s granules, confirming the Scanning Electron Microscopy micrographs and the fractal analysis results. As regards the enhancement of the dissolution profiles, the best result was obtained using β-lactose steam granules followed by PVP K12 ones, even if the reactive dimension values indicated that during the dissolution process PVP K12 granules modified the surface more than β-lactose granules. As regards PVP K90, this excipient was the one less influencing the granule morphology and the dissolution behaviour. Differential Scanning Calorimetry analysis suggested the partial amorphisation of the drug in the granules containing the three excipients. This result was then confirmed by X-ray powder diffraction analysis. Therefore, β-lactose and PVP K12 could be proposed as useful excipients to enhance the dissolution rate of Px from granules prepared using the steam granulation technique.

Keywords: β-Lactose; Polyvinylpyrrolidone; Piroxicam; Wet granulation; Dissolution behaviour

1. Introduction

Wet granulation is the process agglomerating fine powdery materials using a liquid binder to give granules. This can be achieved in a range of different processing equipments such as double-cone blenders, pans, and fluid beds. However, granulation in a high shear mixer is one of the most common methods used in the production of granules [1]. Main reasons are that high shear granulation produces spherical and well-compacted granules in a relatively short time and that the equipment is of a rather simple construction and easily cleaned [2–4].

In previous studies [5,6] we used a one-step high shear granulator (Rotolab®), developed to comply with GMP requirements and able to operate in a closed unit, to obtain accelerated release granules containing piroxicam/β-cyclodextrin and diclofenac/PEG 4000. These granules were made employing the conventional wet granulation and a novel technique based on the use of steam as granulating liquid instead of water. Comparing the granules obtained by traditional wet method and steam granulation, the second one was found to better improve the release from granules, which also had a more porous and irregular surface.

This work was carried out in order to evaluate the use of different excipients, β-lactose and polyvinylpyrrolidone of two molecular weights (PVP K12 and PVP K90), in the production of improved dissolution piroxicam granules, using both water and steam granulation.

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β-Lactose and PVP are the most extensively used pharmaceutical excipients in wet granulation and are generally used as binders or as diluents to study the mechanism of liquid distribution [7–9], of granule growth [10,11] and the optimization of the granulation process through the selection of the best operating parameters [12]. In the present study the effect of these "diluent-binders" on the granule properties, such as average granule size and surface morphology, was examined using Scanning Electron Microscopy (SEM), image and fractal analysis. Then their efficiency to enhance the dissolution rate of piroxicam from the granules was compared. Furthermore, Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD) were used to investigate the possible interactions between the drug and the excipients and to study the solid state of the drug.

2. Materials and methods

2.1. Materials

The examined formulations were: piroxicam (Px)/β-lactose (F1); Px/PVP K12 (F2) and Px/PVP K90 (F3), every one at a 1:9 ratio.

Px (batch number: 105245/b-0129) was purchased in micronized form by CFM S.p.A. (Milan, Italy); β-lactose (Pharmatose® DCL 21) (90% less than 355 μm) was kindly provided by Eigenmann & Veronelli S.p.A. (Milan, Italy) and PVP-s of different molecular weights (Kollidon 12 PF and 90 F) (90% less than 250 μm) were kindly supplied by BASF S.p.A. (Bergamo, Italy). Milli-RX20 grade water (Millipore, Molsheim, France) was used throughout.

2.2. Preparation of the granules

The wet granules were prepared in a laboratory-scale high shear mixer (Rotolab®, Zanchetta s.r.l., Lucca, Italy), described in detail in a previous work [5]. Briefly, the machine is equipped with a hermetically airtight lid and 2 L thermostated vessel, in which the impeller is placed. The airtight lid holds the chopper, the thermocouple sensor, the inlet water and the outlet connected to a vacuum pump. The machine is also equipped with a tilting system, used to move the material during drying.

The batch size was 300 g for both methods. To avoid steam condensation on the walls of the bowl, the jacket of the bowl was preheated to 60 °C; while a temperature of 25 °C was kept in water granulation. The impeller speed was set at 120 rpm for 10 min to mix the powders, then, during the spraying of the granulation liquid, the impeller speed was set at 600 rpm for 1 min to wet the whole powder mixture. Steam was produced by a boiler at a steady flow of 0.75 g/s while the feeding rate of water was 10 mL/min. The amount of water used for the Px/β-lactose mixture was 25 mL for water granulation and 15 mL for steam granulation. In the case of the Px/PVP mixtures it was impossible to granulate using water due to the formation of a very viscous mass, which could hardly be shattered. On the contrary, the use of steam allowed the formation of granules and the amount of water was 10 and 15 mL for PVP K12 and PVP K90, respectively.

The better particle agglomeration was achieved setting the impeller speed at 800 rpm for 7 min in all the formulations; the formation of big lumps was minimized using the chopper during the last 2 min of this step.

Finally, the granules were dried at a reduced pressure and at 60 °C with an impeller speed of 120 rpm for 10 s every 100 s, tilting the bowl to move the granules and to increase their surface exposed to the evaporation process. The drying time of F1, as a function of the water amount used, was 60 and 15 min for water and steam granules, respectively, while only 5 min was necessary to dry the steam granules containing PVP K12 and K90. These drying end times were selected after preliminary granulation tests, during which the moisture content of the granules was measured; the drying time was extended until the residual moisture content did not further decrease. The final residual moisture contents were 0.5 and 2.5% (w/w) for Px/β-lactose steam and water granules, respectively, and 4 and 10% (w/w) for Px/PVP K12 and K90 steam granules, respectively.

Therefore, the total granulation time was 78 and 32 min for β-lactose water granules and β-lactose steam granules, respectively, and 22 min for PVP K12 steam granules and PVP K90 steam granules. The granules were spread out in thin layers allowing them to cool at room temperature, they were then collected and sieved as described in the following section.

For comparison, Px/β-lactose, Px/PVP K12 and Px/PVP K90 physical mixtures were prepared by mixing the components in a mortar for 10 min.

2.3. Characterization of the granules

2.3.1. Size distribution

The granule size distribution was evaluated by sieve analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) at medium vibration level for 20 min and five standard sieves (Scientific Instruments s.r.l., Milan, Italy) in the range 75–750 μm. The fractions were then collected, stored in a dessicator at 25 ± 2 °C (silica gel as drying material) and used for the dissolution and fractal studies.

2.3.2. Determination of drug content

The analysis of the Px content in each fraction was carried out by dissolving 50 mg of granules in 250 mL of pH 7.4 buffer; the amount of the drug was then spectrophotometrically determined (UV2 Spectrometer, Unicam, Cambridge, UK) at 287.0 nm. Each fraction was analysed in triplicate.

2.3.3. Scanning Electron Microscopy

The morphology of the samples was examined by SEM. The samples were sputter-coated with gold using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Philips XL 30) at 10 kV accelerating voltage.

2.3.4. Image analysis

The size and the shape analysis of the F1, F2 and F3 granules, each one granulated with water and steam, were carried out using an image analysis system based on Fourier descriptors, which was described in detail in a previous paper [5]. Briefly, this method measures the coordinates (x, y) of the particle boundary obtained through the digitization of the particle image obtained by SEM. These coordinates, developed to demonstrate deviation from an ideal geometry, the sphere [13], are used to calculate some size parameters, as area, perimeter and equivalent circle diameter (ECD) and some of the shape parameters as shape factor (s) and aspect ratio (a), describing the micro-morphology of the samples.

All these parameters were calculated analysing at least 20 particles for every sample and the mean ± the standard deviation (SD) was reported.

2.3.5. Fractal analysis

The fractal analysis was carried out using SEM interfaced to an IBM PC. The fractal dimension (D) is a measure of the particle surface and it was calculated from the slope of the Richardson's plot (ln of the perimeter length vs ln of the step length) [5,14]: Slope $= 1 - D$. The step length is the unit used to measure the perimeter. The fractal dimension can apply to a line (D_l), such as in the case already described, as well as to a surface (D_s) and it is related to D_s as follows: $D_s = D_l + 1$ [15]. So while D_l is experimentally determined, D_s is a derived parameter and the range of values of D depends on the nature of the geometric parameter considered: $1 < D_l < 2$ and $2 < D_s < 3$; therefore the more irregular and rough a substance is, the higher the value of D.

Furthermore another fractal parameter, useful to analyse the surface which is involved actively in the dissolution process, was calculated and it is defined as reactive dimension [15,16]. To calculate the reactive dimension (D_R) of the granules, the amodelistic parameter, dissolution efficiency (E_d), was calculated from the dissolution profiles obtained for each fraction. D_R was obtained using the expression: $D_R = 3 - S$, where S is the slope of the plot of $ln\ E_d$ versus the ln of the mean particle size [16].

2.3.6. Differential Scanning Calorimetry

The DSC analysis was performed using a Perkin Elmer DSC 6 (Beaconsfield, UK) with nitrogen as purge gas (20 mL/min). The instrument was calibrated for temperature using indium and lead and for enthalpy using indium. The experiments were performed in non-hermetically sealed aluminium pans; the weight of each sample was 8 ± 1 mg and the heating rate was 10 °C/min. The temperature range was 30–250 °C for β-lactose samples and 30–210 °C for PVP samples. Each analysis was performed in duplicated experiments.

2.3.7. X-ray powder diffraction

X-ray patterns of F2 and F3 granules were obtained using a Philips PW 1830 powder diffractometer. The samples were exposed to Cu-K_α radiation ($\lambda = 1.5418$ Å) in the range $5° \leq 2\theta \leq 30°$. The step size was 0.05° every 2 s.

2.3.8. In vitro dissolution studies

In vitro dissolution tests were performed using the USP 24 paddle method (Pharmatest, Steinhein, Germany) rotating at 50 rpm. As dissolution medium, 900 mL of pH 7.4 buffer was used at a temperature of 37 ± 0.1 °C and each sample contained 48 mg of Px. The buffer solution was filtered and continuously pumped (12.5 mL/min) to a flow cell in a spectrometer (UV2 Spectrometer, Unicam, Cambridge, UK). The amount of drug dissolved was analysed at 287.0 nm. The dissolution tests were performed at least in triplicate and the three absorption values were averaged and their SD was then calculated.

2.3.9. Storage stability studies

Dissolution tests and DSC analysis studies were then performed on granule samples after 1 year of storage in a dessicator at 25 ± 2 °C with silica gel as drying material.

3. Results and discussion

To evaluate the effect of β-lactose and PVP (K12 and K90) as diluent-binders in the granulation procedures, the characteristics of the final granules were analysed and compared. The results indicate that these excipients have different behaviour during the wetting process of the mass. The most significant difference between β-lactose and PVP is that, using the first excipient, both steam and water granules were obtained (water granulation required an extra volume of 10 mL with respect to steam granulation, due to the higher diffusivity of steam into the powder mixture [5]). In contrast, when PVP were employed, only steam granules were produced, because the use of liquid water resulted in a very hard and unbreakable mass. This situation can be explained considering that the viscosity of the PVP solution, which was formed during the mass wetting, is a function of the PVP concentration and it is also inversely proportional to its temperature [17]. In fact the added water was at room temperature, while the sprayed steam was at 100 °C; in the first case the viscosity was too high to allow the granule formation; therefore using PVP only steam granules were obtained. In particular, the production of PVP granules required different amounts of water (10 mL for Px/PVP K12 granules vs 15 mL for Px/PVP K90 granules) according to the PVP molecular weight.

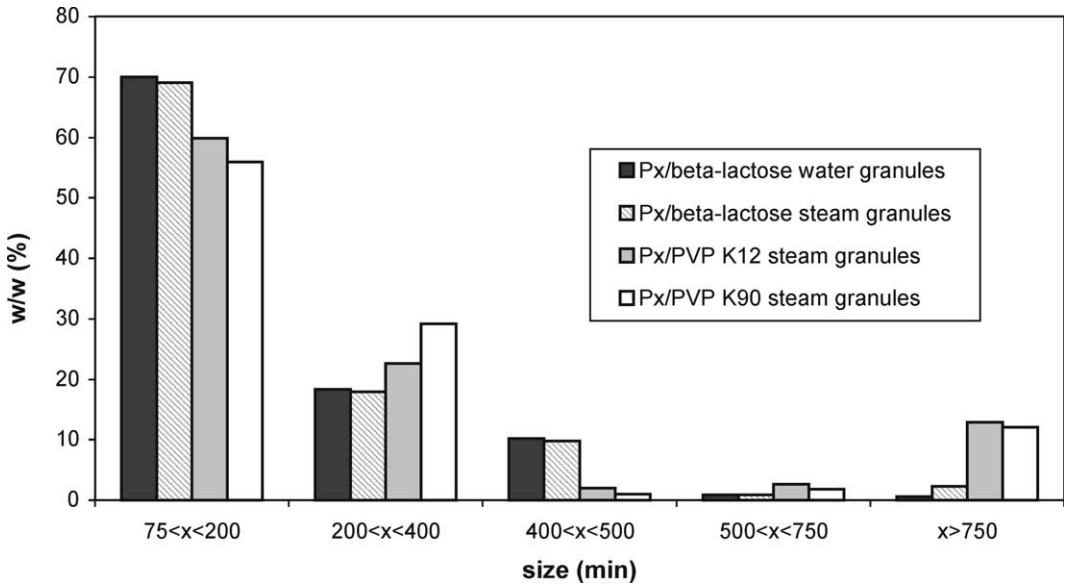

Fig. 1. Size distribution of the granules.

Another difference between the examined excipients when they are used for the production of granules concerned the yield; using PVP, the raw material tended to form compact layers into the bowl of the Rotolab® and, comparing the formulations granulated by steam, Px/β-lactose steam granules provided the better yield (98% w/w) with respect to Px/PVP K12 (93% w/w) and to Px/PVP K90 (90% w/w) steam granules.

3.1. Size distribution and drug content

Fig. 1 shows the size distribution of the granules, in which the prevalent size (more than 55% w/w) ranges from 75 to 200 μm; the use of PVP provided larger granule size ($x > 750$ μm) than β-lactose because of their higher viscosity.

Table 1 reports the Px content in each fraction of the granules. The results indicate the uniform distribution of the drug in the granules both with β-lactose and PVP; in particular, in the formulation containing Px/β-lactose, there were no differences in the drug loading between water and steam granules.

3.2. Morphological studies

The surface morphology of the samples is shown in Fig. 2: the comparison between Px/β-lactose water granules (Fig. 2A) and Px/β-lactose steam granules (Fig. 2B) points out that, although the surface appears quite irregular and rough in both granules, steam granules present a more porous surface compared to water granules, and this fact can contribute to increase the surface area exposed to the dissolution medium. On the contrary, no significant differences were observed in the granule surface using PVP K12 and K90.

In order to gather more information about the micro-morphology of the granules and to correlate their properties to dissolution profiles, image and fractal analysis were performed on the prevalent granule fraction ($75 < x < 200$ μm).

Table 2 reports the results of image analysis in terms of size (area, perimeter and ECD) and shape parameters (shape factor and aspect ratio). The perimeter and area values of Px/β-lactose formulation underline that steam granules had a larger surface area relative to water granules, confirming the SEM micrographs; whereas lower values of these

Table 1
Drug content of the different granule size

μm Fraction	Drug content (% w/w ± SD)			
	Px/β-lactose water granules	Px/β-lactose steam granules	Px/PVP K12 steam granules	Px/PVP K90 steam granules
$75 < x < 200$	10.65 ± 0.56	10.05 ± 0.37	10.38 ± 0.41	10.25 ± 0.18
$200 < x < 400$	9.63 ± 0.84	11.23 ± 0.42	11.23 ± 0.15	9.87 ± 0.38
$400 < x < 500$	11.70 ± 0.25	10.21 ± 0.29	9.84 ± 0.44	10.58 ± 0.71
$500 < x < 750$	10.08 ± 0.07	9.41 ± 0.18	9.67 ± 0.29	9.63 ± 0.14

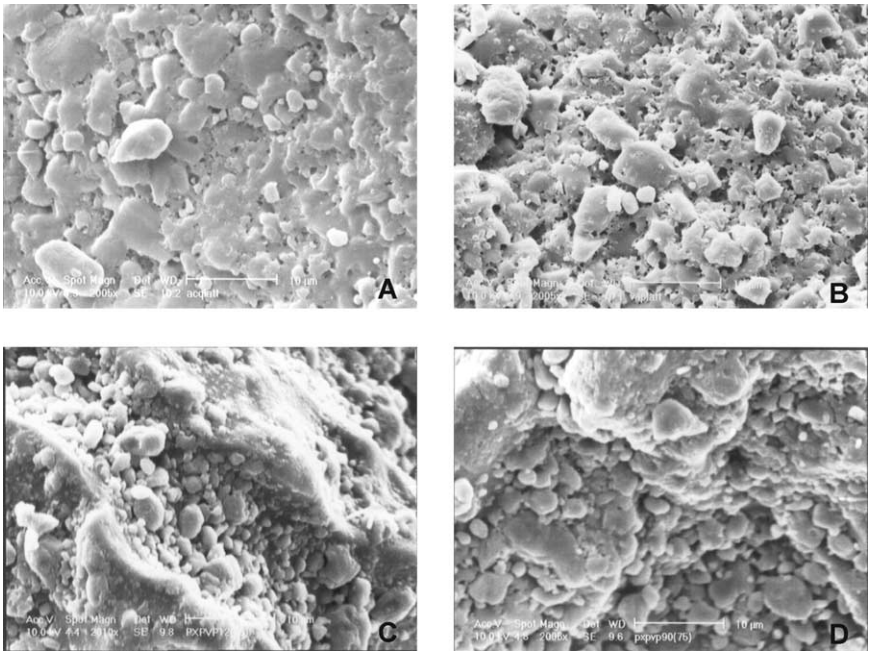

Fig. 2. SEM pictures of the surface of Px/β-lactose granules obtained using water (A) and steam (B), of Px/PVP K12 (C) and Px/PVP K90 (D) steam granules, at a magnification of 2000 ×.

parameters were observed in Px/PVP K12 and K90 steam granules. The values for ECD for each formulation, apparently not correlated to the analysed granule size, show the absence of sphericity (each value is higher than 200 μm); moreover, in all the examined granules, the shape factor (s) values were <1, pointing out the irregular shape of the granules. Finally, for all the examined samples, the aspect ratio (a) values are >1, indicating again a deviation of the granules from the perfect spherical shape, especially for PVP granules.

Fractal analysis is a mathematical tool very useful to describe the nature of the granule surface, as this technique allows to include in a single parameter, the fractal dimension of the surface (D_s), parameters such as roughness or the presence of irregularities on the granule surface, that are difficult to quantify and that cannot be calculated from image analysis.

The results of the fractal dimension ($D_s = 2.9391$ for Px/β-lactose water granules; 2.9632 for Px/β-lactose steam granules; 2.8020 for Px/PVP K12 and 2.7725 for Px/PVP K90 steam granules), calculated from the slope of the Richardson plot (not reported), indicate that the granules had a quite irregular and rugged surface, which could have a positive effect on the dissolution behaviour. In particular, these data reveal that Px/β-lactose steam granules were more rugged and irregular than Px/β-lactose water granules and PVP-s granules; Px/PVP K90 steam granules, showing the lower fractal value, had a smoother surface which was not easily distinguishable from that of Px/PVP K12 granules in SEM micrographs. Therefore, PVP K90 granules should display the slowest release of Px among the examined granules.

3.3. Solid state characterization of the granules

The characterization of the solid state of the granules was performed in order to evaluate possible modifications of the physico-chemical properties of Px or β-lactose and PVP and to study possible interactions between the drug and the excipients. In fact, the wet granulation process itself or

Table 2
Image analysis results of different granules

Parameters[a]	$75 < x < 200$ μm Fraction			
	Px/β-lactose water granules	Px/β-lactose steam granules	Px/PVP K12 steam granules	Px/PVP K90 steam granules
Area ± SD (mm^2)	2.652 ± 0.958	3.163 ± 0.657	0.755 ± 0.294	0.424 ± 0.128
Perimeter ± SD (mm)	2.773 ± 0.784	2.886 ± 0.378	1.715 ± 0.454	1.616 ± 0.508
ECD ± SD (mm)	0.572 ± 0.610	0.631 ± 0.069	0.305 ± 0.060	0.273 ± 0.011
Shape factor (s) ± SD	0.473 ± 0.186	0.488 ± 0.122	0.346 ± 0.122	0.231 ± 0.092
Aspect ratio (a) ± SD	1.633 ± 0.410	1.453 ± 0.220	1.779 ± 0.415	1.709 ± 0.584

[a] The parameters were calculated at a magnification of 30 × ($n = 20$).

the use of steam could lead to a modification of the drug solid state (i.e. transformation from crystalline to amorphous form); furthermore, the presence of PVP in a formulation could promote an amorphisation process [18]. Moreover, β-lactose exhibits different forms (β-lactose or β-anhydrous, α-anhydrous and α-monohydrate) [19]; therefore it is important to evaluate the solid state of both the drug and the excipient in the final granules using DSC and XRD.

DSC curves of Px, β-lactose, their physical mixture and wet granules are shown in Fig. 3(a). Px displays a melting endotherm at 201.18 °C (T peak) indicating that the drug is in a crystalline form ($\Delta H = 107.15$ J/g), while the DSC scan of β-lactose shows an endothermic peak at 238.06 °C, in agreement with Ford and Timmins [20], who reported that β-lactose shows a single endotherm peaking at 240 °C [21]. In the Px/β-lactose physical mixture, Px melts at 199.35 °C with a ΔH of 9.03 J/g, indicating that Px remains in its original state (the amount of drug in the mixture is 10% w/w). On the contrary, the β-lactose endothermic peak shifts to a temperature of 222.15 °C, suggesting the transformation of β-lactose into the α-anhydrous form, which melts around 223 °C [19].

As regards the Px, the curves of Px/β-lactose water and steam granules do not show any modifications of the maximum temperature with respect to the physical mixture;

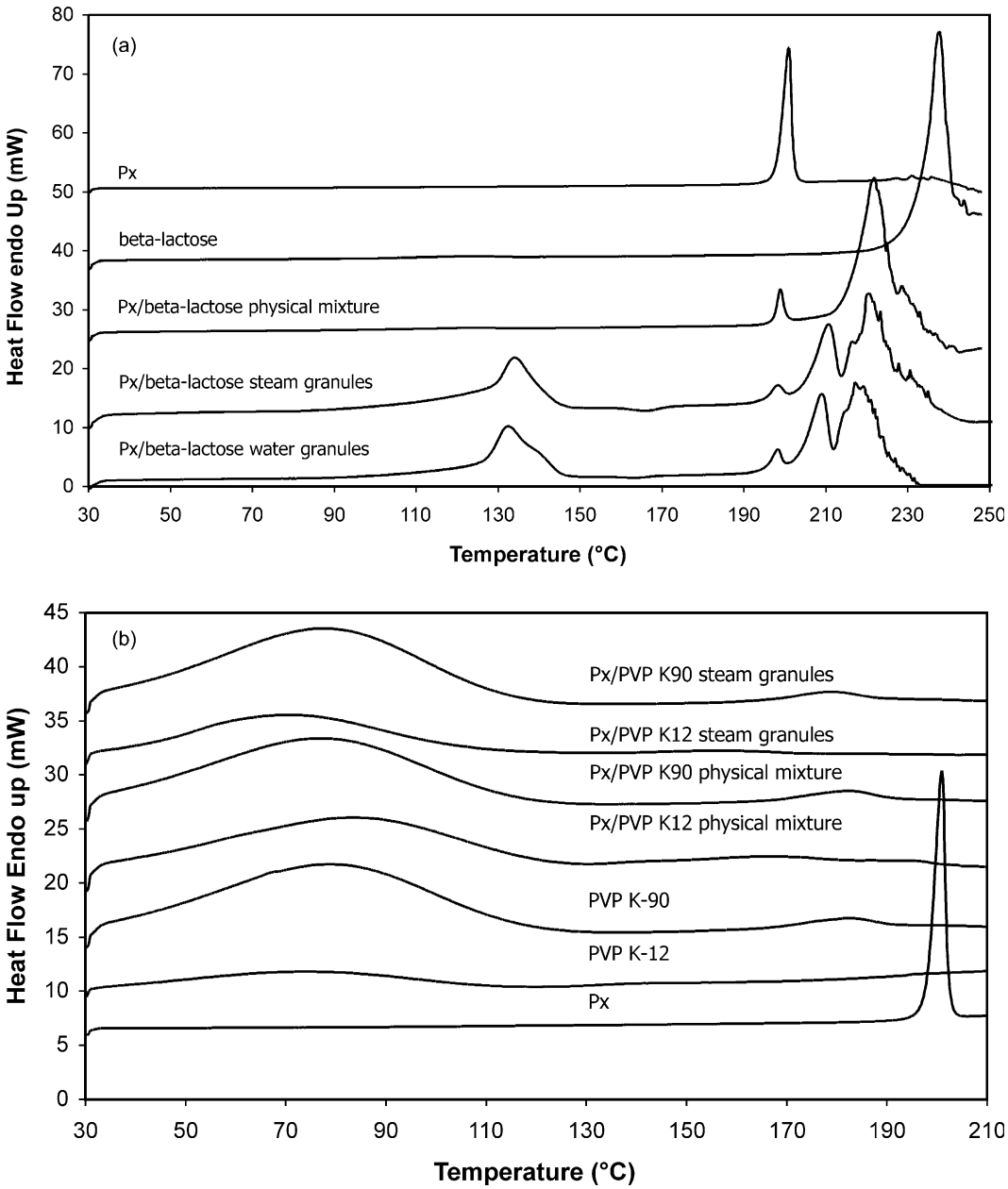

Fig. 3. (a) DSC curves of Px; β-lactose; their physical mixture; steam and water granules. (b) DSC curves of Px; PVP K12; PVP K90; Px/PVP K12 physical mixture, Px/PVP K90 physical mixture; Px/PVP K12 and K90 steam granules.

however, the ΔH values decrease to 5.28 J/g for water granules and to 3.81 J/g for steam granules, suggesting a partial amorphisation of the drug, which could affect the dissolution profile of the drug. The DSC curves of water and steam granules show a further modification of the lactose peak; the excipient exhibits three endothermic peaks, which may be a dehydration endotherm at 133–134 °C and two melting endotherms at 210.66 and 220.96 °C for Px/β-lactose steam granules and at 209.18 and 219.59 °C for Px/β-lactose water granules. These results suggest the transformation of β-lactose into both α-anhydrous and α-monohydrate lactose, which has a broad dehydration endotherm around 140 °C [19] and a melting point at 202 °C. It is known that β-lactose cannot exist as the monohydrate, however, at high humidities it can mutarotate to α-lactose with subsequent incorporation of water. This happens because β-lactose has a highly compact structure that cannot accommodate a water molecule [21]. Therefore, the exposure to water or to water vapour (steam) during the granulation process could form a concentrated solution in which β-lactose mutarotated to α-lactose (anhydrous) and subsequently water was partially incorporated to form the crystalline α-lactose monohydrate. Moreover it was found that the mutarotation from β to α-lactose can also proceed without the dissolution of the excipient: grinding and tabletting β-lactose resulted in α-anhydrous lactose, passing through a state of amorphous structure [21]. This fact could have happened in the case of the physical mixture, which was obtained powerfully c-mixing the components.

Fig. 3(b) reports the DSC curves of Px, PVP K12 and K90, Px/PVP K12 and Px/PVP K90 physical mixtures and Px/PVP K12 and Px/PVP K90 steam granules. The glass transition temperature (Tg) of amorphous PVP lies between 90 and 180 °C, depending on their molecular weight and on their moisture content [22]: the presence of water may also manifest itself as a broad endotherm during the scanning.

PVP K12 displays a change in the baseline between 100 and 120 °C, range in which the Tg of the polymer is included [23]; however, it was not possible to calculate the exact Tg using the selected DSC conditions. PVP K90 shows a broad endotherm between 50 and 120 °C, due to the presence of water and a Tg around 175 °C, as reported by Khougaz and Clas [23].

Both physical mixtures and steam granules containing PVP K12 and K90 reveal the disappearance of the Px peak, suggesting the transformation of the drug in the amorphous form. In order to confirm this hypothesis, the XRD analysis was performed. Fig. 4 shows the XRD diffraction patterns of Px (a), F2-SG (b) and F3-SG (c): Px shows the characteristic peaks of its cubic form at 8.6, 14.5, 17.75, 21.26 and 27.3° 2θ, while PVP diffraction pattern (not shown) is characterized by a broad signal due to its amorphous nature [17]. In the graphs of F2-SG and F3-SG, the characteristic peaks of Px are still present and they are superimposed to the broad signals due to the polymers; these results indicate that in the examined granules the drug is not completely in the amorphous state.

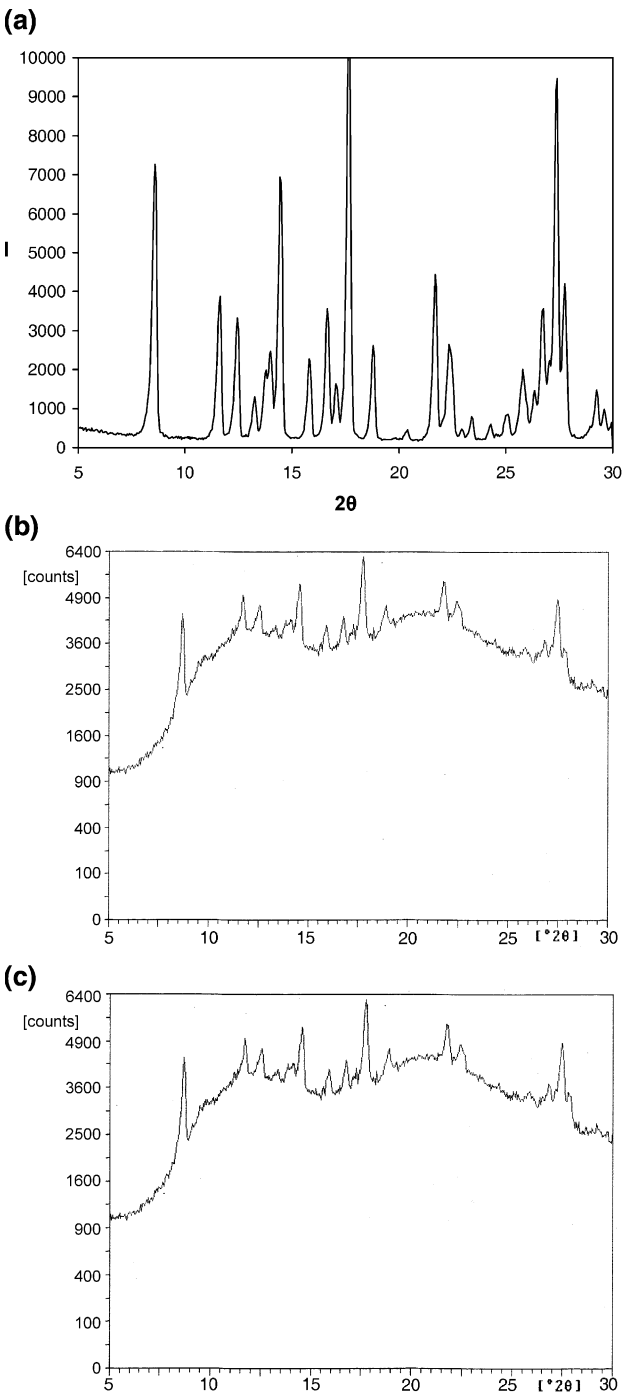

Fig. 4. X ray diffractometer of pure Px (a), Px/PVP K12 (b) and K90 (c) steam granules.

3.4. In vitro dissolution studies

In order to evaluate the efficiency of β-lactose and PVP in improving the dissolution release of Px from the granules, in vitro dissolution profiles of granules, pure drug and

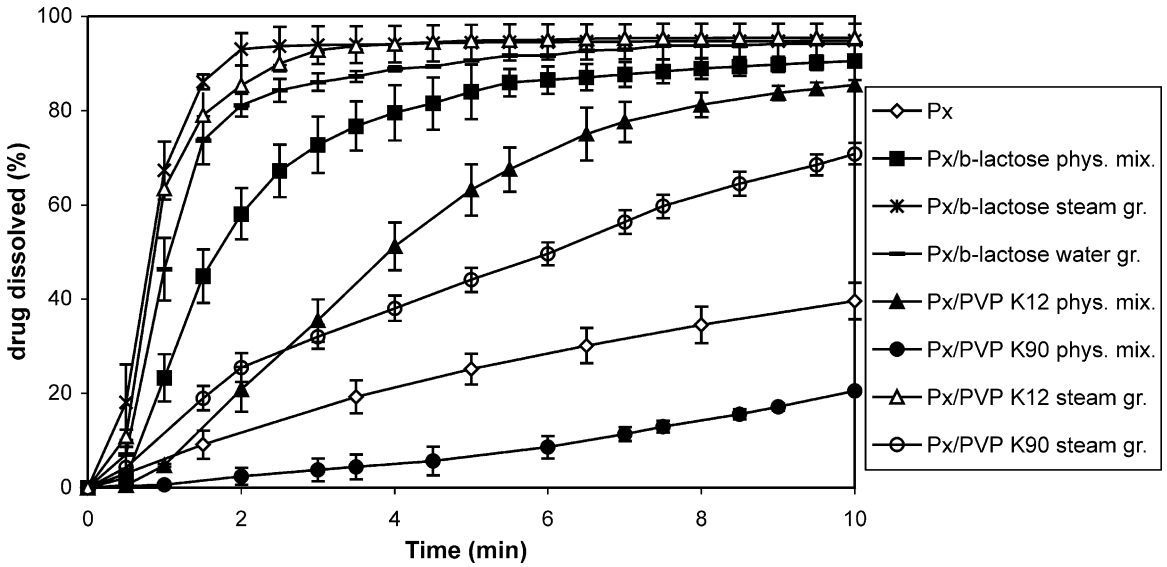

Fig. 5. In vitro dissolution profiles of the samples in pH 7.4 buffer.

physical mixtures of Px/β-lactose, Px/PVP K12 and K90 were compared (Fig. 5).

The dissolution rate of pure Px is quite low: the percentage of drug dissolved in 2 min was 11%; the formation of Px/β-lactose physical mixture improved this value to 58% after 2 min, thanks to the hydrophilic properties of β-lactose. Px/PVP K12 and Px/PVP K90 physical mixtures show a different behaviour: Px/PVP K12 physical mixture released 21% of the drug after 2 min while only 3% of Px was dissolved from Px/PVP K90 physical mixture at the same time. The enhancing effect of Px/PVP K12 physical mixture with respect to the pure drug is due to the hydrophylic nature of the excipient and probably to the partial transformation of Px into the amorphous state. When Px was in mixture with PVP K90, the release was quite slow; this behaviour could be explained considering the high viscosity of this excipient in the dissolution medium; in fact this polymer formed a gelified layer around the particles which reduced the drug dissolution. This effect compensated the increase of Px solubility due to its partial amorphisation.

As regards the granules dissolution profiles, Px/β-lactose steam granules show a better release than water granules (93 and 81% after 2 min, respectively), confirming that the steam granulation technique provided Px-β-lactose granules with rough surface, therefore with a higher surface area in comparison to traditionally wet granulated materials.

Px/PVP K12 steam granules show a significant increase of the dissolution rate in comparison to that of PVP K90, due to the lower viscosity of the PVP K12 solution, as previously observed for the physical mixtures; furthermore the reduction in the crystallinity of Px helped to improve the drug release. Therefore, steam granules of β-lactose and PVP K12 show a great increase in the Px dissolution and their release curves were almost superimposed, being 93 and 85% the amount of drug dissolved after 2 min, respectively.

3.5. Effect of the granule morphology on the dissolution behaviour

As previously described [15,16], the parameter of D_s reflects the morphology of the particle surface, but this surface does not always coincide with the reactive surface, which is actively involved in the dissolution process. Therefore, to differentiate between the geometric morphology of the surface, represented by D_s, and the morphology of the active surface, another fractal parameter D_R (the reactive dimension) has to be considered.

D_R was calculated from the slope of the plot (not reported) of ln of E_d vs ln of the particle size; to calculate E_d the dissolution profiles of the different granulometric fractions of Px/β-lactose and Px/PVP K12 steam granules were performed. The values obtained for D_R were 2.9734 and 2.9821 for β-lactose granules calculated at 2 and 5 min, respectively, and 2.9272 and 2.9770 for PVP K12 granules.

These results show that the reactive surface is higher for Px/β-lactose steam granules than for Px/PVP K12 ones, confirming the image and fractal analysis. Moreover, the results $D_R > D_s$ for all samples revealed that more reactive surface sites arise during the dissolution process. This fact can be correlated to the formation on the particle surface of cracks and pores, which cannot be measured using the Richardson method; therefore, the surface of the steam granules exposed to the dissolution medium can be considered more irregular than that observed by SEM and fractal analysis. In particular, this behaviour is much more evident in PVP K12 steam granules ($D_s = 2.8020$ and $D_R = 2.9272$) than in those containing β-lactose ($D_s = 2.9632$ and $D_R = 2.9734$), suggesting that PVP K12 was more able to widely modify the surface during

the solubilization of the granules than β-lactose, at least in the examined experimental conditions.

3.6. Stability studies

Finally, in order to evaluate the stability of the granules, in vitro dissolution tests and DSC analysis were performed. The dissolution profiles after 1 year storage of granules are very similar to freshly prepared ones; moreover, no differences in the DSC scans were detected (data not shown), according to the well-known property of PVP as inhibitor of drug crystallization [23]. These results suggest the physical stability of the samples, at least for the examined time.

4. Conclusions

The results showed that the use of PVP (K12 and K90) as "diluent-binders" enabled to obtain granules only by the steam technique, while the use of β-lactose produced both steam and water granules. β-Lactose provided granules with a more irregular and porous surface area than PVP, as observed by SEM and confirmed by the values of fractal dimension (D_s). These characteristics reflected on the dissolution behaviour, showing that β-lactose steam granules widely increased the dissolution of Px, followed by PVP K12 granules. This effect could be due to the partial amorphisation of the drug, as confirmed by DSC and XRD analysis. Among the analysed excipients, PVP K90 had the least influence on the granule morphology and the dissolution behaviour.

In conclusion, the findings of this work showed that steam granulation could be an interesting method to improve the dissolution rate of a poorly soluble drug as Px, when associated with a suitable excipient.

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