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Research paper

Improved dissolution behaviour of steam-granulated piroxicam

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Abstract

In this paper we prepared and characterized improved release granulates containing Piroxicam and β-cyclodextrins (1:2.5 molar ratio), obtained by steam-aided granulation, using a one-step rotogranulator, Rotolab®. These granulates were compared to those prepared by traditional wet granulation, to the physical mixture, and to the kneaded and dry granulates. The experimental data showed a significant reduction of the water amount required (50%) and of the working time, with respect to traditional wet granulation. The samples examined by scanning electron microscopy and fractal analysis revealed morphological differences related to the method of preparation: the steam-granulated material showed a diffuse porosity, as confirmed by the porosity test. Differential scanning calorimetry, infrared and X-ray analysis revealed the absence of polymorphs in the solid state of the drug. The results of the dissolution tests suggest that the steam-aided granulation may be considered a useful method to improve the in vitro dissolution rate of Piroxicam, enabling also a considerable reduction in the processing time.

Keywords: Piroxicam; β-Cyclodextrin; Steam granulation; High shear mixer; Improved dissolution rate

1. Introduction

The wet granulation method has been used for a long time in the industrial production of granules. The most frequently used equipment includes traditional shear mixers, high-speed or high-shear mixers/granulators with high tip speeds of the impeller and the chopper (typically 10 m/s or higher) and fluidized-bed granulators [1]. For specific applications other equipment, such as spray dryers and extruders, can also be used [2]. In particular, high-speed mixer granulators are often employed for this process because they allow a short granulation time, high-density and hard granules, and easy machine handling [3,4].

A number of studies has been published describing the effect of the operating conditions on granule quality (size enlargement, size distribution, density, porosity and changes in crystallinity of the pure drug) as a guide to optimize the process [5] and also the performance of nine different high-speed mixers in terms of porosity and size distribution of the granules has been evaluated [6]. Moreover, three different methods to add the liquid were examined and it was found that the method of addition affected both the size distribution and the growth behaviour [1]. It was reported that the strength of granules increased when the supply of water, as granulating liquid, was improved [7]. Furthermore, high shear mixing enabled the production of spherical and smooth pellets, an important feature if they are intended to be coated in a further stage, even though the size distribution of the pellets was larger than for the extruded ones [8].

In this work a steam granulation process was applied to a mixture of Piroxicam (Px) and β-cyclodextrins (β-CD). Px is a poorly water soluble drug [9], so its association with the hydrophilic β-CD can affect its availability by improving the dissolution rate. Many techniques have been developed to prepare suitable Px/β-CD granules, such as kneading, spray drying, grinding and co-precipitation from various solvents [10–12] and recently, a new technology was also patented [13] in which the two substances are co-grinded in a high-energy mill saturated by steam.

The aim of the present research was to study the influence of a steam-aided granulation [14] on the in vitro dissolution rate of Px, from a formulation containing β-CD. The pure Px and its physical mixtures with β-CD were compared with the kneaded product, with the dry granules and with the water and steam granules (WG and SG, respectively).

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2. Materials and method

2.1. Materials

Piroxicam, in micronized (more than 90% of the powder had a particle size less than 10 μm) and anhydrous form, was purchased from C.F.M. SpA (Milan, Italy). β-Cyclodextrins was a commercial sample (Kleptose®) containing 12% w/w hydration water and kindly supplied by Roquette Frères (France). Both samples were used as received.

2.2. Sample preparation

2.2.1. Physical mixture

Px and β-CD were mixed in a glass mortar at a 1:2.5 molar ratio, corresponding to 10.4 and 89.6% (w/w), respectively.

2.2.2. Dry granules

The mixture was compacted into tablets using a single-punch tabletting machine (Korsch, mod EKO, Berlin, Germany) at a compression force of 50 kN/cm^2. The tablets (weight 200 mg, diameter 11 mm, hardness 6 kg) were crushed and sieved, and the 75–200 μm fraction was selected. The hardness of the tablets was determined using an Erweka Type TB24 tester (Erweka-Appareban GmbH, Heusenstamm, Germany).

2.2.3. Kneaded product

Five grams of the physical mixture were milled for 1 h in a mortar using 1 ml water; the paste thus obtained was dried in an oven at 38 °C for 24 h. The final solid was then powdered and sieved, and the 75–200 μm fraction was collected.

2.2.4. Water and steam granules

The granulated material was obtained both with water and steam using a one-step mixer granulator dryer (described below), Rotolab® (Zanchetta SpA, Lucca, Italy). Both WG and SG were sieved and the 75–200 μm fraction was collected and used for all the further tests. These granules and the kneaded product turned yellow during the preparation, due to the transformation of Px into its monohydrate form [9].

2.2.5. Equipment

The diagram of the apparatus is shown in Fig. 1. The main part of the Rotolab® rotogranulator is a hermetically air-tight and 2 l thermostated vessel. All wet granulation tests were carried out using batches of 400 g. The thrust, bearing of the impeller at the bottom of the bowl, incorporates the so called Gas Stripping System (GAST System), a tiny flux of air injected into the bowl, to avoid any entrapping of liquids or solids. The GAST also accelerates the drying step of the granulation. The air-tight lid holds the chopper, the thermocouple sensor, the inlet water and the outlet connected to a vacuum pump (inner residual pressure 0.4 atm). During the drying, the bowl can be tilted in order to mix the material, improving both the heat exchange and the drying rate without damaging the granules mechanically. The steam was produced in a small electric boiler calibrated at a pressure of 3.5 atm. The boiler supplied, through a short thermally insulated tube, a steady steam flow of 0.75 g/s. The steam, carried by a Rilsan® tube (6 × 4 mm), came into contact with the material 5 mm above the impeller. All of the working parameters of the apparatus were accurately pre-set for static or on/off operation and recorded. Moreover, by interfacing the Rotolab® with a PC, a complete batch master file was recorded.

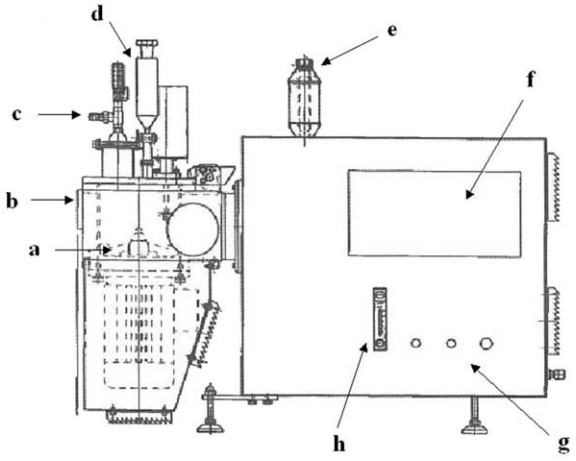

Fig. 1. Diagram of the apparatus: (a) impeller, (b) thermostated vessel, (c) vacuum filter, (d) water and/or steam inlet, (e) jacket heating circuit expansion vessel, (f) control panel, (g) command devices, (h) GAST flow indicator.

2.3. Sample characterization

2.3.1. Morphological analysis

The size distribution of granules was evaluated using a set of vibrating sieves for 20 min and with four standard sieves of 75, 200, 400 and 750 μm (Scientific Instruments s.r.l., Milan, Italy). The morphology of Px, β-CD, physical mixture and Px/β-CD granules was examined with a scanning electron microscope (SEM) (Philips, XL30). The samples were sputter-coated with gold before SEM analysis.

The surface area of water and steam granules was analysed by BET adsorption using a helium porosimeter (Coulter SA-3100), setting the following parameters: gas temperature 25 °C, elapsed time 20 min, sample weight 1.72 ± 0.01 g.

The size (area, p (perimeter) and ECD (equivalent circle diameter)) and shape parameters (major/minor axis, s (shape factor), a (aspect ratio)) are useful to describe the micromorphology of isolated granulates. The ECD is the diameter of the circle that has an area equal to that of a particle and it is calculated using Eq. (1):

$$ECD = 2\cdot\sqrt{\text{area}/\pi} \quad (1)$$

For a circular particle the shape factor is unity, while for all other particles its value is lower than 1; this value is obtained using Eq. (2):

$$s = 4\pi[\text{area}/(p\cdot p)] \quad (2)$$

The ratio of the major and minor axis of the ellipse best fitting the particle is the aspect ratio; it underlines the elongation of the particles and for round and square particles the aspect ratio is unity. For those elongated in the *y*-direction, the ratio is lower than unity, whereas particles elongated on the *x*-axis have a value of larger than unity. All these parameters were calculated analysing at least 20 particles for every sample and the mean ± standard deviation (SD) was reported.

The fractal dimension (*D*), a measure of the particle surface, was calculated from the slope of Richardson's plot (ln of perimeter length vs. ln of step length [15,16]: Slope $= 1 - D$. The step length is the parameter with which we measured the perimeter (1000, 500, 200, 100 and 50 μm).

2.3.2. Solid state characterization

The weight loss by thermal drying of both steam and water granules was determined using a Top Ray thermal balance (Alessandrini, Modena, Italy) at 105 °C for 1 h. Five grams of each sample were heated until constant weight was achieved and this test was repeated three times for each kind of granule.

The differential scanning calorimetry (DSC) tests were performed using a Perkin Elmer DSC 6 using 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.

Studies of infrared (IR) spectra of Px, β-CD and their products were conducted with an IR spectrophotometer (Jasco A200) using the KBr disc method. The powder blends were compressed into a tablet, 10 mm in diameter and 3 mm in thickness, using an hydraulic press for KBr pellets at 300 kg/cm for 1 min.

X-ray patterns were carried out using a Philips powder diffractometer. Samples were exposed to Cu-K_α radiation ($\lambda = 1.5418$ Å) in the range $5° \leq 2\theta \leq 30°$ with a step of 0.5°, and the time for each step was 2 s.

2.3.3. Dissolution studies

Using a wettability tester Lorentzen-Wettre (Sweden), the wettability of the samples was evaluated by direct measurement of the contact angles. Drops of distilled water were placed on the compacted surface by a microsyringe. The contact angle values were derived from the height and the length of the drop image. At least six determinations were carried out for each sample.

Dissolution rate studies were performed using a calibrated USP XXIII paddle apparatus (Pharmatest, Steinheim, Germany), connected by a peristaltic pump (Gilson Minipuls 3, Villiers-le-Bel, France) to a flow-through spectrometer (Unicam UV/Vis spectrophotometer model UV2, Cambridge, UK) and the absorbance at 287 nm was automatically recorded. The pump operated at a rate of 12.5 ml/min and the dissolution medium was a phosphate buffer, pH 7.4. The determinations were performed at a rotational speed of 50 rpm and at a constant temperature of 37 °C. The dissolution tests were performed at least in triplicate.

3. Results and discussion

The main advantages of a wet granulation are: (a) improved flowability and compressibility of the final materials [4]; (b) a change of hydrophobic into hydrophilic surfaces, so improving the bioavailability; (c) an improvement of homogeneity of low dosage forms; and (d) that the adverse influence of poor electrostatic properties of the powder are avoided [7]. In spite of these advantages, the wet granulation processes usually have the disadvantage of requiring several stages [2].

One-step high shear granulators, developed to comply with GMP requirements and to reduce the cross-contamination and the environmental hazards, are able to operate in a closed unit and require only few stages: mixing, primary and secondary granulation, and drying. In the primary granulation the binder solution is sprayed on the powder; in the secondary granulation, the wet product is kneaded in order to produce and to enlarge the granules. The material is finally dried under a suitably low pressure at a moderate temperature.

Water, as a granulating agent, in contrast to organic solvents, is not flammable and does not require expensive safety precautions [2]. However, there are two critical steps associated to the use of water: its distribution uniformity into the solid bed and its elimination, which must be as rapid as possible.

These considerations suggest the possibility of employing steam instead of water in wet granulation: steam provides a higher diffusion rate into the powder and a more favourable thermal balance during the drying step. After condensation of the steam, water forms a hot thin film, requiring only a small amount of extra energy for its elimination, and evaporates more easily [17]. As a consequence, the differences among granules obtained by means of a steam-supplemented Rotolab® and those obtained by more traditional methods (particularly with liquid water granulation) were compared from the chemical-physical point of view and their behaviour to the release of the active agent was examined.

3.1. Evaluation of process parameters

Table 1 compares the pre-set operational parameters used

Table 1
Comparison between the operational parameters used in water and steam granulation

Steps	Process parameters	WG	SG
Mixing step	Time (min)	10	10
Primary granulation	Time (min)	1	1
	Jacket temperature (°C)	25	60
	Water amount (ml)	30	15
	Impeller speed (rpm)	600	600
Secondary granulation	Time (min)	5	7
	Jacket temperature (°C)	25	60
	Impeller speed (rpm)	800	800
Drying step	Time (min)	60	10
	Temperature (°C)	60	60
	Impeller speed (rpm)	120[a]	120[a]
Total time (min)		76	28

[a] 120, 10 s every 100 s.

in water and steam granulation. The analysis of these parameters suggest that in the mixing step there are no differences between water and steam granulation time. This step lasts about 10 min in both cases.

For the primary granulation the amount of water needed is considerably lower with steam than with liquid water (15 vs. 30 ml), due to the higher diffusivity of steam into the dry material. Consequently, steam acts as a stronger and a more efficient binder than liquid water. In fact, the type and the amount of binder added to the formulation play a fundamental role in the uniformity of particles size, hardness, disintegration and compressibility of granules. In particular, our preliminary experiments have demonstrated that inhomogeneous liquid distribution might result in the formation of overwetted lumps, as reported also by Holm [18]. A more homogeneous liquid distribution can be achieved by atomizing water or the binder solution; in any case, the action of steam is more homogeneous and more reliable.

Another important difference is the jacket temperature, which must be kept at 60 °C using steam (as compared to 25 °C in water granulation), to reduce condensation on the inner walls of the bowl; this phenomenon could cause compact layers which lead to a loss of product and to a difficult cleaning of the bowl. The working time for both granulation methods is 1 min.

During the optimization of the two granulation methods, higher dissolution profiles were observed with increasing time of secondary granulation. In particular, 7 min is the optimum for steam granulation, and resulted in granules of homogeneous size. On the contrary, for water granulation the increase of working time does not result in a quicker dissolution rate of the final material and 5 min are sufficient to obtain granules with very good morphological features. Another parameter that can affect the dissolution profile is the impeller speed; previous experiments showed that 800 rpm is the optimum speed for both water and steam granulation. During this phase both granules turned yellow due to the hydration of Px [9], whereby SG displayed a more intense yellow colour than WG. Probably, this behaviour is due to the high thermal energy of steam and to its ability to diffuse into the granules.

The jacket temperature pre-set at 60 °C shortened the drying step with both methods, keeping a discontinuous tilting of the bowl. The time required for this step is a function of the amount of water added during the primary granulation. As a consequence, the drying step is simplified and shortened (10 min) for steam as compared to water granulation (60 min).

3.2. Morphological analysis

The size distribution of WG and SG, illustrated in Fig. 2, provides very similar results: more than 60% of each material is between 75 and 200 μm size and the percentage of lumps ($X > 750$ μm) is very low. Generally, a reproducible granule growth pattern is a consequence of an homogeneous liquid distribution; additionally, in our experiments with the Rotolab® we observed that granule growth is primarily affected by the impeller's speed, by the amount of the liquid and by the processing time. In fact, more than 60% of granules ranging from 75 to 200 μm is achieved with an impeller speed of 800 rpm. Moreover, the content of big lumps (although generally low) was found to be higher with water than with steam, and the size distribution showed that the content of fine granules increased with the mixing time during the secondary granulation in both processes.

Fig. 3 shows the SEM micrographs of the several samples at different magnifications. Px (Fig. 3a) appears to be a bulk of aggregated particles, due to the micronized form of the drug, whereas monolithic blocks with a smooth surface are evident in the β-CD sample (Fig. 3b); physical mixture (Fig. 3c) shows some micro cracks formed by the forces acting on β-CD during the mixing step. In dry granules (Fig. 3d) the cracks on the surface are even more evident and with casual directions, as a consequence of the different forces operating

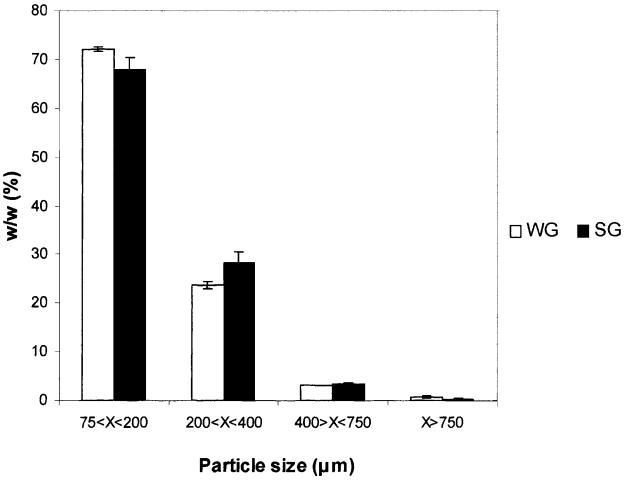

Fig. 2. Particle size distribution of Piroxicam 10.4% and β-CD 89.6% (w/w) granules.

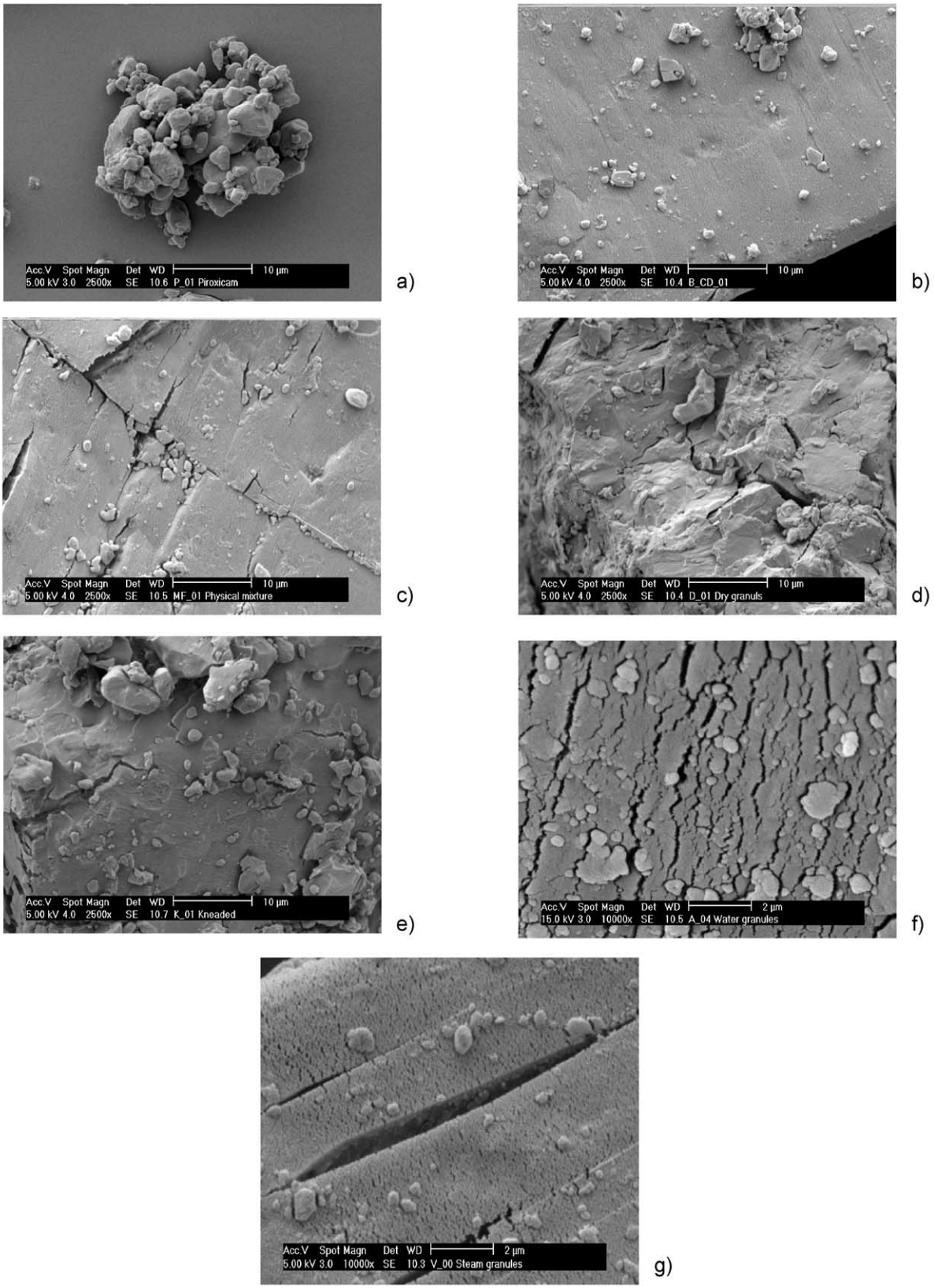

Fig. 3. SEM micrographs of (a) pure Piroxicam, (b) β-CD, (c) physical mixture, (d) dry granules, (e) kneaded product, (f) WG, (g) SG.

Table 2
Image analysis: size and shape parameters of Px/β-CD granules

Parameters (at magnification 30×)	SG ($75 < x < 200$ μm)	WG ($75 < x < 200$ μm)
Area ± SD (mm^2)	1.639 ± 0.576	1.515 ± 0.555
Perimeter ± SD (mm)	1.918 ± 0.646	2.203 ± 0.606
Equivalent circle diameter (ECD) ± SD (mm)	0.444 ± 0.082	0.432 ± 0.082
Shape factor (S) ± SD	0.578 ± 0.180	0.441 ± 0.188
Ellipse major axis ± SD	0.642 ± 0.207	0.588 ± 0.118
Ellipse minor axis ± SD	0.315 ± 0.090	0.328 ± 0.094
Aspect ratio (a) ± SD	2.124 ± 0.727	1.959 ± 0.806

during the compaction and the shattering of the tablets. The morphology of the kneaded product (Fig. 3e) is quite similar to the previous one and is characterized by a sponge-like structure.

The micrographs of WG (Fig. 3f) and SG (Fig. 3g) reveal some important differences in porosity. The material granulated with liquid water is similar to dried mud, characterized by a net of cracks on a compact dry structure. On the contrary the morphology of SG is more complex, being characterized by wider and deeper cracks, which are superimposed to a finer diffuse porosity: in fact steam granules have a higher surface area (0.597 m^2/g) compared with that of WG (0.459 m^2/g), as determined by gas adsorption. This difference of porosity between WG and SG is probably due to the high thermal energy of steam and to the experimental granulating conditions described above; these experimental conditions enhance the evaporation of the moisture, not only on the surface but also from the core of the granules.

Image analysis shows that the granule size (Table 2) is quite independent of the process used: ECD values are comparable in WG and SG samples (0.432 ± 0.082 mm and 0.444 ± 0.110 mm, respectively). The ECD values underline the absence of sphericity; supported also by the values of the major and minor axis of the ellipse best fitting the particle (0.642 ± 0.207 and 0.315 ± 0.090 for SG and 0.588 ± 0.118 and 0.328 ± 0.094 for WG, respectively) and by the values of the aspect ratio (the ratio of these two parameters) and of the shape factor. In spite of this, there

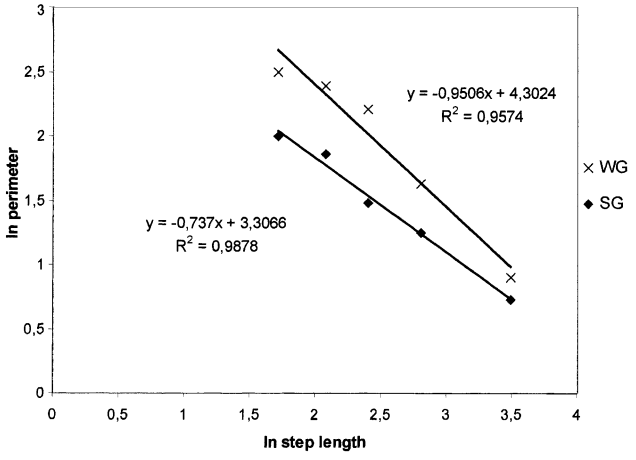

Fig. 4. Richardson's plot of Px/β-CD granules.

are differences in the projected area (1.659 ± 0.776 mm^2 and 1.515 ± 0.555 mm^2 in SG and WG, respectively) and in the perimeter values (1.918 ± 0.646 and 2.203 ± 0.606 mm, respectively). These values underline that SG have a larger surface area than WG.

We determined also the fractal dimension (D), a measure of the particle surface smoothness, which was calculated from the slope of Richardson's plot (shown in Fig. 4).

The results (Table 3) show that D_s value is larger for SG (2.9506) than for WG (2.7370). These values indicate roughness in the SG, in agreement with SEM micrographs and porosity analysis.

3.3. Solid-state characterization

Weight loss by thermal drying show that granules prepared using liquid water contain a higher amount of water (14%) than those prepared by steam (11.6%), as a consequence, the drying rate is higher for WG than for SG.

DSC, IR analysis and X-ray powder diffraction were performed to evaluate possible interactions between the drug and the excipient and to study the solid-state transformations of Px (amorphous and/or polymorphous forms).

DSC thermograms of Px, β-CD, physical mixture, kneaded product, dry granules, WG and SG are shown in Fig. 5. Px displays the melting peak at 198.17 ± 0.06 °C (T onset). DSC thermogram of β-CD shows, in the temperature range considered (30–250 °C), two thermal events: an endothermic peak in the range 60–120 °C, associated with loss of water (about 12%); a minor exothermic peak at 220 °C corresponding to a reversible transformation within the molecule [19].

Thermograms of the physical mixture, the kneaded, WG and SG (Fig. 5), suggest both the lack of physico-chemical interactions between the drug and the excipient and the absence of drug transformation. In fact, in these samples both the temperature at which the thermal events occur and the peak shape of Px and β-CD are unchanged (see

Table 3
Fractal analysis: parameters obtained in the D study

Samples	Slope of the plot	R^2	D_l	D_s
WG	−0.7370	0.9878	1.7370	2.7370
SG	−0.9506	0.9574	1.9506	2.9506

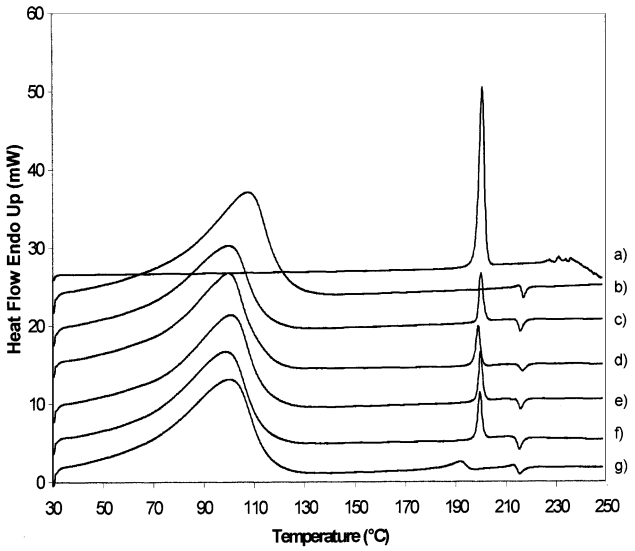

Fig. 5. DSC thermograms of (a) pure drug, (b) β-CD, (c) physical mixture, (d) kneaded product, (e) WG, (f) SG, (g) dry granules. The curves have been separated in the *y*-axis to aid visualization.

Table 4). Furthermore, the ΔH_{melt} values of Px are not very different than for pure Px, after correction for the composition of the samples.

By contrast, in the case of the dry granules, DSC thermogram and data reported in Table 4 show that the endothermic peak of Px shifts from the original value to a lower melting point (184.10 ± 0.52 °C). The shift of the endothermic peak of Px in the dry granulates can be explained by a transformation of Px from its original crystalline form to a polymorphic one, as previously reported by Ghan and Lalla [20]; their study showed that this drug undergoes polymorphic transition, from the *needle*-shaped polymorph to the *cubic* one, during compression.

The IR analysis confirms the DSC results. The IR spectrum (not shown) of pure Px shows that the drug form used in this study was the needle-shaped polymorphic form. In fact the bands of –NH and –OH stretching lie at 3385 cm^{-1}, the value characteristic of the needle form [21]. The IR spectra of the physical mixture, the kneaded product, WG and SG confirm the absence of chemical interactions between the drug and the excipient and of any modification in the solid state of the drug, while the IR spectrum of the dry granules shows the transformation of Px from the needle to the cubic form. In fact the band of –NH and –OH stretching shifts from 3385 to 3330 cm^{-1}, the characteristic frequency of the cubic-shaped polymorph [21]. This change is due to both the compression and friction forces during the grinding of the tablets.

The X-ray patterns of the examined samples are shown in Fig. 6, and they suggest the absence of an amorphous state. The diffraction pattern of Px (Fig. 6a) shows a series of intense peaks which are indicative of its crystallinity. This behaviour was also observed in the physical mixture (Fig. 6b), kneaded product (Fig. 6c), WG (Fig. 6d), SG (Fig. 6e) and dry granules (Fig. 6f).

3.4. Dissolution studies

The wettability of pure Piroxicam is low: the contact angle is 70.45°; wettability increases considerably when Px is in the form of kneaded product, WG, SG and dry granules (19°, 30.25°, 42.9° and 54.7°, respectively).

The low water solubility of Px (0.43 mg/ml in pH 7.4 buffer) explains the dissolution pattern (Fig. 7a) of pure Px and of its physical mixture with β-CD, since the amount of drug dissolved is about 40% after 10 min. The dissolution rate is higher for the kneaded product, WG and for the dry granules than for the physical mixture and for pure drug (the percentage of dissolved Px is about 80%). In the case of SG about the 90% is dissolved after 4 min. The same dissolution profiles are obtained after 1 h, as shown in Fig. 7b.

The increase of the dissolution rate of the kneaded product respect to the physical mixture can be explained by a higher wettability and by a closer contact between the drug and the excipient, as expected from the low value of the contact angle. For the dry granules, it is possible that the polymorphic change from the needle to the cubic form during compression is responsible for the change in the dissolution pattern respect to the physical mixture.

The high dissolution rate of WG and SG is due to the action of both the mechanical energy (shearing stress produced by the impeller) and/or the thermal energy (steam) which causes larger physical interaction between Px and β-CD. Moreover, the good wettability of the WG and mostly the higher porosity and the larger area of the SG can explain better their dissolution behaviour.

From the analysis of these experimental data, we may conclude that the use of steam instead of liquid water in a

Table 4
Differential scanning calorimetric data of the examined samples

Samples	*T* onset (°C)	*T* peak (°C)	Δ*H* (J/g)
Piroxicam	198.17 ± 0.06	201.18 ± 0.01	107.15 ± 0.05
Physical mixture	198.46 ± 0.03	199.99 ± 0.01	10.46 ± 0.18
Kneaded	197.11 ± 0.13	199.00 ± 0.24	9.52 ± 0.25
Water granules	198.09 ± 0.01	199.65 ± 0.01	9.86 ± 0.27
Steam granules	197.89 ± 0.01	199.40 ± 0.12	9.60 ± 0.07
Dry granules	184.10 ± 0.52	191.61 ± 0.12	4.54 ± 0.16

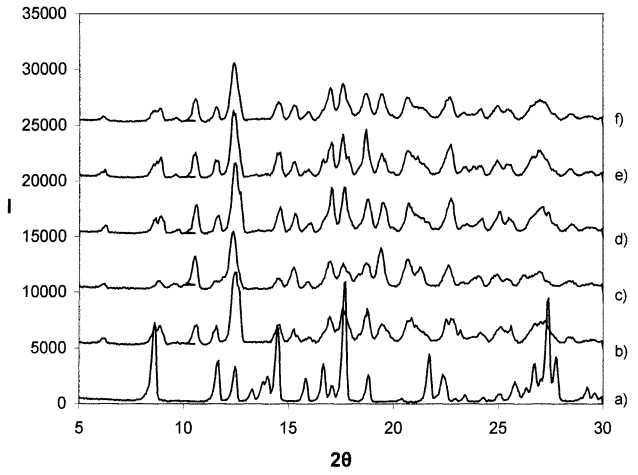

Fig. 6. X-ray diffraction patterns of (a) pure piroxicam, (b) physical mixture, (c) kneaded product, (d) WG, (e) SG and (f) dry granules. The curves have been separated in the *y*-axis to aid visualization.

wet granulation method can considerably decrease the amount of water used and consequently the whole working time. Moreover, despite a shorter drying step, SG have a lower water content. Furthermore, SG displays a higher porosity and a more irregular surface (higher fractal dimension) which increase the surface area exposed to the dissolution process. Thus, the steam-aided granulation of powders may be considered a useful method to increase the dissolution rate of this poorly soluble drug and thus to improve its availability. Further studies are in process to test the use of this technique to improve the dissolution rate of different poorly soluble drugs.

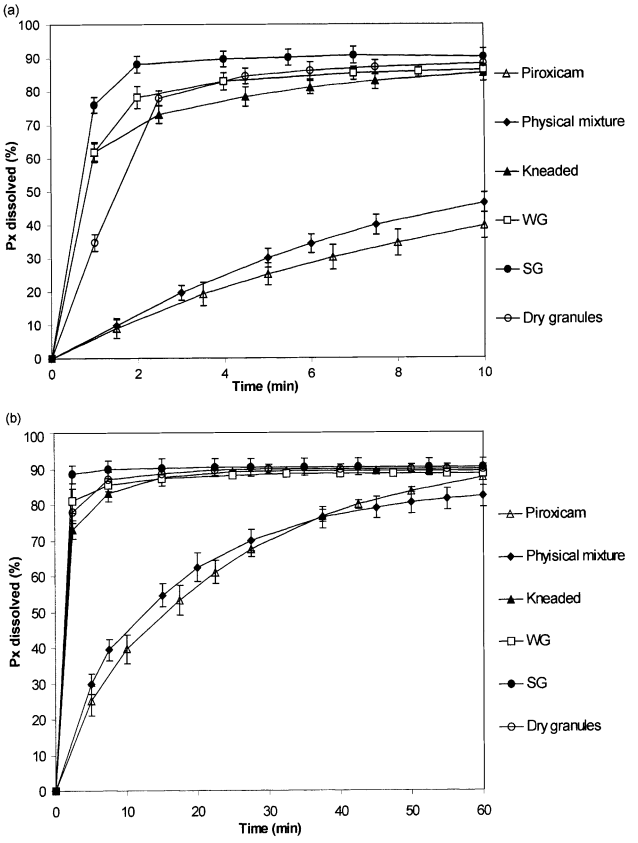

Fig. 7. (a) Dissolution profiles of Piroxicam 10.4% and β-CD 89.6% (w/w) in pH 7.4 buffer (first 10 min). (b) Dissolution profiles of Piroxicam 10.4% and β-CD 89.6% (w/w) in pH 7.4 buffer (1 h).

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