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Note

Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques

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Abstract

The steam granulation is a new wet granulation technique, which involves the use of steam water instead of traditional liquid water as granulation liquid. The aim of this work was to evaluate the possibility of using this new technique to prepare diclofenac–polyethylene glycol 4000 accelerated-release granules. Steam granules were prepared in a laboratory scale high-shear mixer, and their properties were then compared to those of granules, having the same composition, obtained by traditional granulation techniques (wet and melt granulation). The results showed that, selecting the proper process parameters, it was possible to obtain granules using all the three methods; however, the total process time was significantly shorter for steam granulation (30 min) in comparison to traditional wet granulation (70 min), due to the lower amount of used water. The morphological characterization of steam, water and melt granules, performed by scanning electron microscopy (SEM) and image analysis, revealed that steam granules had a more spherical shape and a larger surface area with respect to water and melt ones, suggesting a possible difference in dissolution behavior. Moreover, differential scanning calorimetry (DSC) and X-ray powder diffraction analysis evidenced the transformation of the drug from its originally crystalline form into the amorphous one. Finally, the in vitro dissolution tests showed an increased dissolution rate of the drug from the granules (in particular steam granules) in comparison to pure drug and physical mixture. In conclusion, the results of this study suggested that the steam granulation technique could be considered an interesting alternative to traditional wet granulation to improve the dissolution rate of diclofenac.

Keywords: Steam granulation; Wet granulation; Image analysis; Diclofenac; Polyethylene glycol 4000

Wet granulation is the most used method for the industrial production of granules; it is performed by spraying a liquid binder onto the particles, using a fluidized bed, an high-shear mixer or

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a similar device and then drying the granulated products (Ieveson et al., 2001). Recently, a modification in the wet granulation process has been developed (Raikar and Swartz, 2001): the moist granulation technique. It uses a small amount of granulating fluid, does not require a high-shear mixer and eliminates a costly drying step. Agglomeration takes place when the granulating fluid (water) activates the binder; the remaining ingredients are added with continuous mixing, and the moisture-adsorbing material was added last. Another technique alternative to the traditional wet granulation involves the use of steam as granulating liquid instead of liquid water (Rodriguez, 1999). The use of steam instead of water involves some advantages like a higher distribution uniformity and a higher diffusion rate into the powders and a more favorable thermal balance during the drying step, which suggest the possibility of using steam as a potentially convenient binder in wet granulation.

The aim of this study was to prepare, by steam granulation, granules containing diclofenac (Dic) as model drug (10% w/w) and polyethylene glycol (PEG) 4000 as the excipient (90% w/w). In order to evaluate if this novel technique could be advantageous, granules having the same formulation were obtained using traditional methods like wet and melt granulation, and they were than compared to the steam ones. In particular, PEG 4000, thanks to its physico-chemical features (hydrophilicity and low melting point), was chosen as the excipient suitable both for the wet and melt granulation and to improve the dissolution rate of Dic, a drug having a very low water solubility (17.8 mg/l) (Fini et al., 1999). The in vitro release of the drug from the granules was investigated, and the morphology was studied using scanning electron microscopy (SEM) and image analysis. Furthermore, differential scanning calorimetry (DSC) and X-ray powder diffraction were used to investigate possible interactions between the components.

Dic, kindly supplied by Farchemia s.r.l., Milano, Italy was used as poorly soluble model drug; PEG 4000 (Polichimica, Bo, Italy) was used as diluent and/or binder.

The physical mixture was prepared by mixing Dic and PEG 4000 in a Turbula® mixer for 10 min.

All the granules were prepared in a laboratory scale high-shear mixer (Rotolab®, Zanchetta s.r.l., Lucca, Italy) equipped with an electric-heated jacket; the volume of the bowl was 2 l, and the batch size was 300 g. In steam and wet granulation, the drug and the diluent were mixed in the high-shear mixer for 10 min, using an impeller speed of 120 rpm, and then the granulation liquid was sprayed (25 ml for water granulation and 12.3 ml for steam granulation). Steam was produced in a small electric boiler which supplied a steady steam flow of 0.75 g/sec. During this step the impeller speed was 600 rpm and the granulation time was 10 min; the jacket temperature was 25 °C for water granulation and 50 °C for steam granulation. In the latter case, the temperature was higher to avoid the steam condensation onto the granulating powders. Then the impeller speed was raised up to 800 rpm to chop the big lumps. Finally, the granules were dried at a reduced pressure and at 50 °C in both the methods, to allow the water evaporation. The drying time was 10 min for steam and 50 min for liquid water. Regarding melt granulation, 50% of PEG 4000 was mixed with the drug, while the remaining part was heated separately to 70 °C. After the mixing step, the mixture was heated up by heating the jacket to 50 °C and the molten PEG was added to the substrate. The impeller speed was 800 rpm and the granulation time was 15 min. At the end of the granulation process, water, steam and melt granules were collected and sieved as described in the following section.

The size distribution of granules was evaluated using a vibrating shaker (Octagon Digital, Endecotts, London, UK) and five standard sieves (Scientific Instruments s.r.l., Milano, Italy) in the range 75–1500 μm. The 750–1500 μm fraction was used for the dissolution and image studies. The morphology of the samples was examined using SEM (Philips XL30); the samples were previously sputter-coated with gold. Image analysis was carried out as previously reported (Fini et al., 1996). Briefly, this method calculates a set of shape descriptors, developed to demonstrate deviation

from an ideal geometry (the sphere) (Hickey and Concessio, 1997). The size parameters (projected area and perimeter) and shape parameters (shape factor "*s*" and aspect ratio "*a*") are obtained to describe the micro-morphology of the samples.

The DSC analysis was performed using a Perkin–Elmer DSC 6 with nitrogen as purge gas (20 ml/min). The weight of each sample was 8 ± 1 mg and the heating rate was 10 °C/min. X-ray patterns were obtained using a Philips PW 1830 powder diffractometer. 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.

The analysis of the Dic content in the 750–1500 μm fractions was carried out by dissolving 30 mg of granules in 100 ml pH 7.4 buffer; the amount of drug was then spectrophotometrically determined (UV2 Spectrometer, Unicam, Cambridge, UK) at 273.0 nm. In vitro dissolution tests were performed using USP 24 paddle method rotating at 50 rpm, with a dissolution medium of 900 ml at a temperature of 37 °C. Each sample contained 30.0 mg of Dic; these tests were performed at least in triplicate.

Previous studies (Knight et al., 1998; Ieveson et al., 2001) have demonstrated the importance of the process variables (impeller speed and jacket temperature), the binder viscosity and the liquid distribution for the control of granule nucleation and for consequent growth behavior.

Therefore, to select the proper process parameters, the granulation process was preliminary tested using a placebo formulation. The analysis of the working parameters described above shows that the most important difference between the three methods is the whole process time. A comparison between water and steam granulation shows that 30 min are necessary to obtain the steam-granulated products, with respect to the 70 min required using water as the binder. This significant shortening in working time is the effect of the reduced amount of water in steam granulation with respect to water one (12.3 ml and 25 ml, respectively). As a consequence, also the drying time is shortened (10 min in steam granulation instead of 50 min in water granulation). In melt granulation, the molten PEG acts as a liquid binder, and consequently the use of water is not required, reducing the granulation time to 15 min.

The granule size analysis shows an irregular distribution: each kind of granules has its own prevalent fraction (75–200 μm, 750–1500 μm, 500–750 μm for steam, water and melt granules, respectively); therefore, the 750–1500 μm fraction was chosen for the following studies, exceeding 25% (w/w) in all the samples. The determination of the drug content shows that in the three kinds of samples the amount of Dic in the examined fraction is quite close to the theoretical one, regardless of the granulation method (10.93, 9.96 and 9.69% in water, steam and melt granules, respectively).

The morphology of the granules is shown in Fig. 1. The comparison between water, steam and melt granules points out that steam granules have a more spherical shape in all the samples and the surface is quite irregular. To better analyze the information supplied by SEM and to correlate the morphological granule properties to the dissolution profiles, image analysis was carried out (Table 1). The values of perimeter and area underline that steam granules have a surface area larger than water and melt granules: this difference could result in different behavior in the dissolution rate of Dic. Moreover, steam granules have a lower value of "*a*" (taking into account the standard deviation), suggesting the more spherical shape of these granules, as already shown by SEM. This feature is also confirmed by the value of "*s*".

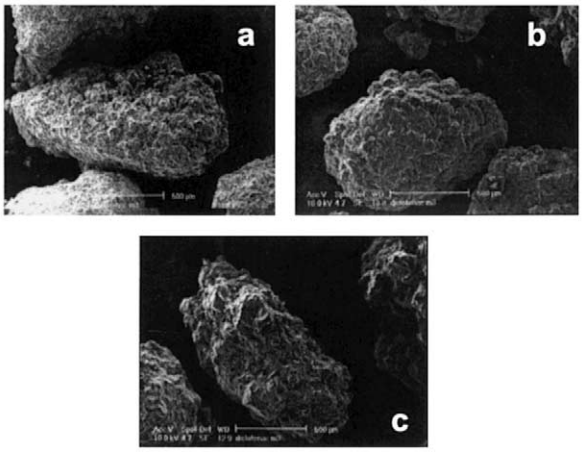

Fig. 1. Electron microscopy images of (a) water, (b) steam and (c) melt granules.

Table 1
Image analysis: size and shape parameters of Diclofenac/PEG 4000 granules.

Samples	Area ± SD (mm^2)	Perimeter ± SD (mm)	Aspect ratio (a) ± SD	Shape factor (s) ± SD
Water granules	19.84 ± 7.94	6.07 ± 3.31	1.44 ± 0.30	0.75 ± 0.27
Melt granules	16.75 ± 4.39	5.60 ± 1.30	1.41 ± 0.32	0.71 ± 0.21
Steam granules	22.96 ± 6.87	5.94 ± 1.37	1.41 ± 0.17	0.83 ± 0.14

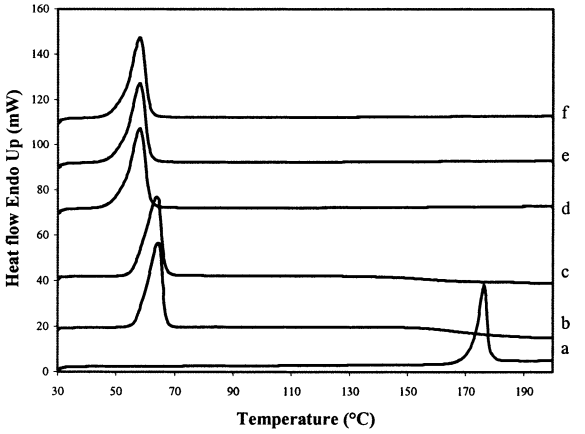

Fig. 2. DSC curves of (a) Dic, (b) PEG 4000, (c) physical mixture, (d) water granules, (e) steam granules and (f) melt granules.

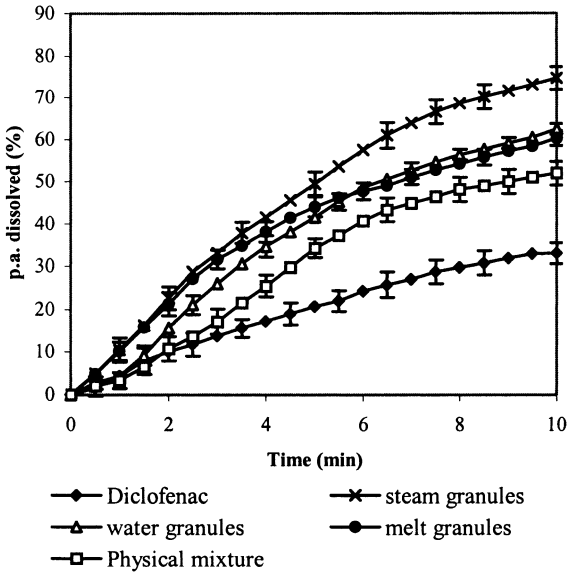

Fig. 3. Dissolution profiles of pure Dic, physical mixture, water, steam and melt granules.

Fig. 2 shows the DSC curves of Dic, PEG 4000, physical mixture, water, steam and melt granules. The DSC curve of Dic shows a melting endotherm at 175 °C, while PEG 4000 has an endothermic peak at 60 °C. In all the other samples the peak of Dic disappears, suggesting the transformation of the drug from its crystalline form into the amorphous one. To confirm this hypothesis, X-ray diffraction studies were carried out; the results (data not reported) show that the drug is crystalline in the physical mixture, while it is almost completely amorphous in the granules.

Finally, Fig. 3 shows the dissolution profiles of pure Dic, physical mixture, water, steam and melt granules. The low water solubility of pure Dic explains its dissolution behavior, since the amount of drug dissolved is about 30% after 10 min; the simple mixture with PEG improves the drug release. All the granules show a higher dissolution rate with respect to the physical mixture; in particular, steam granules release more than 70% of the drug in 10 min, with respect to the 60% of water and melt granules. This effect could be explained by the drug amorphisation, as pointed out by X-ray diffraction, while the best performance of steam granules with respect to water and melt ones could be explained by their larger surface area, as evidenced by image analysis data.

The results suggest that the use of steam in the wet granulation can considerably decrease the amount of water used and consequently the whole working time compared with traditional wet granulation. Furthermore, steam granules have very irregular surface, and this increase of the surface area exposed to the dissolution process is a very important feature for an improved dissolution product.

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