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Melt granulation of pharmaceutical powders: A comparison of high-shear mixer and fluidised bed processes

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ABSTRACT

The main aim of this research was to compare *in situ* melt granulation process in high-shear mixers and fluidised bed equipments with particular attention to the final properties of granules. In addition, the study evaluated the suitability of melt granulation in fluidised bed for improving the dissolution rate of drugs. Agglomerates having identical composition (10%, w/w, of ibuprofen or ketoprofen, 20%, w/w, of PEG 6000 and 70%, w/w, of lactose monohydrate) were produced using both equipments and their morphology, particle size, flowability, friability, drug loading, dissolution behaviors at pH 1.2 and 7.4 and physicochemical properties (DSC and XRD analysis) have been evaluated and compared. The results showed that melt granulation can be successfully performed in both granulators. The utilization of a different equipment had strong impact on the particle size distribution of the granules and on their morphology, while the effect on others physical properties was little, as all the granules possess low friability and excellent flowability. Moreover both the solid state characteristics of the products and the dissolution behaviors of ibuprofen and ketoprofen granules were found to be practically independent of the equipment and all granules showed a significant increase of the drug dissolution rate in acidic conditions. In conclusion *in situ* melt granulation in fluidised beds could be considered a suitable alternative to the melt granulation in high-shear mixers.

1. Introduction

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a substance which melts at relatively low temperature (50–80 °C). This substance can be added to the powders either in the form of a molten liquid (spray-on procedure) or in the form of a solid that melts during the process (*in situ* melt granulation or melt-in procedure) (Wong et al., 2005). In both cases, the molten substance acts like a liquid binding and the dry granules are obtained as the molten binder solidifies by cooling.

In recent years, the interest in melt granulation has increased due to the numerous advantages of this technique over traditional wet granulation. In fact the melt granulation does not require the use of organic or aqueous solvents: the advantages of not using organic fluids are the absence of any risk originating from residuals solvents in the final dosage form and the absence of problems associated with environmental requirement of solvent capture and recycle, while the absence of water results in the elimination of the wetting and drying phases, making the entire process less consuming in terms of time and energy as compared to wet granulation. A further significant advantage of melt granulation is that by an appropriate selection of meltable binders, this technique can be used either to prepare controlled release or enhanced release granules. Examples of hydrophilic binders used to prepare improved-release dosage forms include polyethylene glycols and poloxamers, while hydrophobic binders such as waxes, fatty acids, fatty alcohols and glyceride can be utilized for prolonged-release formulations (Wong et al., 2005).

Utilizable equipments for melt granulation are high-shear mixer and fluidised bed. The first studies on melt granulation in high-shear mixers date back to early 1990s, when the group of Shaefer and Kristensen published a series of papers that extensively investigated the effect of process and formulation variables on melt agglomeration and the mechanisms involved in the growth of the agglomerates (Schaefer et al., 1992a,b,c, 1993a,b). Since then, beside the Shaefer and Kristensen group, others researchers have examined the melt granulation process in high-shear mixer demonstrating that this process can be usefully employed both to enhance the dissolution rate of poorly water soluble drugs (Passerini et al., 2002, 2006; Perissutti et al., 2003) and to control the release of short half-life drugs (Thies and Kleinebudde, 1999; Voinovich et al., 2000a,b).

The interest on melt granulation of pharmaceutical powders in fluidised (or fluid) bed is more recently; the earliest papers, at least at our knowledge, were published by Abberger (2001) and Kojima

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and Nakagami (2001) in 2001. In the period thereafter, considerable amount of work has been performed by Shaefer's group at the Danish University of Copenhagen (Abberger et al., 2002; Seo et al., 2002; Vilhelmsen and Schaefer, 2005), Hounslow' s team at University of Sheffield (Boerefijn and Hounslow, 2005; Tan et al., 2005, 2006), Walker's group at The Queen's University of Belfast (Walker et al., 2005, 2006, 2007a,b, 2009; Zhai et al., 2009) and finally Ansari and Stepanek (2006, 2008) at the Imperial College of London; the four research groups mainly focused their efforts on investigating the detailed mechanism of granule growth and on identifying the overall kinetics during the process. The majority of the works of melt granulation in fluidised bed has been performed using placebo formulations and only very few papers (Walker et al., 2007a) have examined granules containing drugs. Moreover, up till now no paper has demonstrated the potential of melt granulation in fluidised bed for modifying the release behaviors of drugs.

Although high-shear mixers and fluidised beds are suitable equipment for melt granulation of powders, and that the mechanisms of granule formation are different, a comparison of the two processes in terms of granule properties has not been carried out.

The main aim of this research was to compare high-shear mixers and fluidised bed processes with particular attention to the final technological, physicochemical and biopharmaceutical properties of granules. In addition, the study evaluated the suitability of melt granulation in fluidised bed for improving the dissolution rate of drugs. Agglomerates having same composition (a non-steroidal anti-inflammatory agent, ibuprofen or ketoprofen, as model drug, PEG 6000 as hydrophilic meltable binder and lactose as diluent) were produced by *in situ* melt granulation using both equipment and their morphology, particle size, flowability, friability, drug loading, dissolution behaviors and physicochemical properties have been evaluated and compared.

2. Materials and methods

2.1. Materials

Ibuprofen [2-(4-isobutylphenyl)-propionic acid] (Ibu) and ketoprofen [(3-benzoylphenyl)-propionic acid] (Ket) were used as model drugs; both were in the micronized form. Lactose (α-lactose monohydrate) 200 mesh was used as diluent and polyethylene glycol (PEG) 6000 was used as meltable binders; PEG 6000 was in a powder form and the size fraction 250–355 μm was obtained by sieving. All the materials were supplied by Polichimica s.r.l, Bologna, Italy.

2.2. Production of the granules

2.2.1. Melt granulation in fluidised bed (FB)

The experiments were performed using a Mini-Glatt fluidised bed (Glatt GMbH, Binzen, Germany). The conical vessel volume was 0.75 l; the granulator was equipped with three metallic filters, a timing filter blowing (out time fixed set 3 s) and a product temperature probe (±0.1 °C). A single granulation process (batch size 200 g) consisted of three steps: mixing, heating–kneading and cooling. The powders (10% drug, 20% fractionated PEG 6000 and 70% lactose) were placed at the centre of the bottom grid and were mixed by fluidising air with an inlet flow rate of 16.6 m^3/h at ambient temperature; the mixing phase lasted for 5 min. The flow rate of the inlet air was then increased to 23.9 m^3/h and its temperature was raised to 80 °C; as a consequence, the temperature of the powders gradually increased as well (heating phase). Once the product temperature reached 58 °C, the timing of the kneading phase started; after 3 min, the granulation end point was reached. Finally the flow rate of the inlet air was kept constant, while its temperature was decreased to 25 °C to achieve the consolidation of the granules; this cooling phase lasted until the product temperature reached 40 °C. At the end of the granulation process (total processing time was 15 min), the granules were discharged, collected and sieved as described in a following section. The phases and the main process parameters are summarised in Table 1.

2.2.2. Melt granulation in high-shear mixer (HSM)

The granules were prepared in a laboratory scale high-shear mixer (Rotolab®, IMA-Zanchetta, Lucca, Italy), equipped with an electric heated jacket, three blades impeller, a top chopper and a product temperature probe (±1 °C); the vessel volume was 2 l and the batch size was 400 g. The process consisted of three steps: mixing, heating–kneading and cooling. The powders (drug, PEG 6000 and lactose) were mixed in the high-shear mixer for 5 min, using an impeller speed of 120 rpm. Then the impeller speed was increased to 400 rpm and the heating jacket was heated to 70 °C (heating phase): due to the frictional forces and to the heating jacket, the product temperature increased till 57 °C, which was considered the starting point of the kneading phase. After 3 min, the granulation end point was reached. Finally the cooling phase was performed utilising the bowl tilt system and setting an automatic impeller cycle (10 s on, 60 s off) at 120 rpm for 10 min.

At the end of the granulation process (total processing time was 45 min), the granules were collected and sieved as described in a following section. The phases and the main process parameters are summarised in Table 1.

2.3. Characterization of the granules

2.3.1. Granule size analysis

The size distribution of granules was evaluated by sieves analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) and six standard sieves (Scientific Instruments s.r.l., Milano, Italy) in the range 100–1400 μm. The mass of the granules used for the analysis was 100 g and the sieving time was 10 min. The fractions were then collected and stored in a closed glass container at 25 ± 2 °C.

Table 1
Process parameters of the melt granulation in fluidised bed (FB) and high-shear mixer (HSM) granulator.

Phase	Parameters for FB				Parameters for HSM			
	Inlet air flow rate (m^3/h)	Inlet air temperature (°C)	Product temperature (°C)	Time (min)	Impeller speed (rpm)	Jacket temperature (°C)	Product temperature (°C)	Time (min)
Mixing	16.6	25	25.0–30.0	5	120	25	25–30	5
Heating	23.9	80	25.0	4	400	70	25	27
Kneading			58.0	3			57	3
Cooling	23.9	25	58.0–40.0	3	120[a]	70–25	57–40	10
Total time				15				45

[a] Automatic impeller cycle: 10 s on–60 s off.

2.3.2. Yield

The yield of the granulation process was calculated by dividing the total weight of the granules in the range 100–1400 μm by the weight of the initial powder (in percentage).

2.3.3. Determination of Carr index (bulk and tapped densities)

The granules were weighted and poured into a 100-ml graduated cylinder. The bulk volume V_b and the tapped volume V_t were determined by a tap density apparatus (Erweka SVM 12, Erweka GmbH, Germany) and used to calculate the bulk density d and the tapped density D. Then, the Carr index (or Compressibility Index, CI%) values were calculated as follows:

$$\mathrm{CI} = \frac{100(D-d)}{D}$$

2.3.4. Determination of the friability

The friability of the granules was determined by introducing 10 g of the granules (250–1000 μm) together with 20 stainless steel beads (mean diameter 3 mm) in a friabilator (Erweka TA20, Erweka GmbH, Germany)) for 10 min at a rotational speed of 25 rpm. After 250 rotations, the beads were removed and the granules were sieved over a 250-μm sieve. The friability value was calculated as the percentage of the final weight of after sieving to the initial weight of the granules.

2.3.5. Scanning electron microscopy

The morphology of the granules was examined using scanning electron microscopy (SEM); (Philips XL30); the samples were previously sputter-coated with gold.

2.3.6. Determination of drug content

The analysis of the drug content in the different fractions of granules was carried out by dissolving 100 mg of granules in 250 ml of deionized water; the amount of drug was then spectrophotometrically determined (UV2 Spectrometer, Unicam, Cambridge, UK) at 222.0 nm for ibuprofen granules and at 260.0 nm for ketoprofen ones. Each sample was analysed at least in triplicate. Statistical analysis of the drug content was then performed using one-way analysis of variance (ANOVA); a post hoc comparison between the means of individual groups was performed by the Tukey–Kramer multiple-comparison test. The differences were considered to be statistically significant when $p < 0.05$.

2.3.7. In vitro dissolution studies

In vitro dissolution tests were performed using the USP Apparatus 2 (paddle) (Pharmatest, Steinheim, Germany) rotating at 50 rpm. As dissolution media, 900 ml of pH 1.2 solution or pH 7.4 phosphate buffer were used at a temperature of 37 ± 0.5 °C. Samples of pure drug or of granules (fraction 500–750 μm), containing an amount of drug (10 mg) chosen to assure sink conditions (C < 0.2 Cs), were added to the dissolution medium. The solution was filtered and continuously pumped (12.5 ml/min) to a flow cell in a spectrometer (UV2 Spectrometer, Unicam) The amount of drug dissolved was analysed at 220.0 nm (pH = 1.2) or 222.0 nm (pH = 7.4) for ibuprofen samples or at 260.0 nm for ketoprofen ones both at pH = 1.2 and pH = 7.4. The dissolution tests were performed at least in triplicate.

The dissolution profiles were compared using f_2 similarity factor (Moore and Flanner, 1996). The similarity factor is a logarithmic reciprocal square-root transformation of the sum of squared error and is a measurement of the similarity in the percentage of dissolution between two curves:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where n is the sampling number, R_t and T_t are the percent dissolved of the reference and test products at each time point t. The similarity factor fits the result between 0 and 100. Two dissolution profiles are considered similar when the f_2 value is greater than or equal to 50. For the f_2 calculation, sampling number lower than 95% of drug released were considered.

2.3.8. Differential scanning calorimetry (DSC)

The DSC analysis was performed using a PerkinElmer DSC 6 (PerkinElmer, 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 pan; the weigh of each sample was 13 ± 1 mg and the heating rate was 10 °C/min.

2.3.9. X-ray powder diffraction (XRD) analysis

Samples were studied by means of XRD technique using a X'Pert PRO (PANanalytical B.V., Almelo, The Netherlands) diffractometer with Cu Kα radiation, monochromatised by a secondary flat graphite crystal. The scanning angle ranged from 5 to 30° of 2θ, steps were of 0.02° of 2θ, and the counting time was of 100 s/step. The current used was 20 mA with a voltage of 40 kV.

2.3.10. Storage stability test

Samples of melt granules were stored at 25 ± 2 °C and 60 ± 5% relative humidity (R.H.); DSC analysis and X-ray powder diffraction studies were then performed on these samples after 1 year of storage.

3. Results and discussion

3.1. Influence of the equipment on the morphological and technological properties of the granules

As mentioned in the introduction, melt granulation can be performed using two procedures: the spray-on method involves the spraying of a molten binder onto the powders, while the *in situ* melt granulation employs a solid binder which is heated above its melting point by hot air (fluidised bed) or by impeller frictional forces and heating jacket (high-shear mixer). In this research the *in situ* melt procedure has been utilised because, avoiding hot-melt flows, it is preferable in industrial granulation process.

In the preliminary part of the work, numerous tests on placebo formulations both in fluidised bed and in high-shear mixer were

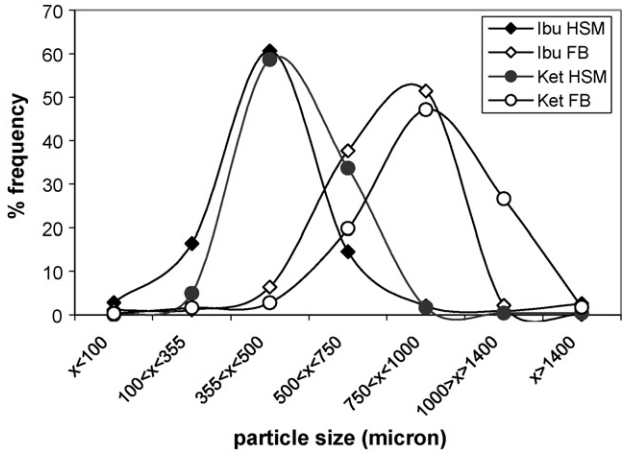

Fig. 1. Size distribution of ibuprofen and ketoprofen granules produced by fluidised bed (FB) and by high-shear mixer (HSM) equipment.

necessary to select the proper (suitable) operative conditions for the production of granules by *in situ* melt granulation. As regards the process in the fluidised bed, experiments were carried out varying the temperature and the flow rate of fluidising air, the product temperature, which have been reported (Walker et al., 2005, 2006) to be the most important process parameters in fluidised bed granulator. In analogy, preliminary tests were carried out in the high-shear mixer by varying the critical (Schaefer et al., 1992a, 1993a; Voinovich et al., 2000b) operating parameters (impeller speed, jacket temperature and kneading time).

Once good operative parameters have been found, four batches of granules containing ibuprofen or ketoprofen as model drugs have been produced in fluidised bed and in high-shear mixer using the operating parameters reported in Table 1. Worthy of note, the total

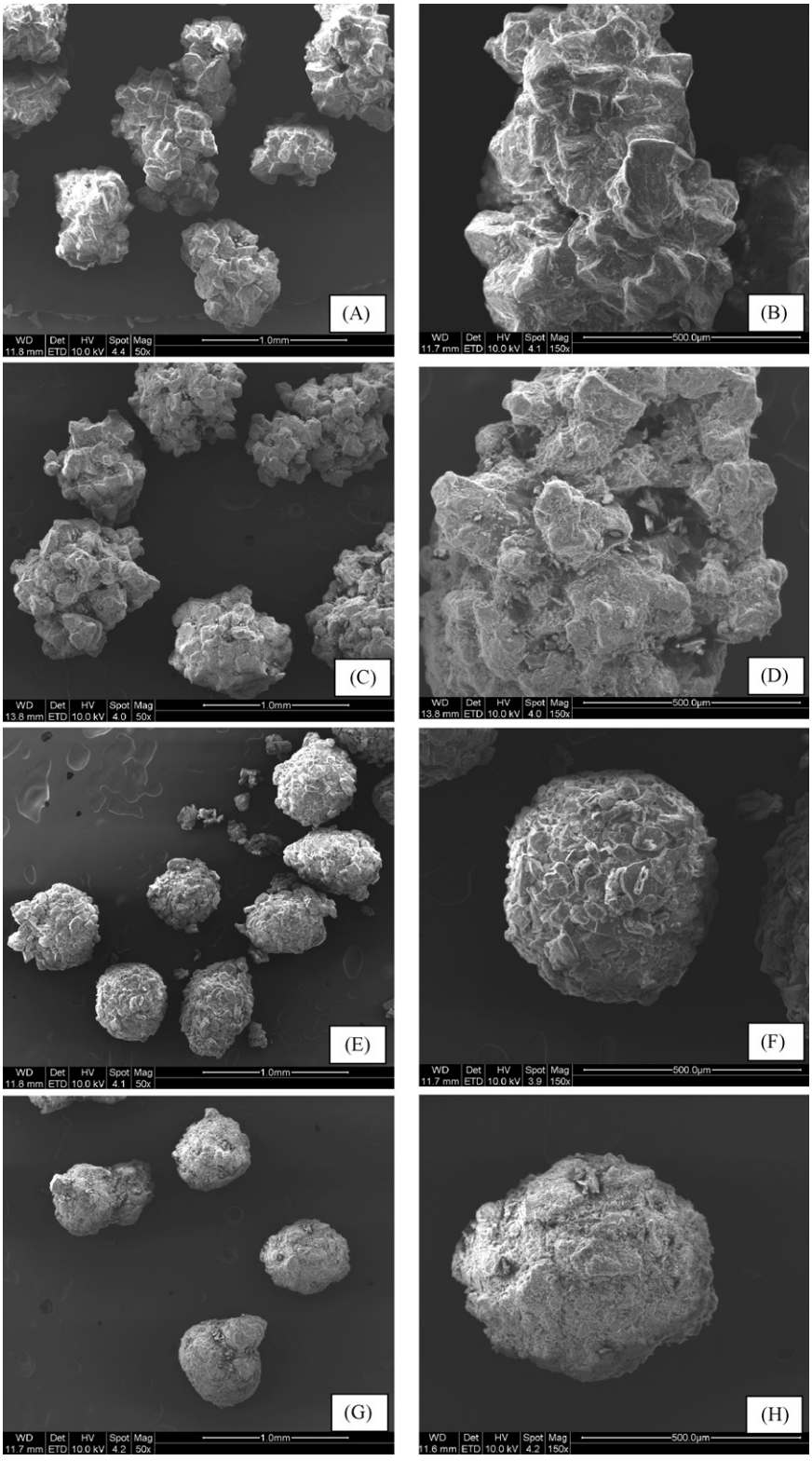

Fig. 2. SEM images of FB ibuprofen (A and B), FB ketoprofen (C and D), HSM ibuprofen (E and F) and HSM ketoprofen (G and H) granules at two different magnifications.

Table 2
Technological properties of the granules.

	Yield (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Carr's index (%)	Friability (%)
Ibu FB	86	0.464	0.497	6.7	0.73 ± 0.16
Ibu HSM	96	0.490	0.509	3.6	4.25 ± 0.47
Ket FB	96	0.555	0.588	5.6	0.89 ± 0.09
Ket HSM	99	0.649	0.667	2.5	1.67 ± 1.67

processing time for the melt granulation in fluidised bed was significantly shorter than in high-shear mixer due to the considerably shorter heating (4 min versus 27 min) and cooling (3 min versus 10 min) phases.

Fig. 1 shows the particle size distribution of the granules: all the samples have a low amount of fine powder (size < 100 μm) and of big lumps (size > 1400 μm), confirming that the parameters used for both processes were corrected. The particle size distribution of the granules is of Gaussian type; the prevalent size is in the range 355–500 μm for HSM samples, while FB granules have bigger particle size (main fraction is 750–1000 μm).

SEM analysis (Fig. 2) showed that the equipment had a strong influence on the morphology of the granules. Both ibu and keto granules manufactured with FB were quite irregular in shape (Fig. 2A and C) and appeared quite porous (Fig. 2B and D), while the ibu and keto granules produced in HSM were regular with a spherical shape (Fig. 2E and G) and possessed a more homogenous structure (Fig. 2F and H). The differences in morphology can be correlated to different granulation mechanisms: the FB irregular shaped granules could be indicative of a coalescence type mechanism, where the initial small nuclei increase in size by agglomerating with other nuclei to form larger granules, in accordance with the granulation mechanism proposed by Walker's group (Walker et al., 2005, 2006, 2007a,b, 2009). On the contrary, the morphology of HSM granules suggested the hypothesis of an immersion dominant growth mechanism (Abberger et al., 2002, Vilhelmsen and Schaefer, 2005). Nevertheless a kinetic study would be necessary to verify the dominant growth mechanism in FB and HSM.

Table 2 reports the yields and the physical properties of the four batches of granules; the yield were lower for FB processes compared to HSM, however the values were good for all batches. The HSM samples showed bulk and tapped densities slighter lower than FB granules and lower Carr's index; as the Carr's index is dependent upon size, size distribution and shape of the granules (regularly shaped particles have better flow properties than irregularly shaped ones, while the decreasing of the particle size in general corresponds to lower flowability), the results suggested that in our case the regular spherical shape of HSM more affected the flowability than granule size. In any case, all FB and HSM granules possessed Carr's index < 10, indicating excellent flowability. In addition, all the samples showed friabilities widely below 30%, value considered as indicative of acceptable granule strength (Van Melkebeke et al., 2008). These results confirmed that both high-shear mixers and fluidised bed processes allowed the production of granules having good technological properties.

Table 3 reports the drug content of the main fractions for ibu and keto granules produced by FB and HSM; both drugs were uniformly distributed in the different granule fractions both in the samples manufactured in FB and in HSM. However the granules produced by FB showed an actual drug content lower than the theoretical ones; this result can be explained considering that both drugs utilized in this study were in micronized form, therefore their dimensions were considerably lower respect to PEG 6000 and lactose. During the initial phases of the process in fluid bed, micronized drugs tended to float upward and a certain amount of particles could adhered to the filters, causing the loss of the drugs. On the other hand, the granulation process in HSM allowed the production of granules having actual drug content very close to the theoretical one.

Table 3
Drug content for the different granule fractions.

	Drug content (% ± S.D.) for the different fractions (μm)		
	355–500	500–750	750–1000
Ibu FB	7.84 ± 0.10	7.45 ± 0.07	8.06 ± 0.33
Ibu HSM	10.95 ± 0.49	10.60 ± 0.60	10.69 ± 0.45
Ket FB	8.14 ± 0.10	7.98 ± 0.02	7.91 ± 0.40
Ket HSM	11.14 ± 0.13	11.17 ± 0.21	11.31 ± 0.13

3.2. *In vitro dissolution studies of the granules*

In the following part of the study, *in vitro* dissolution tests have been performed with the aims to assess either if the melt granulation is an effective method to increase the dissolution rate of poorly water soluble drugs and to evaluate the influence of the equipment on the biopharmaceutical properties of the granules. As the model drugs, ibuprofen and ketoprofen, are weakly acid molecules (pK_a around 4.4–4.6), they have a pH-dependent solubility, therefore the dissolution studies have been performed at two different pH.

Fig. 3A showed that the dissolution rate of pure ibuprofen at pH 1.2 was very low, as expected, being the percentage of drug dissolved less than 5% and 15% in 30 min and in 2 h, respectively.

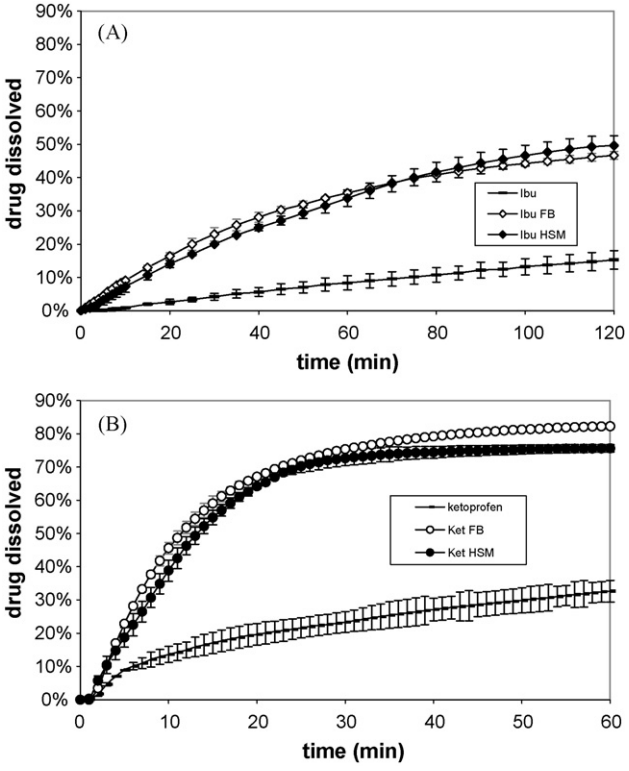

Fig. 3. (A) Dissolution profiles of pure ibuprofen and of FB and HSM granules containing ibuprofen at pH 1.2. (B) Dissolution profiles of pure ketoprofen and of FB and HSM granules containing ketoprofen at pH 1.2.

The granules produced by melt granulation showed a significant increase of these values: the amount of ibuprofen dissolved from both FB and HSM granules was about 20% in 30 min and 50% in 2 h, suggesting that melt granulation could be an industrial method to enhance ibuprofen dissolution rate. Interestingly, the dissolution profiles of the granules, having the same particle size, produced using different equipments were almost superimposable, evidencing that the different morphology of granules had no effect on the dissolution rate. Similar results were obtained for the samples containing ketoprofen (Fig. 3B): the amounts of pure drug dissolved at pH 1.2 were 23% and 32% in 30 min and in 2 h, respectively. Both FB and HSM granules showed a significant dissolution enhancement, being the percentage of ketoprofen dissolved higher than 75% after only 30 min.

Fig. 4A and B reported the dissolution profiles in pH 7.4 phosphate buffer of ibuprofen and ketoprofen samples, respectively. As expected, both pure drugs showed a fast dissolution rates ($t_{50\%} < 3$ min and $t_{90\%} = 6$ min for ibuprofen, $t_{50\%} < 4$ min and $t_{90\%} = 14$ min for ketoprofen), according to the high solubility of the molecules in a dissolution medium at pH above their pK_a. The comparison between the dissolution profiles of ibuprofen granules produced in FB and in HSM indicated that also at pH 7.4 the dissolution behavior of the granules were not influenced by the equipment ($f_2 = 64.45$); analogous results ($f_2 = 72.88$) were obtained by comparing ketoprofen FB and HSM dissolution data.

Therefore, the results of dissolution tests indicated that *in situ* melt granulation using both fluidised bed and high-shear mixer is a useful technology to enhance the dissolution rate of ibuprofen and ketoprofen in acidic conditions. Moreover, although the different granulation mechanism involved in the formation of granules in FB and in HSM produced granules having different morphology, the dissolution behaviors of ibuprofen and ketoprofen granules were found to be practically independent of the equipment. These results are similar to that obtained by Gao et al. (2002) by comparing granules produced by wet granulation in fluidised bed and high-shear mixer and confirmed that *in situ* melt granulation in fluidised beds can be considered a suitable alternative to melt granulation in high-shear mixers.

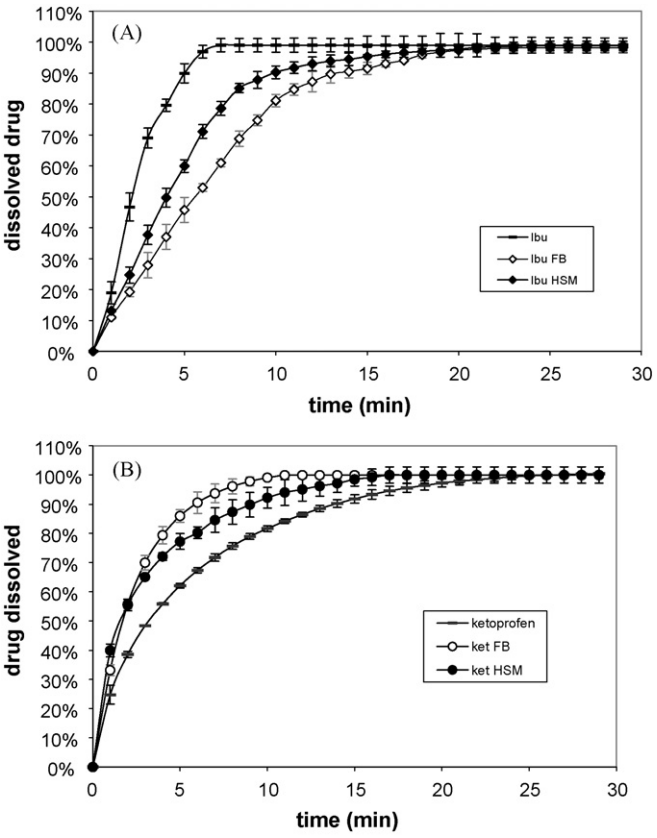

Fig. 4. (A) Dissolution profiles of pure ibuprofen and of FB and HSM granules containing ibuprofen at pH 7.4. (B) Dissolution profiles of pure ketoprofen and of FB and HSM granules containing ketoprofen at pH 7.4.

3.3. Solid state characterization of the granules

Finally, the solid state characterization of the granules was performed with the aim of verifying whether the melt granulation process modified the original physical form of the meltable binder and/or of the drug (e.g. transformation from the original crystalline form into a different polymorph or an amorphous state).

Fig. 5 reports the DSC curves of Ibu, PEG 6000, lactose monohydrate, their physical mixture and granules produced in fluidised bed and high-shear mixer. DSC curve of pure Ibu shows a single melting endothermic peak at 79.0 ± 0.1 °C, in accordance with Walker et al. (2007a). PEG 6000 has a melting endothermic peak at 67.7 ± 0.2 °C,

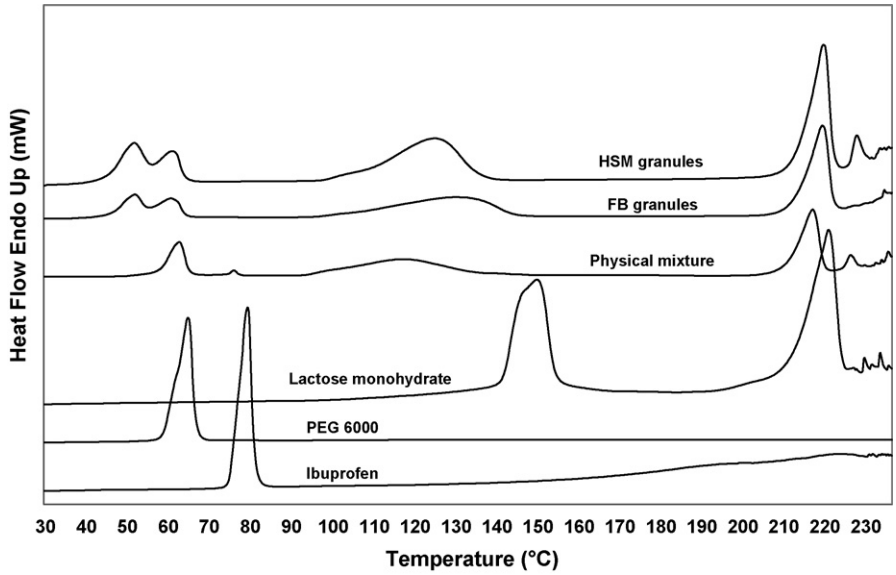

Fig. 5. DSC curves of raw ibuprofen, PEG 6000, lactose monohydrate, physical mixture, FB granules and HSM granules.

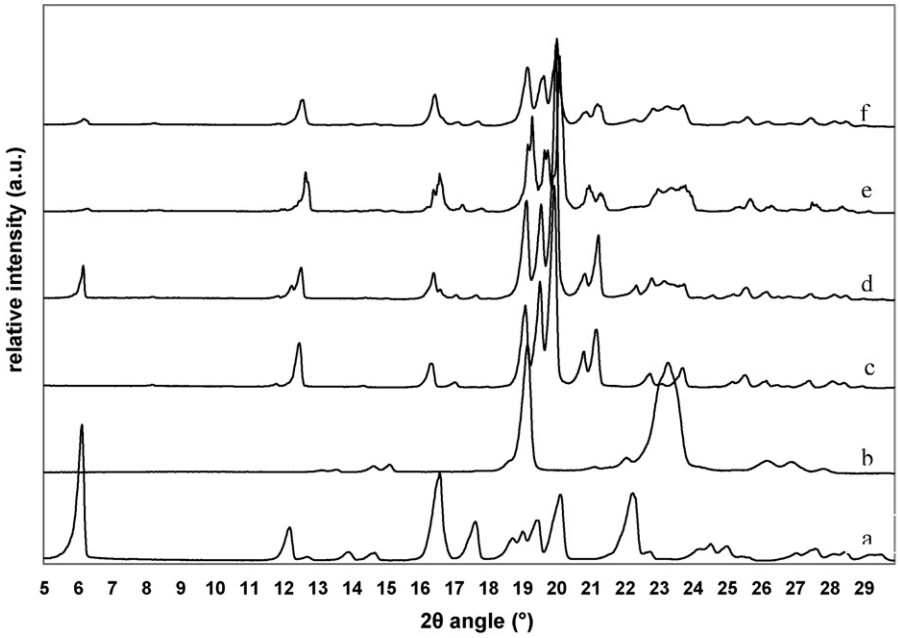

Fig. 6. XRD patterns of raw ibuprofen (a), PEG 6000 (b), lactose monohydrate (c), physical mixture (d), FB granules (e) and HSM granules (f).

indicating that the chains of raw binder are in the extended stable conformation (Lloyd et al., 1997), while DSC curve of lactose monohydrate shows an endothermic peak at 149.9 ± 0.3 °C, due to the loss of hydration water, and a melting endothermic peak with decomposition at 220.9 ± 0.6 °C.

In the DSC curve of physical mixture, the characteristic peaks of Ibu, PEG 6000 and lactose monohydrate are unchanged, indicating the absence of strong interactions between the drug and the excipients. The thermogram of FB granules is quite similar to that of HSM granules, suggesting that the equipment does not influence the physicochemical properties of the products. However both DSC curves are very different from physical mixture one, evidencing that the melt granulation process modifies the solid state of meltable binder and/or of the drug; in particular it is possible to notice a new endothermic peak at 51.9 ± 0.3 °C and the absence of ibuprofen melting peak at 79.0 °C.

These results can be explained with different hypothesis: the new peak could indicate that, after the melting of the PEG during the granulation process, the binder partially recrystallised in the folder chain conformation which melts at lower temperature with respect to the extended conformation (Lloyd et al., 1997), or it could suggest the formation of an eutectic system between ibuprofen and PEG 6000, as widely reported in literature (Law et al., 2002; Vippagunta et al., 2007). The absence of the ibuprofen melting peak could be explained by the formation of the eutectic mixture or by a reduction of drug crystallinity (by the transformation of the crystalline ibuprofen into the amorphous state) after the melt granulation process.

XRD analysis was then necessary to verify these suppositions; Fig. 6 shows the XRD patterns of ibuprofen, PEG 6000, lactose, their physical mixture and of FB and HSM granules. The raw ibuprofen (a) is crystalline, as demonstrated by numerous sharp and intense diffraction peaks at 6.2, 16.6, 20.1 and 22.4° of 2θ. PEG 6000 (b) exhibits two main peaks at 19.2 and 23.3° of 2θ, while raw lactose (c) displays the typical pattern of lactose monohydrate (Perissutti et al., 2003). The XRD trace of the physical mixture (d) shows the

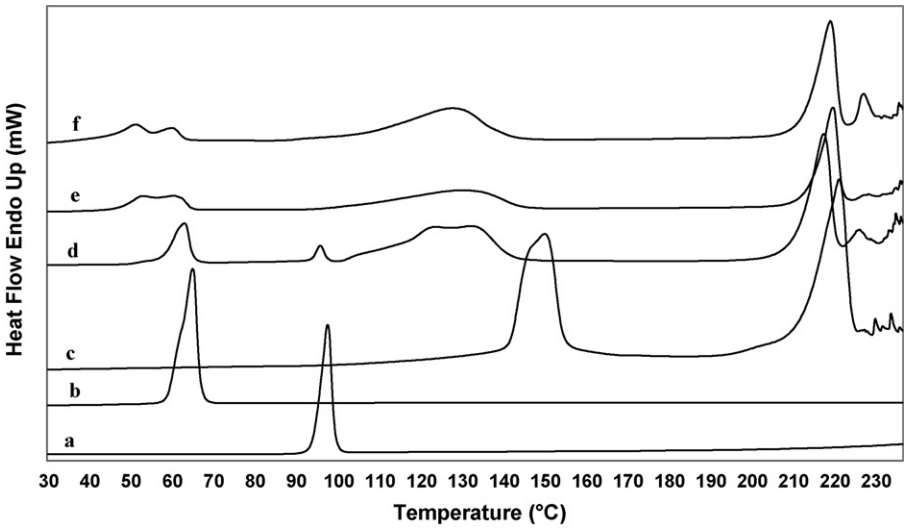

Fig. 7. DSC curves of raw ketoprofen (a), PEG 6000 (b), lactose monohydrate (c), physical mixture (d), FB granules (e) and HSM granules (f).

characteristic peaks of all the components, in particular the drug peaks at 6.2 and 22.4° of 2θ are still evident. On the contrary, the XRD patterns of both FB granules (e) and HSM products (f) display a marked reduction of the ibuprofen peaks (very evident for the peak at 6.2 of 2θ) compared to the trace of the physical mixture having the same composition, suggesting that the melt granulation process causes a reduction of the drug crystallinity, in accordance with the findings of Walker et al. (2007a).

Similar DSC and XRD results were obtained for ketoprofen samples. Fig. 7 shows that DSC curve of ketoprofen (a) has a melting endothermic peak at 97.0 ± 0.1 °C, indicative of the crystalline form of the raw drug. The drug melting peak is still present in the DSC curves of the physical mixture (d), while it is not detectable in the DSC traces of FB and HSM granules, which show the new peak around 52 °C. XRD results of ketoprofen samples (Fig. 8) are in agreement with ibuprofen XRD findings, confirming a partial drug amorphization in the granules in comparison with the physical mixture.

The results of ibuprofen and ketoprofen XRD analysis supported the hypothesize that the disappearance of the ibuprofen and ketoprofen peaks in the DSC curves of the granules was due to a reduction of drug crystallinity, while the new peak around 52 °C could be reasonably due to the partial transformation of the extended conformation of PEG to its folder chain conformation. It

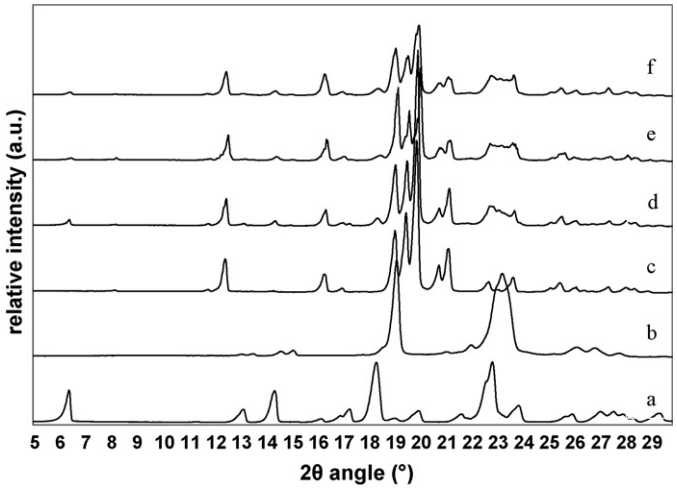

Fig. 8. XRD patterns of raw ketoprofen (a), PEG 6000 (b), lactose monohydrate (c), physical mixture (d), FB granules (e) and HSM granules (f).

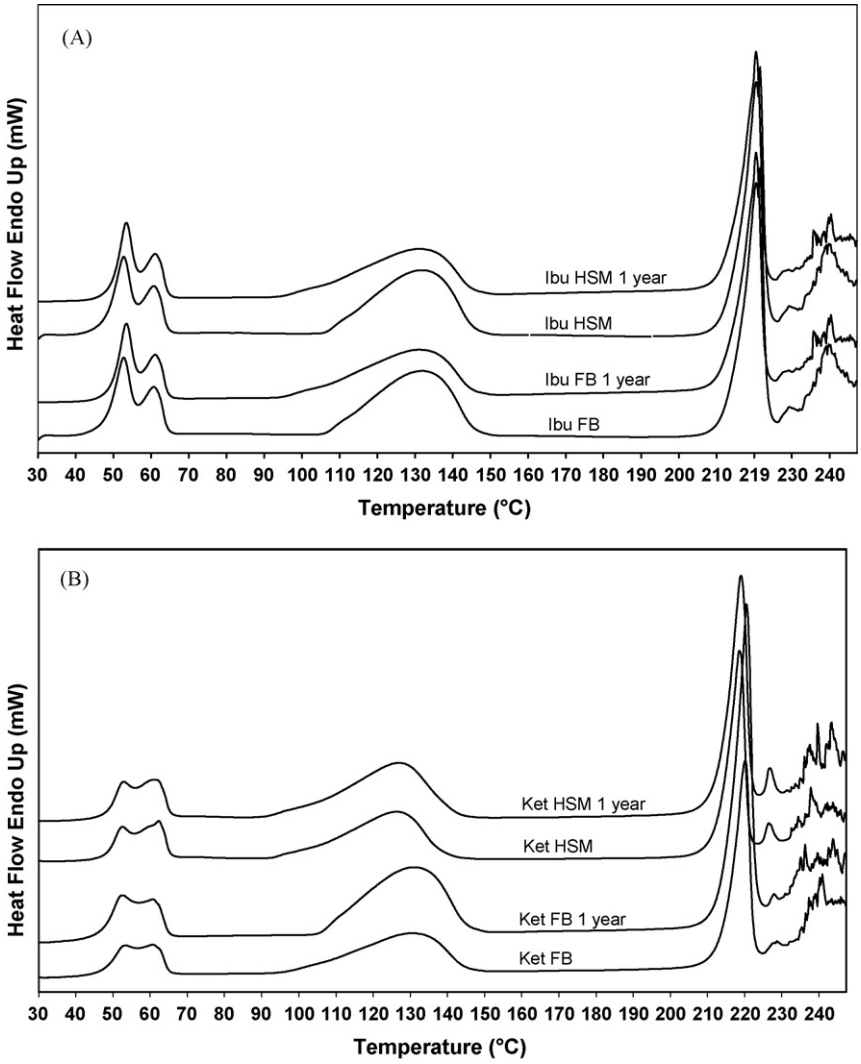

Fig. 9. (A) DSC curves of FB and HSM ibuprofen granules freshly prepared and after 1 year of storage at 25 °C. (B) DSC curves of FB and HSM ketoprofen granules freshly prepared and after 1 year of storage at 25 °C.

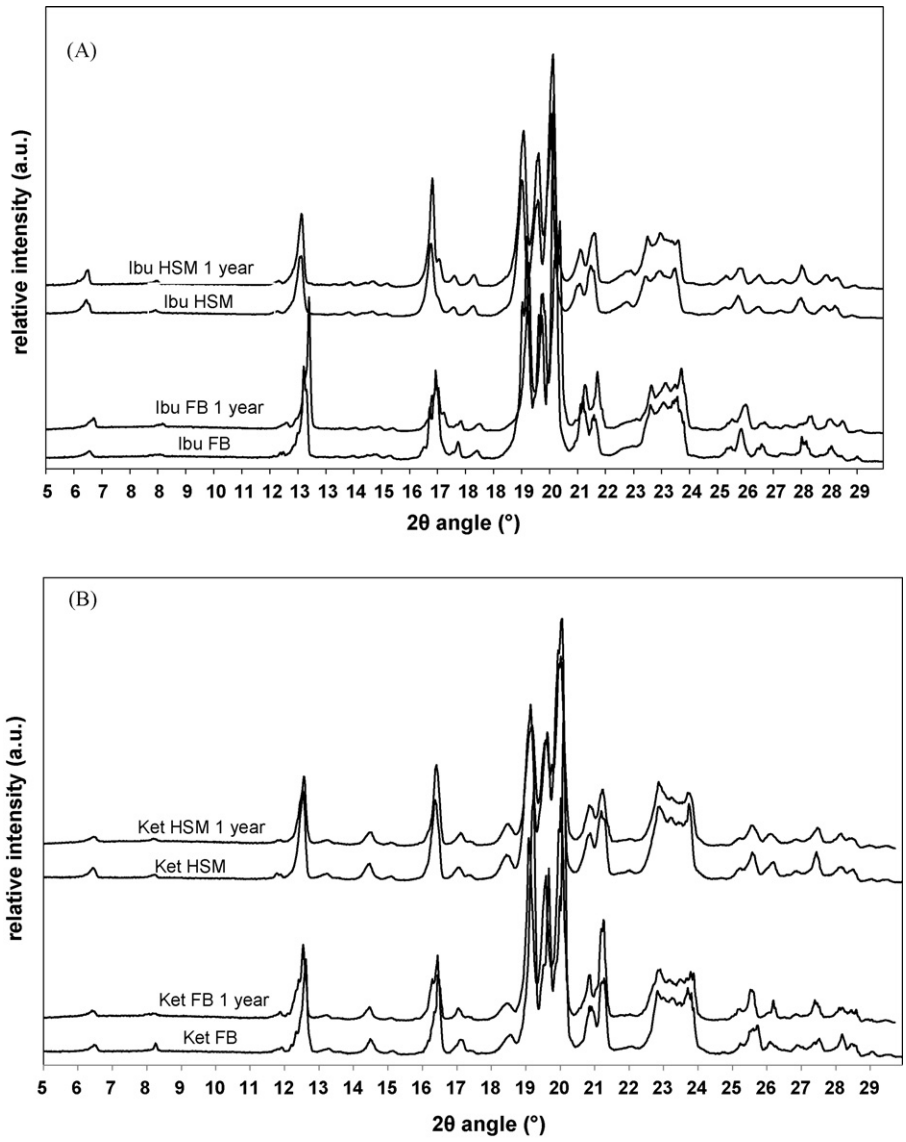

Fig. 10. (A) XRD patterns of FB and HSM ibuprofen granules freshly prepared and after 1 year of storage at 25 °C. (B) XRD patterns of FB and HSM ketoprofen granules freshly prepared and after 1 year of storage at 25 °C.

is important to notice that these modifications of the solid state of both the excipients and the drugs were due to the melt granulation process, independently from the equipment used for the production of the granules.

Finally, in order to evaluate the stability of the granules, solid state analysis were performed on the samples after 1 year of storage at 25 °C; no differences in the DSC (Fig. 9A and B for ibuprofen and ketoprofen granules, respectively) and X-ray graphs (Figs. 10A,B and 9B for ibuprofen and ketoprofen granules, respectively) can be detected for the drugs. These results suggested the physical stability of the samples, at least for the examined time.

4. Conclusions

The results of this research show that *in situ* melt granulation of pharmaceutical powders can be successfully performed in both high-shear mixer and fluidised bed granulators. Due to the different mechanism of granule growth, the utilization of a different equipment has strong impact on the particle size distribution of the granules and on their morphology. On the contrary, the equipment effect on others technological properties is little, as all the granules possess low friability and excellent flowability. Moreover either the solid state characteristics of the products and the dissolution behaviors of ibuprofen and ketoprofen granules are found to be practically independent of the equipment and all granules show a significant increase of the drug dissolution rate in acidic conditions. Although the results obtained for 10% ibuprofen and ketoprofen granules need to be assessed for higher drug loadings and for drugs with different properties, *in situ* melt granulation in fluidised beds can be considered a suitable alternative to melt granulation in high-shear mixers. This finding is very important as it indicates that in pharmaceutical industry, if necessary, it can be possible to switch from one equipment to another maintaining constant the biopharmaceutical properties of the granules.

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