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In situ fluidized hot melt granulation using a novel meltable binder: Effect of formulation variables on granule characteristics and controlled release tablets

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ABSTRACT

In situ fluidized hot melt granulation (FHMG) for different (ternary) formulations based on glyceryl palmito-stearate as non-conventional meltable binder and ibuprofen as model drug was examined for controlled release applications. The process was robust, lasted only 15 min, and enabled to attain high yields (95–98 wt.%). The obtained granules presented a bimodal size distribution, having the major mode of 200 μm and good flow properties, thus avoiding the necessity to add other lubricants for tablet compaction. The crystalline structure of ibuprofen and of the non meltable excipients was retained, and that of glyceryl palmito-stearate was recovered in the final granules. The resulting ibuprofen tablets had good pharmacotechnical properties. The granulation process did not modify release profiles from the tablets. The main factor influencing the release profiles was the content of glyceryl palmito-stearate in the formulations. A high drug load (50 wt.%), which is particularly important in the case of high dose active pharmaceutical ingredients, was achieved. Glyceryl palmito-stearate performed a triple function in the tablet formulation: as a meltable binder, as a controlled release matrix and as a lubricant.

1. Introduction

Growing environmental regulations are driving the search for more efficient processes free of organic solvents to improve current processing of powdered materials in the manufacture of solid dosage forms [1–3]. In this direction, fluidized hot melt granulation (FHMG) is emerging as an innovative process, currently under development worldwide [4,5]. In FHMG, both the active pharmaceutical ingredient and all the excipients, including the binding agent, are introduced in the bed in the form of powders. Its distinguishing feature lies in the *in situ* phase transition (solid–liquid) of the binder [6]. FHMG presents comparative advantages over conventional granulation methods [6–9]. FHMG is a quick process that involves a single step. The absence of aqueous phase avoids potential hydrolysis problems, favors a higher binder to substrate ratio, and can generate granules with higher density and reduced porosity. FHMG also results in savings in energy consumption and operation times since it does not require a drying step and solidification occurs almost instantaneously. In addition, it is particularly suitable for drugs unstable in solution, and an appropriate choice of the granulation excipients may allow controlling drug release rate [10,11].

The literature about FHMG is still scarce and generally involves conventional fusible agents [6,7,10,12,13], or the molten binder is sprayed on the fluidized bed particles [14]. Likewise, those publications involving the binder in solid state, are mainly devoted to examine hydrodynamic or kinetic aspects on granule formation [13,15–18] and have barely explored the formation of granules containing drugs [2,5,19,20]. The design and implementation of melt processing depend on the physicochemical properties of the active ingredient and the excipients used, as well as on the desired properties of the final product [14].

One aspect which requires further research concerns binders involved in melt granulation, since the application of this type of processing has been limited by the complex behavior of the carriers, associated with their physicochemical properties, which can lead to changes in the final product and/or have adverse effects during storage. To overcome these drawbacks, the use of novel fusible excipients has raised special interest in recent years. In particular Gelucires, consisting of mixtures of glycerides and fatty acid esters of polyethylene glycol (PEG), have received attention as innovative excipients. They have shown a better performance in controlled release systems obtained by using laboratory melting–solidification techniques compared to conventional meltable

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Table 1
Formulations evaluated in FHMG experiments and process yields.

Formulation	Drug	wt.%	Excipient 1	wt.%	Excipient 2	wt.%	Yield wt.%
0	Ibuprofen	80	Glyceryl palmito-stearate	20	–	–	62
1	Ibuprofen	50	Glyceryl palmito-stearate	10	Granulac 200	40	95
2	Ibuprofen	50	Glyceryl palmito-stearate	20	Granulac 200	30	97
3	Ibuprofen	50	Glyceryl palmito-stearate	30	Granulac 200	20	95
4	Ibuprofen	50	Glyceryl palmito-stearate	20	Talc	30	96
5	Ibuprofen	50	Glyceryl palmito-stearate	20	Granulac 140	30	98
6[a]	Ibuprofen	50	Glyceryl palmito-stearate	20	Granulac 200	30	100

[a] This formulation was not granulated (control).

binders [21]. The nature and proportion of Gelucires' components determine the hydrophilic–lipophilic balance (HLB) and melting point (33–70 °C), both properties with technological and biopharmaceutical impacts. Although Gelucires have shown potentialities for the design of floating controlled release matrix systems [22,23], they rarely have been tested in melt granulation in a fluidized bed.

In this context, the present study aims at examining FHMG using glyceryl palmito-stearate, as meltable binder, and ibuprofen as model drug for controlled release applications. The resulting granules from different formulations as well as tablets prepared with the granules were characterized.

2. Materials and methods

2.1. Materials

Ibuprofen (61 μm median volume particle size) was donated by Unifarma SA, Buenos Aires, Argentina. Glyceryl palmito-stearate, commercialized as Precirol® ATO 5 or Gelucire 54/02 (indicative particle size of 50 μm) was generously provided by Gattefossé (Ferromet SA, Argentina). Lactose monohydrate for granulation (Meggle AG trademarks Granulac 140 and Granulac 200) was a donation of EtilFarma SA, Buenos Aires, Argentina. The size specification for Granulac 140 was no more than 40% w/w <32 μm and no less than 80% w/w <100 μm; for Granulac 200 it was 45–75% w/w <32 μm and no less than 90% w/w <100 μm). Talc was supplied by Droguería Prest SA, Buenos Aires, Argentina (100% w/w less than 44 μm). All the materials employed were of pharmacopoeial grade.

2.2. Methods

2.2.1. Fluidized hot melt granulation

Granulation experiments were performed in a laboratory size Mini Glatt fluidized bed system (Glatt GMBh, Binzen, Germany). The system working volume was 50–750 mL. The chamber was equipped with an air distribution plate at the bottom and three metal filter cartridges at the top and a temperature probe with an accuracy of ±0.1 °C. No inserts or spray nozzles were used. A scheme of the system is provided in the Supplementary information. From preliminary experiments, it was determined that an inlet air flow rate of 25 $m^3\ h^{-1}$ allowed good fluidization of the powders. Accordingly, this flow rate was used for all the experiments reported. A filter blowing interval of 3 s was used. The batch size was 100 g. All materials were passed through a 149 μm opening sieve (100 U.S. Standard mesh) before loading the equipment.

The granulation process consisted in 1 minute mixing at room temperature, and then inlet air temperature was raised to 80 °C. After approximately 9 min the sample temperature reached 51 °C; this was considered as the onset of the 1 minute granulation. Finally, inlet air temperature was lowered to ambient temperature for 4 min, with final sample temperature below 40 °C. The total process time lasted 15 min.

The yield of the fluidized bed granulation process was calculated as the weight of the resulting granules divided by the weight of the initial powders, multiplied by 100.

2.2.2. Characterization of granules

Size distribution of the granules was evaluated by sieve analysis, employing a vibrating shaker Zonytest LR2006 (Rey & Ronzoni S.R.L., Buenos Aires, Argentina) equipped with 10 sieves covering the range

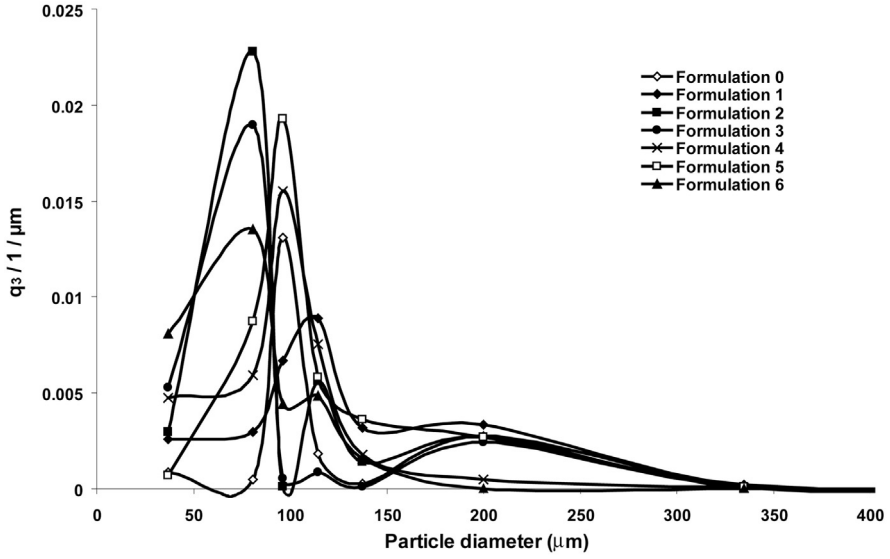

Fig. 1. Size fractional mass density distribution of the granules produced by fluidized bed hot melt granulation (small fractions of particles of size rather larger than 400 μm were also obtained).

74–2000 μm. 50 g of the granules was used keeping vibration time for 10 min.

Measurements by differential scanning calorimetry were performed in a SDT Q600 (TA Instruments) thermal analyzer, under nitrogen flow (100 mL min^{-1}). Experiments were carried out with 7–8 mg of samples in open aluminum oxide crucibles. The heating rate was 10 °C min^{-1} from 25 to 600 °C.

Samples were characterized by means of X-ray powder diffraction (XRD) using a Siemens D5000 diffractometer with Cu Kα radiation (λ = 1.54056 Å), equipped with a curved graphite crystal monochromator. The scanning angle was in the range 5–60° of 2θ (steps of 0.05°). The counting time was 2.0 s $step^{-1}$.

FT-IR was performed in a PerkinElmer Spectrum BX II FT-IR spectrophotometer (PerkinElmer Inc.) employing the KBr disc method; the range measured was 4000–650 cm^{-1} and 32–64 scans were taken with a resolution of 2–4 cm^{-1}.

Scanning electronic microscopy (SEM) of gold metallized samples was performed in a Zeiss DSM 982 Gemini microscope (Carl Zeiss) equipped with a field emission gun (FEG) and an in-lens secondary electron detector (SE). Acceleration voltage was 4 kV. Magnification ranges were between 200× and 50,000×.

Flowability of the granules was evaluated semi-quantitatively by measuring the static angle of repose [24]. A funnel filled with the granules was maintained 2 cm above a graduated surface; the funnel was drained and the angle of repose was calculated measuring the diameter of the cone formed.

2.2.3. Preparation of tablets

Tablets were prepared in a Sanchez SC2 single punch tablet press (Talleres Sanchez S.R.L., Buenos Aires, Argentina). 6 mm wide round unscored convex tablets were prepared. The press was adjusted in order to obtain weights of 150 mg and hardness values in the range 5–6 kp for all the formulations. The hardness of the tablets was determined using a Vanderkamp VK200 tablet hardness tester.

2.2.4. Characterization of tablets

Weight variation of 10 tablets was determined, using an analytical balance. (Mettler AL 204, Mettler-Toledo Int. Inc., Greifensee, Switzerland).

Friability of the tablets was assessed weighing accurately around 6.5 g of tablets before and after placing the tablets in a tablet friability apparatus (Alycar Instrumentos, Argentina), which rotated at 25 ± 1 rpm for 4 min.

The ibuprofen content was determined spectrophotometrically at 221 nm (Cary 1E, Varian Inc., Palo Alto, CA, USA). Previous studies indicated that the excipients did not interfere with the determination of the model drug. The mean of three determinations is reported.

2.2.5. Drug release from tablets

The IBF release profiles were determined using a USP compliant Apparatus II (paddle) dissolution tester (Alycar Instrumentos, Argentina). The rotating speed was 50 rpm and a temperature of 37.0 ± 0.5 °C was used. The dissolution medium was 1000 mL 0.05 M phosphate buffer of pH 7.2 ± 0.05 (total release time of 8 h) [24]. Aliquots of 3 mL of solution were taken every 30 min; the reduction of the total volume was taken into account to calculate the concentrations. The amount of IBF released was determined spectrophotometrically at 221 nm. The results informed for each kind of tablet are the mean of twelve determinations.

Dissolution profiles were compared employing the difference factor, f_1, and the similarity factor, f_2 [25]. Ideally, $f_1 = 0$ indicates that both curves are identical. Since this is not possible from a practical point of view, values between 0 and 15 are considered acceptable.

The difference factor was calculated employing the expression:

$$f_1 = \left\{ \left[\sum_{t=1}^{n} |R_t - T_t| \right] \div \left[\sum_{t=1}^{n} R_t \right] \right\} \times 100 \quad (1)$$

where n is the number of sampling time points, and R_t and T_t are dissolution percentages at each time point t of the reference and of the test product, respectively.

The similarity factor was calculated according to:

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

where the meaning of the terms in this equation is the same as in Eq. (1). Values of the similarity factor are in the range 0–100. Two dissolution profiles are considered similar when f_2 is greater than or equal to 50. For calculation of f_2, sampling points up to 95% of drug release were considered.

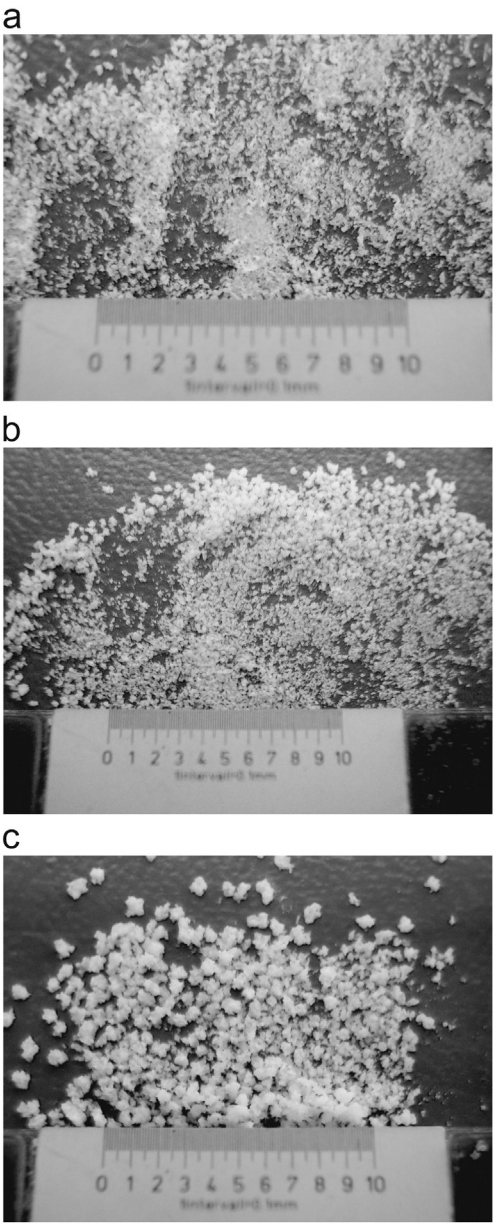

Fig. 2. Optical images of granules for Formulation 1 (ibuprofen 50 wt.%, Glyceryl palmitostearate 10 wt.% and Granulac 200 40 wt.%, air flow rate of 25 m^3 h^{-1}, 15 min total process time and granulation temperature of 51 ± 1 °C) corresponding to size fractions of 149–250 μm (a), 250–420 μm (b), 420–500 μm (c). Full scale bars diplayed in the images correspond to 1 cm.

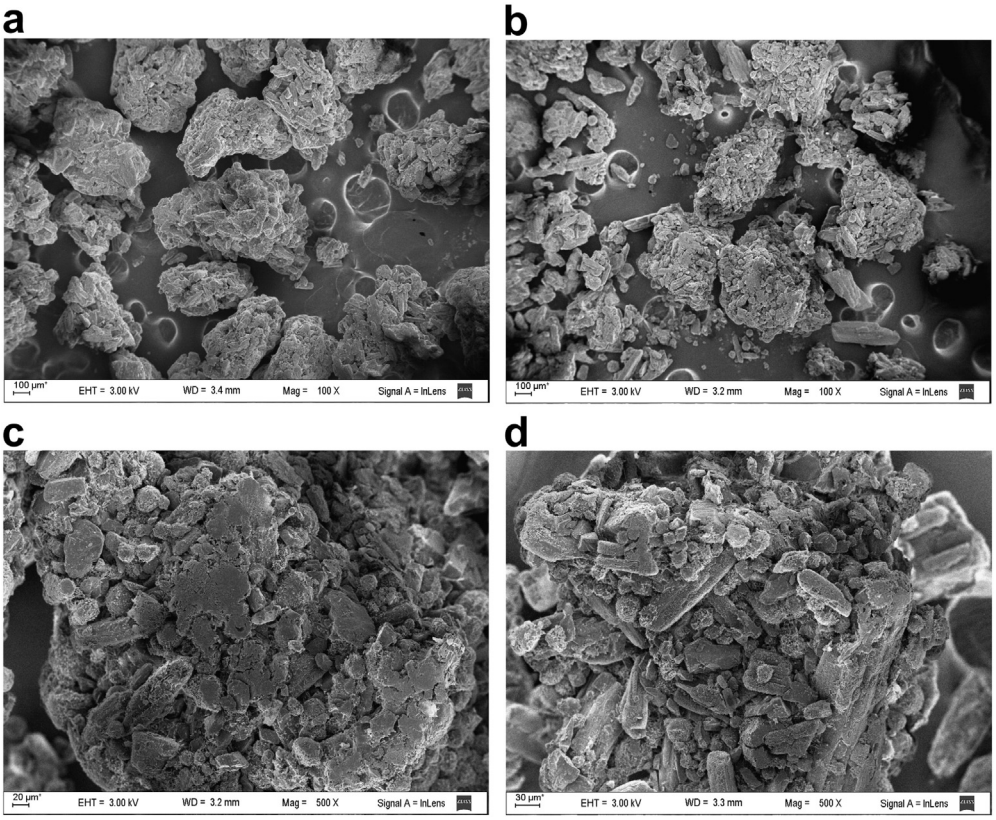

Fig. 3. Scanning electronic micrographs of the 420–500 µm fraction of Formulation 1 (a), and the 420–500 µm fraction of Formulation 5 (b, c and d).

3. Results and discussion

Table 1 shows the different formulations subjected to the FHMG process. Formulation 0 contained only ibuprofen and glyceryl palmito-stearate (20 wt.%), whereas all the other formulations contained ibuprofen (50 wt.%) and two other excipients. Formulations 1, 2 and 3 contained 10, 20, and 30 wt.% of glyceryl palmito-stearate, respectively, and lactose (Granulac 200) as the third component. In Formulations 4 and 5 glyceryl palmito-stearate at 20 wt.% was also used, but Granulac 200 was replaced by Granulac 140 or by talc, respectively. Formulation 6 was employed as a control, and had the same composition as Formulation 2. It consisted of the physical mixture of the components.

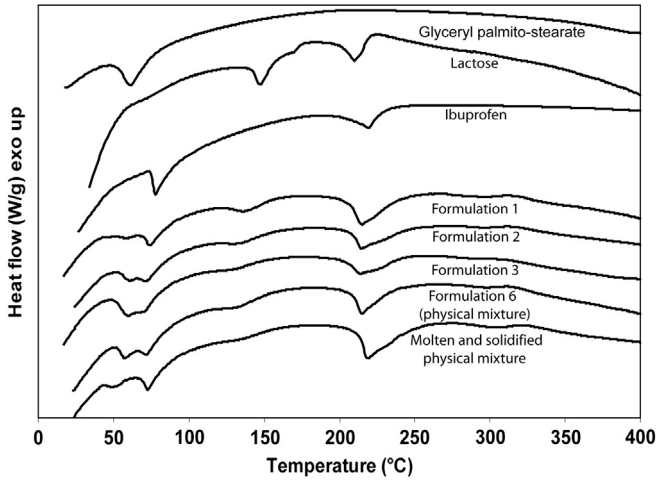

Fig. 4. DSC curves of glyceryl palmito-stearate, lactose monohydrate, ibuprofen, Formulations 1, 2, 3, 6 (physical mixture), and molten and solidified physical mixture.

Yields of the granulation process were high (95–98 wt.%) (Table 1). Only the yield for Formulation 0 was low (62 wt.%) as that mixture (80 wt.% ibuprofen plus 20 wt.% glyceryl palmito-stearate, without any other excipients) adhered to the gas distribution plate, the walls of the fluidized bed chamber and especially to the metal filter cartridges. For this reason, a non meltable excipient was included.

Fig. 1 presents the size distribution of the granules obtained for the different formulations. Only the data up to 400 µm are shown in this figure, since very small fractions of particles of larger size were obtained. Size fractional mass density distribution ($q_3/1/\mu m$) is represented in terms of particle diameter (µm) of the granules obtained for Formulations 1–6. From these results, the occurrence of granulation was confirmed. The granules presented a bimodal size distribution; the second mode was 200 µm. As it can be appreciated, quantitative variations in the formulation (Formulation 1 to 3) or changes in the excipient particle diameter, such as the substitution of the lactose by a lactose of larger diameter (Formulation 5) or by talc of finer diameter (Formulation 4), did not influence the average size of the granulated fractions. The physical mixture (Formulation 6) had an average size of 81 µm. Granules of similar sizes and distribution patterns have been reported employing ballotini beads with poloxamer as the meltable binder [9].

Images of fractions of different sizes for Formulation 1 are shown in Fig. 2. As already mentioned in the granulation experiment, process conditions employed were an air flow rate of 25 $m^3\ h^{-1}$, 15 min total process time and granulation temperature of 51 ± 1 °C. The material appears as rounded particles with variable sphericity. This appearance is similar for all the granulated formulations tested. Representative SEM images (Fig. 3) show that granules are composed of the individual components stuck together by the binder. Ibuprofen can be distinguished at the higher magnification as oblong particles, whereas lactose presents polyhedral shape.

Fig. 4 shows the DSC curves of pure glyceryl palmito-stearate, lactose, ibuprofen, Formulations 1, 2, 3, and 6 (physical mixture), and the molten and solidified physical mixture. Glyceryl palmito-stearate

Table 2
Onset temperatures (°C) and heats of transition (J g^{-1}) detected in DSC curves of glyceryl palmito-stearate, lactose monohydrate, ibuprofen, Formulations 1, 2, 3, and 6 (physical mixture), and molten and solidified physical mixture.

Sample	Onset temperature (°C)	Heat (J g^{-1})	Onset temperature (°C)	Heat (J g^{-1})	Onset temperature (°C)	Heat (J g^{-1})
Glyceryl palmito-stearate	52.40	155.7				
Lactose					142.60	51.3
Ibuprofen			75.40	133.7		
Formulation 1	51.06	17.2	70.02	65.3	125.66	21.1
Formulation 2	51.62	33.5	66.95	67.0	120.72	15.9
Formulation 3	51.47	44.6		66.7	121.66	10.5
Formulation 6 (physical mixture)	51.72	35.1	66.83	64.9	120.73	14.3
Molten and solidified physical mixture	41.97	30.5	65.79	57.2	118.86	12.5

presents a melting endothermic peak at 52.4 °C (calculated as the onset temperature in all cases) and a heat of fusion of 155.7 J g^{-1}, while the DSC curve of lactose monohydrate shows an endothermic peak at 142.6 °C, due to the loss of hydration water, with an associated heat of 68.0 J g^{-1} and a melting endothermic peak with decomposition at 202.2 °C. DSC curve of pure ibuprofen shows a melting endothermic peak at 75.4 °C and a heat of fusion of 133.7 J g^{-1}, followed by decomposition and evaporation of breakdown products above 180 °C. These results are in agreement with previous studies [2,22,26–28]. In Formulations 1, 2, and 3, the peaks of the raw materials are maintained indicating the absence of strong interactions between the drug and the other components (Fig. 4, Table 2). The results in Table 2 indicate that in these formulations heats of fusion of glyceryl palmito-stearate and ibuprofen, and heats associated with lactose water loss approximately maintain the proportionality according to their theoretical composition. However, the temperature corresponding to the melting of glyceryl palmito-stearate and ibuprofen decreased slightly as a consequence of impurification caused by the presence of the other components in the granules. It is worth mentioning that the melting temperature of glyceryl palmito-stearate is much lower in the molten and solidified physical mixture (41.83 °C) than in Formulation 6 (physical mixture, 52.74 °C) and in Formulation 2 (54.73 °C), all three of the same composition, possibly due to the more intimate contact among the components in the molten and solidified physical mixture. Heats of transition of the molten and solidified physical mixture are also lower than those expected by the proportion of its components (Table 2).

In Fig. 5 the X-ray diffractograms of the raw materials, granulates and the physical mixture are presented. Glyceryl palmito-stearate shows three peaks at 2θ angles of 19.5°, 21.5° and 23.5° [21] while Granulac 200 (lactose monohydrate) displays a pattern with the more intense peaks at 19.1°, 19.5° and 19.95° of 2θ [29]. The diffraction pattern of ibuprofen is crystalline, with numerous sharp and intense diffraction peaks at 6.2°, 16.6°, 20.1° and 22.4° of 2θ [2]. X-ray diffractograms of Formulations 1 and 2 present the peaks of all their components with intensities according to their relative contents, not evidencing loss of crystallinity. The diffractogram of Formulation 2 is very similar to Formulation 6 (physical mixture). In contrast, the molten and solidified physical mixture shows a decrease in crystallinity as evidenced by broader peaks of lower intensity.

Fig. 6. shows FT-IR spectra of glyceryl palmito-stearate, ibuprofen, lactose and Formulations 1, 2 and 6 (physical mixture). For glyceryl palmito-stearate, peaks were recorded at 1730 cm^{-1} (C=O stretching) and

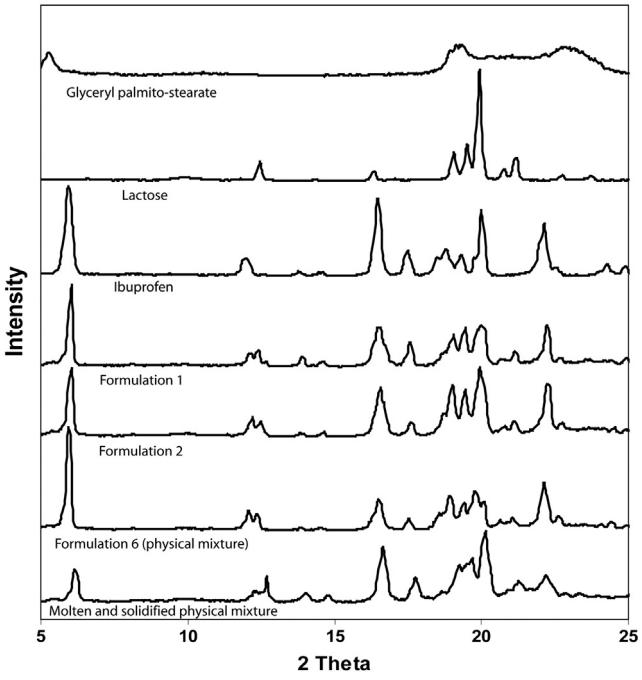

Fig. 5. XRD patterns of glyceryl palmito-stearate, lactose monohydrate, ibuprofen, Formulations 1, 2, 6 (physical mixture) and molten and solidified physical mixture.

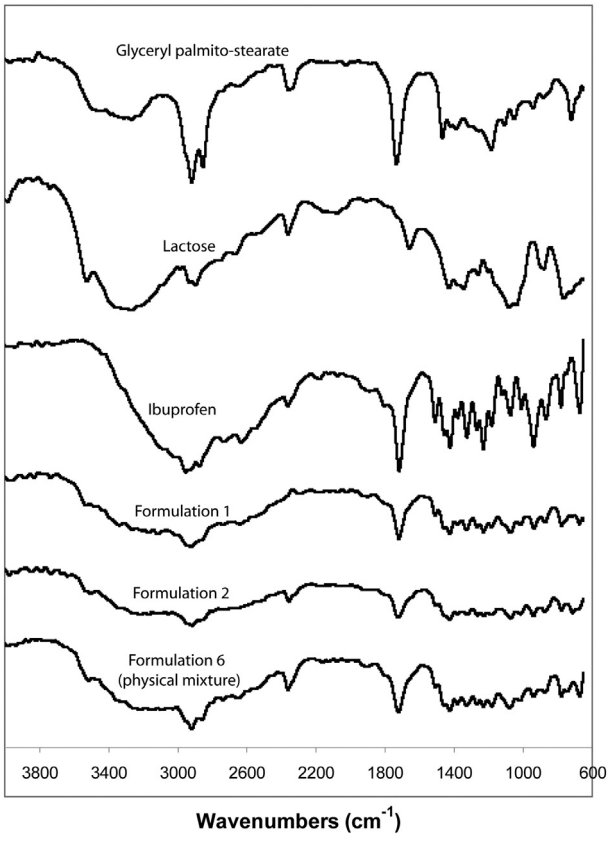

Fig. 6. FT-IR spectra of glyceryl palmito-stearate, lactose monohydrate, ibuprofen, Formulations 1, 2, and 6 (physical mixture).

strong peaks in the region 2850–3000 cm^{-1} (C–H stretching). Lactose has a broad absorption peak at 3250 cm^{-1}, which represents O–H stretching; other peaks correspond to C–O stretching (1335 and 1032 cm^{-1}) and C–H bending and ring vibrations (874 and 750 cm^{-1}). Ibuprofen spectrum presents the characteristic peaks at 2951 cm^{-1} (O–H stretching), 1715 cm^{-1} (C=O stretching), 1506 cm^{-1} (C–C ring vibration), 1456 cm^{-1} (C–H asymmetric bending of the CH_3 group and C–H scissoring of the CH_2 group), 1267, 1228 and 1182 cm^{-1} (C–O stretching and O–H bending) [5,30–32]. The FT-IR spectra of the formulations can be considered as the addition of peaks of the constituents, with intensities in agreement with their relative composition. A comparison of Formulation 2 and Formulation 6 reveals that the granulation process did not modify the position and intensity of the peaks.

From DSC, XRD, and FT-IR data, it can be inferred that in the experimental FHMG conditions employed, the crystalline structure of ibuprofen, a model drug of low melting point, was not lost; the structure of lactose was also maintained and glyceryl palmito-stearate appeared to return to its original physical state after melting and solidification. Besides, the components of the granules seem not to present strong solid state interactions, indicating a good compatibility among the components.

Fluidity of granules (Table 3) was considered as "good", according to the flow property classification of USP [24], with the exception of Formulation 0 whose flow was "Fair — aid not needed". However, Formulation 6 (physical mixture) was classified as "Poor — must agitate, vibrate". Comparing Formulation 6 with Formulation 2, it can be seen that the angle of repose improved 18° (from 51° to 33°) as a consequence of the granulation process. Due to its deficient flow, only in the preparation of tablets with the physical mixture, it was necessary to feed the die manually as powder did not flow from the hopper of the tablet press.

The preparation of tablets involved an initial setting of die load and applied force of the tablet press; this was performed employing Formulation 1. The settings were not altered for the other formulations in order to make comparisons. Tablets achieved proper and similar hardness values applying low compression forces and the variability of weight was acceptable (Table 4). Due to the low yield attained in the granulation process and of the poor flow, Formulation 0 was not further studied. The lowest hardness value was achieved for this formulation. The content of ibuprofen assayed by UV spectroscopy was in the range 99.1–100.3% of the theoretical value, for all the formulations. The ibuprofen dissolution profiles from Formulations 1–6 are illustrated in Fig. 7. Experimental data were used to calculate the Difference (f_1) and Similarity Factors (f_2), employing Formulation 2 as reference (Table 5). From these factors it can be inferred that the granulation process did not substantially modify the release profiles ($f_1 = 9.3$ and $f_2 = 71.0$ for Formulation 2/Formulation 6). It has been previously reported that drug dissolution profiles are practically independent of the melt granulation method (FHMG or high shear mixer) in the case of formulations involving ibuprofen, lactose and PEG6000 [2]; on the other hand, glyceryl palmito-stearate matrices prepared by hot fusion released theophylline slower than the same drug prepared by a manual ethanol granulation [33]. Differences in the granulometry of lactose also led to similar formulations ($f_1 = 10.4$ and $f_2 = 67.8$ for Formulation 2/Formulation 4). However, the variation in the percentage of meltable binder modified release profiles, especially when glyceryl palmito-stearate was decreased from 20% to 10% ($f_1 = 39.7$ and $f_2 = 29.5$ for Formulation 2/Formulation 1 and $f_1 = 16.8$ and $f_2 = 59.7$ for Formulation 2/Formulation 3). As expected, a higher percentage of lipophilic binder was associated with a lower drug release [19,34]. The increase in glyceryl palmito-stearate also implied a corresponding decrease in lactose composition (Table 1). The substitution of talc instead of lactose was another factor that modified release profiles even though in a lesser way and differently than could be expected preliminarily, based on the characteristics of both excipients ($f_1 = 30.5$ and $f_2 = 71.0$ for Formulation 2/Formulation 5). Talc being water insoluble as opposed to lactose, its higher release can be explained by an increase in total surface area [35] associated with the bulk erosion observed in the dissolution flasks, since the first hours of the tests. Tablet disintegration occurred approximately after 4 h, in line with the jump in the release that appears in the dissolution profile at this time (Fig. 7). It should be hypothesized that in all cases, granulation takes place predominantly through a distribution mechanism, considering that all the powders and drops of the binder are of similar sizes and that solid, compact granules are obtained. Nevertheless, an immersion mechanism could also contribute to granule formation in the case of Formulation 5. In this one, talc involving smaller particle size was used. In these conditions, the binder would be preferably consumed in the granulation of talc, leaving ibuprofen in the granules more accessible to the dissolution medium. This would lead to a different granular structure and to the disintegration and enhanced release [5,36].

The comparison of release values during the first 30 min (first experimental point) with those corresponding to equivalent successive intervals, allows detecting the presence or the lack of a "burst release" effect from a dosage form; this effect is difficult to predict *a priori* [37]. Burst release in monolithic matrices could be due to some drug trapped on the surface of the matrix during compression, especially in the case of high drug loads, such as those employed in these experiments (50 wt.%), leading to immediate drug release. In all the formulations evaluated almost no burst release was observed, even with values as low as 10 wt.% of meltable binder, showing the effectiveness of glyceryl palmito-stearate as a controlled release matrix. These results are noteworthy, especially when compared with matrices based on carnauba wax, glyceryl monostearate, stearic acid, cetyl alcohol, or cetostearyl alcohol which reportedly present noticeable burst effect at concentrations of 25 and 50 wt.% [36].

The dissolution profiles were fitted to a semi-empirical model based on previous proposals (Model I) [38,39]. Accordingly, experimental data corresponding to fractions of drug released ≤60% were employed. The model equation is given by:

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t/M_∞ is the fraction of the total drug released, k, the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery device, t, the time elapsed from the start of the dissolution test, and n, the release exponent. Model characteristic

Table 3
Static angles of repose and flow properties of Formulations 1–6 granulates.

Formulation	Static angle of repose (°)	Flow properties
0	37	Fair — aid not needed
1	35	Good
2	33	Good
3	34	Good
4	34	Good
5	33	Good
6	51	Poor — must agitate, vibrate

Table 4
Weights, hardness and friability of tablets obtained from the different formulations.

Tablets from formulation	Mean weight (mg)	CV %	Hardness kP	Friability %
0	129.43	2.12	3.1	60
1	151.84	2.31	6.1	0.26
2	149.21	0.80	5.5	0.34
3	153.44	0.76	5.6	0.10
4	150.53	1.37	6.0	0.17
5	147.49	3.16	5.5	0.12
6	148.84	2.12	5.6	0.20

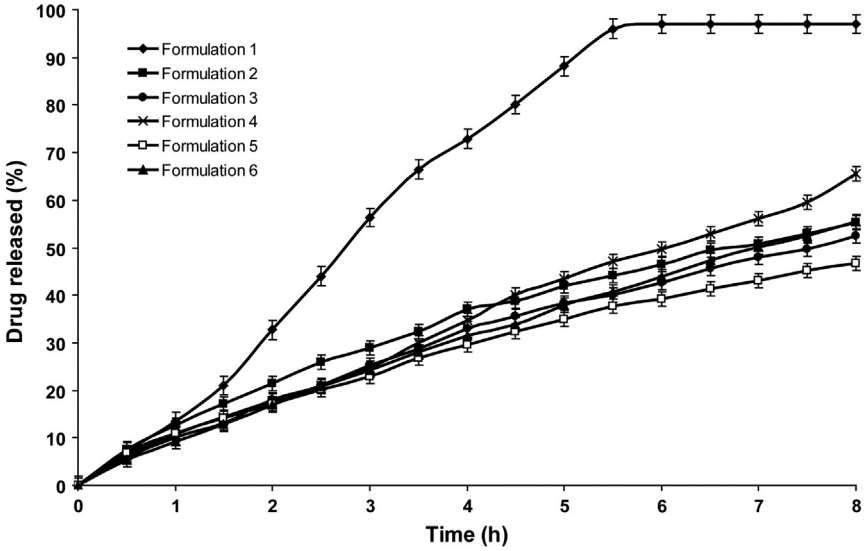

Fig. 7. Release of IBF from the tablets prepared from Formulations 1–6.

parameters (k, n), as evaluated by non-linear regression analysis are shown in Table 6.

As can be inferred from R^2 values ($\geq$0.979), Model I appropriately describes the experimental data. Assuming cylindrical geometry for the tablets prepared in the study, a release exponent (n) of 0.45 points to Fickian diffusion transport, whereas values of n between 0.45 and 0.89 suggest non-Fickian transport. In turn, values of n of 0.89 indicate that the system releases the drug with a zero order kinetics (case II transport) independently of the real drug release mechanism [38,39]. Values above 0.89 are described as super case II transport.

As can be seen in Table 6, n values were in the range 0.62–0.99. Formulation 1 release suggests super case II. From Formulation 1 (10% glyceryl palmito-stearate) to Formulation 2 (20 wt.% glyceryl palmito-stearate), k decreased. An increase in the binder content to 30 wt.% in Formulation 3 almost did not modify the k parameter; however, the release from Formulation 3 was lower at the expense of a lower k value. The release from Formulations 2, 3, 5 and 6 could be classified as non-Fickian (anomalous) transport. The n value of 0.90 for Formulation 4, where lactose was replaced by talc (20 wt.%) could point to zero order release.

To further study the possible mechanisms involved in drug release, the experimental profiles were also fitted to a second model (Model II) reported in the literature [38,39]. The equation representing the model is as follows:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{4}$$

The meaning of the terms M_t/M_∞ and t, is the same as for Model I. The model characteristic parameters k_1, k_2, and m, evaluated by non-linear regression analysis, are presented in Table 6. As shown in Table 6, R^2 values were greater than or equal to 0.998. Accordingly, Model II seems to adequately describe the experimental release data from glyceryl palmito-stearate matrices. The first term on the right side of Model II equation represents Fickian diffusional contribution, F, whereas the second term represents case II transport, R. For glyceryl palmito-stearate lipophilic matrices the last mechanism is assumed to be due to surface erosion [37] as swelling is reported to be negligible [40,41]. This is reflected in the very low k_2 values obtained for Model II fitting. The ratio of both contributions can be calculated as follows:

$$\frac{R}{F} = \frac{k_2 t^m}{k_1} \tag{5}$$

The model characteristic parameters estimated in Table 6 and the experimental data from the different formulations were used to build Fig. 8, namely to represent the R/F ratio versus the drug release percentage.

The results depicted in Fig. 8 indicate that in general, the contribution of Fickian diffusion was dominant for all formulations and, therefore, use of Model I enables to represent properly the experimental data. In turn, for a particular drug release percentage, the contribution of matrix relaxation was relatively more important for Formulation 1 (10% glyceryl palmito-stearate) than for the other formulations. In addition, for each formulation, case II transport also became more important when the percentage of drug release increased.

4. Conclusions

Different formulations containing ibuprofen as model drug were granulated by fluidized hot melt granulation, employing glyceryl palmito-stearate as a meltable binder, in a single stage. Yields were high (95–98 wt.%) and the complete process lasted only 15 min. The major mode of particle size distribution was 200 μm. The crystalline structure of ibuprofen and the non meltable excipients was not lost, and that of glyceryl palmito-stearate was recovered in the final

Table 5
Difference and similarity factors for the different formulations, with regard to Formulation 2.

Formulation	Difference factor (f_1)	Similarity factor (f_2)
1	39.7	29.5
3	16.8	59.7
4	10.4	67.8
5	30.5	46.2
6	9.3	71.0

Table 6
Model characteristic parameters of Model I and Model II.

Formulation	Model I			Model II			
	k (h^{-n})	n	R^2	k_1 (h^{-m})	k_2 (h^{-2m})	m	R^2
1	17.66	0.99	0.979	14.80	2.02	0.90	0.999
2	13.74	0.68	0.997	47.71	0.08	0.68	0.998
3	11.21	0.72	0.998	28.91	0.06	0.72	0.999
4	9.89	0.90	0.997	12.29	0.06	0.91	0.998
5	10.76	0.62	0.996	42.63	0.07	0.62	0.998
6	9.53	0.85	0.999	14.14	0.05	0.85	0.999

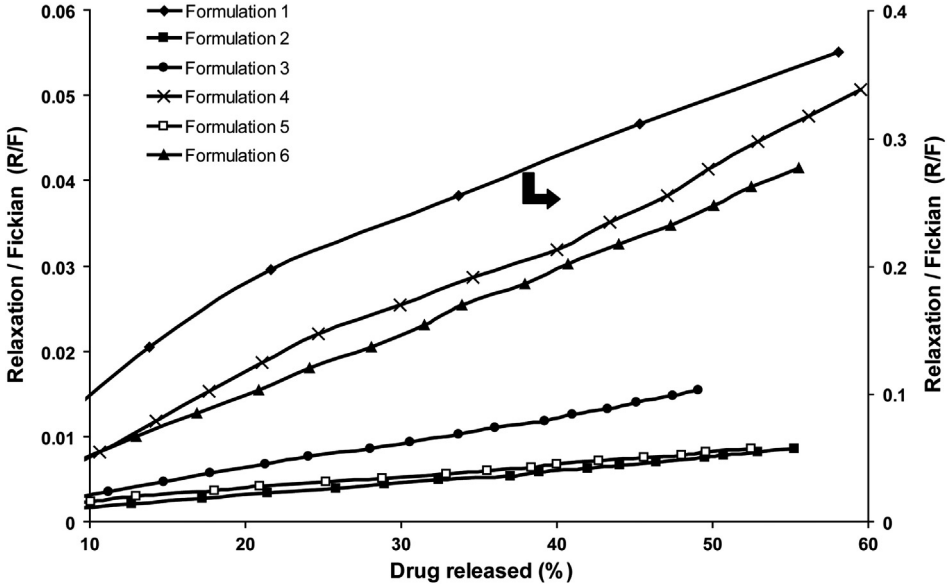

Fig. 8. Ratio between matrix relaxation and Fickian diffusion contributions (R/F), for Formulations 1–6. Values for Formulation 1 are presented in the secondary axis.

granules. The granules presented good flow properties and, therefore, it was not necessary to add other lubricants to obtain ibuprofen tablets. The tablets showed good pharmacotechnical properties. The granulation process did not modify release profiles from the tablets. The main factor influencing the release profiles was the content of glyceryl palmito-stearate in the formulations. A high drug load was achieved; this is particularly important in the case of high dose active pharmaceutical ingredients. Glyceryl palmito-stearate performed a triple function in the tablet formulation: as a meltable binder, as a controlled release matrix and as a lubricant.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.powtec.2014.05.058.

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