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An investigation into the effect of formulation variables and process parameters on characteristics of granules obtained by in situ fluidized hot melt granulation

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ABSTRACT

The aim of this study was to investigate the influence of binder content, binder particle size, granulation time and inlet air flow rate on granule size and size distribution, granule shape and flowability, as well as on drug release rate. Hydrophilic (polyetilenglycol 2000) and hydrophobic meltable binder (glyceryl palmitostearate) were used for in situ fluidized hot melt granulation. Granule size was mainly influenced by binder particle size. Binder content was shown to be important for narrow size distribution and good flow properties. The results obtained indicate that conventional fluid bed granulator may be suitable for production of highly spherical agglomerates, particularly when immersion and layering is dominant agglomeration mechanism. Granule shape was affected by interplay of binder content, binder particle size and granulation time. Solid state analysis confirmed unaltered physical state of the granulate components and the absence of interactions between the active and excipients. Besides the nature and amount of binder, the mechanism of agglomerate formation seems to have an impact on drug dissolution rate. The results of the present study indicate that fluidized hot melt granulation is a promising powder agglomeration technique for spherical granules production.

1. Introduction

Melt granulation (MG) is an emerging technique based on the use of binders that have relatively low melting point (between 50 and 80 °C) and act as a molten binding liquid. The equipment that can be used for melt granulation includes: high-shear mixers, fluid bed granulators, extruders. Significant advantages of this technique over conventional granulation methods have led to increased interest in application of meltable binders. Considering that solvent is not required, process is simple, rapid, cost effective, no risks associated with residual solvents in the final product, suitable for moisture-sensitive drugs (Andrews, 2007; Heng and Wong, 2006; Wong et al., 2005). By selecting the suitable binder, MG can be used either to prepare modified (Evrard and Delattre, 1996; Hamdani et al., 2002; Pauli-Bruns et al., 2010; Thies and Kleinebudde, 1999; Voinovich et al., 2000; Zhou et al., 1996) or immediate release dosage forms (Borini et al., 2009), and also to improve bioavailability of poorly water soluble drugs (Passerini et al., 2002, 2006, 2010; Perissutti et al., 2003; Vilhelmsen et al., 2005; Yang et al., 2007).

The possibility of using molten binder liquid for agglomeration in high shear mixer was introduced in the early 1980s (Rubinstein and Musikabhuma, 1980), and intensive studies begun in the 1990s with the work of Schæfer et al. (1990, 1993a,b). Interestingly, MG in fluidized beds has provoked research interest more recently, with the earliest research papers, at least to our knowledge, published in 2001 and 2002 (Abberger, 2001; Abberger et al., 2002; Kidokoro et al., 2002; Kojima and Nakagami, 2001; Seo et al., 2002). These studies have announced a significant potential of fluidized hot melt granulation (FHMG) for the preparation of granules with excellent flow properties and suitable for compression into tablets. Depending on the method of binder addition, two procedures have been proposed: spray on (molten binder being added through a nozzle) and in situ (melt-in, co-melt) procedure (meltable binder being initially included as discrete particles within the fluidized bed). Despite the considerable differences between high-shear mixers and fluidized beds, particularly the lower shear forces in fluidized beds, similar mechanisms of the agglomerate growth have been suggested. Schæfer and Mathiesen (1996) proposed for agglomerate growth in high shear mixer two different nucleation mechanisms: distribution (molten binder is distributed on the surface of the solid particles) and immersion mechanism (solid particles are immersed into the surface of the molten binder droplets). In these early studies on FHMG it was found that prevalence of one or the other mechanism is mainly governed by the ratio

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between the size of molten binder droplets and size of solid particles. Nucleation by immersion and subsequent layering is promoted by larger molten binder droplets, and nucleation by distribution and further growth by coalescence occurs when the molten binder droplets are not greater than the solid particles.

From 2005 onwards significant efforts have been made to elucidate the exact granulation mechanism and kinetics of the process of agglomerate growth in fluidized beds (Ansari and Stepanek, 2006; Vilhelmsen et al., 2004; Walker et al., 2005, 2006, 2007a,b,c, 2009; Zhai et al., 2009). Majority of the reported results were obtained for placebo formulations and only few papers are dealing with granulates that contain active substance (Borini et al., 2009; Passerini et al., 2010; Pauli-Bruns et al., 2010; Vilhelmsen et al., 2005; Walker et al., 2007a).

FHMG has some advantages compared to melt granulation in high shear mixers, such as better control of the product temperature, which simplifies the whole process allowing the cooling phase to be performed easily and quickly in the same piece of equipment. Due to the higher shear forces, agglomerates produced in high shear mixers are usually more spherical. On the other hand, as a result of lower shear forces in fluid bed processor, it is capable to produce the agglomerates with higher binder content than high-shear mixer and rotary processor (Vilhelmsen et al., 2004). The rotary processors are proposed as an alternative equipment for melt pelletization, and it was suggested that conventional fluid bed processors might be unsuitable for pelletization (Vilhelmsen et al., 2004). Recent studies showed that highly spherical pellets can be obtained in fluid bed granulator when dominant mechanism of agglomeration is immersion and layering (Pauli-Bruns et al., 2010) and that despite some differences in particle size distribution and morphology of the granules, in situ FHMG can be a suitable alternative to melt granulation in high-shear mixers (Passerini et al., 2010).

The objective of the present study was to investigate the influence of formulation and process parameters on granules and tablets characteristics. The suitability of conventional fluid bed granulator as an alternative equipment for melt pelletization was investigated. Two different binders were used, glyceryl palmitostearate as hydrophobic and polyetilenglycol 2000 as hydrophilic meltable binder.

2. Materials and methods

2.1. Materials

Paracetamol (Acros Organics, Geel, Belgium) was used as the model drug. Lactose monohydrate (Carlo Erba Reagents, Milan, Italy) was used as diluent. Glyceryl palmitostearate (Precirol® ATO 5), kindly supplied by Gattefosse (Saint-Priest Cedex, France), was used as hydrophobic meltable binder. Polyethylene glycol (PEG) 2000 (Fluka AG, Buchs, Switzerland) was used as hydrophilic meltable binder. Sodium Hydroxide (Merck, Darmstadt, Germany) and potassium phosphate monobasic (Sigma–Aldrich Chemie GmbH, Steinheim, Germany) were used for dissolution media preparation. Polyvinylpyrrolidone (Kollidon® K 25, BASF, Ludwigshafen, Germany) was used as a wet granulation binder.

2.2. Methods

2.2.1. Characterization of primary materials

Lactose and paracetamol particle size was determined in triplicate by laser diffraction (Mastersizer S, Malvern Instruments Ltd., Worcestershire, UK) using a 300RF lens and a small volume dispersion unit (1500 rpm). Ethanol was used as a dispersion media for lactose and cyclohexane as a dispersion media for paracetamol.

The melting range and the melting onset temperature of meltable binders were estimated by a differential scanning calorimeter DSC 1 (Mettler-Toledo GmbH, Gießen, Germany) equipped with STARe Software. Samples of about 10 mg were non-hermetically sealed in a 40 μl aluminum pan, and scanned between 25 and 150 °C at a heating rate of 10 °C/min under nitrogen atmosphere (50 ml/min).

The viscosities of molten binders were estimated at 65 °C within the shear rate range 0–200 s^{-1} using the rotational rheometer Rheolab MC 100 UM (Paar Physica, Stuttgart, Germany) coupled with the rotating cylinder measuring device Z3.

2.2.2. Contact angle measurements

Compacts of the powders (200 mg) were prepared using a round stainless steel punch and die assembly (d = 13 mm) in a Specac hydraulic press (Specac Ltd., Kent, England) with a 30 s dwell time at a force of approximately 49 kN. The contact angle was measured using Krüss DSA100 (Krüss GmbH, Hamburg, Germany). The molten binder was preheated to 65 °C and then dropped onto the solid (lactose and paracetamol), the contact angle was measured using circle method on at least five samples.

2.2.3. Granule preparation

Granulation process (in situ FHMG) was performed in Mycrolab fluid bed processor, OYSTAR Hüttlin, connected to a personal computer allowing the process parameters to be monitored and recorded. The batch size was 200 g. Meltable binders were finely ground to give a mass mean particle size of ≈247.5 μm (180–355 μm sieve fraction) or a mass mean particle size of ≈650 μm (500–800 μm sieve fraction). All the ingredients, paracetamol (20%), binder (5% or 15%) and lactose, were filled into the processing chamber, fluidized and preheated to product temperature of 65 °C. The start of granulation time was defined as the point where product temperature reached 65 °C. After specified time (10 or 30 min) the inlet air heating was switched off. The inlet air flow rate was kept constant at 35 and/or 50 m^3/h. Filters were shaken for 0.2 s in alternating mode during the whole process. When the product temperature decreased below 30 °C the fluid bed processor was stopped and the product removed.

2.2.4. Experimental design

Binder particle size, binder content, granulation time, and the inlet air flow rate were set as investigated variables. Considering that the inlet air flow rate did not show significant influence on response variables in the experiments with PEG 2000, it was kept constant in the experiments with Precirol® ATO 5. Accordingly, formulations with PEG 2000 were prepared according to 2^{4-1} fractional factorial design, while formulations with Precirol® ATO 5 were prepared according to 2^3 full factorial design. Real and coded values of the evaluated factors are given in Table 1. All experiments were performed in randomized order (Table 2). The experimental results were analyzed by analysis of variance (ANOVA), at the 0.05 level of significance, using the Design-Expert® software (Version 7.0, Stat-Ease Inc., Minneapolis, USA).

The response variables were: mass median particle diameter (d_{50}), span (S_{75-25}), aspect ratio (AR), projection sphericity (PS), circularity (C), Carr index (CI), time required for 40% (T_{40}) and 80% (T_{80}) drug release.

2.2.5. Granule size analysis

The size distribution of granules was evaluated by sieves analysis, using the vibratory sieve shaker (Retsch GmbH, Haan, Germany) and a set of standard sieves in the range of 50–2000 μm. Sieve analyses were performed on samples of 100 g and the sieving time was 10 min.

Table 1
Real and coded values of evaluated factors.

Factors	Symbol	PEG 2000		Precirol® ATO 5	
		Low level (−1)	High level (+1)	Low level (−1)	High level (+1)
Binder particle size (μm)	X_1	247.5	650	247.5	650
Binder content (%)	X_2	5	15	5	15
Granulation time (min)	X_3	10	30	10	30
Inlet air flow rate (m^3/h)[a]	X_4	35	50	–	–

[a] The inlet air flow rate was kept constant at 35 m^3/h in the experiments with Precirol ATO 5.

Median particle diameter (d_{50}) was calculated by linear interpolation of the cumulative percentage frequency curve. The span was determined as a quotient of difference between the agglomerate sizes corresponding to the quartile points at 75% and 25% and mass median diameter.

2.2.6. Determination of Carr index

The granules were weighted and poured into a 100 ml graduated cylinder. The bulk and tapped densities were obtained before and after tapping (1250 taps) the granulate using a VanKel Tap Density Tester (VanKel Technology Group, Cary, USA). The values of these two densities were used to calculate the Carr index.

2.2.7. Image analysis

The granule shape was examined using Olympus BX50 microscope (Olympus Corporation, Tokyo, Japan) coupled with a Sony DXC-950P digital camera (Sony, Tokyo, Japan). Image analyses were performed on at least 200 agglomerates, using image processing software AnalySIS® (Soft Imaging System GmbH, Münster, Germany). Measurements were performed at 40× magnification corresponding to a pixel length of 4.12 μm. Representative samples of agglomerates from the size fraction 315 to 2000 μm were used for image analysis.

In order to characterize and estimate the shape of the agglomerates following parameters were calculated: the aspect ratio (AR), the circularity (C) and the projection sphericity (PS). The aspect ratio is defined as the maximum Feret diameter (maximum caliper distance of 180 measurements around the particle using 1° steps) divided by the maximum Feret diameter perpendicular to it (AnalySIS User's Guide, 1998). The projection sphericity indicates how spherical the particle is, and can be calculated using the following equation (Podczeck et al., 1999):

$$\mathrm{PS} = \frac{4A}{\pi d_m^2} \quad (1)$$

where A is the projected area of two-dimensional particle outline, and d_m is the maximum Feret diameter of a particle.

The circularity as a measure of particle roundness, but also an indication of the particle smoothness, is given by the following equation (Bouwman et al., 2004; Podczeck et al., 1999):

$$C = \frac{4\pi \times A}{P^2} \quad (2)$$

where P is the overall perimeter of two-dimensional particle outline.

The investigated parameters values close to 1, indicate high sphericity of the particles obtained.

2.2.8. Scanning electron microscopy (SEM)

The morphology of the agglomerates was investigated by SEM (Supra 35VP, Carl Zeiss, Oberkochen, Germany) with an acceleration voltage of 1 kV and a secondary detector. Both, whole and cut granules, were deposited on double-adhesive carbon tape and pictures were taken.

2.2.9. Tablet compression

Tablets were prepared by direct compression method. A flat-faced punches with a diameter of 13 mm were used to compress granules using an eccentric tablet machine (EKO Korsch, Berlin, Germany). Tablet weight was set to 500 mg.

2.2.10. In vitro dissolution studies

Dissolution studies were performed in the paddle apparatus (Erweka DT 600, Heusenstamm, Germany) at 50 rpm using 900 ml of USP phosphate buffer pH 5.8 as a dissolution media. Dissolution media samples were withdrawn at the predetermined time intervals, appropriately diluted and assayed UV spectrophotometrically (Evolution 300 spectrophotometer, Thermo Fisher Scientific, Madison, USA) at 243 nm. All determinations were performed in triplicate. T_{40} and T_{80} were determined by linear interpolation of the dissolution curves.

Table 2
The experimental design matrix and values of response variables.

Granulate	Run no.	X_1	X_2	X_3	X_4	d_{50} (μm)	d'_{50} (μm)[a]	S_{75-25}	AR	PS	C	CI (%)	T_{40} (min)	T_{80} (min)
A1	6	−1	−1	−1	−1	361.5	587.4	1.36	1.17	0.76	0.92	12.5	3.0	7.4
A2	5	+1	−1	−1	+1	724.9	1166.2	1.52	1.18	0.74	0.84	10.3	2.9	7.4
A3	2	−1	+1	−1	+1	682.1	686.8	0.79	1.23	0.69	0.87	3.6	12.5	31.4
A4	3	+1	+1	−1	−1	1697.4	1746.2	0.69	1.20	0.71	0.82	5.2	10.3	26.7
A5	8	−1	−1	+1	+1	382.6	565.3	1.28	1.17	0.75	0.92	12.9	3.2	10.5
A6	7	+1	−1	+1	−1	729.0	1169.6	1.53	1.16	0.76	0.84	12.2	6.3	14.3
A7	1	−1	+1	+1	−1	639.2	646.4	0.83	1.26	0.65	0.80	3.2	11.9	34.0
A8	4	+1	+1	+1	+1	1158.8	1179.8	0.65	1.22	0.70	0.88	3.9	9.5	19.8
B1	3	−1	−1	−1	–	104.7	286.1	0.88	1.14	0.78	0.94	23.3	71.7	280.1
B2	8	+1	−1	−1	–	128.7	813.7	4.36	1.26	0.66	0.88	20.7	63.9	177.3
B3	6	−1	+1	−1	–	416.8	418.6	0.33	1.23	0.68	0.85	9.7	162.8	476.3
B4	4	+1	+1	−1	–	1040.7	1067.0	0.33	1.11	0.83	0.85	8.3	119.0	288.4
B5	5	−1	−1	+1	–	91.5	293.3	0.72	1.18	0.75	0.92	21.5	61.2	236.4
B6	7	+1	−1	+1	–	100.5	877.1	6.03	1.21	0.71	0.90	19.7	57.3	116.3
B7	2	−1	+1	+1	–	399.2	400.2	0.34	1.22	0.70	0.89	10.7	146.0	465.9
B8	1	+1	+1	+1	–	961.2	993.4	0.32	1.13	0.80	0.93	11.5	118.4	232.2

[a] d'_{50} is a mass median particle diameter obtained when fraction of particles < 180 μm was exluded from calculations.

2.2.11. Differential scanning calorimetry (DSC)

DSC analyses of single components and granulates were performed as described for characterization of the binders. Thermograms were obtained at a heating rate of 10 °C/min over a temperature range of 25–250 °C.

2.2.12. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded using a Nicolet iS30 FTIR Spectrometer (Thermo Fisher Scientific, Madison, USA). Scanning range was 650–4000 cm^{-1}.

2.2.13. X-ray powder diffraction (XRPD)

Samples of single components, granules and corresponding physical mixtures were studied by XRPD technique using a Siemens D5000 X-ray diffractometer (Siemens, Munich, Germany) with Cu Kα radiation. The scanning angle ranged from 3° to 37° of 2θ, scan steps were 0.04 of 2θ, and the counting time was 1 s/step.

2.2.14. Taste evaluation study

Taste evaluation was performed by the panel of 14 human volunteers, seven male and seven female (26–35 years of age), from whom informed consent was firstly obtained. The following granulates were used in the study: those prepared by FHMG with Precirol (15%, 10%, or 5%) or with 15% PEG 2000, and granulate prepared by conventional wet granulation method with 5% aqueous polyvinylpyrrolidone (PVP) solution, as a reference. The volunteers were asked to rank these five granulates according to bitter taste intensity, with number 1 assigned to granulate that is not bitter (or the least bitter among the tested granulates), and number 5 assigned to granulate with strong bitterness (i.e. the most pronounced bitterness among the tested granulates). Taste evaluation was performed as follows: 500 mg (equivalent of 100 mg paracetamol) of each granulate was put on the center of the tongue, held in the mouth for 10 s, and then spat out. The mouth was rinsed thoroughly with deionized water and the next granulate was tested after a 15 min break.

3. Results and discussion

3.1. Material properties

The median particle diameter for lactose was found to be 33.4 μm, while $d_{(0.1)}$ and $d_{(0.9)}$ were found to be 0.6 μm and 41.4 μm, respectively. Paracetamol median particle diameter was 66.6 μm, with $d_{(0.1)}$ and $d_{(0.9)}$ being 20.6 μm and 89.4 μm, respectively. Two binders exhibited different melting behavior. PEG 2000 had a melting peak at 53 °C, and melting range of 49–58 °C. Precirol® ATO 5 showed the melting peak at 61 °C, and the melting range of 53–66 °C. The viscosity of PEG 2000 was 134.0 mPa s, and Precirol® ATO 5 viscosity was 34.3 mPa s. Binder viscosity values were obtained at shear rate 94.8 s^{-1}.

3.2. Granule size and size distribution

The results of particle size analysis are presented in Table 2. It was shown that with larger initial binder particle size and higher binder content larger agglomerates were obtained.

It was found that binder content and the binder particle size had statistically significant influence on the size of the granules prepared with PEG 2000 (Table 3). Both factors had positive effect on median particle diameter. Similar results were obtained when Precirol was used as a binder, but the two-factor interaction between binder content and particle size was found to be significant factor as well. The influence of the initial Precirol particle size was more pronounced at higher Precirol content, the possible reason being that lower binder content resulted in a large fraction of fines regardless of binder particle size.

Considering that d_{50} values were estimated from entire particle size distribution, it should be taken into account that these values were affected by the fraction of ungranulated material. When fraction of fines (particles < 180 μm) was excluded from calculation, median particle diameters estimated for the formulations with 5% binder were considerably higher, while they remained practically the same in the case of formulations with 15% binder (Table 2). The results obtained indicate that size of the granules was governed mainly by initial binder particle size. The binder content and the binder particle size were found to significantly influence recalculated values of median particle diameter (d'_{50}), but the impact of binder particle size was now higher in case of both binders (Table 3).

The amount of PEG 2000 used for granulation had statistically significant effect on the width of particle size distribution. Higher binder content resulted in narrower agglomerate size distribution, i.e. lower S_{75-25}. Size distribution of agglomerates prepared with Precirol was significantly influenced not only by binder content but also by binder particle size and interaction of these factors. With 15% Precirol quite narrow particle size distribution was achieved, while granulation with 5% Precirol resulted in considerable amount of fines and consequently broader particle size distribution. Particularly high values of S_{75-25} were obtained for formulations prepared with larger initial binder particles, and that is the consequence of difference between the size of fine particles and the size of agglomerates.

Ansari and Stepanek (2006) found that granule size is dependent only on the binder particle size, and that the amount of the binder controls the fraction of fines rather than the agglomerate size. However, the results of the present study revealed the influence of the binder content on agglomerate size as well. Immersion and layering was dominant mechanism of agglomerate growth for all formulations they tested, which might be the reason for these differences. The results obtained in the present study indicate that width of particle size distribution is mainly affected by the amount of the binder, and quite narrow particle size distribution for a given binder particle size can be achieved if the amount of binder is sufficient (Ansari and Stepanek, 2006; Pauli-Bruns et al., 2010; Vilhelmsen et al., 2004; Walker et al., 2006). Granulation time and the inlet air flow rate did not show significant impact on granule size and granule size distribution. This is in accordance with literature findings showing that these parameters are of minor influence if the particles are fully fluidized and granulation time is close to the time that corresponds to the equilibrium particle size (Pauli-Bruns et al., 2010; Walker et al., 2005, 2006; Zhai et al., 2009).

Granulation process with both, PEG 2000 and Precirol ATO 5, showed similar trends in terms of median granule diameter and width of particle size distribution. It is interesting, however, that granules prepared with PEG were somewhat larger than those prepared with Precirol, and that the values of S_{75-25} were higher in the case of formulations with PEG 2000 (Table 2). Binder viscosity is shown to significantly influence granule growth and the mechanism of agglomerate formation (Kidokoro et al., 2002; Schæfer and Mathiesen, 1996; Walker et al., 2006). Namely, if the viscosity of the binder is lower it will be easier for solid particles to migrate to the interior of the binder droplet, and also the molten binder will be more easily drawn to the surface of the nuclei formed either by immersion or distribution, leading to further agglomerate growth. However, the viscosity of PEG 2000 at granulation temperature is almost 4-fold greater than that of Precirol, suggesting that viscosity of the binder was not the dominant factor controlling the agglomerate growth. It may be postulated that different wetting properties of the melts were the reason for differences in granule size. Contact angle measurements showed considerably better wetting of the granulate components with PEG (with contact angle being 30.2°

Table 3
Effects of the independent variables on response variables: median particle diameter (d_{50}, d'_{50}), span (S_{75-25}), aspect ratio (AR) and projection sphericity (PS).

Factors and interactions	d_{50} (μm) (r^2 = 0.9715)[a]		d'_{50} (μm) (r^2 = 0.9683)[b]		S_{75-25} (r^2 = 0.9352)		AR (r^2 = 0.8263)		PS (r^2 = 0.7993)	
	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value
PEG 2000										
Intercept	0.0387	–	0.0012	–	1.0818	–	1.1984	–	0.7196	–
X_1	−0.0067	0.0002	−0.0004	<0.0001	–	–	–	–	–	–
X_2	−0.0058	0.0004	−0.0001	0.0406	−0.3415	<0.0001	0.0294	0.0018	−0.0321	0.0027
Factors and interactions	d_{50} (μm) (r^2 = 0.9965)		d'_{50} (μm) (r^2 = 0.9906)		S_{75-25} (r^2 = 0.9966)[b]		AR (r^2 = 0.9982)		PS (r^2 = 0.9859)	
	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value
Precirol ATO 5										
Intercept	405.41	–	643.67	–	1.89	–	1.1868	–	0.7399	–
X_1	152.38	0.0002	294.13	<0.0001	-0.25	0.0022	−0.0086	0.0292	0.0118	0.0564
X_2	299.06	<0.0001	76.12	0.0022	1.16	<0.0001	−0.0132	0.0127	0.0125	0.0484
X_1X_2	144.12	0.0002	–	–	0.28	0.0013	−0.0446	0.0011	0.0510	0.0010
X_1X_3	–	–	–	–	–	–	−0.0068	0.0455	–	–
$X_1X_2X_3$	–	–	–	–	–	–	0.0143	0.0109	-0.0166	0.0235

[a] The inverse square root transformation of response values was applied in order to improve the statistical properties of the analysis.
[b] The inverse transformation of response values was applied in order to improve the statistical properties of the analysis.

for lactose, and 31.0° for paracetamol) than with Precirol (with contact angle being 117.0° for lactose, and 92.8° for paracetamol). Namely, PEG 2000 is more hydrophilic compared to Precirol and in spite of higher viscosity the spreading is greater and, therefore, the agglomerate growth will not be hindered.

3.3. Granule shape and morphology

The aspect ratio (AR) is often used as parameter for granule shape analysis (Passerini et al., 2002; Pauli-Bruns et al., 2010; Vilhelmsen et al., 2004). However, it is a measure of elongation of the particle, and it might be more useful in processes where oblong granules can be obtained, e.g. extrusion–spheronization (Bouwman et al., 2004; Podczeck et al., 1999). Besides the aspect ratio, the projection sphericity (PS) and the circularity (*C*) were used in the present study in order to evaluate the shape of the granules. PS is useful in estimation of the sphericity of granules, and *C* includes the granule roughness as well, because the overall perimeter is used for its calculation.

AR and PS were significantly influenced by binder content, and no significant influence of any of the tested variables on *C* was found in case of granules prepared with PEG (Table 3). Considering that these experiments were performed as fractional factorial design and that somewhat lower r^2 values were obtained (Table 3), further analysis may be needed.

However, AR and PS obtained for formulations with Precirol were significantly affected not only by the binder content but also by the interaction between the binder content and the binder particle size and by third order interaction between binder content, binder particle size and granulation time. AR was also significantly influenced by the interaction between the binder particle size and granulation time. Again, no statistically significant effects on C were found. The highly spherical granules were obtained with 15% Precirol (initial particle size ≈ 650 μm). At higher binder content granules were more spherical when larger binder particles were used. On the contrary, at lower binder content, more spherical granules were obtained when smaller binder particles were used. Interestingly, the differences in the sphericity of granules as a function of binder particle size were less pronounced with prolonged granulation time (Fig. 1).

Scanning electron micrographs revealed presence of the hollow core in the samples prepared with larger binder particle size (Fig. 2), which indicates that immersion and layering was dominant agglomeration mechanism (Abberger, 2001; Ansari and Stepanek, 2006; Pauli-Bruns et al., 2010). On the other hand, when smaller binder particles were used it seems that coalescence of primary nuclei followed by adherence of ungranulated powder occurred (Fig. 3), which is in agreement with previous findings that immersion and distribution mechanisms are expected to occur simultaneously when the binder droplet size is similar to the size of solid particles (Abberger et al., 2002). Different mechanisms involved in agglomerate formation might be the reason for observed differences in sphericity. Granules formed by immersion mechanism have more regular and spherical shape than those formed by coalescence (Walker et al., 2009; Zhai et al., 2009), which can explain the results of the shape analysis at higher binder content.

However, complex factor interaction influencing granule shape is not yet fully elucidated. In agglomeration process that involves coalescence lower binder content corresponds to more spherical granules (Walker et al., 2007b, 2009; Zhai et al., 2009). On the other hand, when immersion is dominant mechanism lower binder content means a larger number of solid particles that compete to immerse in a molten binder particle. SEM micrographs (Fig. 4), indeed, show that lower binder content has led to formation of granules with more solids attached to the surface or immersed into the binder particle. It can be assumed that these granules need somewhat more time to get nearly spherical shape.

Conventional fluid bed granulators are often considered as unsuitable for production of highly spherical granules (Passerini et al., 2010; Vilhelmsen et al., 2004). However, results of the present study indicate considerable potential of in situ FHMG for preparation of agglomerates that are quite regular and spherical in shape. The relevant shape factor values are presented in Table 2.

3.4. Granule flowability

The Carr index, as an indicator of powder flowability, was calculated, and the values obtained are given in Table 2. Granule flowability was significantly influenced by binder content (Table 4). Higher binder content resulted in better flowability of granules, i.e. lower Carr index values as presented in Table 2. Interestingly, granulates prepared with PEG showed better flow properties, likely as a result of differences in granule size. For example, Carr index values obtained for granulates prepared with 15% PEG were less than 6,

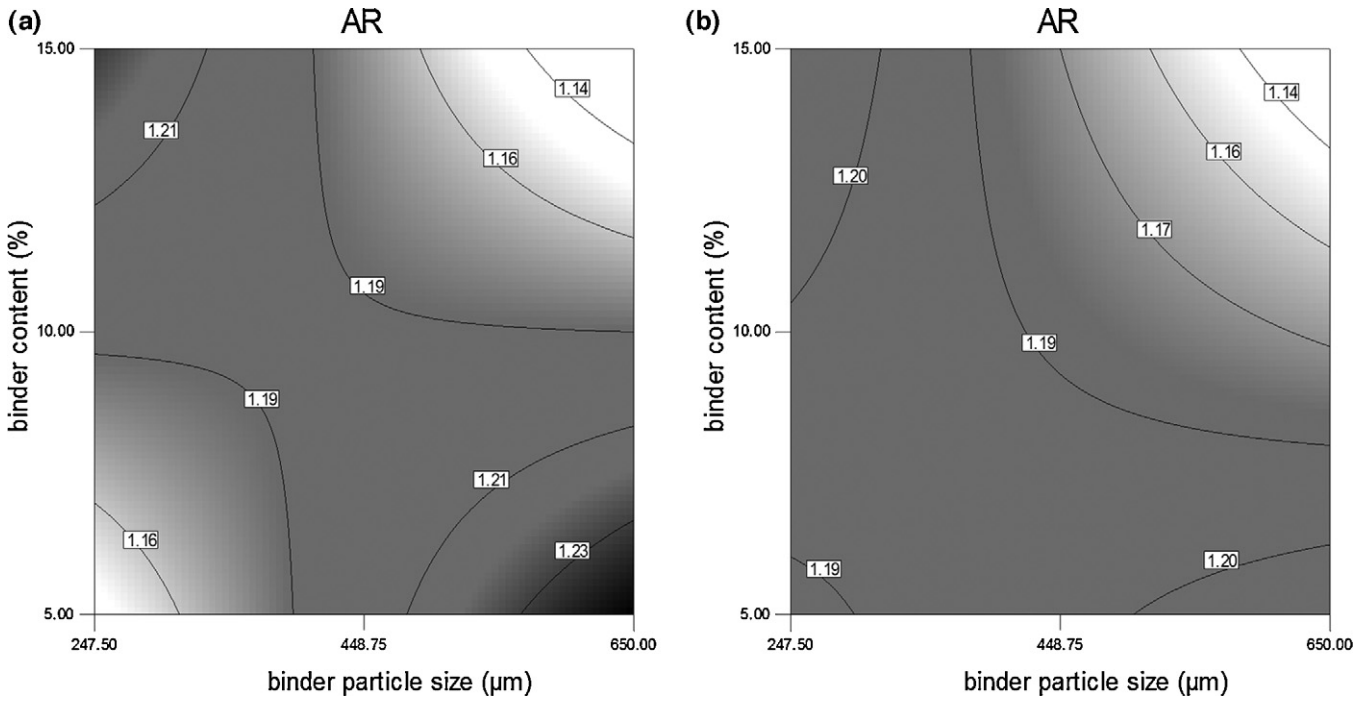

Fig. 1. Contour plots of AR as a function of Precirol ATO 5 particle size and content: (a) granulation time – 10 min; (b) granulation time – 30 min.

and for granulates prepared with 15% Precirol these values were between 8 and 12. However, when present in sufficient amount both binders enabled production of granules with excellent flow properties.

3.5. Solid state analysis

Solid state characterization of the granules was performed in order to determine whether the granulation process altered the

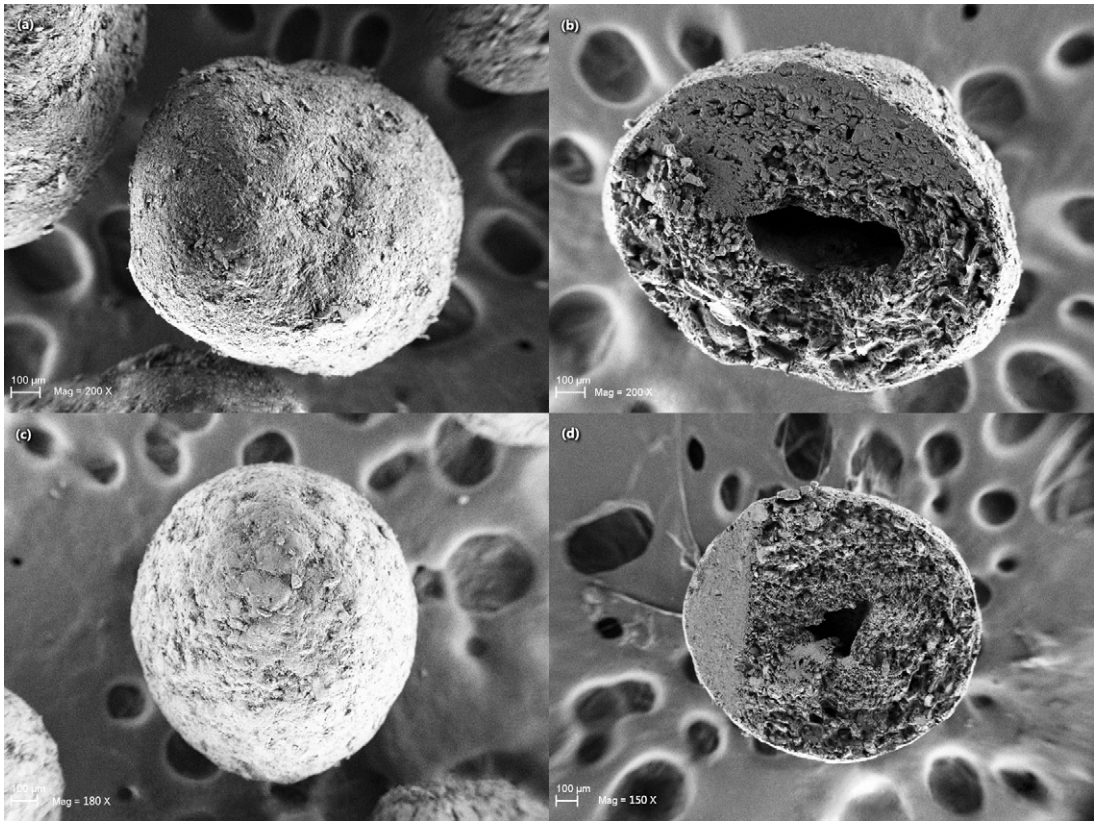

Fig. 2. SEM micrographs of: (a) a single granule and (b) cross section of granule prepared with 15% PEG 2000 (initial binder particle size ≈ 650 μm); (c) a single granule and (d) cross section of granule prepared with 15% Precirol ATO 5 (initial binder particle size ≈ 650 μm).

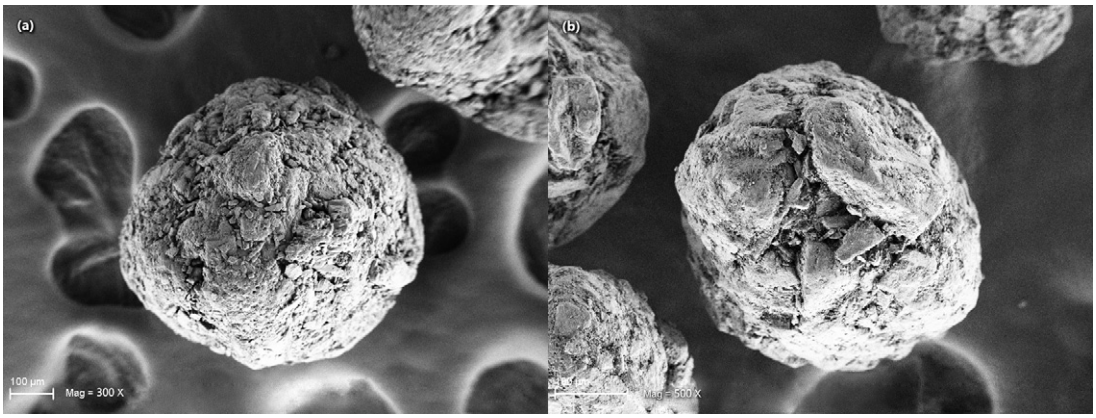

Fig. 3. SEM micrographs of: (a) a single granule prepared with 15% PEG 2000 (initial binder particle size ≈ 247.5 μm); (b) a single granule prepared with 15% Precirol ATO 5 (initial binder particle size ≈ 247.5 μm).

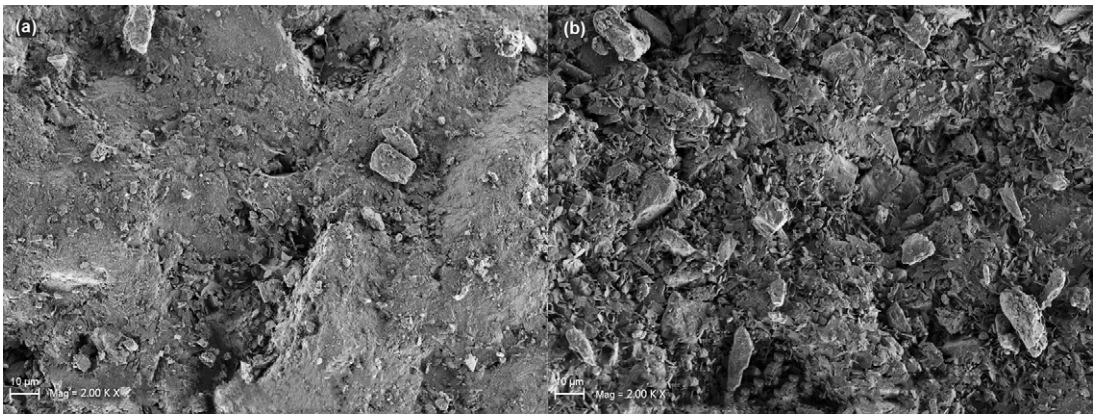

Fig. 4. SEM micrographs of: (a) surface of granule prepared with 15% Precirol ATO 5 (granulate B8) and (b) surface of granule prepared with 5% Precirol ATO 5 (granulate B2).

original physical form of the meltable binder and/or of the drug, as well as to investigate whether any interaction between the active and the excipients occurred.

Fig. 5 represents DSC thermograms of pure components and granulates. DSC thermogram of pure paracetamol showed single sharp melting endothermic peak at 172 °C, which corresponds to characteristic melting peak of paracetamol form I (Qi et al., 2008). DSC curve of PEG 2000 exhibited melting peak at 53 °C, while Precirol showed somewhat wider melting range with melting peak at 61 °C. Standard DSC curve of lactose monohydrate was observed, similar to those reported (Ilić et al., 2009). Thermograms of granulates prepared with PEG 2000 showed characteristic peaks of the binder and lactose. Melting peak of paracetamol can be easily indentified in DSC curve obtained from granulate with 5% binder, but its intensity is considerably lower in DSC curve of granulate with 15% binder. It may be hypothesized that paracetamol crystals partially dissolve in the molten hydrophilic binder during DSC analysis. At 15% binder only a small fraction of paracetamol remained undissolved and therefore the endothermic peak around 170 °C is barely noticeable. Similar explanations were proposed for praziquantel-Gelucire 50/13 (Passerini et al., 2006) and for UC-781-PEG 6000 systems (Damian et al., 2000). To confirm these assumptions, further solid state characterization was performed by means of XRPD and FTIR.

Table 4
Effects of the independent variables on response variables: Carr index (CI), time required for 40% (T_{40}) and 80% (T_{80}) drug release.

Factors and interactions	CI (%) (r^2 = 0.9549)		T_{40} (min) (r^2 = 0.8819)		T_{80} (min) (r^2 = 0.8141)	
	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value
PEG 2000						
Intercept	7.97	–	7.45	–	18.94	–
X_2	−4.01	<0.0001	3.58	0.0005	9.05	0.0022
Factors and interactions	CI (%) (r^2 = 0.9514)		T_{40} (min) (r^2 = 0.9822)		T_{80} (min) (r^2 = 0.9932)	
	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value	Coefficient estimate	*p*-Value
Precirol ATO 5						
Intercept	15.69	–	100.05	–	284.11	–
X_1	–	–	−10.38	0.0164	−80.56	0.0008
X_2	−5.61	<0.0001	36.53	0.0002	81.57	0.0007
X_3	–	–	–	–	−21.40	0.0332
X_1X_2	–	–	−7.49	0.0452	−24.85	0.0225

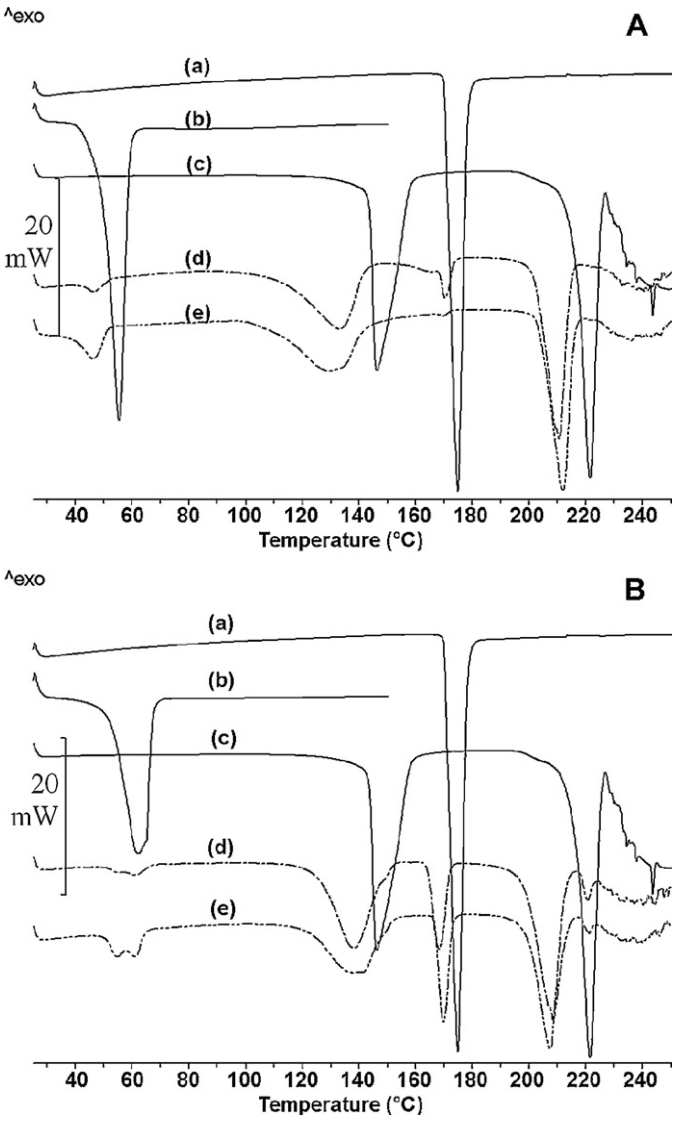

Fig. 5. DSC thermograms of (A): paracetamol (a), PEG 2000 (b), lactose monohydrate (c), granulate with 5% PEG 2000 (d), and granulate with 15% PEG 2000 (e); and (B): paracetamol (a), Precirol ATO 5 (b), lactose monohydrate (c), granulate with 5% Precirol ATO 5 (d), and granulate with 15% Precirol ATO 5 (e).

In DSC thermograms of granulates containing Precirol characteristic peaks of all components can be identified. Interestingly, the additional lower melting endotherm of Precirol was observed, suggesting the presence of less-stable polymorphic form of Precirol. The presence of two melting endotherms, was previously reported for freshly solidified samples (Evrard et al., 1999; Hamdani et al., 2003).

Fig. 6 shows the XRPD diffractograms of pure paracetamol, granulates and corresponding physical mixtures. Pure paracetamol is crystalline, as demonstrated by sharp and intense diffraction peaks at 15.5, 18.2 and 24.4° of 2θ. The XRPD diffractograms of granulates, both with PEG 2000 and Precirol, and of their corresponding physical mixtures showed the characteristic peaks of the drug. Comparison of diffractograms of granulates and the corresponding physical mixtures revealed the same peak diffraction angles with comparable intensity, indicating that the crystal form of the active ingredient remained unaltered after the melt granulation process.

FTIR analysis was performed to determine whether there was any interaction between the components of granulates (Fig. 7). The FTIR spectrum of paracetamol showed characteristic

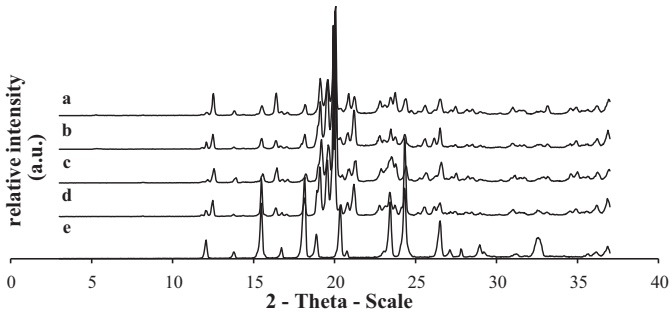

Fig. 6. X-ray powder diffraction patterns of: (a) granulate with 15% Precirol ATO 5, (b) physical mixture with 15% Precirol ATO 5, (c) granulate with 15% PEG 2000, (d) physical mixture with 15% PEG 2000, and (e) paracetamol.

peaks at 1220–1250 cm^{-1} assigned to the amide group, in the 1500–1560 cm^{-1} region for the N—H bending and C—N stretching, at 1650 cm^{-1} due to the stretching of the amide carbonyl group, in the 3100–3200 cm^{-1} region for the OH group, at 3300–3350 cm^{-1} for the N—H stretching band. PEG 2000 exhibited the absorption bands that are characteristic for its chemical structure (Mansur et al., 2004). The major IR peaks observed in the spectrum of Precirol were in the 1700–1750 cm^{-1} region due to the stretching vibration of the carbonyl group, and the strong peaks typical for the hydrocarbon stretching region (2850–3000 cm^{-1}). The FTIR spectrum of lactose monohydrate was in agreement with the IR spectrum of α-lactose monohydrate reported in the literature (Kirk et al., 2007). Characteristic peaks of the drug, as well as of the binders and diluent, are evident in the FTIR spectra of granulates, suggesting the lack of interactions.

3.6. *In vitro dissolution studies*

Tablets prepared from granules with PEG 2000 showed fast drug release (Fig. 8a), and the only factor that had statistically significant effect on dissolution rate was the binder content (Table 4). Higher PEG content resulted in longer time required for 40% or 80% drug release. Formulations with Precirol showed considerably slower drug release compared to the formulations with PEG 2000. Dissolution profiles of tablets prepared from granules with Precirol are presented in Fig. 8b. Concerning the response variables T_{40} and T_{80}, the binder content and the binder particle size, as well as two-factor interaction between these factors, were found to be significant factors (Table 4). T_{80} was also significantly influenced by the granulation time and this factor had negative effect on the time required for 80% paracetamol release. Higher content of lipid binder caused slower drug release. Time required for 40% and/or 80% drug release was longer when initial binder particle size was lower, and the influence of binder particle size was more pronounced when Precirol content in formulation was higher. An explanation for the observed effect of binder particle size on dissolution rate might be different mechanisms of agglomerate formation. Schæfer and Mathiesen (1996) reported that distribution and coalescence mechanism results in more uniform distribution of the binder within the granules than the immersion and layering mechanism. The more uniform binder distribution is, more tightly the drug particles are entrapped in lipid matrix, which may explain slower dissolution from formulations prepared with smaller binder particles. Pauli-Bruns et al. (2010) did not find any influence of the binder particle size on dissolution time, but the immersion mechanism was dominant for the investigated formulations, and consequently the agglomerates had similar structures. On the other hand, Vilhelmsen et al. (2005) reported pronounced influence of mechanism of agglomerate formation, and therefore

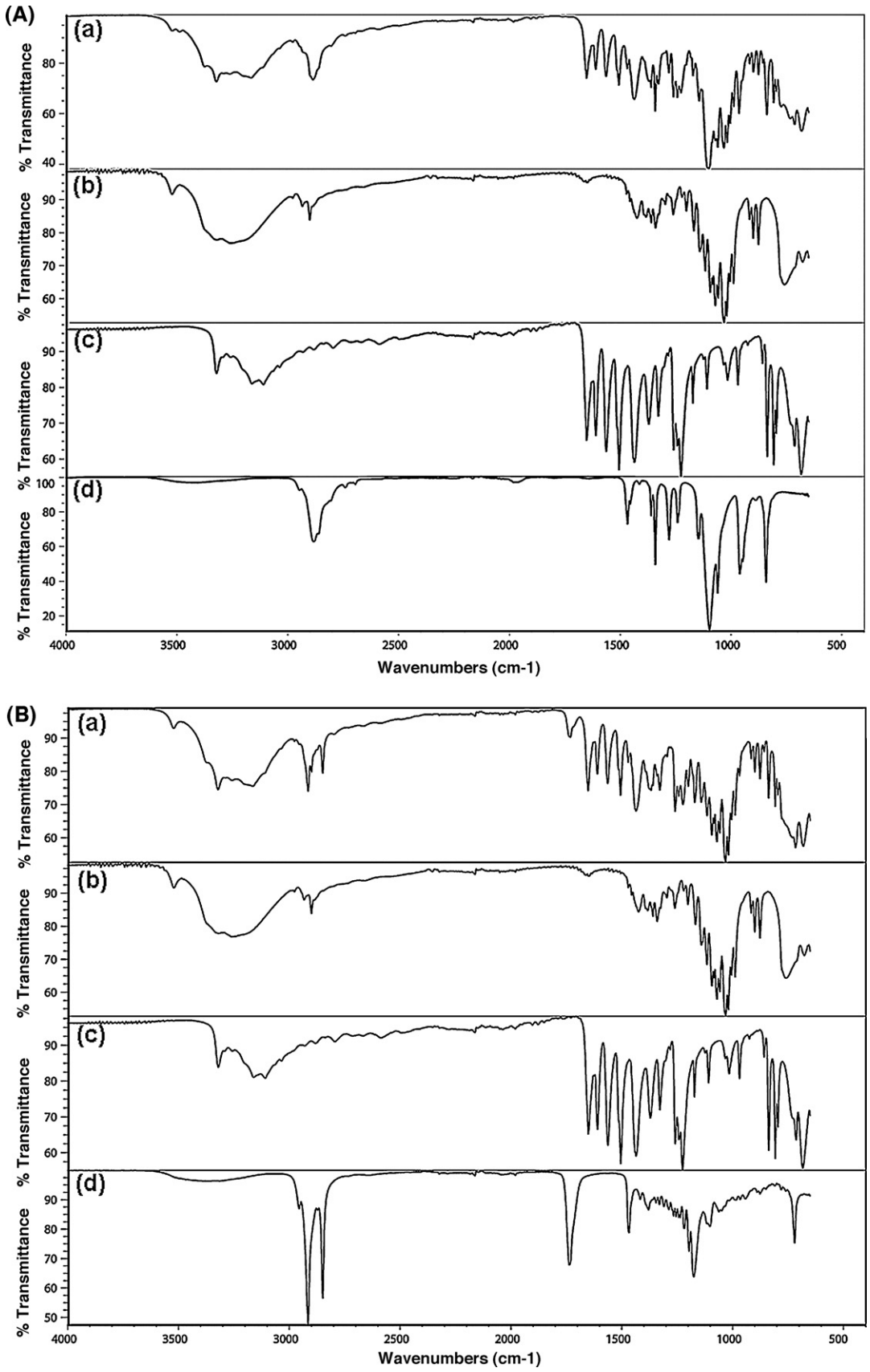

Fig. 7. FTIR spectra of (A): granulate with 15% PEG 2000 (a), lactose monohydrate (b), paracetamol (c), PEG 2000 (d); and (B): granulate with 15% Precirol ATO 5 (a), lactose monohydrate (b), paracetamol (c), Precirol ATO 5 (d).

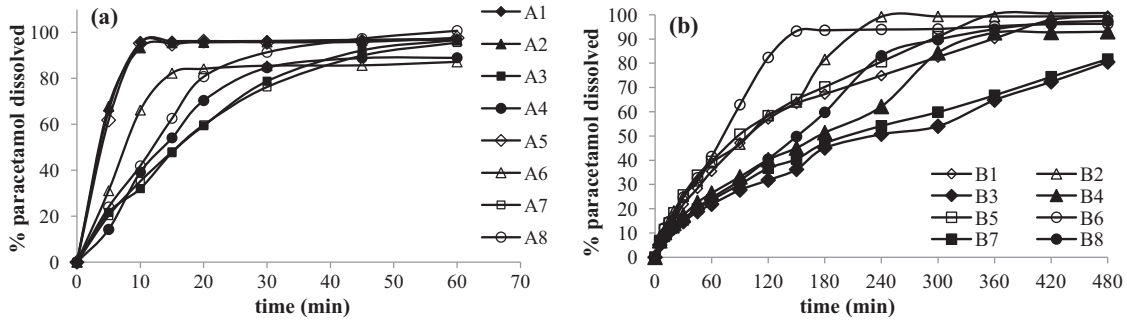

Fig. 8. In vitro dissolution profiles of tablets prepared from granules with PEG 2000 (a) and Precirol ATO 5 (b). Standard deviation bars were omitted for the sake of clarity.

Table 5
Results of the taste evaluation.

Granulate	Bitter taste intensity[a]
15% Precirol (FHMG)	2.07
10% Precirol (FHMG)	1.29
5% Precirol (FHMG)	3.00
15% PEG 2000 (FHMG)	4.14
PVP (WG)	4.50

[a] Results are the mean of 14 observations.

different intragranular distribution of the active, on dissolution rate.

3.7. Taste evaluation study

FHMG has been proposed as an approach to taste masking of bitter drugs (Kidokoro et al., 2002). In the present study the capability of hydrophobic meltable binder to suppress the bitter taste of model drug was evaluated.

The results of taste evaluation study are presented in Table 5. The study revealed that hydrophobic meltable binder, such as Precirol, may provide the effective taste masking. At 10% or 15% Precirol efficient granulation was achieved, and granulates exhibited no bitterness or slight bitterness. When granulates were prepared with PEG 2000 or by conventional wet granulation with PVP the bitter taste of paracetamol was not suppressed.

The results obtained indicate that FHMG may be a suitable approach for taste masking which does not require additional excipients (such as corrigents, polymers with pH-dependent solubility) or time consuming technological processes. FHMG might be an elegant way to achieve a lot of functionalities, including the suppression of bitter taste, but it merits further assessment for higher drug loadings, as well as further work in order to achieve rapid drug release at the same time.

4. Conclusions

Experimental data obtained in this study suggest that conventional fluid bed granulators could be an alternative to high shear mixers or rotary processors for the melt agglomeration. Highly spherical agglomerates with smooth surface were obtained, particularly when immersion and layering was dominant mechanism of granule growth. Complex factor interaction was found to affect the granule shape parameters and further, more detailed, analysis is needed to fully clarify the factor interplay. Granule size was primarily dependent on binder particle size, while it was shown that narrow size distribution and good flow properties can be achieved if the binder amount is sufficient. Dissolution rate was influenced by the binder type and content but also seems to be affected by mechanism involved in agglomerate formation.

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