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Characterization of agglomerated carvedilol by hot-melt processes in a fluid bed and high shear granulator

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ABSTRACT

The purpose of this study was to prepare and characterize granulated carvedilol by melt-in and spray-on melt granulation in a fluid bed and a high shear granulator. Granulates having comparable particle size distribution and good flow properties were obtained with proper adjustment of process parameters for each binder (poloxamer 188, polyethylene glycol 4000, and gliceryl monosterate), procedure (spray-on and melt-in) and equipment (fluid bed and high shear granulator). In-line probes for particle size measurements proved to be a useful tool for determining the end point of melt granulation. The product temperature during melt granulation was found to be the critical process parameter for achieving appropriate granulate particle size distribution. The results showed that melt granulation using hydrophilic binders is an effective method to improve the dissolution rate of carvedilol. The method of binder addition to the powders (melt-in or spray-on procedure) was found to strongly influence the dissolution rate of carvedilol. The highest dissolution rates were obtained when the spray-on procedure is used, independently from the type of granulator used. The results also suggest that the most probable explanation for the increase in the dissolution rate of granulated carvedilol is improvement of the wettability through intimate contact between hydrophilic binder and hydrophobic drug.

1. Introduction

Melt granulation is a process by which agglomeration of pharmaceutical powders is efficiently promoted using meltable binders which melts or softens at relatively low temperature (50–80 °C). Cooling of the agglomerated powder and the resultant solidification of the molten or soften binder complete the granulation process. The addition of low melting binders to the starting powder mixture can be either in the form of a solid particles that melt during the process (melt-in procedure or in situ melt granulation) or in the form of a molten liquid, optionally containing the dispersed drug (spray-on or pump-on procedure), which indicate a variety of options to design final granulate properties. More specifically, the melt-in procedure of melt granulation process involves heating a mixture of drug, binder and other excipients to a temperature within or above the melting range of the binder, while the spray-on procedure involves spraying of a molten binder, optionally containing the drug, onto the heated powders (Abberger, 2001; Seo et al., 2003; Wong et al., 2005).

Melt granulation offers several advantages compared to the conventional granulation processes. It is a good alternative to wet granulation for water sensitive materials. Generally, no organic or aqueous solvent is required in the melt granulation process, so the environmental requirements of organic solvent capture and recycling are eliminated, while the absence of water enables that the wetting and drying phases are eliminated, making the entire process less energy and time consuming (Aulton, 1992; Wong et al., 2005). Melt granulation method can be efficiently utilized to enhance stability of moisture sensitive drug and also to improve the poor physical properties of the drug substance (Matsunga et al., 1997; Kowalski et al., 2009). There are also some limitations when using melt granulation processes. The major drawback is the required high temperature during the process which can cause degradation and/or oxidative instability of the ingredients, especially of thermolabile drugs. In contrast to extensive studies on wet and dry granulation processes, there is still a lack of knowledge with regard to the predictability and modelling of the melt granulation processes (Walker et al., 2005, 2007a; Zhai et al., 2010).

Suitable commercial excipients that can be used in the melt granulation processes can be divided into two basic groups: hydrophilic and hydrophobic low-melting binders. Mostly, hydrophilic binders include polyethylene glycols (PEGs) 2000–20000, poloxamer 188 and 407, polyoxylglycerides, and

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esters of polyethylene glycols, whereas hydrophobic binders include fats (i.e., glyceryl behenate, glyceryl palmitate, glyceryl palmitostearate, glyceryl monostearate), waxes (beeswax, carnauba wax, microcrystalline wax, paraffin wax), cetostearyl alcohol, stearic alcohol, stearic acid, and hydrogenated castor or cottonseed oil (Heng and Wong, 2007). The selection of a meltable binder with a hydrophilic/hydrophobic character is crucial for the dissolution behaviour of the drugs. Recently, some authors have described melt granulation technique using hydrophilic binders as an effective method to improve the dissolution rate of poorly water soluble drugs, such as ibuprofen (Passerini et al., 2002; Walker et al., 2007b), carbamazepine (Perissutti et al., 2003), diazepam (Seo et al., 2003), praziquantel (Passerini et al., 2006), and griseofulvin (Yang et al., 2007). Furthermore, by selecting suitable hydrophobic binders, the melt granulation may be used to prepare controlled release granules (Thies and Kleinebudde, 1999; Voinovich et al., 2000; Pauli-Bruns et al., 2010; Ochoa et al., 2011).

Equipment used for melt granulation technologies must be modified to promote melting and prevent unwanted solidification of the product on exposed equipment surfaces. Nowadays, high shear and fluid bed granulators are most suitable equipment for melt granulation of pharmaceutical powders. In both cases, a gradual build-up of granules occurs during the process. The marked difference between the methods is the absence of shearing forces in the fluid bed processes, whereas high shearing forces are generated in high shear mixing/granulating (Walker et al., 2005, 2007b). Recently, it was demonstrated that in situ melt granulation can be successfully performed in both high shear and fluidized bed granulators maintaining constant biopharmaceutical properties of the final granules (Passerini et al., 2010). However, there are no reports in the literature regarding the comparison of high shear and fluid bed melt granulation including both melt-in and spray-on procedure.

Carvedilol, an arylethanolamine type α_1 and β adrenergic receptor antagonist used for patients with hypertension and congestive cardiac failure, is a drug that has a low level of solubility in gastrointestinal fluids and is extensively metabolized in liver (Morgan, 1994). Carvedilol is practically insoluble in water and exhibits pH-dependant solubility. Its solubility is <1 μg/mL above pH 9.0, 23 μg/mL at pH 7, and about 100 μg/mL at pH 5 at room temperature (Brook et al., 2007). However, up to fourfold improvement of carvedilol bioavailability could be achieved by increasing the carvedilol solubility (Wei et al., 2005). Some of the reported methods for enhancing the dissolution rate of carvedilol include formation of the cyclodextrin inclusion complex (Bhutani et al., 2007; Hirlekar and Kadam, 2009), preparation of self-emulsifying drug delivery systems (SEDDS) or self-microemulsifying drug delivery systems (SMEDDS) (Wei et al., 2005; Mahmoud et al., 2009), co-grinding technique (Swamy et al., 2010) and preparation of solid dispersions with porous silica (Planinšek et al., 2011).

The aim of the present study was to prepare granules of poorly soluble drug carvedilol by fluid bed (FB) and high shear (HS) melt granulation using melt-in and spray-on procedure monitored by in-line probes for particle size measurements. The in-line probes were used to ensure comparable particle size distribution of final granules, regardless of the equipment and procedure used. Prepared granules were primarily evaluated in terms of feasibility of type of equipment (fluid bed or high shear granulator), method of binder addition to the powders (melt-in or spray-on procedure) and type of hydrophilic binder (polyethylene glycol 4000 or poloxamer 188) for production of granules having appropriate technological properties and improved dissolution rate of carvedilol. Additionally, hydrophobic binder gliceryl monostearate was used to examine all used types of melt granulation techniques for technological comparison with above mentioned hydrophilic binders. The obtained granules were characterized in terms of technological properties, morphology, thermal behaviour, solid-state analysis, wettability properties, drug/excipients solid-state distribution, drug content, dissolution rate and solubility enhancement of poorly soluble drug, and basic storage stability.

2. Materials and methods

2.1. Materials

Lactose monohydrate (lactose, lactose monohydrate 200 mesh, DMV, Germany) and microcrystalline cellulose (MCC, Avicel PH 101, FMC, Germany) were used as fillers. Polyethylene glycol 4000 powder (PEG 4000, Clariant, Germany), poloxamer 188 powder (P188, Lutrol® F68, BASF, Germany) and gliceryl monostearate powder (GMS, Cutina® GMS-V, Cognis, Germany) were used as meltable binders for the melt-in procedure. In all three cases binder sieved fraction with particle size less than 315 μm was used in order to ensure comparable particle size of final granules for both granulators and procedures. Based on the preliminary trials with placebo mixtures in fluid bed granulator it was found out that using higher binder sieved fraction (>315 μm) the undesired fraction of un-granulated fines markedly increased as already reported in the literature (Ansari and Stepanek, 2006). Unfractionated meltable binders were used for the spray-on procedure. Carvedilol (Krka, Slovenia) was used as a poorly soluble drug with a particle size d_{v10}: 18.9 μm, d_{v50}: 80.1 μm, and d_{v90}: 190.3 μm measured by laser diffraction method. All other materials used were of pro analysis quality.

2.2. Preliminary studies

2.2.1. Differential scanning calorimetry (DSC)

In order to estimate carvedilol solubility in different molten binders phase diagrams of binary mixtures (binder and drug) were constructed using the peak melting points determined by DSC described in detail in Section 2.4.3. Samples were heated from 20 °C to 140 °C at a rate of 10 °C/min.

DSC was also used to simulate the process of heating and cooling during spray-on procedure of melt granulation. Samples of binary mixtures (75% binder and 25% drug) were heated from 20 °C to 85 °C at a rate of 10 °C/min, thermostated at 85 °C for 15 min, and then cooled back to 20 °C at a rate of 10 °C/min.

2.2.2. Hot stage microscopy (HSM)

Melting events of binder and binder/drug dispersion in actual ratio (3/1, w/w) were observed using a hot stage system (FP82HT, Mettler Toledo, Switzerland) and microscope (BX50, Olympus, Japan). Samples were heated from 20 °C to 85 °C at a rate of 10 °C/min.

2.2.3. Determination of carvedilol solubility in molten binders

The solubility of carvedilol was examined by determination of the carvedilol concentration in the clear saturated supernatant of the sedimentated dispersion of carvedilol in the molten binders at 85 °C, which was solidified to ambient temperature before spectrophotometrical analysis at 285 nm (Agilent 8453, Germany).

2.2.4. Rheology measurements

The viscosities of the molten binders and molten binders with homogeneously dispersed drug in actual mass ratio 3:1 were measured with a rheometer Physica MCR 301 (Anton Paar, Austria) at constant shear rate 3700 s^{-1} (value according to the estimated shear rate for dispersion at the tip of the nozzle) and temperature range 75–90 °C (working conditions during spray-on experiments).

2.3. Composition and preparation of granulate

The melt granulation process for both types of granulator and procedures was optimized on the basis of preliminary trials with placebo mixtures. The batch size of final granulate was in all cases 1200 g, consisting of 800 g of lactose, 200 g of microcrystalline cellulose, 150 g of binder, and 50 g of carvedilol. The suitable granulation process parameters were set in accordance with each binder melt properties as stated below for both granulators and procedures used. Moreover, operative process parameters were promptly adjusted for each binder/equipment/procedure in order to obtain aimed granule particle size distribution with mass median particle diameter around 400 μm and span values below 2 for all experiments.

2.3.1. Fluid-bed melt granulation

The granules were prepared in a laboratory scale fluid-bed granulator BX CGD 1 (Brinox Process Systems, Slovenia). Granulation was performed using process chamber "Tornado" with bottom spraying and specific air distribution plate. Focused beam reflectance measurement (FBRM) probe (FBRM® C35, Mettler Toledo, Switzerland) was used within the process chamber for real time in-line particle size analysis during the melt granulation.

Binder addition by melt-in procedure: The fillers, binder and drug were placed in the process chamber, the fluidizing inlet air temperature was set to 80 °C, and the fluidizing air flow rate to 65 m^3/h. The product end-point temperature was 57 °C, 60 °C and 65 °C for P188, PEG 4000 and GMS formulation, respectively. The granulation process was stopped, when the granulate reached the previously mentioned temperatures (57 °C, 60 °C and 65 °C for samples with P188, PEG 4000 and GMS as binders).

Binder addition by spray-on procedure: Carvedilol was dispersed in melted binder at 85 °C. The obtained suspension was constantly fed (feed rate: 10, 18 and 25 g/min for P188, PEG 4000 and GMS formulation, respectively) to the atomizing nozzle with an orifice diameter 0.8 mm using peristaltic pump (1B.1003-R/65, Petro Gas, Germany) via tubing heated by a temperature controller (Digi-Sense, Cole Parmer, USA) and sprayed at atomizing air pressure 1.5 bar over the fillers. The atomization air temperature was set to 100 °C. The fluidizing air flow rate was set to 65 m^3/h and inlet temperature of 52 °C and 57 °C for P188, and PEG 4000, respectively. The spraying process was started when powder mixture in the product bowl reached temperature of 47 °C and 52 °C for P188 and PEG 4000 formulation, respectively.

Immediately after reaching the granulation endpoint as determined by the FBRM probe, the cooling of the product was started by opening the by-pass airway, setting the fluidizing inlet air temperature to ambient temperature and increasing the fluidizing air flow rate to 100 m^3/h. The process was stopped when the product temperature reached 40 °C.

2.3.2. High-shear melt granulation

The granules were prepared in a laboratory scale high-shear mixer (Collette Gral 10, Belgium), equipped with hot water heated double jacket. Spatial filter velocimetry (SFV) probe (Parsum IP70-SE, Malvern, UK) was used within the process chamber for real time in-line particle size analysis during the melt granulation.

Binder addition by melt-in procedure: The fillers, binder and drug were mixed using an impeller speed of 305 rpm and heated up by heating the jacket to 58 °C, 60.5 °C and 65.5 °C for P188, PEG 4000 and GMS, respectively. When the product reached the preselected temperature i.e. to 58 °C, 60.5 °C and 65.5 °C for samples containing P188, PEG 4000 and GMS, respectively the process was stopped.

Binder addition by spray-on procedure: The fillers were mixed using an impeller speed of 305 rpm and heated up by heating the jacket to 45 °C, 50 °C and 53 °C for P188, PEG 4000 and GMS, respectively. When the temperature of the powder mixture in the product bowl reached the above temperatures the spraying of the binder/drug dispersion was started. Melted binder with homogeneously dispersed drug was kept at 85 °C during the spraying and was constantly fed (feed rate: 5, 9 and 12.5 g/min for P188, PEG 4000 and GMS formulation, respectively) to the spraying nozzle with an orifice 3 mm using peristaltic pump (1B.1003-R/65, Petro Gas, Germany) via tubing heated by a temperature controller (Digi-Sense, Cole Parmer, USA).

Immediately after reaching granulation end point as determined by the SFV probe, the granules were collected, spread in thin layers on stainless steel trays, and allowed to cool to the ambient temperature.

2.4. Characterization of the prepared granules

2.4.1. Particle size distribution and flow properties of granules

The size distribution of the obtained granules compared to starting materials was determined by the vibrating sieve analysis, using seven sieves in the range 0.071–1.25 mm (Air Jet Sieve 200 LS-N, Hosokawa Alpine, Germany). Linear interpolation of the cumulative percentage frequency curve was used to determine the mass median particle diameter (d_{50}), 10th percentile (d_{10}), and 90th percentile (d_{90}) of the cumulative granulate size distribution, respectively. The span is defined as the difference between d_{90} and d_{10} relative to d_{50}.

The flow properties of the obtained granules and starting materials were evaluated by Carr index (CI) and Hausner ratio (HR), which were determined using Stampfvolumeter STAV 2003 (JEL Engelsmann AG, Germany) with a 250 mL glass-measuring cylinder. All analyses were performed in triplicate.

2.4.2. Scanning electron microscope (SEM)

The morphology of prepared granules and starting carvedilol was examined by SEM. The samples were deposited on adhesive double-sided carbon tape (width 8 mm, Agar Scientific Ltd., UK). A SEM (Ultra Plus, Carl Zeiss, Germany) was used with an acceleration voltage of 1.00 kV and a secondary electron detector.

2.4.3. Differential scanning calorimetry (DSC)

DSC curves were recorded with calorimeter DSC 1 (Mettler Toledo, Switzerland). A 3–6 mg samples were weighted and sealed in aluminium pan. Samples were heated from 20 to 240 °C at a rate of 20 °C/min under nitrogen flow 40 mL/min. The instrument was calibrated with indium.

2.4.4. X-ray powder diffraction (XRPD)

X-ray diffractograms were obtained using a Philips PW3040/60X'Pert Pro MPD (Philips Electronic Instruments, USA) with Cu K0 radiation (I = 1.5418 Å) at 40 kV and 30 mA. The scanning angle ranged from 3° to 32.5° of 2θ, the steps were 0.04° of 2θ, and the counting time was 10 s/step.

2.4.5. Fourier transform-infrared spectroscopy (FT-IR)

FT-IR spectra were performed with FT-IR spectrometer (System Spectrum GX, Perkin Elmer, UK). The samples were mixed with IR grade dry potassium bromide and then compressed using a hydraulic press (Perkin Elmer, Germany) at 8 t for 1 min. The spectra of prepared samples were scanned over a frequency range 4000–400 cm^{-1} with a resolution of 4 cm^{-1}.

2.4.6. Contact angle measurement

The contact angle (θ) was measured using static contact angle analyser DSA 100 (Krüss, Germany). A 250 mg sample was weighed and compressed at a compression force 550 N. A 0.5 μL drop of a phosphate buffer solution (pH 6.8, Ph. Eur.) was put on compressed

Table 1
The physical properties of the molten binder and binder/drug dispersion at 3/1, w/w ratio.

Binder	Solubility of carvedilol at 85 °C (w/w%)	Binder viscosity at 85 °C (mPa s)	Dispersion viscosity at 85 °C (mPa s)	Binder solidification onset temp. (°C)	Dispersion solidification onset temp. (°C)
P188	26.7	417	424	38	29
PEG 4000	31.3	175	205	43	35
GMS	7.1	19	96	58	56

plate and the initial contact angle was measured. At least triplicate determinations were carried out for each sample.

2.4.7. Raman mapping

For each given sample small amount of granulate was transferred onto microscopic glass and then pressed to get flat surface of material. Granulate chemical analysis was done by Raman point-by-point mapping experiments using Senterra dispersive Raman microscope (Bruker Optics, Germany) equipped with 785 nm laser using maximum laser power (100 mW). Integration time was set to 10 s per spectrum with 2 co-additions. Objective used was 20× confocal objective (Olympus Microscope, Japan) with 50 μm pinhole. The analysed surface was 800 μm × 1050 μm with step size in *x*-axis 20 μm and in *y*-axis 21 μm which in total gave 2091 points (spectra). All Raman spectra were acquired in area from 1800 to 450 cm^{-1}. All the data were acquired and manipulated by Bruker Optics software OPUS version 6.5.

2.4.8. Determination of drug content

The carvedilol content in the granulates was determined by suspending in a suitable quantity of methanol. Quantification of the drug in the filtered solution was determined using a UV-spectrophotometer (Agilent 8453, Germany) at a wavelength of 285 nm. The standards used to construct the calibration curves were prepared using the same media. All analyses were performed in triplicate. Results were expressed as percent of theoretical content ± relative standard deviation (mean value ± RSD).

2.4.9. Solubility and dissolution studies

The solubility of carvedilol was determined by the following procedure: weighted samples of granulates and pure drug were magnetically stirred in beaker containing 100 mL of phosphate buffer solution (pH 6.8, Ph. Eur.) thermostated at 37 °C in non-sink conditions. At prespecified time point (48 h) dissolution medium samples were collected, filtered through a 0.45 mm pore filter and analysed spectrophotometrically at 285 nm (Agilent 8453, Germany). The measurements were performed in triplicate.

In vitro dissolution studies were performed using a USP type II apparatus (VK 7000, VanKel, USA), equipped with standard glass vessels and paddles. Samples equivalent to 25 mg of carvedilol (the maximum single drug dose) were placed in a dissolution vessel that contained 900 mL of phosphate buffer solution (pH 6.8, Ph. Eur.) at 37 ± 0.5 °C and stirred with 50 rpm. Samples were collected periodically, filtered through a 0.45 mm pore filter (Minisart RC 25, Sartorius, Germany) and replaced with a fresh dissolution medium. The concentration of carvedilol was determined spectrophotometrically at 285 nm (Agilent 8453, Germany). All the dissolution experiments were carried out in triplicate.

2.4.10. Storage physical stability test

Samples of prepared granules were stored at 25 °C and 65% relative humidity for 6 months. Stored samples were analysed by DSC, XRPD and by dissolution studies.

3. Results and discussion

3.1. Preliminary studies

From industrial point of view for melt granulation process the melt-in procedure is favoured over the spray-on procedure due to avoiding the hot-melt flows. Nevertheless, different addition of binder/drug during melt granulation may markedly influence on the improvement of dissolution rate of poorly soluble drug (Vilhelmsen et al., 2005). In comparison to melt-in procedure, the spray-on procedure involves additional stage to spray molten binder with dispersed drug over the pharmaceutical powders. To better elucidate the differences between the different types of binders and their addition methods, predicted solubility of carvedilol in each molten binder, viscosity and approximate solidification temperature of binder and binder/carvedilol (3:1, w/w) dispersion, were determined in the scope of the preliminary investigations and are summarized in Table 1.

Solubility of carvedilol in each low melting binder and drug was verified using DSC curves by changes in the melting endotherm of the drug as widely reported in the literature (Ford and Timmins, 1987; Mura et al., 1998). Phase diagrams were constructed in order to predict carvedilol solubility in the binder (data not shown). The phase diagrams for P188 and PEG 4000 showed that carvedilol had a maximum solubility of around 25% (w/w) in these two binders. On the other hand carvedilol maximum solubility in molten GMS was estimated to be around 5% (w/w). The phase diagrams of all three drug–excipient combinations did not show the presence of an eutectic. Moreover, it was confirmed that carvedilol is completely dissolved in molten binder only in a lower drug concentration region of the phase diagram. However, the phase diagrams can be considered as a special type of a eutectic in which the liquid and the solid curve have become superimposed (Damian et al., 2000). DSC analysis was complemented by HSM, which allows visualization of both melting events and optionally dissolution of drug in melted binder. The HSM results demonstrated that carvedilol was completely dissolved in molten P188 or PEG 4000 when drug/binder ratio was 1:3. On the contrary there was observed only partially dissolving of carvedilol in molten GMS (data not shown). Additionally, the differences in above mentioned findings regarding carvedilol solubility in different binders were confirmed by the results of content of carvedilol in clear liquid obtained by centrifugation of drug dispersions in melted binders.

The viscosities of melted binders at a given temperature interval were in the following rank order: P188 > PEG 4000 > GMS (Fig. 1). As expected, the viscosity of all three molten binders is inversely proportional to the temperature. The viscosity of binder/drug dispersions may be influenced by solubility of the drug in the molten binder as described in the literature (Hawley et al., 1992; Kattige and Rowley, 2006). We have found out that the viscosity of GMS/carvedilol dispersion was approximately fourfold of pure GMS, on the other hand the addition of carvedilol to the molten P188 or PEG 4000 showed minor impact onto the viscosity compared to the pure binders. This rheological behaviour is in accordance with aforementioned findings suggesting the solid dispersion of carvedilol in molten GMS and solution in case of P188 and PEG 4000.

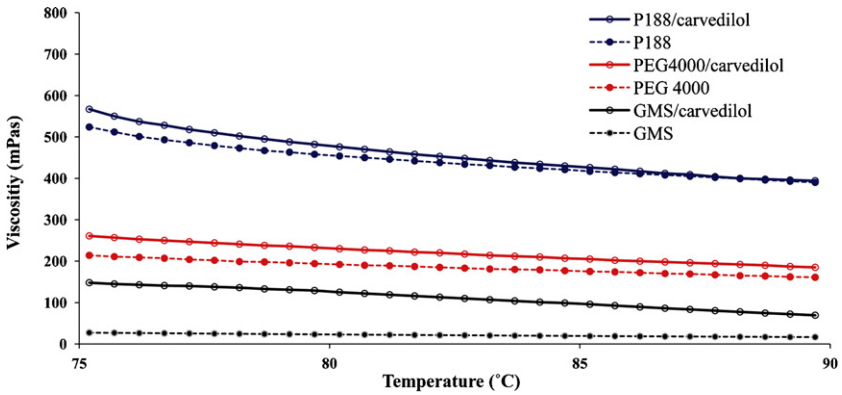

Fig. 1. Effect of temperature on the viscosity of molten P188, PEG 4000, and GMS and their corresponding molten dispersion with carvedilol.

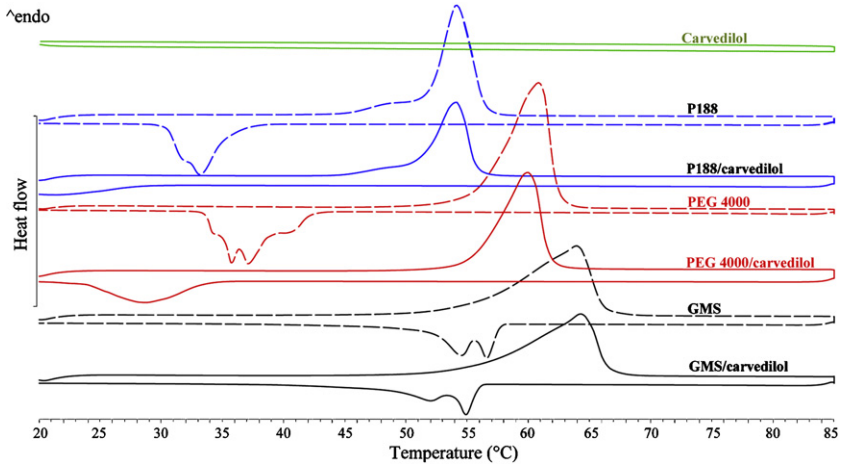

Fig. 2. DSC heating/cooling stages for carvedilol, binders (P188, PEG 4000, GMS) and their corresponding binary mixtures.

From the DSC curves in Fig. 2 simulating heating/cooling behaviour of carvedilol each binder and its corresponding actual binary mixture with carvedilol during spray-on melt granulation it was found that GMS mixture has the highest solidification onset temperature, which is close to GMS melting point, whereas the solidification onset temperature of PEG 4000 and P188 mixtures is approximately 15 °C lower from pure binder melting points. Addition of the carvedilol to the molten binder shifted the exothermic peak of dispersion crystallization to the lower temperature, particularly for the P188 and PEG 4000 dispersion. This phenomenon was already described in the literature, and is more common in cases where the substance is completely dissolved in the molten binder (Chatham, 1987). Shift of solidification point was in case of carvedilol and GMS mixture less pronounced due to lower solubility of drug in the excipient in comparison with P188 and PEG 4000.

3.2. Preparation and physical characterization of granules

Due to nozzle clogging at the start of the spraying process in case of FB spray-on granulation procedure with GMS we could not prepare this sample and was excluded from further experimental plan. As can be seen in Table 1 and Fig. 2 molten GMS with or without dispersed carvedilol indicate relatively high solidification temperature compared to PEG 4000 and P 188 and therefore this could be the main reason for solidifying of binder/drug dispersion within atomizing nozzle at operating temperature. The use of higher operating temperatures to avoid nozzle clogging was not possible due to limitations of equipment used in our experiments that allows the atomization air temperature up to 100 °C. The impurity profile analysis which was performed on the all granulate samples showed that used melt granulation processes did not cause any chemical degradation of the carvedilol (data not shown).

The granule growth kinetics during melt granulation process and the granulation end point were determined by in-line FBRM in a fluid bed and SFV probe in the case of high shear granulator. In order to minimize the impact of differences in granule particle size on dissolution rate, it was necessary to obtain similar granule particle size distribution for all experiments. The melt granulation process parameters of each equipment/procedure were promptly adjusted to the end point of in-line measurements of granule particle size during the preliminary experiments with placebo, and finally containing carvedilol. Firstly, the FB spray-on and melt-in processes were optimized regarding the appropriate FBRM chord length distribution (CLD) representing granule particle size distribution. Afterwards, the obtained granules were examined with at-line SFV probe ensuring reference SFV CLD, which represent the reference end granulation point for experiments in high shear granulator. The comparison of cumulative frequency curves of the square weighted chord length for P188 granules in Fig. 3 suggesting that the in-line FBRM and SFV probe proved to be an useful tool for determining end point of melt granulation ensuring comparable granule particle size distribution in fluid bed and high-shear granulator using spray-on and melt-in procedure.

It is noteworthy that product temperature during melt granulation was the main process factor for appropriate granulate particle size preparation and was mainly influenced by impeller speed and jacket temperature in HS granulator, fluidizing air flow and air inlet

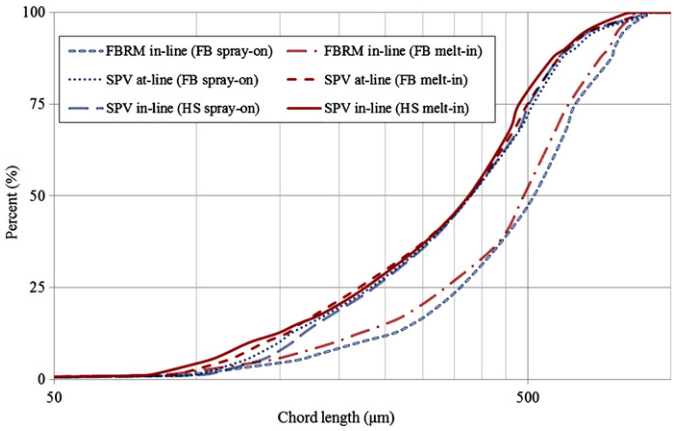

Fig. 3. Comparison of cumulative frequency curves of the square weighted chord length for P188 granules.

temperature in FB granulator, and additionally starting chamber temperature and feed rate of molten dispersion in case of using spray-on procedure in both FB and HS granulator. Furthermore, in order to obtain granules of the desired particle size from the melt-in experiments, it was necessary to use binder size fractions below 315 μm in all cases. To obtain granules of the desired size from the spray-on experiments, different dispersion feed rate had to be used for different binders. This can be explained by different viscosity of each binder or binder/drug dispersion at operating temperature identified during preliminary investigations (Table 1). In case of spray-on procedure in FB and HS granulator, P188/carvedilol dispersion with the highest viscosity was sprayed at the lowest feed rate.

Generally, the yield for all successfully performed experiments was found to be within range 95–100%. As shown in Table 2, the mass median particle diameter of the granules ranged between 369.7 and 426.2 μm for all the granules prepared. Moreover, d_{10} and d_{90} values for all examined granules were similar and in expected size ranges, which indicate low amount of fine powder and low amount of coarse particles, and therefore confirm that the used process parameters were correctly determined according to aimed particle distribution of granules. Span values representing the width of granule size distribution are below 2.0 for all the examined granules indicating again similar and relatively narrow particle size distribution of all obtained granules. The values of Carr index (CI) were within range 5–15% and Hausner ratio (HR) below 1.25, which means that all prepared granules showed good flow properties. Additionally, all granules that were prepared using the same technological procedure and method of binder addition have comparable bulk and tapped densities (Table 3). Granules of the same composition, prepared using HS procedure, have higher ($p = 0.05$) bulk densities then those prepared by FB procedure, when the same binder addition method is used. Within the FB procedure of granule preparation, method of binder addition will influence the bulk density of granules, with granules prepared by melt-in method of binder addition having higher bulk densities. The same cannot be claimed for HS procedure. Same general trends as in case of bulk densities can be observed also in case of tapped densities. Results of apparent densities for granules (Table 3), having the same composition, indicate that granules prepared with HS procedure have, due to higher values of apparent densities, also more open pore structure with less closed intragranular pores, when compared to those prepared with FB technique. Indirect estimation for trend of closed pore ratios is however not reflected in the results of the dissolution studies (Fig. 5), where the method of binder addition seems to be the prevalent factor.

SEM micrographs of FB/HS spray-on/melt-in P188 granules were utilized to compare their shape and surface morphology characteristics. Fig. 4(a) and (b) reveals that pure carvedilol exists as thin plates of single crystal. On the other hand, the photomicrographs of the prepared P188 granules using FB spray-on (Fig. 4c), FB melt-in (Fig. 4d), HS spray-on (Fig. 4e), and HS melt-in (Fig. 4f) procedure showed comparable, relatively spherical and quite porous structure of granules in which the individual surface properties of the carvedilol were lost during melt granulation. However, similar structure of the granules prepared by different equipments/procedures for melt granulation suggested the hypothesis of comparable granule growth mechanism. Nevertheless, a kinetic study (Tan et al., 2006) would be necessary to confirm the prevalent granule growth mechanism during melt granulation for both examined equipments and procedures.

It can be concluded that by tuning of critical process conditions the aimed end point of granule particle size distribution, measured by in-line probes, can be achieved. The granules having similar particle size distribution and good flow properties can be obtained in this manner.

3.3. Drug content, solubility and dissolution studies

The actual drug content of carvedilol in granules was between 97.7% and 101.1% of theoretical drug content with RSD values below 1% for all successfully obtained granules indicating the uniform distribution of drug in the granules. This means that actual drug content in granules can be expected to be equal to theoretical value, regardless of the equipment and procedures for melt granulation.

Table 2
Comparison of particle size distribution and flow properties of prepared granules.

Sample		Particle size distribution (μm)				Flow properties	
Binder	Equipment/procedure	$d(0.1)$	$d(0.5)$	$d(0.9)$	Span	CI (%)	HR
P188	HS melt-in	77.2	374.1	759.3	1.82	13.8	1.16
	HS spray-on	79.4	381.8	823.3	1.95	13.0	1.15
	FB melt-in	85.6	397.2	774.7	1.73	14.5	1.17
	FB spray-on	101.4	426.2	811.6	1.67	9.9	1.11
PEG 4000	HS melt-in	94.3	401.2	803.4	1.77	11.5	1.13
	HS spray-on	69.7	379.8	827.4	1.99	14.5	1.17
	FB melt-in	95.5	392.2	793.0	1.78	13.8	1.16
	FB spray-on	87.7	419.9	808.4	1.72	11.5	1.13
GMS	HS melt-in	81.4	381.6	743.9	1.74	13.0	1.15
	HS spray-on	65.4	369.7	772.7	1.91	12.3	1.14
	FB melt-in	98.2	407.9	841.7	1.83	12.3	1.14
	FB spray-on	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]

[a] Not available due to nozzle clogging at the start of the spraying process.

Table 3
Bulk, tapped and apparent densities ($n = 3$) of prepared granules.

Sample		ρ_{bulk} (g/cm^3)	ρ_{tapp} (g/cm^3)	ρ_{app} [b] (g/cm^3)
P188	HS melt-in	0.60 ± 0.02	0.69 ± 0.02	1.5393 ± 0.0011
	HS spray-on	0.57 ± 0.01	0.65 ± 0.01	1.4651 ± 0.0009
	FB melt-in	0.56 ± 0.01	0.65 ± 0.01	1.4644 ± 0.0007
	FB spray-on	0.47 ± 0.02	0.52 ± 0.01	1.3973 ± 0.0012
PEG 4000	HS melt-in	0.59 ± 0.01	0.66 ± 0.01	1.5144 ± 0.0006
	HS spray-on	0.56 ± 0.01	0.66 ± 0.01	1.4702 ± 0.0014
	FB melt-in	0.56 ± 0.01	0.64 ± 0.02	1.4638 ± 0.0015
	FB spray-on	0.45 ± 0.01	0.51 ± 0.01	1.4106 ± 0.0010
GMS	HS melt-in	0.57 ± 0.01	0.66 ± 0.02	1.5217 ± 0.0009
	HS spray-on	0.57 ± 0.01	0.65 ± 0.01	1.4803 ± 0.0006
	FB melt-in	0.54 ± 0.01	0.62 ± 0.01	1.4598 ± 0.0004
	FB spray-on	–[a]	–[a]	–[a]

[a] Not measurable due to nozzle clogging at the start of the spraying process.
[b] Measured using He pycnometer.

As already mentioned in the introduction, carvedilol is water poorly soluble drug with reported solubility in aqueous media with pH 7.0 of 0.023 mg/mL. Our measured solubility of pure carvedilol in phosphate buffer with pH 6.8 was 0.020 mg/mL. Solubility of carvedilol using drug-loaded granules prepared by melt granulation was also measured, because it was expected that hydrophilic binders may solubilize the drug in solution. Measured solubility of carvedilol in case of P188 and PEG 4000 granules were 0.089 mg/mL and 0.058 mg/mL, respectively. No significant differences were observed between saturation solubilities of carvedilol for drug-loaded granules prepared by different equipment/procedure for each binder. The improvements in carvedilol solubility represent

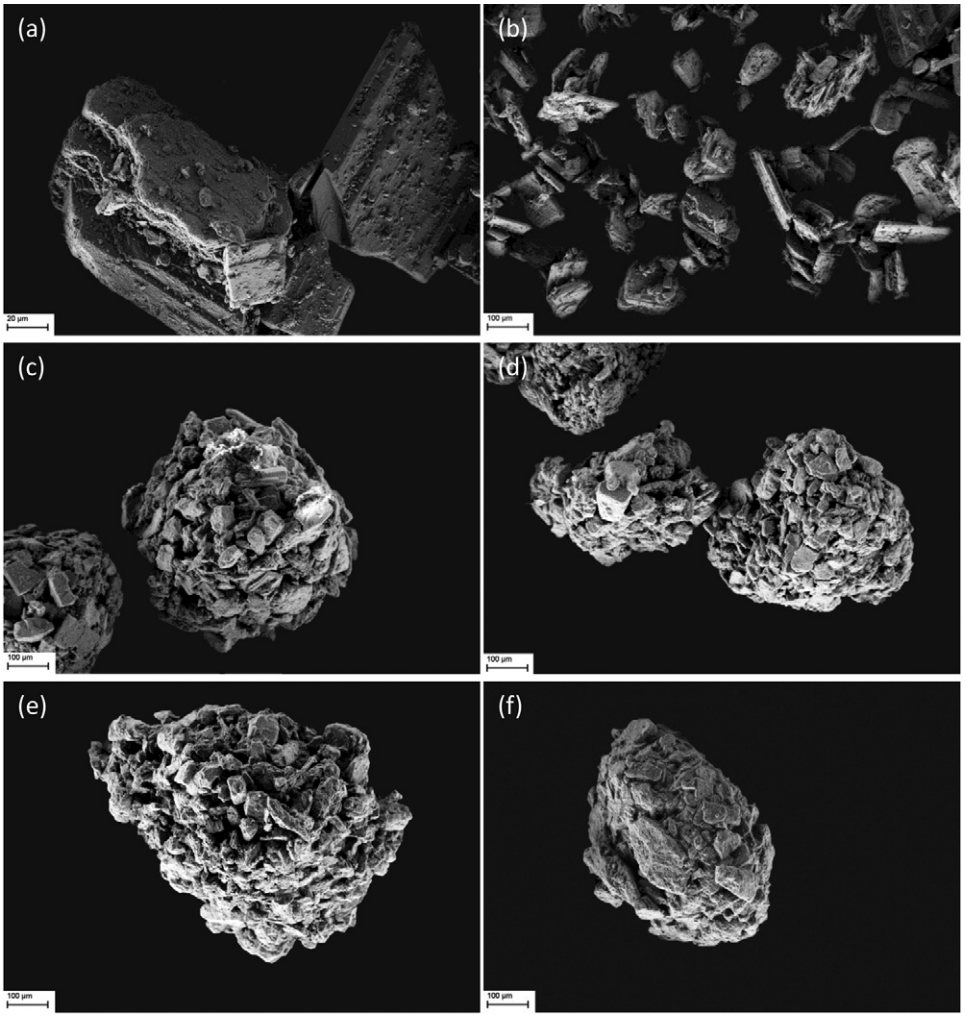

Fig. 4. SEM micrographs of (a, b) crystalline carvedilol and (c) FB spray-on, (d) FB melt-in, (e) HS spray-on and (f) HS melt-in P188 granules. Magnification 500× (a) and 100× (b–f).

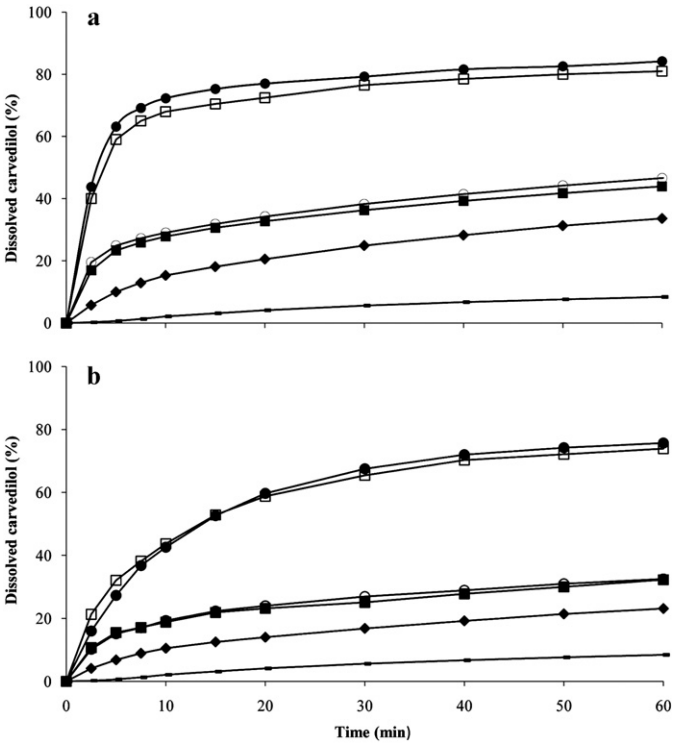

Fig. 5. Dissolution profiles of powders/granules in buffer at pH 6.8 for (a) P188 and (b) PEG 4000 formulations. Crystalline carvedilol: -, physical mixture: ♦, and granules HS melt-in: ■, HS spray-on: □, FB melt-in: ○, and FB spray-on: ●.

about 4.5-fold increase of solubility using P188 as hydrophilic binder and about 3-fold increase using PEG 4000 as hydrophilic binder. Solubilization capacity for carvedilol is greater when P188 is used compared to PEG 4000, as already described for other poorly soluble drug (Passerini et al., 2006; Ahuja et al., 2007). This can be explained with poloxamer amphiphilic chemical structure hypothesizing the formation of polymeric micelles able to solubilize poorly soluble drug.

The in vitro dissolution profiles of P188 and PEG 4000 granules containing carvedilol compared to that of pure drug and corresponding physical mixture are summarized in Fig. 5. The dissolution experiments were not carried out under sink conditions and the drug was not completely dissolved in 60 min, but under conditions such that the dissolution study was most discriminatory and in our opinion physiologically relevant. The dissolution rate of pure carvedilol was very low, with the amount of drug dissolved in 60 min being less than 15%. The in vitro dissolution rate of all prepared granules using both hydrophilic binders (P188 or PEG 4000) was higher as compared to the pure drug and their corresponding physical mixture, where P188 enhanced the dissolution rate of carvedilol to a greater extent. The differences in the dissolution behaviour of granulated carvedilol were generated within the first 15 min and strongly correlated with binder type and method of its addition to the starting powder. After initial burst dissolution, which determined the overall dissolution performance, carvedilol was then relatively slow and linearly dissolved throughout the remaining time, independently of sample type. However, the comparison between the dissolution profiles of carvedilol granules produced in FB and HS granulator indicated that the dissolution behaviour of both P188 (Fig. 5a) and PEG 4000 (Fig. 5b) granules was not influenced by the equipment. On the contrary, the method of binder addition to the powders (melt-in or spray-on procedure) was found to strongly influence the dissolution rate of carvedilol from prepared granules. The highest dissolution rates from granules are obtained when the spray-on procedure (spraying of a molten binder/drug dispersion onto the heated powders) is applied, independently from the equipment used. The dissolution profiles obtained from granules after 6 months of storage at 25 °C did not change during examined period.

From the comparison of saturation solubility and dissolution study results it can be assumed that an improvement in the dissolution rate of P188 and PEG 4000 granules up to 60 min, as shown in Fig. 5, cannot be only the result of improved solubility. It can be therefore expected that also other parameters such as wettability of the particle surface, particle size of the drug, solid state of the drug, are responsible for the enhanced dissolution rate of granules containing carvedilol, which is discussed in the following paragraphs.

3.4. Study of solid state and dissolution mechanism enhancement

3.4.1. Solid state analysis

To characterize the solid state of the carvedilol in the granules, DSC curves were obtained from binders (P188 and PEG 4000), fillers (lactose and MCC) (data not shown), and pure crystalline carvedilol, as well as from prepared P188 granules and their corresponding physical mixtures (Fig. 6). The crystalline carvedilol was characterized by a single, sharp melting endotherm peak at 117.7 °C, a characteristic of the polymorph II (Beyer and Reinholz, 1999). P188 and PEG 4000 has a melting endothermic peak at 56.6 °C and 60.3 °C, respectively, while DSC curve of lactose monohydrate exhibit endothermic peak at around 155 °C representing the loss of hydration water, followed by the melting endothermic peak of decomposition near to 220 °C. Furthermore, the DSC curves of P188 granules prepared by FB melt-in, FB spray-on, HS melt-in, and HS spray-on procedures were quite similar to each other, suggesting that the procedure as well as the equipment do not influence the thermal behaviour of final P188 granules. However, no significant differences were found between the obtained DSC diagrams of granules and their corresponding physical mixture. In both cases the absence of the carvedilol melting endotherm could be explained by dissolving of the drug in molten P188 as it was previously found out in preliminary investigation. The similar results were obtained for PEG 4000 granules prepared by all four melt granulation methods and their corresponding physical mixture (data not shown), indicating that neither procedure nor the equipment do not influence the thermal behaviour of final PEG 4000 granules.

Fig. 7 shows the XRPD patterns of pure carvedilol, lactose, MCC, P188, FB/HS spray-on/melt-in granules with P188 as a binder and its corresponding physical mixture. Pure carvedilol is in crystalline form (Fig. 7a), as demonstrated by the sharp and intense diffraction lines corresponding to form II of the drug (Beyer and Reinholz, 1999). Diffractograms of carvedilol containing granules (Fig. 7f–i) exhibited predominating signals for α-lactose monohydrate (66.7% in formulation) (Fig. 7b) and are in agreement with the literature data (Brittain et al., 1991). MCC (Fig. 7c) and P188 (Fig. 7d) show broad diffraction lines (at 14.5–18.5°, and 23.05–26.0° of 2θ) and (at 20.5°, and 24.0–25.5° of 2θ), respectively, which all disappear already in case of physical mixture (Fig. 7e). Relatively low-intensity peaks (at 5.9°, 14.8°, 17.6°, 18.4°, and 24.4° of 2θ) in diffractograms of physical mixtures (Fig. 7e) and granules (Fig. 7f–i) correspond to form II of carvedilol. The low intensity of these diffraction lines reflects the low drug concentration (4.2%, w/w) in measured samples. Comparison of P188 granules (Fig. 7c–f) and P188 physical mixture (Fig. 7b) indicate that they have analogous diffraction pattern with comparable intensity of the lines. It can be assumed that the crystallinity of the carvedilol was not essentially reduced by melt granulation process regardless of the equipment and procedures. In case of spray-on procedure, where carvedilol is

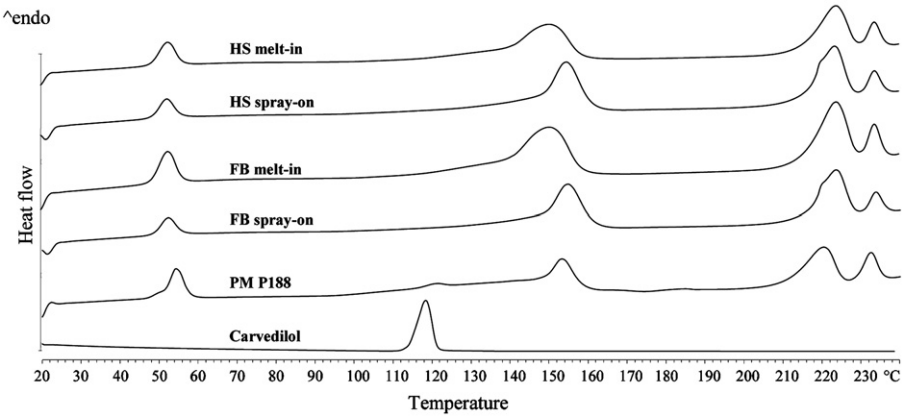

Fig. 6. DSC curves of carvedilol, P188 physical mixture and P188 granules prepared by FB spray-on, FB melt-in, HS spray-on and HS melt-in procedures.

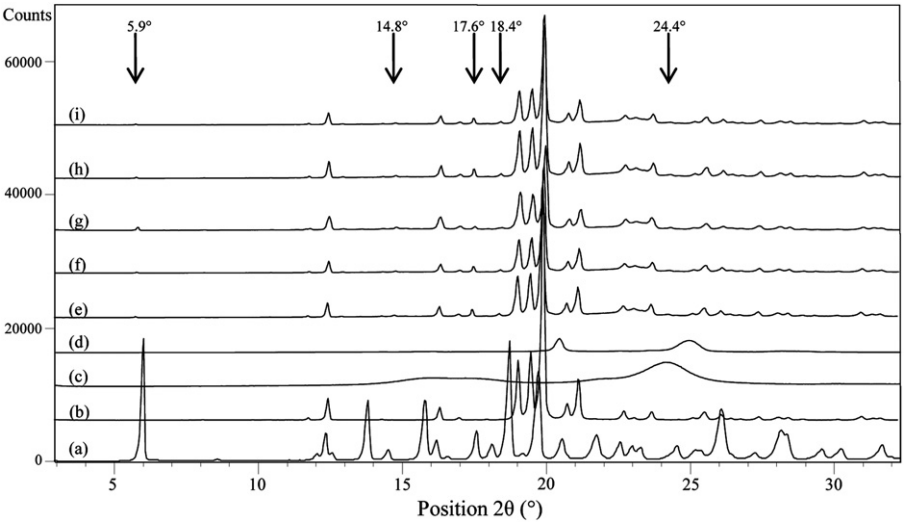

Fig. 7. XRPD data of (a) crystalline carvedilol, (b) lactose, (c) MCC, (d) P188, (e) physical mixture with P188, and P188 granules prepared by (f) FB spray-on, (g) FB melt-in, (h) HS spray-on and (i) HS melt-in procedures.

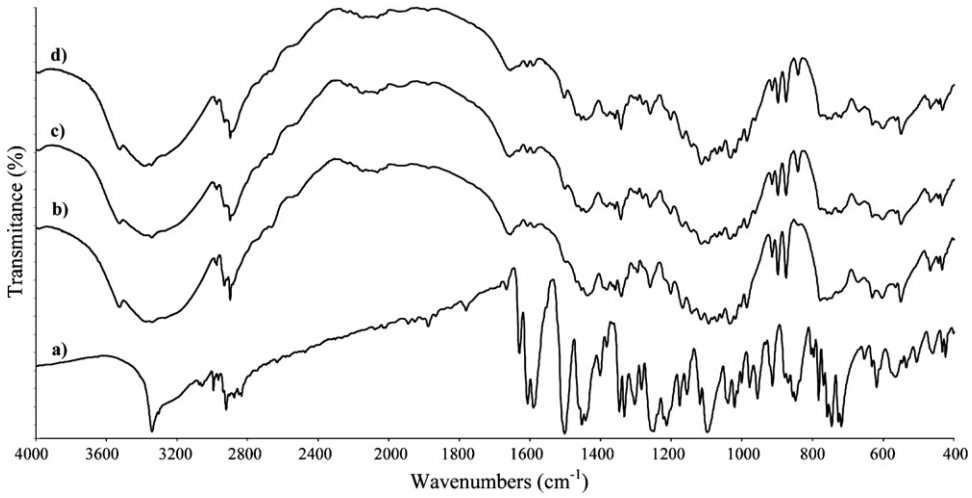

Fig. 8. Comparison of FT-IR spectra of (a) carvedilol, (b) P188 physical mixture, (c) FB melt-in and (d) FB spray-on P188 granules.

Table 4
Wetting properties of carvedilol, prepared granules and their corresponding physical mixtures.

Sample	Contact angle (°)
Carvedilol	85 ± 5
Pure P188	19 ± 3
Pure PEG 4000	20 ± 2
P188 granules	
FB melt-in	22 ± 2
FB spray-on	18 ± 1
HS melt-in	21 ± 4
HS spray-on	17 ± 2
P188 physical mixture	27 ± 3
PEG 4000 granules	
FB melt-in	27 ± 3
FB spray-on	24 ± 3
HS melt-in	28 ± 4
HS spray-on	21 ± 1
PEG 4000 physical mixture	33 ± 4

dissolved in molten hydrophilic binder as confirmed in preliminary study, it can be hypothesized that drug recrystallized during cooling phase of melt granulation. This could be attributed to the relatively slow rate of cooling of the molten mixture during solidification which allows longer time for crystal growth phase.

Finally, in order to evaluate the stability of the granules, DSC and XRPD analysis were performed on the samples of prepared FB/HS melt-in/spray-on P188 and PEG 4000 granules after 6 months of storage at 25 °C and 75% relative humidity (data not shown); no significant differences were detected between starting ($t = 0$) and stored samples ($t = 6$ months) suggesting the physical stability of samples, i.e. carvedilol crystalline state, at least for the examined time.

To study the possibility of the interaction between carvedilol and binder/fillers in the solid state, FTIR analysis was carried out. FTIR spectrum of pure crystalline carvedilol (Fig. 8a) showed intensive characteristics peaks at 3340 cm^{-1} (N—H and O—H stretching vibrations merged together), 3074–3037 cm^{-1} (C—H aromatic stretching vibrations) 2995–2922 cm^{-1} (C—H aliphatic stretching vibrations), 1630 cm^{-1} (N—H bending vibrations) and 1251 cm^{-1} (C—O stretching vibrations). The FTIR signals corresponding to the above stated bond vibrations for physical mixture (Fig. 8b) and P188 granules, prepared by FB melt-in and spray-on procedure (Fig. 8c and d), did not change intensity nor position with respect to the pure carvedilol signal (Fig. 8a). No differences were found between spectra of physical mixture and examined P188 granules. The absence of significant shift in the position of carvedilol characteristics peaks and the nearly equivalent spectra of both P188 granules and their corresponding physical mixture intensifies the idea of absence of solid-state interactions between carvedilol and binder/fillers in the final granules (Newa et al., 2008).

3.4.2. Wetting study

A series of contact angle measurements were performed on powder plates compacted from pure drug, physical mixtures, and all prepared granules using melt granulation as shown in Table 4, where the results of wetting analysis are summarized. Wetting properties of the examined samples are represented as the value of initial contact angle of dissolution media phosphate buffer solution (pH 6.8, Ph. Eur.) on the surface of powder comprimates. The highest initial contact angle was measured for pure drug reflecting surface hydrophobicity of carvedilol. On the other hand, the presence of hydrophilic binders (P188 or PEG 4000) in granules prepared by melting and physical mixtures showed marked reduction in the measured contact angle. However, the values of contact angle for both P188 and PEG 4000 physical mixtures are slightly higher in comparison to prepared granules for each binder. Granulate samples obtained by spray-on procedure indicate slightly lower contact angles than in case of melt-in samples. In addition, the contact angle of formulations containing P188 showed slightly better phosphate buffer wettability compared to PEG 4000 formulations, what was expected due to surfactant properties of P188. These results prove that inclusion of hydrophilic binder has a noticeable benefit of improving the wettability of hydrophobic drug.

3.4.3. Raman mapping

The spatial dimension introduced by Raman mapping has been largely utilized to assess drug and excipients distribution within samples, as widely reported in the literature (Docoslis et al., 2007; Furuyama et al., 2008; Fujimaki et al., 2009). In this study Raman mapping was used to identify and estimate the ingredients distribution inside the granules, as well as the particle size of carvedilol, in order to give insight into the internal structure of granules containing carvediol solid dispersion and to compare different manufacturing procedures used in this study with particular attention to the dissolution properties of the final granules containing P188. The results of Raman mapping analysis of P188 granules representing the distribution of individual components inside the granules are summarized in Fig. 9. Raman analysis of individual components was done by integration of characteristic Raman peaks of carvedilol (1653–1608 cm^{-1}), lactose (865–836 cm^{-1}) and MCC (529–499 cm^{-1}). From the above Raman mapping images it can be concluded that method of binder addition (spray-on or melt-in procedure) determines the granules internal structure. FB/HS melt-in granules showed homogeneous distribution of ingredients (lactose, MCC, carvedilol) and presence of carvedilol particles in the range of 80–200 μm. On the other hand, FB/HS spray-on granules showed that carvedilol particles are significantly smaller (app. up to 10 μm) and homogeneously distributed on the surface of starting materials (MCC and lactose), what is in accordance with applied technological procedure. It was not possible to include P188 distribution in the results of Raman analysis due to low intensity and overlapping characteristics peaks with remaining ingredients. Nevertheless, it can be speculated that P188 is homogeneously distributed with other ingredients in case of melt-in procedure and surrounding the carvedilol on the surface of starting materials in case of spray-on procedure. However, the findings obtained in Raman mapping study are expected and in accordance with applied procedures.

Finally, considering all results obtained in the present study, it is believed that the most probable explanation for the increase in the carvedilol dissolution rate from granules (Fig. 5) is the improvement of the wetting of carvedilol through intimate contact between hydrophilic binder and hydrophobic drug. For BCS class II drugs, wetting would be an important mechanism contributing to the drug dissolution rate (Löbenberg and Amidon, 2000). Furthermore, dissolution rate is probably improved by the increase in carvedilol solubility due to the influence of hydrophilic and/or surface active binder. In addition, the inhibition of fine drug particle aggregation within prepared granules could contribute to enhanced dissolution rate of carvedilol. Raman mapping analysis demonstrated markedly reduced crystalline drug particle size in the case of granules prepared by spray-on procedure. This was effectively reflected in the high dissolution rate of carvedilol, which can be assigned to the increased effective surface area of the drug particles exposed to the dissolution medium. On the other hand, by using the melt-in procedure the drug particle size was not essentially reduced. Moreover, from the Raman study of granule samples it can be assumed that drug particles are surrounded by hydrophilic ingredients, which enable improved wetting properties of carvedilol and consequently enhanced dissolution rate of the drug. Due to higher specific surface of carvedilol in case of spray-on granulation procedure, drug is in even better intimate contact with hydrophilic excipients of

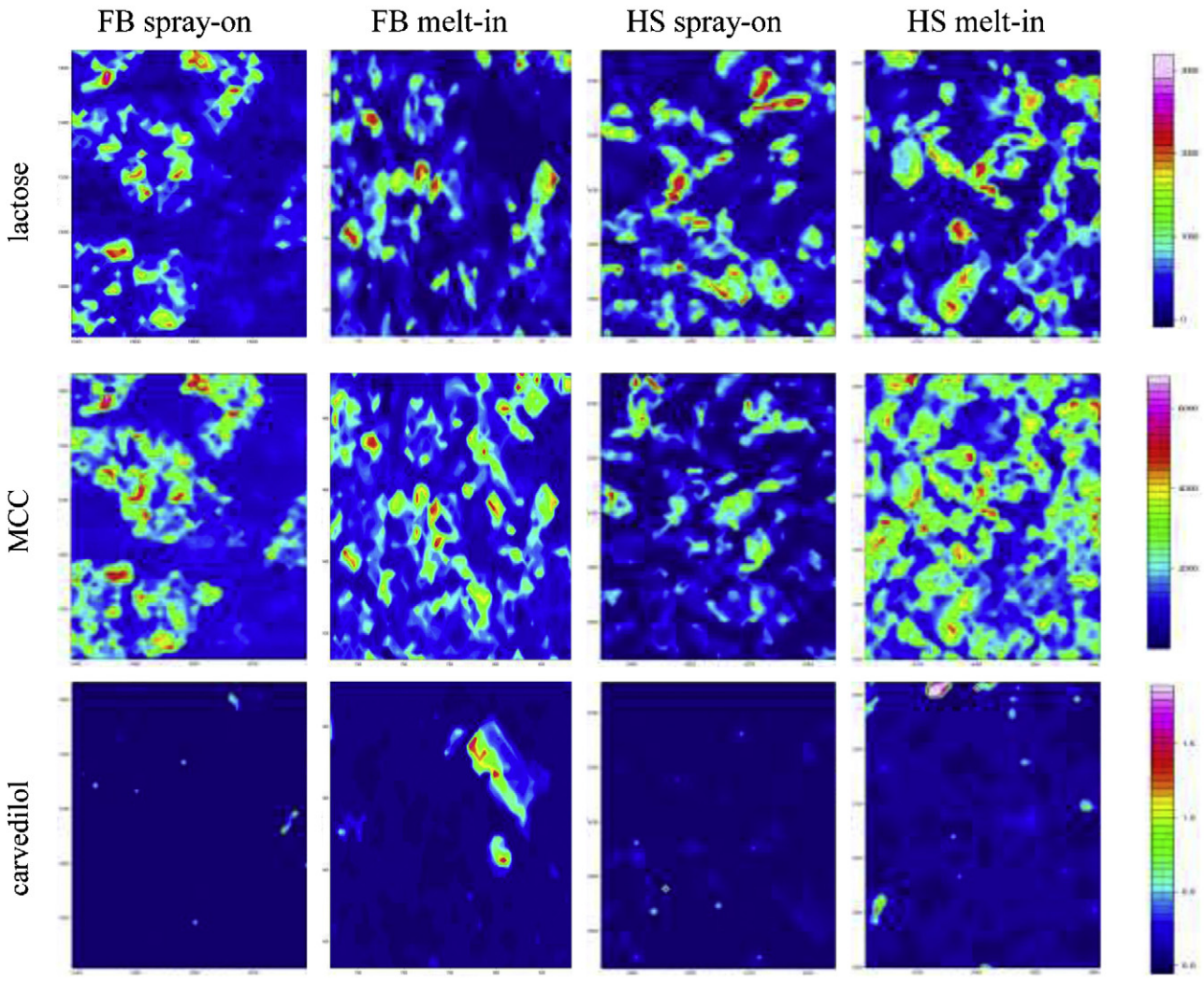

Fig. 9. Micro-Raman XY scans of P188 granules prepared by FB spray-on, FB melt-in, HS spray-on and HS melt-in procedures (green to pink areas are identified as lactose in upper, MCC in middle and carvedilol in lower row).

the granule. This along with marked reduction of drug particle size could be the main reason for a higher dissolution rate of carvedilol from the granules prepared by spray-on compared to melt-in procedure used in this study.

4. Conclusions

The obtained results demonstrated that FB and HS melt granulation using spray-on or melt-in procedures can be successfully used for preparing carvedilol granules having appropriate technological properties. The optimal operating parameters for the production of granules were set according to each binder melt properties and used equipment/procedure. Our results confirmed the usefulness of FBRM and SFV probe for in-line granule particle size measurement and determination of melt granulation end point in both FB and HS granulator based on aimed particle size distribution. SEM pictures revealed similar morphology of the prepared granules, regardless of the equipment and procedure used. It has been shown that melt granulation using hydrophilic binders is an effective method to improve the dissolution rate of poorly water soluble drug. The binder addition procedure was found to influence the dissolution profile obtained from granules produced in both FB and HS granulator. The spray-on procedure resulted in a higher dissolution rate of carvedilol from the granules. On the contrary, the dissolution behaviour was found to be practically independent of the equipment while maintaining similar particle size distribution. Solid state analysis of pure carvedilol and prepared granules showed the presence of carvedilol form II polymorph and no evident change in crystal form was detected due to technological process of granule preparation. Moreover, it was confirmed that there are no significant solid-state interactions between carvedilol and other binders/fillers in final granules. Wetting properties of prepared granules, along with saturation solubility and Raman mapping studies, confirmed that various mechanisms are involved in improvement of dissolution rate of poorly soluble drug.

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