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Highlights

- HME ASD's smoother surface contributed to better flowability compared to granules.
- Rough and porous surface of HS granules was beneficial for dissolution properties.
- PEG 6000 was a better alternative to Soluplus® for HS melt granulation purpose.

The comparison of melt technologies based on mesoporous carriers for improved carvedilol dissolution

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Abstract

High-shear (HS) melt granulation and hot melt extrusion (HME) were compared as perspective melt-based technologies for preparation of amorphous solid dispersions (ASDs). ASDs were prepared using mesoporous carriers (Syloid® 244FP or Neusilin® US2), which were loaded with carvedilol dispersed in polymeric matrix (polyethylene glycol 6000 or Soluplus®). Formulations with high carvedilol content were obtained either by HME (11 extrudates with polymer:carrier ratio 1:1) or HS granulation (6 granulates with polymer:carrier ratio 3:1).

DSC and XRD analysis confirmed the absence of crystalline carvedilol for the majority of prepared ADSs, thus confirming the stabilizing effect of selected polymers and carriers over amorphous carvedilol. HME produced larger particles compared to HS melt granulation, which was in line with better flow time and Carr index of extrudates. Moreover, SEM images revealed smoother surface of ASDs obtained by HME, contributing to less obstructed flow. The rougher and more porous surface of HS granules was correlated to larger granule specific surface area, manifesting in faster carvedilol release from Syloid® 244FP-based granules, as compared to their HME counterparts. Regarding dissolution, the two HS-formulations performed superior to pure crystalline carvedilol, thereby confirming the suitability of HS melt granulation for developing dosage forms with improved carvedilol dissolution.

Keywords: mesoporous carrier, melt granulation, hot melt extrusion, PEG 6000, Soluplus®, amorphous solid dispersion

1. Introduction

Poor drug water-solubility has been an ongoing challenge in the recent history of pharmaceutical industry, which gave a rise in different technological and formulation strategies, to address the solubility improvement. One of such drugs is carvedilol, as it belongs to Biopharmaceutics Classification System (BCS) class II (poor solubility, good permeability). By non-selectively blocking β adrenergic receptors, the drug inhibits sympathetic effect on cardiovascular system. It also undergoes an extensive 1st pass liver metabolism, as it is a good substrate for CYP enzymes, in that way lowering drug concentration in the bloodstream (Parker et al. 2018; Morgan 1994).

Various approaches were studied to improve the bioavailability of carvedilol, including production of polymeric and lipid nanoparticles (Sharma et al. 2019; Mishra et al. 2016), nanosuspensions (Liu et al. 2012), cyclodextrin complexes (Aljimaee et al. 2015), niosomal carriers (Arzani et al. 2015), mixed micelles formulations (Öztürk et al. 2022) in addition to lipid based formulations (Singh et al. 2012; Mandić et al., 2019; Choi et al. 2021) and amorphous solid dispersion (ASD) (Sharma and Jain, 2010; Kumar Potluri et al. 2011; Genina et al., 2018; Krstić et al. 2020, Ravikumar et al. 2022), including such with sustained release (Halder et al. 2020). When comparing the last two industrially applicable approaches, lipid formulations, such as self-emulsifying drug delivery systems offer an additional benefit by their ability to reduce the first-pass metabolism effect as well as improve membrane permeability (Čerpnjak et al. 2013; Feeney et al. 2016). Nevertheless, ASD seem to have better perspective from the carvedilol loading capacity and stability point of view. Namely, carvedilol content in self-microemulsifying granules did not exceed 6 % *w/w*, despite the high liquid load of the granules, which resulted in large mass of final self-microemulsifying tablet (Kovačević et al. 2022; Mandić et al. 2020). In addition, carvedilol instability was reported in self-microemulsifying systems, where amide products can be formed between nucleophilic secondary amine of carvedilol and fatty acids, a common component of lipid phase (Mandić et al. 2021).

ASD preparation techniques are commonly divided into solvent evaporation method, methods based on supercritical fluids, melt-based techniques and other miscellaneous methods (Pandi et al. 2020). Preparation of ASDs of carvedilol by solvent evaporation in a vacuum evaporator or by direct adsorption from acetone solution resulted in carvedilol amorphization and improved drug dissolution. Moreover, porous silica, which was used as carrier, contributed to the maintenance of amorphous state, in that way preserving the advantage of improved solubility (Kovačič et al. 2011; Planinšek et al. 2011). More recently, wet milling method (Bolourchian

and Panah, 2022) and melt based technique (Genina et al. 2018) were used to prepare ASD of carvedilol without the use of organic solvent. Since carvedilol is a thermostable active ingredient, melt based approach including melt granulation, hot melt extrusion and direct adsorption of melts into mesoporous carriers is particularly promising. It is a one step process as there is no need for solvents addition (e.g. as granulation liquid), which results in the absence of drying phase, and overall shorter processing time and reduced production costs (Becker et al., 2015). In case of melt granulation, polymers with relatively low melting point (50–80 °C) are heated above that temperature and used as binders due to solidification of the molten bridges (Morin et al. 2014; Osborne et al. 2011; Chen et al. 2014). When considering granulation method, it is important to note that agglomerates produced in high-shear granulator usually have more spherical shape and more uniform particle size in addition to lower porosity as granules produced in the fluid bed device, due to higher shear forces obtained during the process (Aleksić et al. 2020). Such differences could also manifest in granules flow, leading to improved flowability, which is critical for successful further processing into tablets or capsules. Possibly time-consuming development and optimization of such process linked to the fact that the impact of process parameters variation can only be visible at the end of the process could be outwitted by hot-melt extrusion (HME), which was applied for continuous manufacturing of carvedilol-loaded mesoporous silica (Genina et al. 2018). Moreover, it can easily be scaled-up, in that way lowering not only the overall process optimization time but also material loss (Laitinen et al. 2013).

Apart from polymer binders, mesoporous carriers can also be used in preparation of next generation ASDs due to stabilizing effect of drug-carrier interactions established during absorption of drug into the carrier's pores as well as adsorption onto its surface. In addition to preventing the drug recrystallization, high specific surface area and large pore volume of mesoporous carriers enable loading of liquid into the pores up to three times of their own mass, while still maintaining good flow properties (Chandhari et al. 2017; Baumgartner and Planinšek 2021; Knapik-Kowalczuk et al. 2020; McCarthy 2016).

Considering the lipids formulation-linked carvedilol stability issues observed in our previous study (Mandić et al. 2021), the present study aimed to compare high-shear (HS) melt granulation and hot melt extrusion as two competing technologies for preparation of amorphous solid dispersion, developed to improve carvedilol solubility. In keeping with this, carvedilol was dissolved in the melt of tested polymers (polyethylene glycol (PEG) 6000 vs. Soluplus®) and loaded into Syloid 244® FP or Neusilin® US2 to merge the advantages of mesoporous carriers and melt technologies for improving dissolution properties of poorly water-soluble

drugs. Prepared ASDs were critically compared according to their physico-chemical characteristics and obtained drug release profiles to identify the most perspective formulations and the parameters that predominantly influence the product performance from the dosage form design point of view.

2. Materials and Methods

2.1. Materials

Carvedilol (CTX Life Sciences Ltd., Gujarat, India) was used as a BCS II model drug.

PEG 6000 (Krka, Novo Mesto, Slovenia) and Soluplus® (BASF, Ludwigshafen, Germany) were used as polymeric binders within the melt technology processes.

Neusilin® US2 (Fuji Chemical Industries Co. Ltd., Japan), the amorphous magnesium aluminometasilicate, and silica Syloid® 244FP (Grace GmbH & Co. KG, Worms, Germany) were used as mesoporous carriers, due to their high liquid adsorbing capacity. These two carriers have the following physical characteristics, where first value is associated with Neusilin® US2 and second value with Syloid® 244FP: specific surface area (m^2/g) 300–342 vs 359, median particle size / d_{50} (µm) 106–108 vs 2.4–3.7, mesopores radius (nm) 8.0–12.7 vs 10.7, oil/water adsorbing capacity (mL/g) 2.4–3.4 vs 1.6–3.0 (Fuji Chemical Industries 2015; Grace 2015; Kostelanská et al. 2022). In shots, both carriers have similar specific surface area, mesopores radius and liquid adsorbing capacity, while they differ a lot in median particle size.

For preparation of dissolution media, KH_2PO_4 (Merch KGaA, Germany), NaOH (Merck KGaA, Germany), HCl (37%, Panreac Quimica S.A.U. Barcelona, Spain) and purified water (reverse osmosis, Faculty of Pharmacy, Ljubljana, Slovenia) were used.

2.2. Methods

2.2.1. Preparation of preblends for melt extrusion and melt granulation

All preblends for melt extrusion were prepared with polymer-to-carrier ratio 1:1, while the balance (Mettler Toledo, Columbus, Ohio, USA). Firstly, the preblend containing only mesoporous carrier (Syloid® 244FP or Neusilin® US2) and melting polymer (PEG 6000 or Soluplus®) was mixed in the turbula mixer (Turbula T2F, Willy A. Bachofen, Basel, Switzerland) for 10 minutes at 60 rpm. For the second round of mixing and to obtain homogenous preblend for extrusion, the compounds were added to the mixing container in the following order: ½ of polymer-carrier mixture, followed by carvedilol, and the other ½ of polymer-carrier mixture. Finally, the loaded container was mixed for 15 minutes at 60 rpm.

In case of melt granulation, the preblend preparation differed in the formulation composition, since 1:1 polymer-to-carrier ratio wasn't suitable for this particular melt technique. Instead, the optimal ratio of polymer-to-carrier ratio needed to enable the process proved to be 3:1. Nevertheless, carvedilol loads and mixing process remained the same, as described above.

2.2.2. Preparation of carvedilol solid dispersion by melt extrusion

Preblends (~100 g) were placed into the twin screw feeder (DDW-MDO-MT-1-HYD, Kubota Brabender Technologie GmbH, Duisburg, Germany), attached to laboratory Tabletop extruder (2E9 HMI Three-Tec GmbH, Seon, Switzerland) with the total length of screw configuration 180 mm. The configuration consisted of 90 mm-length conveying section, made of 10 elements with 9 mm screw pitch and 9 mm screw length, followed by first kneading section of 18 mm-length, with 60° angle between kneading elements. Following, an intermediate 18 mm conveying section was placed to facilitate the flow of the melt towards the second 60° kneading section. Each formulation was extruded through the 1 mm die out on the conveyor belt (Geppert band GmbH, Jülich, Germany). The process parameters (shown in Table 1) were adjusted to each formulation, to obtain product with suitable characteristics. After the process steady state was reached, the product was collected.

Produced extrudates were milled by Cryomill (SPEX Sample Prep, Metuchen (NJ), USA) to obtain micronized powder, which were further compared to melt granulates obtained by HS granulator. The milling process involved 2 milling cycles, each consisting of: 10 minutes of pre-cooling, followed by 15 seconds milling (milling rate was 15 counts/s), and finally sieving through 1 mm sieve. Milled products were then stored in labeled cup-container, wrapped with parafilm.

2.2.3. Preparation of carvedilol solid dispersion by high-shear melt granulation

Melt granulation in HS granulator (4M8-Trix, Pro Cept, Zele, Belgium) was used for production of carvedilol solid dispersion. The target temperature of the process was obtained by using the granulation bowl with a heatable double-jacket, connected to a water-heater (Ministat 125, Huber, Offenburg, Germany). This device was used for both preheating the bowl, to avoid premature formation of granules, and to maintain the target temperature during the granulation step.

More specifically, the granulation process was started by adding ~50 g of the preblend (section 2.1.1.) into the preheated, one-liter glass bowl. The target temperature was obtained by heating the circulating water above the melting temperature of applied polymers. In the case of PEG 6000 it was varied between 65 and 75 °C during process development phase and finally set to

62 °C. In the case of Soluplus®, the water temperature was set to maximal value of 98°C. While the chopper speed was kept constant at 2000 rpm, the impeller speed was adjusted to the carrier type, ranging from 400 rpm (Syloid® 244FP) to 500 rpm (Neusilin® US2). Finally, granulation endpoint was determined by visual appearance of the granules and the feeling under fingertips (in reference to previous granulation experience). The granules were then sifted through a sieve with mesh size of 1 mm and cooled down to ambient temperature (~25 °C).

2.2.4. Loss on Drying

The loss on drying of extrudates and granules obtained by both melt techniques was measured by thermogravimetric analytical balance (HC103/01, Mettler Toledo, Switzerland). Samples were placed on the aluminum pan to cover its surface in a thin layer, and the measurement conditions were set to 85 °C, until constant sample weight was reached. The final result was presented as the percentage of moisture in the product.

2.2.5. Particle size and Size Distribution Measurement

The size and size distribution of the prepared extrudates and granules as well as the initial mesoporous carrier powders were measured using the Mastersizer 3000 device (Malvern Panalytical Ltd, Malvern, UK) by placing approximately 1 g of the sample into an Aero S dispersion cell. Measurement conditions were set to 1.5 bar of air pressure and 20 % feed rate. Mastersizer 3000 uses laser diffraction to obtain the results, which are presented as d_{10}, d_{50} and d_{90} values (particle size in μm) as well as SPAN (distribution width).

2.2.6. Evaluation of Flow Properties and Compressibility

Granule and extrudate flow properties were evaluated according to Ph. Eur. 11th (2.9.16 Flowability, 2.9.34 Bulk density and tapped density of powders and 2.9.36. Powder flow (Ph. Eur. 11th Ed.)). For the flow time measurement, about 15 g of the sample was poured into a pharmacopoeia standard glass funnel and the time needed for the entire sample to flow out was measured and expressed as the flow time in s/100 g of sample. Then, height and diameter of the powder cone were measured, and angle of repose was calculated from the results. Measurements of flow time and angle of repose were repeated 10 times and expressed as average values.

For the evaluation of Carr's index, between 30 and 40 g of sample was accurately weighted and gently placed into a 100 mL plastic cylinder. The volume of the sample was measured as the bulk volume. Then, the cylinder was tapped 1250 times with a tap density tester (VanKel 50–1100, VanKel Technology Group, Cary (NC), USA) to determine the tapped volume. Bulk and

tapped volumes were used for the calculation of bulk and tapped densities, and Carr's index as an indicator of the samples flow. All measurements were performed in triplicate and expressed as average values.

2.2.7. Determination of Carvedilol Content

Carvedilol content in granules and extrudates was determined using UV spectroscopy (UV/VIS spectrophotometer Varian Cary® 50; Agilent Technologies Inc, Santa Clara (CA), USA), by measuring the absorbance at 284 nm wavelength, according to the procedure already described in the literature (Kovačević et al. 2023; Mandić et al. 2019).

Precisely weighed samples with theoretical content of 12.5 mg of carvedilol were quantitatively transferred into a 500 mL measuring flask, with 70 mL of methanol used as cosolvent, and filled with pH 1.2 HCl solution up to ¾. Thereafter, the flask was sonicated for 30 min, followed by 30 min stirring at 50 °C, and an additional 30 min of sonication. For the final sample preparation, the flask was filled up with the medium to the volume mark.

Then, 10 mL of the prepared sample was filtered into a cuvette through a 0.45 μm RC membrane filter. The absorbance of the sample was measured at 284 nm, in reference to the medium used as a blank. The concentration of carvedilol in the sample was calculated based on the previously determined carvedilol calibration curve, which was further calculated to express the carvedilol content mg/g of solid granules.

2.2.8. Particles Surface Morphology

The surface morphology of melt-granules and milled-extrudates was evaluated using a scanning electron microscope (Supra 35VP, Carl Zeiss, Oberkochen, Germany) at 1 kV accelerating voltage using SE2 detector under 250 and 1000 × magnification. The prepared samples consisted of small number of particles, carefully sprinkled onto a double-adhesive carbon tape, that was previously glued to a metal holder.

2.2.9. Assessment of Carvedilol Physical State

The physical state of carvedilol and amorphous carvedilol stability in extrudates and granules was examined by differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis. To assess their drug loading potential, crystalline carvedilol, pure polymers and mesoporous carriers were also evaluated in addition to their binary (carvedilol:polymer in ratios 2:1, 1:1 and 1:2) physical mixtures. Using a DSC (DSC1 STARe System, Mettler Toledo Columbus, Ohio, USA), the samples (5–7 mg) were heated in an aluminum pan with perforated lid, from 25 °C to 150 °C (heating rate of 10 °C/min), kept isothermal for 1 min, then cooled

down to 0°C (cooling rate of 10 °C/min), while maintaining a nitrogen gas flow of 50 mL/min. An empty aluminum pan was used as a reference. Finally, the output data was evaluated by STARe V9.30 software program (Mettler Toledo, Columbus, Ohio, USA). In the case of extrudates, different DSC device (Netzsch, Selb, Germany) and software program (Software Netzsch Proteus 80) were used, since that part of the experiments was conducted within collaboration with Research Centre for Pharmaceutical Engineering in Graz, Austria.

XRD analysis of the pure excipients, crystalline carvedilol and granules was performed using an X'Pert powder diffractometer (Malvern Panalytical Inc, Westborough (MA), USA) equipped with a graphite monochromator in the diffracted beam. Cu Kα radiation was used (40 mA, 40 kV) and the spectra was obtained in the range 3°–30° 2θ (Bertoni et al. 2023). In case of extrudates, other X-ray scattering device was used (Hecus X-Ray Systems GmbH, Graz, Austria), with measurements performed in wide angle region of 17−27° 2θ, using high-resolution camera (S3-Micorpix, Hecus, Graz), a point-focusing detector (PSD-50, 54 μm/channel; Hecus) and a Cu Kα X-ray source, with an instrumental setting of 50 kV/1 mA. The powder samples were filled in the quartz capillary with an internal diameter of 2 mm and sealed with wax. The capillary was rotating (0.2 Hz) while being exposed to an X-ray beam to allow for angular averaging of the powder scattering patterns. The counting time employed during the measurement was 600 s. All measurements were performed in triplicate.

2.2.10. In Vitro Carvedilol Release Testing

In vitro dissolution testing of granules and extrudates was conducted using Ph. Eur. Apparatus 2 dissolution tester with rotating paddles (VanKel VK 7010 Tablet Dissolution Tester, VanKel Technology Group, Cary (NC), USA; Ph. Eur. 11th 2.9.3. Dissolution test for solid dosage forms (Ph. Eur. 11th Ed.).

The amount of tested granules and extrudates was adjusted to contain 12.5 mg of carvedilol, and the results were presented as average value with corresponding standard deviation. Pure crystalline carvedilol was used as a reference. The dissolution vessels were filled with selected medium (900 ml of diluted HCl solution with pH 1.2 or phosphate buffer with pH 6.8) and heated to 37 ± 0.5 ◦C with stirring rate of 50 rpm. Upon reaching the required medium temperature, the samples were quantitatively transferred into the vessels. 5 mL of samples was withdrawn and filtered through a 0.45 μm pore RC (regenerated cellulose) membrane filters at predetermined time intervals (i.e. 5, 10, 20, 30, 45, 60, 90, 120, 180 min, plus additional sampling time points at 240, 300 and 360 min for pH 6.8 media). The withdrawn medium was replaced with the same volume of fresh medium, to maintain the same total volume. Final

sampling was conducted after an additional 5 min *infinity spin* with paddles rotating with maximal speed of 250 rpm, to ensure the complete drug release. Samples were further analyzed using UV spectroscopy, and the absorbance was measured at 284 nm wavelength. Carvedilol concentration was determined in relation to the calibration curves obtained in both media; the *in vitro* release profile was plotted as the cumulative percentage of released carvedilol versus time.

2.2.11. Stability testing

The stability study was conducted for melt-based granules stored under controlled accelerated conditions (40°C, 75% RH; Memmert GmbH HPP110, Schwabach, Germany) in closed container. Carvedilol content and the presence of impurities were determined with HPLC system (Series 1100/1200, Agilent Technologies, Santa Clara (CA), USA), using methods described in our previous study (Mandić et al., 2021) within the time points of 0, 4, 6 and 12 weeks of storage under controlled accelerated conditions.

3. Results and Discussion

Two melt-based techniques, i.e. HS melt granulation and HME, were studied with the aim of improving the dissolution of carvedilol by preparing mesoporous carrier-based solid dispersion. Two different polymeric binders were selected based on their characteristics and stabilizing ability, and the characteristics of obtained products were critically compared between the two technologies. PEG 6000, a semicrystalline polymer, was used due to its relatively low melting temperature suitable for melt granulation (ranging between 60 °C and 80 °C, depending on the processing conditions and the polymer purity (Rowe et al. 2009). Other polymer applied was Soluplus®, a thermoplastic amorphous excipient, mostly used within HME, and with glass transition temperature (Tg) around 70 ° (Cho et al. 2015; Linn et al. 2012). Solid dispersions were prepared by adsorbing the dispersions of carvedilol in the polymer matrix melt into the pores of either Neusilin® US2 or Syloid® 244FP, selected as mesoporous carriers. In the first part of the research we focused on the preparation of carvedilol ASDs with desired flow properties and drug release by selection and/or screening of optimal excipients and optimization of melt process parameters.

3.1. Optimization of melt technology process and solid dispersion formulation

For easier understanding, samples were named with regard to carvedilol loading, polymer and carrier type as well as melt technique used; the name of each formulation starts with the

numbers **20**, **30** or **40**, presenting the loading of incorporated carvedilol (% *w/w*), which is followed by mesoporous carrier name (abbreviated as **Neu** (for Neusilin® US2) or **Syl** (for Syloid® 244FP)) and polymer (abbreviated as **Sol** (for Soluplus®) or PEG (for PEG 6000)) included in the formulation. The suffix of the sample name reveals the melting technique used for preparation of specific formulation, with - **HME** presenting hot melt extrusion and – **HS**, high-shear melt granulation technology.

3.1.1. Hot melt extrusion

To investigate the influence of polymers and mesoporous carriers on product characteristics, all HME formulations contained the same weight ratio between polymer and carrier (1:1), while carvedilol load was varied (20, 30 and 40 % *w/w*). The suitable process parameters utilized for each are reported in Table 1.

Table 1. The values of optimized process parameters used for HME; each formulation was named with regard to carvedilol share (20, 30 or 40 *w/w* %), carrier (Neusilin® US2 or Syloid® 244FP) and polymer (PEG 6000 or Soluplus®) used as well as the melt technology (HME or HS melt granulation).

Formulation	Feed rate (g/min)	Screw speed (rpm)	Barrel temperature (°C)	Conveyor belt speed (m/min)
20NeuSol–HME 30NeuSol–HME 40NeuSol–HME	**100**	**100**	**115**	**6.06**
20NeuPEG–HME	**100**			
30NeuPEG–HME	**100**	**50**	**50**	**1.72**
40NeuPEG–HME	**75**			
20SylSol–HME	**40 – 80**	**75 – 150**	**105 – 115**	
20SylSol–HMEm	**manual**	**75**	**105 – 130**	**4.40**
30SylSol–HME	**50**	**75**	**115**	
40SylSol–HME	**50**	**100 – 120**	**105**	

20SylPEG–HME	**manual**		**75 - 100**	
30SylPEG–HME	**50**	**75**	**80**	**1.72**
40SylPEG–HME	**50**		**75**	

The preblend composed of the drug, polymer and carrier was placed in the feeder, which was attached to the extruder with an already preheated barrel above polymer melting temperature. In the hot barrel the polymer was softened/molten and mixed with other components by screw rotation carrying the mixture towards the 1 mm extrusion die. Temperature was identified as the most critical process parameter, as overheating the drug can induce product degradation (Talvani et al. 2014).

With regard to processability, Neusilin® US2 proved to be more suitable for HME, compared to Syloid® 244FP. The process optimization was timesaving, as the initially optimized process parameters found to be applicable for all three formulations containing Soluplus® as a polymer. However, PEG 6000-based formulations were more challenging, requiring extrusion at particularly lower extrusion temperatures of 50 °C. Above 50 °C, the extrudate, coming out of the die to the conveyor, was sticky and as such couldn't solidify quick enough even at the lowest conveying rate. In this case, the use of mesoporous carriers with high liquid loading capacity proved to be of great advantage, as it enabled the extrusion process despite very low melting point of the polymer.

The biggest challenge was processing the formulations containing high amounts of Syloid® 244FP, used as a solid carrier. In case of formulation 20SylSol-HME, the highest torque value of 11-14 Nm was obtained, in addition to creaking sound of the screwing elements. Even with the temperature increased to 130 °C and manual feeding, an appropriate product couldn't be obtained. It was assumed that this formulation was on the limit of processability due to high torque, which was attributed to high amount of the carrier (40 % *w/w*) with relatively small particle size (~3.5 μm) and low bulk density (Solomon et al. 2021). By decreasing the amount of Syloid® 244FP, within formulations 30SylSol-HME and 40SylSol-HME, acceptable values of ~9.5 and 4.5 Nm of torque were generated (respectively) and the yellowish extrudate could be collected.

3.1.2. High-shear melt granulation

In order to investigate the influence of melt technology on product characteristics, the same formulation composition was also applied within the HS granulation process. In this case, the three-component preblend was placed in the granulation bowl and heated above polymer melting temperature. As a result, carvedilol dissolved in polymer matrix melt was assumed to

load into the carrier pores, resulting in ASDs with amorphous drug form stabilized by presence of binding polymer and mesoporous carrier.

The initial granulation temperature was set to 75 °C (above the PEG 6000 melting temperature), due to expected temperature loss linked to circulating the hot water through the silicon tubes connecting the heating device and the heating water jacket of granulation bowl. As no granules were formed after more than 60 minutes of mixing, the amount of polymer in the formulation was considered as too low as well as the amount of solid carrier was too high, that overall led to complete absorption of molten polymer into the pores of a carrier instead of forming the liquid bridges between the particles. To find the optimal amount of polymer needed for the most effective granules formation (i.e. without residues of non-granulated material), formulations with higher polymer-to-carrier ratios up to 5.5:1 were tested (Table S1). The addition of insufficient amount of Neusilin® US2 (polymer:carrier ratio of 5.5:1) resulted in a semisolid state of the product due to the lack of solid surfaces capable of absorbing the excess of molten polymer dispersion. Adequate granules were produced with intermediate polymer-to-carrier ratio (i.e. 3:1), which could be detected visually as well as by the fingertips touch. Therefore, all carvedilol ASDs were optimized to this polymer:carrier ratio.

However, the process still needed some optimization, as the processing time was too short (4 min and 42 sec, Table S1) to follow the granule growth and correctly determine the granulation endpoint. Therefore, the temperature was decreased to slow down granule growth and enable more reliable detection of its final point. More specifically, it was decreased towards the temperature of the onset of PEG 6000 melting peak. Lowering the granulation temperature from 75 to 62 °C contributed to improved process control and enabled the preparation of granules, as presented at Table 2.

In addition to PEG 6000, Soluplus® was also tested as binding polymer in HS granulation due to its widespread use in (hot) melt extrusion processes. Nevertheless, processability of Soluplus® was a great challenge, due to limitation of the granulation bowl highest temperature, controlled by heating water jacket. Upon initially setting the granulation temperature to 90 °C, it was soon increased to 98 °C as highest possible temperature of water-jacket to melt the polymer and enable formation of granules. As no changes were observed in the granulation bowl implying pure Soluplus® being unsuitable for HS granulation with our equipment. Therefore, its overall processability was expected to increase by lowering its Tg onset in mixtures with PEG 6000.

Table 2. The values of optimized formulation and process parameters used for HS melt granulation; each formulation was named with regard to carvedilol share (20, 30 or 40 *w/w* %), carrier (Neusilin® US2 or Syloid® 244FP) and polymer (PEG 6000 or Soluplus®) used as well as the melt technology (HME or HS melt granulation).

*The ratio between Soluplus® and PEG 6000, within the polymer share.

Formulation	Polymer:carrier ratio	Temperature (°c)	Granulation time (min:sec)
20NeuPEG-HS	**3:1**	**62**	**08:22**
30NeuPEG-HS			**08:17**
40NeuPEG-HS			**05:18**
20SylPEG-HS			**15:28**
30SylPEG-HS			**20:19**
40SylPEG-HS			**15:41**
20NeuSol1PEG1	**(1.5:1.5)*:1**	**98**	**13:49**
20NeuSol1PEG2	**(1:2)*:1**		**04:14**

In keeping with this, formulations consisting of Soluplus® and PEG 6000 as granulating polymers (used in 1:1 and 1:2 ratios; Table 2) and Neusilin® US2 (at 3:1 ratio in favor of polymers) were used for preparing granules by HS melt granulation. Despite this adjustment, a significant amount of ungranulated material remained after granulation, therefore Soluplus®-based granules were omitted from further experiments.

Overall, considering the specific characteristics of compared melt-based technologies, we can conclude that the use of mesoporous carriers contributed to the HME-formulation processability of PEG 6000. Likewise, extrusion would be more favorable in the case of products containing Soluplus®, since the polymer couldn't be processed by HS melt granulation. In order to obtain adequate product by HS granulation, all PEG 6000-based formulations were optimized to contain polymer-to-carrier ratio 3:1.

3.2. The comparison of HME and HS melt-based technology

With the aim to further investigate the influence of melt technology on the products characteristics, HS melt-based granules and their HME counterparts were compared for their physico-chemical characteristics and drug release profiles.

3.2.1. The impact of the studied melt technologies on the surface morphology and flow properties of obtained products

Formulations obtained either by HS melt granulation or HME, followed by cryo-milling of extrudates, were sieved and submitted for further characterization. The results of scanning electronic microscope (SEM) analysis are presented in Figures 1 and 2. All formulations prepared by HME had relatively smooth surfaces. Even though all formulations are based on mesoporous solid carriers with high specific surface area, the carrier pores were not visible in the SEM images and are most likely filled by the molten PEG 6000 (Figure 1) or Soluplus® (Figure 2). Apart from the smooth surfaces, some sharp edges of 30SylPEG-HME particles were also noticed, probably caused by cryo-milling of spaghetti-like extrudates (Figure 1d). Contrary to this, HS granules were round and with more porous structure and rougher surfaces (Figures 1a and 1b). It seems that their pores were not completely filled with the melt, possibly due to high-shear forces pushing the melt deeper inside the carrier pores. Thus, based on SEM images we can conclude that the porous structure of the carriers was preserved in case of products obtained by HS melt granulation, contrary to formulations produced by HME technology.

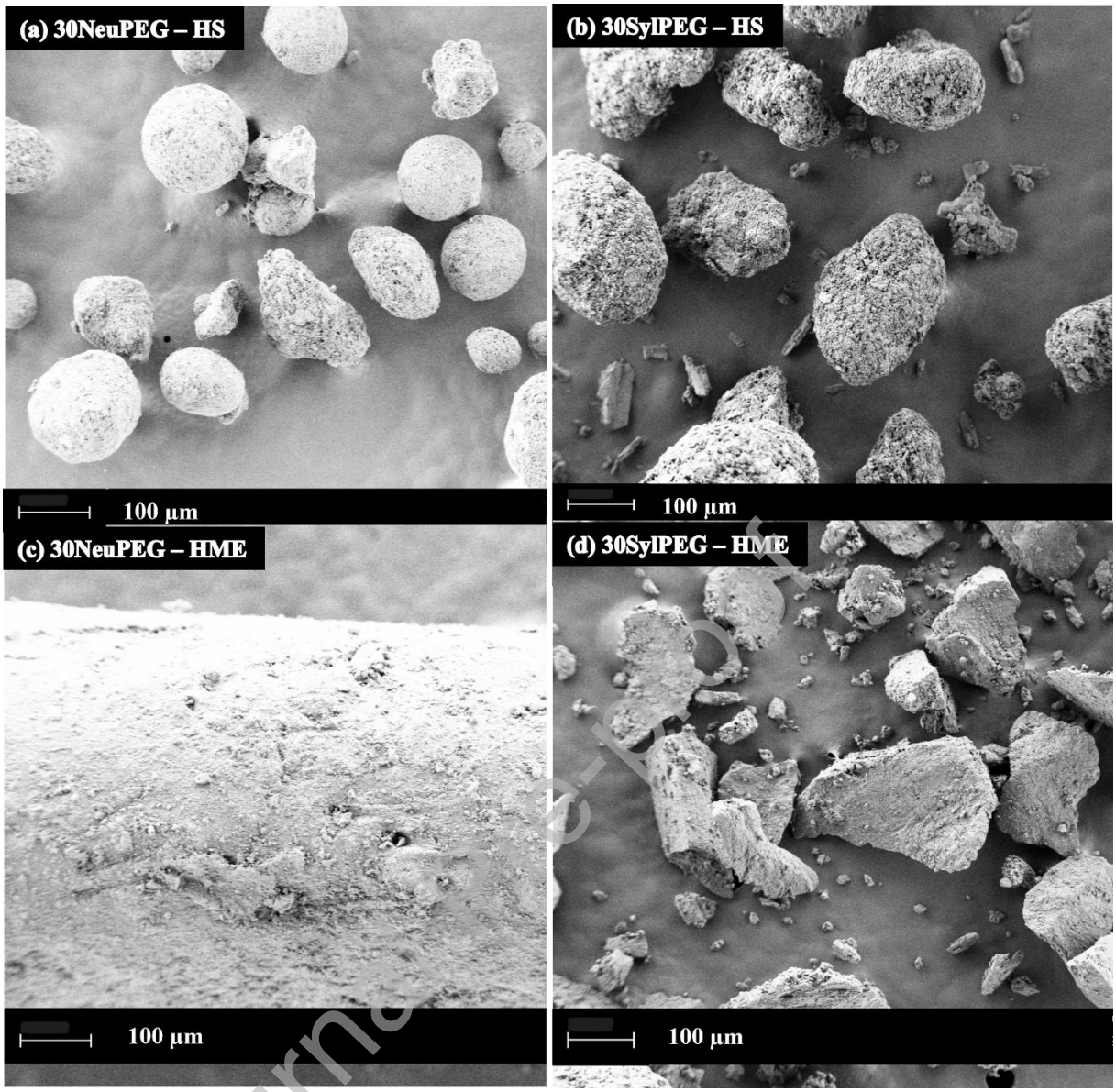

Figure 1. The comparison of surface morphology between products obtained by HS melt granulation and HME: SEM images of 30NeuPEG-HS (a), 30SylPEG-HS (b), 30NeuPEG-HME (c) and 30SylPEG-HME (d), under magnification of 250 ×.

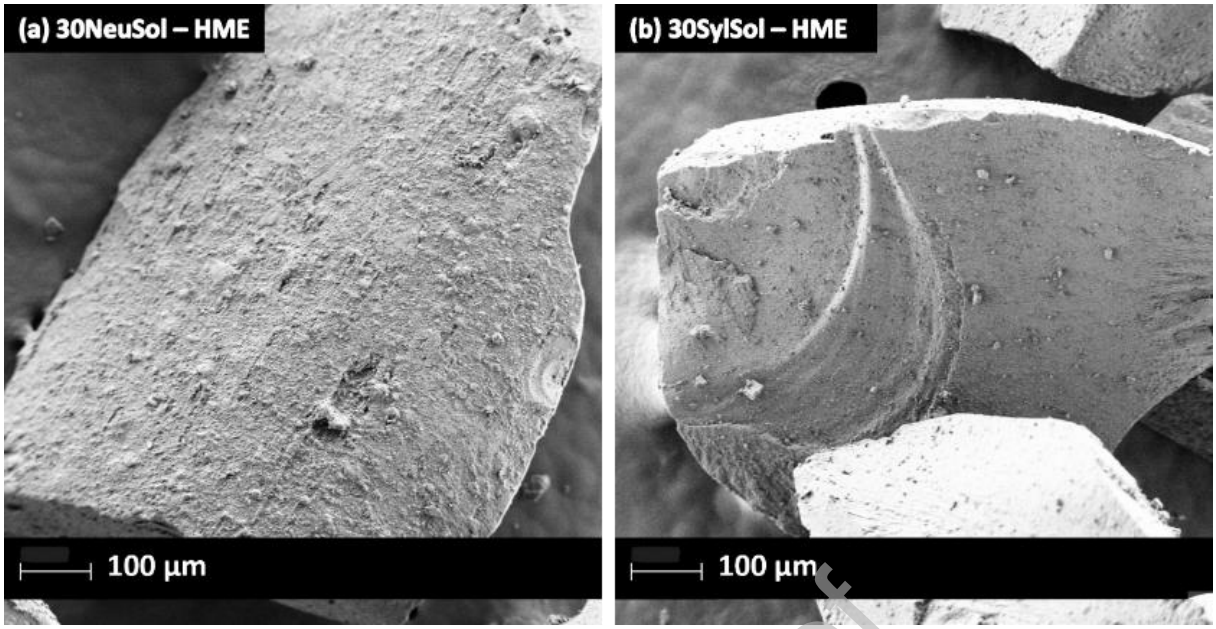

Figure 2. SEM images of HME-particles: 30NeuSol-HME (a) and 30SylSol-HME (b), under magnification of 250 ×.

Laser diffraction measurements showed narrow distribution of HS granules (SPAN values 0.8-1.2, with one outlier with value of 1.6), d_{50} between 540 to 800 µm (Table 3). The only exception regarding the low SPAN value was formulation 40SylPEG-HS, which was identified for residues of insufficiently granulated material as seen from d_{10} value of 126 µm. All other formulations had minimal residual non-granulated material seen from d_{10} values of over 260 µm.

The results of their HME counterparts are presented in Table 4. Overall, they were characterized as fairly bigger, with median granule size ranging from 880 to 1060 µm and with generally slightly broader size distribution (SPAN values 1.0-1.3).

Larger size of HME products also contributed to improved flow time as compared to their HS granulation produced counterparts (4.5 - 6.3 vs. 9.3 – 12.3 seconds, respectively). Likewise, CI values were slightly better as HME resulted in product with fair-to-good, while by HS granulation only fair flow properties were obtained (see Tables 3 and 4). This was contrary to our expectations, as the use of high-shear equipment usually results in granules with higher bulk and tapped densities as well as more spherical shape due to high-shear forces applied during processing. Therefore, to complement flowability characterization, particle surface morphology was investigated.

Better flowability of HME-particles was also supported by the results of SEM analysis, as smoother particle surface could contribute to more unobstructed product flow. Moreover, possible explanation for the highest CI value of 30SylPEG-HME (of all HME products) could

be complemented by irregular particle shape, visible on Figure 1, which could impair the flow characteristics.

Table 3. Characteristics of granules obtained by HS melt granulation: median particle size (d_{50}) and distribution width (SPAN), flow properties (flow time, angle of repose, Carr index - CI) and moisture content.

Formulation	d_{10} (µm)	d_{50} (µm)	SPAN	Flow properties		Moisture content (%)
				Flow time (s)	Carr's Index (%)	
20NeuPEG- HS	260	546	1.19	12.3 ± 0.3	18.4 ± 0.9	2.6
30NeuPEG- HS	478	714	0.82	11.7 ± 0.2	19.6 ± 0.8	2.3
40NeuPEG- HS	482	688	0.76	10.8 ± 0.2	17.6 ± 0.8	2.3
20SylPEG- HS	466	718	0.89	9.3 ± 0.2	16.9 ± 0.8	3.1
30SylPEG- HS	573	796	0.68	10.7 ± 0.3	18.6 ± 1.0	1.7
40SylPEG- HS	126	536	1.59	10.1 ± 0.2	18.4 ± 0.9	1.9

Table 4. Characteristics of products obtained by HME followed by cryo-milling: median particle size (d_{50}) and distribution width (SPAN), flow properties (flow time, angle of repose, Carr index - CI) and moisture content.

Formulation	d_{10} (µm)	d_{50} (µm)	SPAN	Flow properties		Moisture content (%)
				Flow time (s)	Carr's Index (%)	
20NeuPEG- HME	637	1060	1.17	6.3 ± 1.7	19.1 ± 1.8	2.4
30NeuPEG- HME	642	974	0.97	6.0 ± 1.0	15.2 ± 0.0	2.3
40NeuPEG- HME	523	956	1.26	5.5 ± 0.7	16.4 ± 1.1	2.6
30SylPEG- HME	533	876	1.01	5.6 ± 0.5	19.4 ± 0.9	2.0
40SylPEG- HME	617	1030	1.17	5.2 ± 0.3	15.3 ± 0.6	1.8
20NeuSol- HME	583	996	1.22	4.7 ± 0.4	13.5 ± 2.0	2.3
30NeuSol- HME	485	881	1.22	4.7 ± 1.1	18.2 ± 1.8	2.9
40NeuSol- HME	410	819	1.26	4.5 ± 1.2	12.8 ± 1.1	2.8
30SylSol- HME	547	968	1.21	4.5 ± 0.4	/	1.9
40SylSol- HME	538	1010	1.24	4.6 ± 0.9	16.8 ± 0.5	1.6

3.2.2. Carvedilol physical state in melt-based products and stability

DSC analysis was performed for two main reasons: (1) as part of preliminary study, to assess possible interactions between the components and more importantly, to estimate the amount of carvedilol dissolving within the molten polymer, as in such state it would be loaded into the carrier pores. For that purpose, DSC curves of pure components, binary and ternary physical mixtures were measured; (2) to characterize carvedilol physical state within melt-based products and determine possible residue of crystalline carvedilol, whose poorer water-solubility could impair the dissolution behavior.

As shown on DSC curves (Figure 3), pure crystalline carvedilol had a pronounced endothermic peak with onset at ≈116 °C, indicating melting of the drug crystal (form II). During cooling cycle, a Tg was observed at ≈43 °C, suggesting complete amorphization of carvedilol. Thermogram of pure PEG 6000 shows a melting endothermic peak with onset at ≈63 °C and a recrystallization exothermic event starting at about ≈46 °C during cooling cycle.

In cases of binary physical mixtures with PEG 6000, this peak was either shifted towards lower temperatures (2:1 and 1:1 ratios) or absent (1:2 ratio), indicating that carvedilol dissolved in a molten polymer indicating the amorphization potential. Moreover, on the physical mixture 1:2 cooling curve, recrystallization of PEG 6000 was observed. To optimize the formulation composition, it was essential to estimate the maximum amount of carvedilol dissolved in PEG 6000, which proved to be between 33 % (no carvedilol peak observed at ratio 1:2) and 50 % (small carvedilol peak observed at ratio 1:1). In keeping with this amorphous state of carvedilol was expected in all formulations containing 20 % of the drug (corresponding to 33 % carvedilol-to-polymer share in HME). Oppositely, formulations with 40 % of carvedilol (corresponding to 57 % carvedilol-to-polymer share in HME) were expected to exceed drug solubility in PEG 6000, in particular those prepared by HME, due to smaller share of polymer in formulation.

Contrary to PEG 6000 physical mixtures, no shift of carvedilol melting peak towards lower temperature was observed in mixtures containing Soluplus® (Figure S1). Accordingly, the process temperature used during HME was high enough to enable amorphization of the drug.

All granules produced by HS granulation and HME were submitted to DSC analysis to evaluate the physical state of carvedilol in obtained solid dispersions. In most of samples, no thermal events corresponding to crystalline carvedilol were detected on thermograms (Figures 4 and 5), which is in line with expectedly amorphous state of incorporated carvedilol. Nonetheless, between 90 and 110°C, a very mild and broad peak was observed for 40NeuPEG-HS and 40SylPEG-HS, which could correspond to remaining of some crystalline carvedilol (Figure 4).

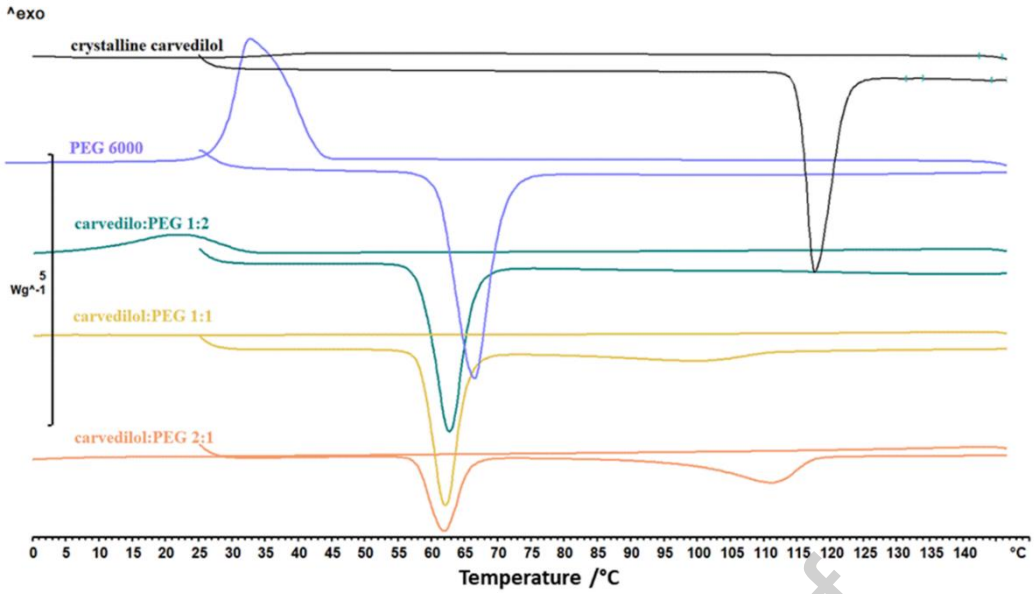

Figure 3. DSC thermograms of pure crystalline carvedilol and of binary physical mixtures with PEG 6000, in ratio 2:1, 1:1 and 1:2.

Interestingly, the melting of PEG 6000 residues was absent in case of 20SylPEG-HME and 40SylPEG-HME but observed within its Neusilin® US2 counterparts (Figure 5). This was unexpected, since the amount of PEG 6000 in the formulation 20SylPEG-HME was 3-fold higher than carvedilol amount and therefore, the excess of semi-crystalline polymer should be seen as exothermic event. A possible explanation for the lack of PEG 6000 melting peak is fully amorphous state of PEG 6000 within these samples, which is in line with the absence of its recrystallization peak during cooling phase in Figure 3 (2:1 and 1:1 ratio).

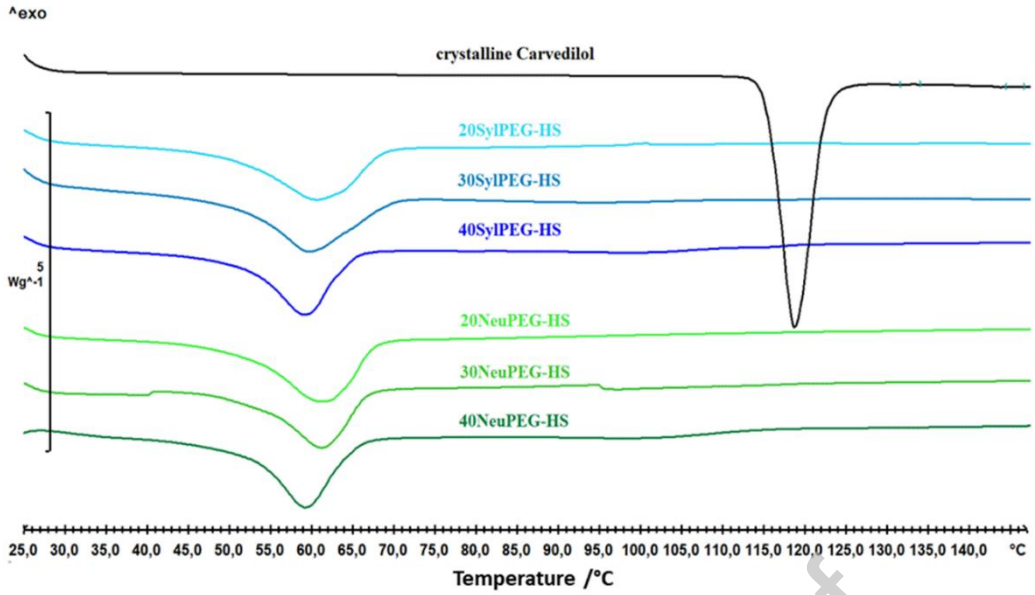

Figure 4. DSC curves of pure crystalline carvedilol and carvedilol solid dispersion produced by HS melt granulation: 20NeuPEG-HS, 30NeuPEG-HS, 40NeuPEG-HS, 20SylPEG-HS, 30SylPEG-HS and 40SylPEG-HS.

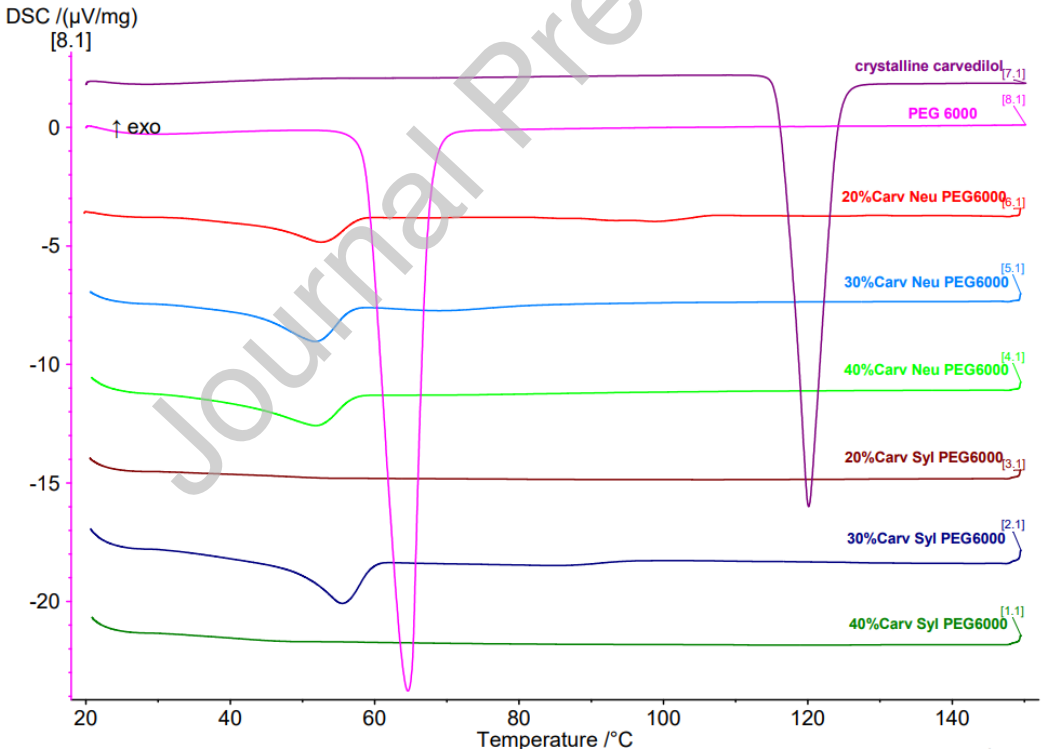

Figure 5. DSC thermograms of pure crystalline carvedilol, PEG 6000 and carvedilol solid dispersion produced by HME: 20NeuPEG-HME, 30NeuPEG-HME, 40NeuPEG-HME, 20SylPEG-HME, 30SylPEG-HME and 40SylPEG-HME.

As seen in Figure 5, the carvedilol melting peak is absent on the DSC curves of HME products, including those with 40 % drug content (i.e. 40NeuPEG-HME and 40SylPEG-HME). This allowed us to presume that, as it couldn't be molecularly dispersed within the polymer, carvedilol was amorphized during HME process. Although in some HME experiments the process temperature was set below the drug melting temperature, carvedilol did eventually melt, due to additional heating of the barrels linked to mechanical energy produced by screw rotation in the kneading area.

The possible presence of crystalline carvedilol was further investigated by XRD analysis, with pure crystalline carvedilol, the corresponding pure polymers and carriers used as reference samples. XRD diffractograms of Neusilin® US2- and Syloid® 244FP-based HS granules are presented in Figures 6 and 7, respectively. Likewise, XRD diffractograms of their HME counterparts are shown in Figures 8 and 9. Both mesoporous carriers showed a distinct 'halo', typical for amorphous state solids, while diffractogram of pure carvedilol showed diffraction peaks typical for its crystalline state. Some weak diffraction lines, corresponding to crystalline drug, were observed for 20NeuPEG-HS, while in case of 40 % carvedilol loading, these peaks were the most pronounced, indicating the amount of crystalline carvedilol residues was depended on the drug loading. Similar trend was also observed within Syloid® 244FP formulations, with the exemption of 20SylPEG-HS, as the only HS-formulation with no crystalline diffraction lines visible.

In the case of NeuPEG-based HME, crystalline carvedilol diffraction lines were observed in the samples with 30 and 40 % drug loading, while for Syloid® 244FP-based just for 30SylPEG-HME. Likewise, Syloid® 244FP performed better than Neusilin® US2 also in case of HME. With the absence of crystalline drug in 20SylPEG-HME and 40SylPEG-HME, Syloid® 244FP overperformed Neusilin® US2 as more suitable mesoporous carrier for production of amorphous solid dispersion of carvedilol. Moreover, Syloid® 244FP-based HME was superior compared to HS melt granulation, as the drug was mostly present in amorphous state and/or dispersed within PEG 6000 and captured within the pores of the carrier, apart from HS granulation, where the residues of crystalline carvedilol could act as a nucleus and induce crystal growth.

Apart from crystalline carvedilol, two pronounced peaks at 19° and 23° were observed in the case of semi-crystalline PEG 6000 as well. Interestingly, these peaks were visible for all formulations, except 20SylPEG-HME and 40SylPEG-HME, as shown on Figure 9. Therefore, XRD complemented the results of DSC analysis, confirming the absence of PEG 6000 crystals within the same samples. A possible explanation may be that the recrystallization of remaining

polymer was inhibited by limited molecular mobility inside the pores of the carrier, due to hydrogen bonding with the surface of silanol groups (Solomon et al. 2021). In keeping with this, smaller size of Syloid® 244FP particles, compared to Neusilin® US2 (measured d_{50} value was 106 vs. 3.5 μm), and shallower pores (14.5 vs. 10.7 nm (Trivedi et al. 2023; Kostelanská et al. 2022; Krupa et al. 2015)) could be linked to better stabilization effect, since the crystal growth within narrower pore is more difficult.

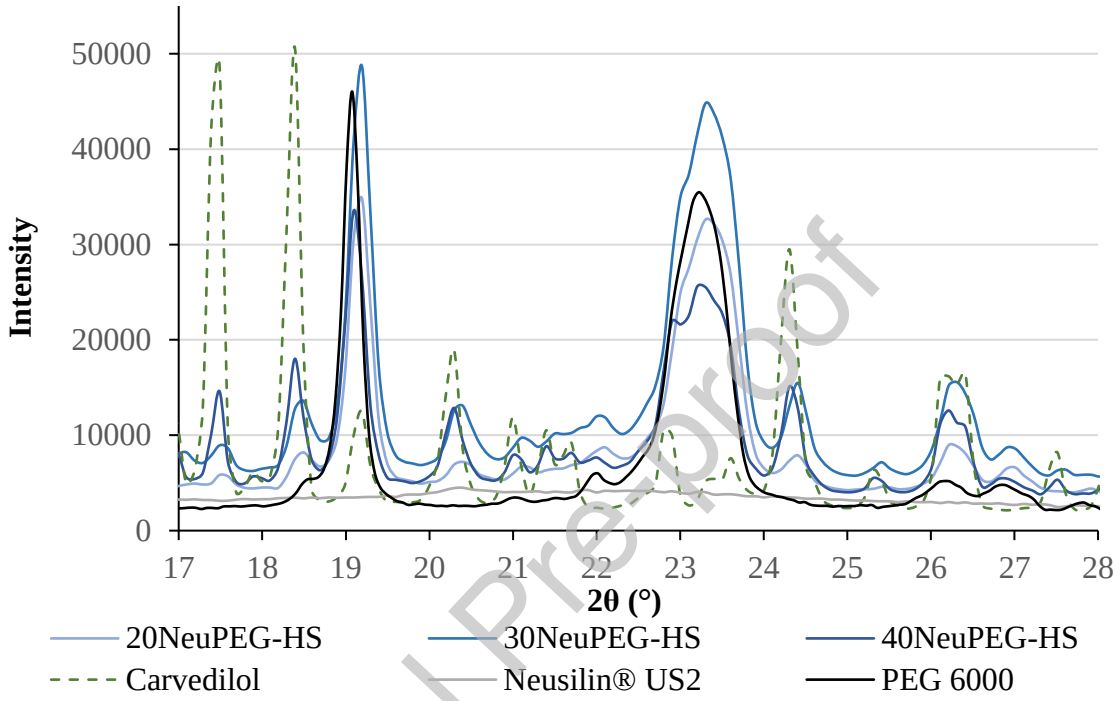

Figure 6. XRD diffractograms of pure crystalline carvedilol, Neusilin® US2, PEG 6000 and carvedilol solid dispersions prepared by HS melt granulation (20NeuPEG-HS, 30NeuPEG-HS and 40NeuPEG-HS).

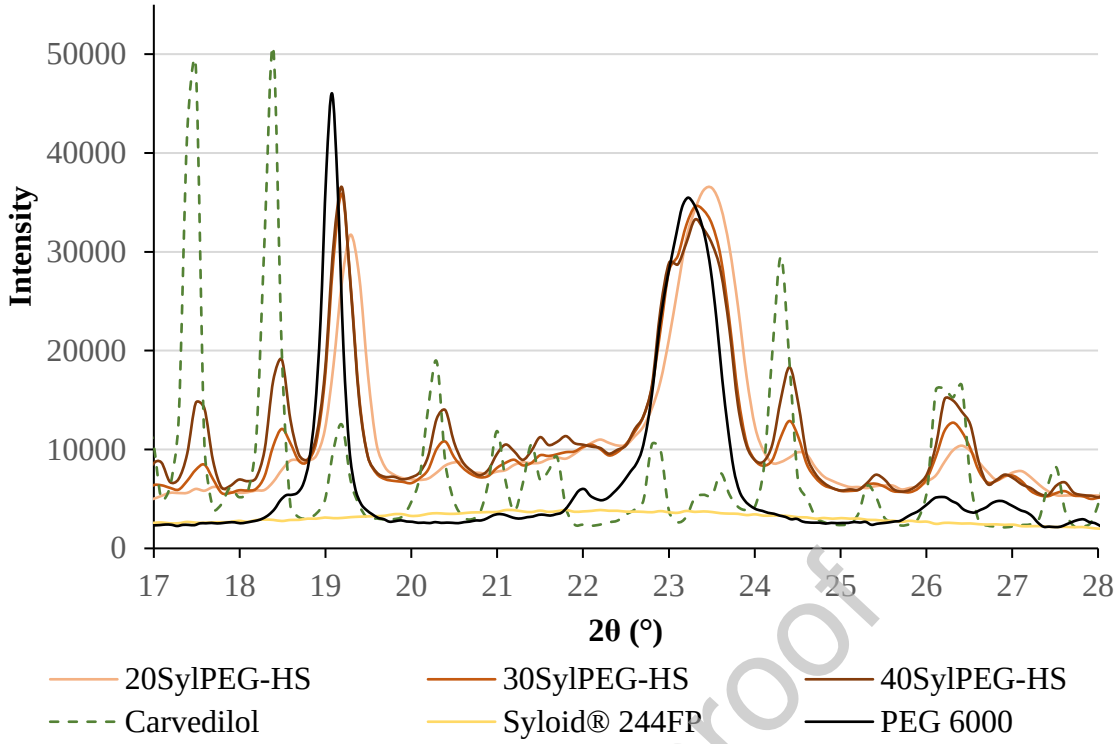

Figure 7. XRD diffractograms of pure crystalline carvedilol, Syloid® 224FP, PEG 6000 and carvedilol solid dispersion prepared by HS melt granulation (20SylPEG-HS, 30SylPEG-HS and 40SylPEG-HS.).

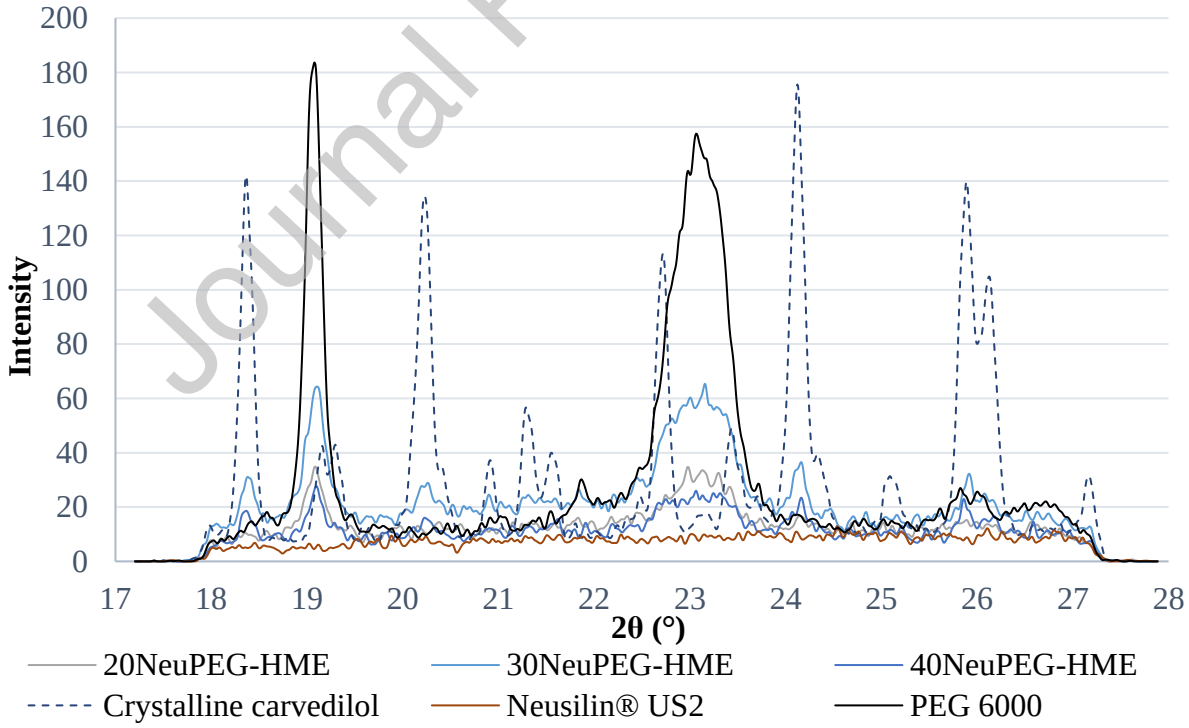

Figure 8. XRD diffractograms of pure crystalline carvedilol, PEG 6000, Neusilin® US2 and carvedilol solid dispersion prepared by HME (20NeuPEG-HME, 30NeuPEG-HME and 40NeuPEG-HME).

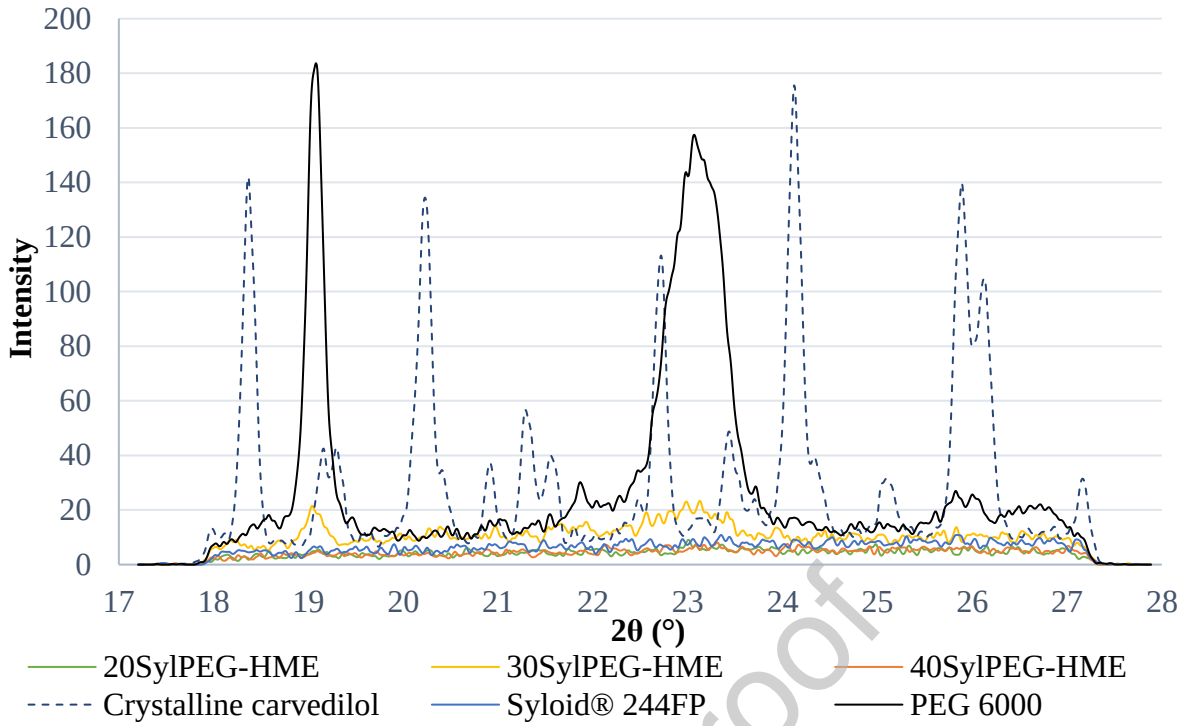

Figure 9. XRD diffractograms of pure crystalline carvedilol, PEG 6000, Syloid® 244FP and carvedilol solid dispersion prepared by HME (20SylPEG-HS, 30SylPEG-HME and 40SylPEG-HME).

Solid state properties of carvedilol in HME formulations containing Soluplus® was evaluated solely by XRD analysis due to its lower detection limit in comparison to DSC analysis. Accordingly, no diffraction peaks typical of crystalline carvedilol were visible on corresponding XRD curves (Figures S2 and S3), implying complete amorphization of carvedilol during the HME process.

Overall, the results of DSC and XRD analysis indicate that initial drug loading positively correlated with the amount of crystalline carvedilol residuals. Nevertheless, the absence of crystalline form was confirmed within most of formulations, due to addition of polymer matrix and mesoporous carrier, in that way preserving the advantage of improved dissolution linked to such state. HME stood out as better melt technology for preparing carvedilol ASD due to higher amount of the drug in amorphous state.

The stability study was conducted for melt-based granules that were stored under controlled accelerated conditions (40°C, 75% RH). Carvedilol content was assessed using validated HPLC method within the predetermined time points of 0, 4, 6 and 12 weeks. After 12 weeks of storage, the amount of carvedilol in melt-based granules decreased by 10 % in Syloid® 224FP based product and only 4 % in Neusilin® US2-based product (Figure S5). From stability point of view, ASDs of carvedilol were confirmed superior to be superior compared to lipid-based drug delivery system, where formation of amides was reported due to in situ reaction of the drug and fatty acids present in the lipid phase of formulation (Mandić et al. 2021).

3.2.3. The impact of melt technology on in vitro carvedilol release

As amorphous solid dispersions were designed to improve the dissolution of poorly-water soluble drugs in the gastro-intestine, carvedilol *in vitro* release profile was determined for all melt-based products in two media, diluted HCl solution with pH 1.2 (Figure 10) and phosphate buffer solution with pH 6.8 (Figure S4).

As seen on Figure 10, the total amount of carvedilol released from HME products wasn't influenced by carvedilol loading, as comparable *in vitro* release profiles were obtained for products containing 20, 30 and 40 % of carvedilol within all polymer-carrier combinations. While the results of the influence of mesoporous carrier on dissolution behavior were contradictory and we couldn't determine which of two melt technologies performed better, the type of polymer used for preparation of solid dispersions (i.e. PEG 6000 vs. Soluplus®) showed significant impact, with faster drug release obtained with PEG 6000 based products. Despite the complete amount of carvedilol in amorphous state (XRD results) in Soluplus®-based products, those formulations exhibited the slowest release, inferior even to crystalline carvedilol during the first two hours.

Drug release was also affected by applied melt granulation technology. While all three NeuPEG-HME formulations exhibited very rapid and complete drug release within the first 20 minutes, carvedilol release from their HS counterparts was somewhat slower. Focusing at 10-minute timepoint, 20NeuPEG-HME and 30NeuPEG-HME showed 88% and 101% of released drug, respectively, while 20NeuPEG-HS and 30NeuPEG-HS showed 81 and 80% of the released drug, respectively. In addition, formulation 40NeuPEG-HS stood out with much slower and incomplete release compared to its HME counterpart, which was most likely linked to residues of crystalline carvedilol left upon granulation, as confirmed by XRD analysis. Even though some crystalline remaining were also observed within the Syloid® 244FP counterpart

(40SylPEG-HS), such dissolution behavior wasn't expressed. Due to differences in granules size and distribution width (Table 3), such Syloid 244FP-based granules, with the lowest d_{10} value of 126 μm, exhibit the greatest specific surface area which is available to dissolution media.

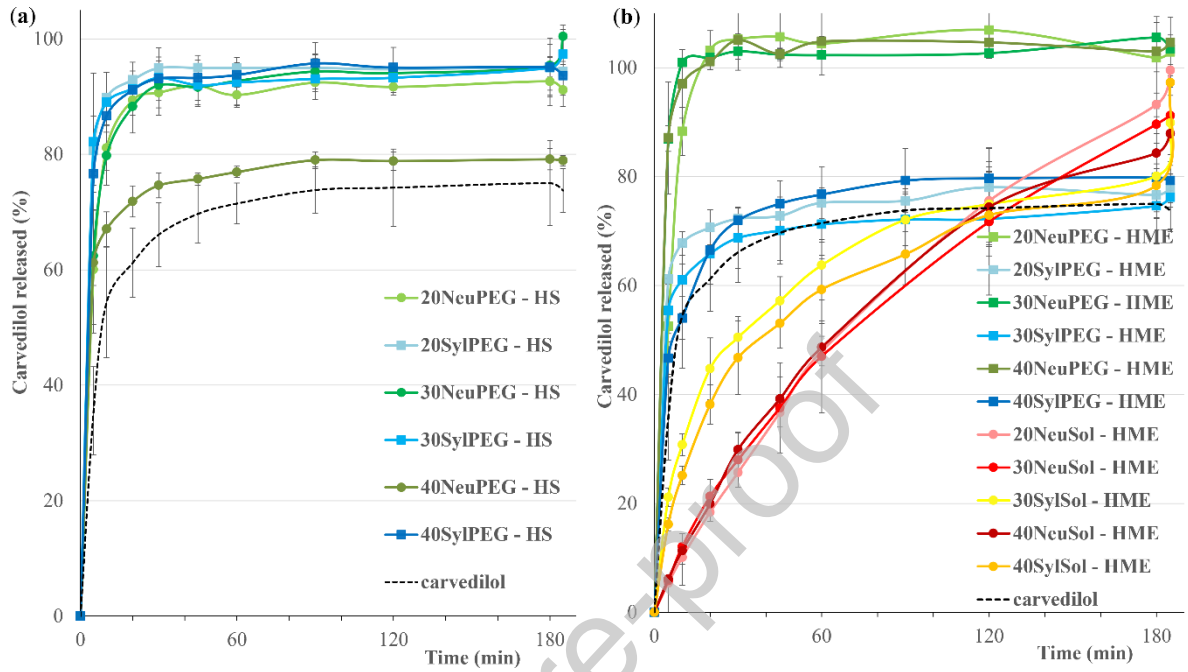

Figure 10. *In vitro* carvedilol dissolution profiles at pH 1.2 for all solid dispersions prepared either by (**a**) HS melt granulation or (**b**) HME.

For Syloid® 244FP-based formulations the opposite effect of preparation technology was observed, though. Namely, granules obtained by HS granulation exhibited better *in vitro* dissolution characteristics as compared to their HME counterparts (Figure 10). In keeping with the results of SEM analysis, less favorable dissolution properties were assumed for HME products with smaller particle surface area available for the contact with dissolution media. Due to more porous structure and smaller size of HS granules they have larger specific surface area as their HME counterparts, resulting in faster and more complete drug release in dissolution media with pH 1.2.

Moreover, among all tested products, only HS formulations 20SylPEG-HS and 20NeuPEG-HS were performing superior to crystalline carvedilol in pH 6.8 media, with Syloid® 244FP-based formulation resulting with most extensive drug release. In other HME products a slower drug release than pure carvedilol was observed (Figure S4). The slower dissolution rate of carvedilol was expected in the test medium with pH 6.8, due to the drugs' properties of weak base (amine group in the structure).

Considering the drug release characteristics, the choice of polymer is crucial for development of solid dispersions capable of overcoming poor drug solubility challenges by melt technology approach. Hydrophilic PEG 6000 was therefore identified as polymer of choice for preparing carvedilol solid dispersion. The production technology also influenced the drug release characteristics of obtained products, with HS melt granulation generally resulting in porous granules with better release properties, considering both dissolution media. Our results indicated that selection of mesoporous carrier should be adjusted to applied production technology.

4. Conclusion

The study compared two melt-based formulations loaded into mesoporous carriers, prepared by HS melt granulation and HME for improved dissolution of carvedilol, with the main focus on the impact of melt technology choice on products characteristics. During the process, carvedilol was dissolved/dispersed within the molten polymer (either PEG 6000 or Soluplus®), and the melt was loaded into the pores of either Neusilin® US2 or Syloid® 244FP. Due to differences in the processes, two techniques varied in polymer-to-carrier ratio. For HS melt granulation, the optimal ratio was found to be 3:1, while in case of HME, it was 1:1. Nevertheless, all processed formulations contained high amounts of carvedilol, with 20, 30 and 40 *w/w* % of drug load. DSC and XRD analysis confirmed the absence of crystalline drug form for majority of prepared ASDs. In this way the stabilizing effect of selected melting polymers and mesoporous carriers was confirmed, in addition to preserving the advantage of improved dissolution of amorphous carvedilol.

ASD of carvedilol prepared by HME found to be great alternative to HS granulation, considering larger amount of amorphous drug in the final product. However, the advantage of melt-based formulations, had been disproved by the results of *in vitro* dissolution testing in medium with pH 6.8, since only two formulations produced in HS granulator (20SylPEG-HS and 20NeuPEG-HS) exhibited faster release than pure crystalline carvedilol, and therefore being the only ones within which carvedilol dissolution improved in both dissolution media. Less favorable dissolution properties of HME extrudates were supported by the results of surface morphology assessment, since due to lower surface porosity, smaller particle surface area was available for the contact with dissolution media, in that way slowing down the drug release.

Overall, taking into consideration all the characterized properties of melt-based products, hydrophilic PEG 6000 stood out as a better alternative to Soluplus®. Apart from facilitated

processability in HS granulator, 20SylPEG-HS performed the best, exhibiting the shortest flow time of all HS granules (9.3 g/100 g), in addition to achieving complete carvedilol amorphization, that further reflected in superior dissolution properties of this formulation.

Author contributions: Conceptualization – M.K., A.Z.P. and I.G.I.; Investigation & Methodology – M.K., O.Z. and C.A.; Data curation & Formal analysis – M.K., I.G.I. A.P. and A.Z.P.; Visualization – M.K.; Supervision – A.Z.P., I.G.I. and A.P.; Writing – original draft, M.K.; and Writing – review & editing, I.G.I., A.Z.P., O.P., A.P., N.P., S.B., O.Z. and C.A.; A.Z.P. and I.G.I. equally contributed to the manuscript and share the corresponding authorship.

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Graphical Abstract