The effect of polymeric binder type and concentration on flow and dissolution properties of SMEDDS loaded mesoporous silica-based granules

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PII: S0928-0987(23)00212-9
DOI: https://doi.org/10.1016/j.ejps.2023.106582
Reference: PHASCI 106582

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 7 July 2023
Revised date: 7 September 2023
Accepted date: 11 September 2023

Please cite this article as: Mila Kovačević , Alenka Zvonar Pobirk , Ilija German Ilić , The effect of polymeric binder type and concentration on flow and dissolution properties of SMEDDS loaded mesoporous silica-based granules, *European Journal of Pharmaceutical Sciences* (2023), doi: https://doi.org/10.1016/j.ejps.2023.106582

Highlights

- Incorporation of higher molecular weight binders results in slower *in vitro* drug release from solid SMEDDS.
- High binder concentration is related to faster *in vitro* drug release from solid SMEDDS.
- Higher binder amount has favorable effect on flow properties, although flowability of all SMEDDS granules is good for further tableting.
- Both high-shear granulation and tableting have a (slight) negative effect on drug release rate.
- SMEDDS granules and tablets preserved self-microemulsifying properties.
- Povidone K30 is the best polymeric binder candidate for further research.

The effect of polymeric binder type and concentration on flow and dissolution properties of SMEDDS loaded mesoporous silica-based granules

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Abstract

Self-microemulsifying drug delivery systems (SMEDDS) are lipid-based formulations, designed to improve the solubility of poorly-water soluble drugs. Mesoporous silica is frequently used for SMEDDS solidification by various techniques. One of them is wet granulation, which enables achieving both high SMEDDS load and good flow properties. This study investigated the effect of six polymeric binders' addition to granulation dispersion (GD) (povidone K30, povidone K90, copovidone, Pharmacoat® 603, Pharmacoat® 615 and Methocel™ K100 Premium LV) on characteristics of produced SMEDDS granules, prepared by wet granulation. By incorporation of polymer in GD, it was possible to produce mesoporous silica-based free-flowing granules, with preserved self-microemulsifying properties, responsible for improved *in vitro* release of carvedilol. The incorporation of higher molecular weight binders resulted in slower *in vitro* release, while high binder concentration was related to faster drug release. The highest release rate was achieved with povidone K30 at 7.45 % binder concentration, as corresponding granules exhibited complete drug release already in 5 minutes. Granulation method (manual vs. high-shear) influenced the release rate of carvedilol as it was released slower from SMEDDS granules prepared using the granulator.

Finally, SMEDDS tablet formulation was optimized to achieve maximum granule content and adequate tablet hardness. Increased granule content found to negatively influence tablet hardness, as maximum granule content of 25 % was needed to obtain appropriate hardness. Such tablets exhibited short disintegration time, so this final prototype can be considered as orodispersible tablet.

Keywords: SMEDDS, high-shear granulation, mesoporous carrier, polymeric binder, SMEDDS tablets

Introduction

Good aqueous solubility is a key prerequisite for complete drug absorption upon oral administration. Unfortunately, pharmaceutical industry has been facing a drastic increase in the number of poorly water-soluble new drug entities, belonging to BSC classes II and IV. Such developments urged the formulation scientists to come up with various coping strategies such as chemical modifications, particle design changes and various drug delivery systems [1–4]. Self-microemulsifying drug delivery systems (SMEDDSs) have recently been intensively researched as a lipid-based formulations, that spontaneously form fine oil-in-water dispersion with nanometer-sized droplets in aqueous environment [5–7]. Due to their liquid consistency, SMEDDS are preferably transformed to solid state dosage forms, usually by filling them into soft capsules, which is also the only available dosage form of solid SMEDDS on the market, for example Sandimunne Neoral®, Norvir®, Fortovase®[8]. Considering such production of soft capsules is a relatively demanding and expensive multi-step process, other solid single-dose solid dosage forms (e.g. tablets) could improve the processability and stability as well as provide better patient compliance [9]. Particular challenge of SMEDDS solidification lies with ensuring an adequately high liquid load, which negatively affects the needed flow properties for the tableting [10,11]. Even when using solid carriers with high specific surface area, direct

ads[illegible]ct with poor flowability, inappropriate for further processing by tableting [12–14]. However, high-shear wet granulation proved to have beneficial effect, as good flow properties were maintained along with high liquid load [15].

In such wet granulation process, the granulation dispersion (GD) is based on aqueous SMEDDS dispersion, consisting of SMEDDS, water and a binder polymer. The choice of binder and its concentration plays an important role in achieving appropriate GD viscosity, required for the granulation process. Therefore, different binders can be used and it is expected that such variation of GD can affect the properties of produced granules [16–18]. Also, due to their physicochemical properties, some binder polymers can show a beneficial effect on precipitation inhibition, since upon dispersion of SMEDDS in water, formulations with high drug-loading may result in unwanted drug precipitation [19,20].

Therefore, the present study aimed to investigate the influence of the variation GD composition (through different binder types and concentrations) for SMEDDS solidifications on relevant technological and biopharmaceutical characteristics of the solid SMEDDS granules, with a particular focus on flow and dissolution properties. Carvedilol (BSC class II) was used as poorly water-soluble model drug, while six polymeric binders (povidone (PVP) K30 and K90, copovidone, as well as three hypromellose subtypes of different viscosities) were used for SMEDDS wet granulation using high-shear method along with mesoporous carrier Syloid 244® FP. Such systematic research was necessary to adding an important piece of knowledge towards improvement in SMEDDS industrial applicability. With that in mind, the most promising SMEDDS granules were compacted into SMEDDS tablets, optimizing the formulation, since low hardness and large mass of SMEDDS tablets proved to be a major drawbacks in previous research [11,13,15].

Materials and Methods

1. Materials

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

Liquid SMEDDS was composed of mixture of Capmul® MCM EP/NF (mono-diglyceride of medium chain fatty acids, Abitec Corporation, Columbus, Ohio, USA), refined castor oil (Ph. Eur. Grade, Caesar & Loretz GmbH, Hilden, Germany), Kollisolv® PEG E 400 (Sigma-Aldrich, St. Luis, MO, USA) and Kolliphor® RH 40 (polyoxyl 40 hydrogenated castor oil, Sigma-Aldrich, USA). Syloid® 244 FP (silica with average particle size 3.5 µm, Grace GmbH & Co. KG, Worms, Germany) was used as solid mesoporous carrier for liquid SMEDDS.

Different binder types and concentrations were used in GD: PVP K30 (BASF, Ludwigshafen, Germany), PVP K90 (BASF, Germany), copovidone VA64 (Kollidon® VA64, BASF, Germany), hypromellose Pharmacoat® 603 (Shin-Etsu Chemical Co. Ltd., Tokyo, Japan), hypromellose Pharmacoat® 615 (Shin-Etsu Chemical Co. Ltd., Japan) and hypromellose Methocel™ K100 Premium LV (DuPont, Wilmington, Delaware, USA).

For SMEDDS tablet production the following materials were used: Kollidon® VA64 as a dry binder, croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer, Philadelphia, PA, USA) as a disintegrant, microcrystalline cellulose (Avicel® PH 200, FMC Biopolymers, USA) as a filler, and magnesium stearate (Merch KGaA, Darmstadt, Germany) as a lubricant and antiadhesive agent.

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

2. Methods

2.1. Preparation of Carvedilol-Loaded Liquid SMEDDS

Carvedilol-loaded liquid SMEDDS was prepared according to our previously published research [10]. SMEDDS formulation consisted of 40 % w/w of Kolliphor® RH 40 as nonionic surfactant, 40 % w/w PEG 400 as cosolvent, 10 % w/w of castor oil and 10 % w/w of Capmul® MCM EP. Crystalline carvedilol was added to homogenous mixture of SMEDDS (100 mg/1 g of SMEDDS), then the mixture was heated to 50 °C and stirred until the drug completely dissolved (for approximately 3 h, with stirring speed of 60 rpm). The prepared carvedilol-loaded SMEDDS was transparent and yellowish liquid.

2.2. Granulation Dispersion Preparation

GD consisted of SMEDDS and water in the ratio of 70:30 with a variable addition of binding polymer in concentrations range of 0.00, 0.23, 0.45, 0.90, 1.85, 3.60, 5.10 and 7.45 % w/w. Six different polymers were used as binders, three hypromellose types (Pharmacoat® 603, Pharmacoat® 615 and Methocel™ K100) with varying viscosities and three vinylpyrrolidone-(co)polymers (PVP K30, PVP K90 and copovidone). GD was prepared in the paten, by adding the appropriate amount of carvedilol-loaded liquid SMEDDS and water to the binder, mixing the components until homogeneous.

2.3. Determination of Granulation Dispersion Rheological Properties

The viscosity of GD was assessed in accordance with Section 2.2.3. of our previous research study [15],using a rotational rheometer (Physica MCR 301, Anton Paar GmbH, Graz, Austria) with cylindrical measurement system (CC27/T200/SS), at 25 °C temperature and shear rate from 1 to 100 s^{-1}. The viscosity between the samples was compared at shear rate 10 s^{-1}.

2.4. Preparation of SMEDDS Granules by Wet Granulation

SMEDDS granules were prepared according to descriptions of manual and high-shear (HS) wet granulation method described by our previous work [15], with some modifications as described below. As a reference for successful SMEDDS granulation, particle size distribution measurement (Mastersizer 3000, Malvern Panalytical, Malvern, United Kingdom) was used. Initially, all granules were prepared manually in order to optimize binder content in the granules. Then, the process was scaled-up to HS granulator (4M8-Trix; ProCept, Zele, Belgium) where the following process parameters were used: impeller speed 400 rpm, chopper speed 2,000 rpm, the GD flow rate of 4.3 g/min and gas flow rate of 0 L/min (no gas flow), as GD was added drop-by-drop onto the carrier, due to clogging of the nozzle.

Firstly, solid mesoporous carrier Syloid® 244FP was weighted into paten used as a granulation bowl, and GD was added drop-by-drop while thoroughly mixing with pestle. In the case of manual granulation, the endpoint was determined visually (by observing the size of formed particles and the touch by fingertips), while in the case of HS endpoint was based on the amount of GD previously added in manual granulation. Upon reaching the endpoint, the wet mass was kneaded for additional 2 minutes, to evenly distribute the liquid among particles. Afterwards, the wet mass was sifted through 1000 µm mesh sieve and dried on a laboratory tray dryer (SP45; Kambič, Semič, Slovenia) at 70 °C, until a moisture content 1.5–3.5 % was achieved (approximately 20–25 min for manual or 50-55 minutes for HS granulation).

2.5. Loss on Drying

SMEDDS granules loss on drying was measured in accordance with Section 2.2.6. of our previous research study [15], using thermogravimetric analytical balance (BÜCHI Moisture Analyzer B-302), with measurement conditions of 85 °C for 15 min.

The size and size distribution of the produced SMEDDS granules were measured using the Mastersizer 3000, according to the method described in Section 2.2.7. of our previous research study [15]. Measurement conditions were 1.5 bar of air pressure with 20% feed rate.

2.7. Evaluation of SMEDDS Granules Flow Properties and Compressibility

SMEDDS granule's 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) [21]. For the flow time measurement, about 15 g of the sample was gently transferred 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. For the angle of repose, a ruler was used to measure the height and the radius on the formed granule heap from which the angle of repose was then calculated. Measurements of flow time and angle of repose were performed about 10 times and expressed as average values, along with corresponding standard deviations. For the evaluation of the granules' Carr index (CI) properties, the same amount of granules was accurately weighted and gently transferred into a 100 mL plastic cylinder. The volume of the sample was measured as the bulk volume. Further, 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. All measurements were performed in triplicate and expressed as average values, along with corresponding standard deviations. Bulk and tapped volumes were used for the calculation of bulk and tapped densities, and CI as an indicator of the produced granules flow.

2.8. Determination of Carvedilol Content

The carvedilol content in SMEDDS granules and tablets was determined using UV spectroscopy (UV/VIS spectrophotometer Varian Cary® 50; Agilent Technologies Inc, Santa Clara (CA), USA) according to the procedure already described in the literature [10,15]. Precisely weighed samples with theoretical content of 12.5 mg carvedilol were quantitatively transferred into a 500 mL flask, with 70 mL of methanol, used as a cosolvent, and filled with diluted HCl solution with pH = 1.2 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 against carvedilol calibration curve, which was further calculated to express the carvedilol content (mg) per g of solid granules.

2.9. Granules Surface Morphology

The surface morphology of SMEDDS granules was evaluated using a Supra 35VP scanning electron microscope (SEM; Carl Zeiss, Oberkochen, Germany) at 1 kV accelerating voltage using SE2 detector under 250 × magnification. The prepared samples consisted of small amount of granules, carefully sprinkled onto a double-adhesive carbon tape, that was previously glued to a metal carrier.

2.10. Assessment of Carvedilol Physical State

Differential scanning calorimetry (DSC) analysis was used for evaluation of carvedilol physical state in produced SMEDDS granules, in addition to crystalline carvedilol, Syloid® 244FP, polymeric binders and their ternary physical mixtures in ratio 1:1:1). Using a differential scanning calorimeter (DSC1 STARe System, Mettler Toledo Columbus, Ohio, USA), the samples (5–7 mg) were heated in an aluminum pan with

per[illegible]e, an empty aluminum pan was used. Finally, the output data were evaluated by STARe V9.30 software program (Mettler Toledo).

2.11. Compaction into SMEDDS Tablets

Tablets were prepared from HS granules using a single-punch tablet press (Kilian SP 300; IMA, Cologne, Germany). The tableting mixture consisted of 25 %, 30 %, or 38 % w/w of SMEDDS granules, 5 % w/w of copovidone (Kollidon® VA64), 5 % w/w of sodium croscarmellose (Ac-Di-Sol®), 1 % w/w of magnesium stearate and the rest of microcrystalline cellulose (Avicel® PH-200), used as filler. SMEDDS tablets were prepared with compression forces of 9-17 kN, using a 12 mm flat face round punch, with each tablet containing approximately 12.5 mg of carvedilol.

2.12. Evaluation of SMEDDS Tablets

All SMEDDS tablets were evaluated for hardness (VanKel 200 Tablet Hardness Tester, VanKel Technology Group, Cary (NC), USA), disintegration time (Erweka ZT4; Erweka GmbG, Langen, Germany) and friability (Erweka TAR 10), according to the procedure and criteria in corresponding Ph. Eur. 11th monographs (2.9.1. Disintegration of tablets and capsules; 2.9.7. Friability of uncoated tablets; 2.9.8. Resistance to crushing of tablets) [21].

2.13. Evaluation of Self-Microemulsifying Properties

The assessment of SMEDDS granules and tablets self-microemulsifying properties was conducted following the method described in Section 2.2.14. of our previous research study [15], at 25 °C using Zetasizer Ultra. Three different media were used: purified water, diluted HCl solution with pH 1.2 and phosphate buffer with pH 6.8.

2.14. *In Vitro* Carvedilol Release Profile

In vitro dissolution testing of SMEDDS granules and tables was conducted using Ph. Eur. apparatus 2 dissolution tester with rotating paddles (VanKel VK 7010 Tablet Dissolution Tester, VanKel Technology Group, Cary (NC), USA) according to Ph. Eur. 11th monograph 2.9.3 Dissolution test for solid dosage forms [16].

All samples (containing 12.5 mg of carvedilol) were tested in triplicate, and the result presented as an average value with corresponding standard deviation. Pure crystalline carvedilol and liquid SMEDDS were used as references. The dissolution vessels were filled with selected medium (diluted HCl solution with pH = 1.2 or phosphate buffer with pH = 6.8) and heated up to 37 ± 0.5 °C with paddles rotating at 50 rpm. Upon reaching the required medium temperature, samples were quantitatively transferred into the vessels. 10 mL of sample was withdrawn and filtered through a 0.45 µm pore RC membrane filter at predetermined time intervals (5, 10, 20, 30, 45, 60, and 120 min, and additional sampling point time point at 240 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 15 min with paddles rotating with maximal speed of 250 rpm (so-called *infinity spin)*, to ensure the complete drug release.

Samples were further analyzed using UV spectroscopy, and the absorbance was measured at 284 nm wavelength. The 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.

Results and Discussion

Six different polymeric binders, belonging to two large groups of polymers – hypromellose and vinylpyrrolidone-(co)polymers, were chosen for SMEDDS solidification by wet granulation, aiming to identify their influence on products' flow and dissolution properties. Binder concentration in SMEDDS granules was varied from 0.00 (no binder added) to 7.45 % w/w, where this maximum value was determined as optimal amount in our previous study [15]. The characteristics of the produced SMEDDS granules were compared with regard to the used polymeric binder type and concentration, as well as the granulation method used (manual or HS granulation).

1. Wet Granulation with SMEDDS-based Granulation Dispersion

All granulations were conducted by adding appropriate amount of GD, in order to granulate all Syloid® 244FP particles, which was used as solid carrier. The initial part of the research was focused on determination of minimal binder amount, needed to obtain good flowability of SMEDDS granules.

1.1. The influence of polymer type and concentration on SMEDDS granule flow properties

According to the results of SMEDDS granules flow properties presented in Table S1, the angle of the repose wasn't influenced by either polymer concentration or type influenced, as all granules exhibited excellent flow properties according to Ph. Eur. 11th criteria. Regardless of the angle of repose results, flow time and Carr index were more influenced by GD variation. Considering the flow time, the influence of polymer concentration was pronounced at concentrations of 1.85 % of the binder in GD and above, as flowability improved in case of SMEDDS granules with PVP K30, PVP K90 and Pharmacoat® 615 in comparison to the granules with a 0.90 % of the polymer (Tables 1 and 2). Analogue trend was not observed in case of other three binders, as those SMEDDS granules had comparable flow time across all binder concentrations.

Tab[illegible]al granulation: median particle size (d_{50}) and flow properties (flow time and CI) at different concentration of binder in GD from 0.00 to 7.45 % w/w.

	PVP K30			PVP K90			copovidone		
% binder w/w	**d_{50} (µm)**	**flow properties**		**d_{50} (µm)**	**flow properties**		**d_{50} (µm)**	**flow properties**	
		Flow time (s)	**CI (%)**		**Flow time (s)**	**CI (%)**		**Flow time (s)**	**CI (%)**
0.00	632	7.6 ± 0.2	17.8 ± 0.2	632	7.6 ± 0.2	17.8 ± 0.2	632	7.6 ± 0.2	17.8 ± 0.2
0.45	654	7.0 ± 0.3	18.2 ± 0.3	660	7.2 ± 0.3	18.6 ± 0.4	665	7.3 ± 0.3	16.3 ± 1.5
0.90	671	8.2 ± 0.2	18.5 ± 1.0	668	8.5 ± 0.3	22.2 ± 0.9	700	6.8 ± 0.3	16.7 ± 1.1
1.85	610	5.3 ± 0.1	21.4 ± 0.6	679	6.6 ± 0.1	22.0 ± 0.4	678	6.7 ± 0.2	16.7 ± 1.6
3.60	617	5.1 ± 0.4	21.9 ± 1.5	705	7.0 ± 0.2	15.8 ± 1.3	700	7.6 ± 0.3	16.8 ± 1.9
5.10	601	5.7 ± 1.6	21.0 ± 1.2	649	5.0 ± 0.4	21.5 ± 1.0	738	7.4 ± 0.1	17.5 ± 0.9
7.45	507	5.2 ± 0.3	17.4 ± 1.5	610	5.6 ± 0.1	23.9 ± 1.4	705	7.2 ± 0.1	23.6 ± 1.3
Average values*	610	6.1 ± 1.3	19.7 ± 1.9	662	6.7 ± 1.2	20.7 ± 2.9	698	7.2 ± 0.4	17.9 ± 2.8
*Average values were calculated for all binder-based SMEDDS granules, excluding 0.00 % binder.									

Table 2. Results of the characterization of hypromellose-based SMEDDS granules obtained by manual granulation: median particle size (d_{50}) and flow properties (flow time and CI) at different concentration of binder in GD from 0.00 to 7.45 % w/w.

	Pharmacoat® 603			Pharmacoat® 615			Methocel™ K100		
% binder w/w	**d_{50} (µm)**	**flow properties**		**d_{50} (µm)**	**flow properties**		**d_{50} (µm)**	**flow properties**	
		Flow time (s)	**CI (%)**		**Flow time (s)**	**CI (%)**		**Flow time (s)**	**CI (%)**
0.00	632	7.6 ± 0.2	17.8 ± 0.2	632	7.6 ± 0.2	17.8 ± 0.2	632	7.6 ± 0.2	17.8 ± 0.2
0.45	434	6.6 ± 0.2	10.0 ± 0.4	418	7.6 ± 0.4	16.4 ± 0.3	371	5.2 ± 0.3	15.9 ± 0.9
0.90	523	6.5 ± 0.9	10.6 ± 0.9	493	7.5 ± 0.5	12.0 ± 0.6	513	5.5 ± 0.5	16.8 ± 0.8
1.85	542	6.9 ± 0.4	12.9 ± 0.3	392	4.5 ± 0.4	12.7 ± 1.7	363	5.5 ± 0.3	12.8 ± 0.4
3.60	429	5.6 ± 0.3	20.1 ± 0.2	509	5.3 ± 0.6	14.1 ± 1.0	347	5.5 ± 0.4	14.4 ± 1.1
5.10	462	5.1 ± 0.6	15.2 ± 1.7	526	5.9 ± 0.5	16.0 ± 0.4	434	4.9 ± 0.3	17.0 ± 0.5
7.45	560	5.1 ± 0.6	14.4 ± 1.3	548	5.5 ± 0.3	17.0 ± 0.4	288	4.9 ± 0.3	19.6 ± 0.9
Avrage values*	492	6.0 ± 0.8	13.9 ± 3.7	481	6.1 ± 1.2	14.7 ± 2.1	386	5.3 ± 0.3	16.1 ± 2.3
*Average values were calculated for all binder-based SMEDDS granules, excluding 0.00 % binder.									

Altogether, Methocel™ K100-based granules exhibited the shortest average flow time of 5.3 s, which was also the best result of all hypromellose polymers. A possible explanation could be that Methocel™-based granules were less greasy to the touch in comparison to Pharmacoat®s, which was observed during manual granulation process. The production of such SMEDDS granules could also explain the positive correlation between the efficiency of granulation process and binder concentration. At lower concentrations of binder, some larger aggregates were formed which stuck to the mesh while pushing the wet mass through the sieve. Therefore, from perspective of higher yield (Table S2), the most favorable SMEDDS granules were made with a higher binder concentration.

Interestingly, in case of hypromellose-based polymers, the improvement in flow properties with increasing binder concentrations was noticed, as granules with higher binder concentrations had slightly shorter flow

tim[illegible]d therefore would have better flow properties, as somewhat expected and previously reported [16].
The concentration dependent trend previously shown, couldn't' be confirmed by CI values results. Despite this, CI values turned out to be a good descriptor to distinguish between the two polymeric binder types. Namely, PVP-based granules in average exhibited fair flowability (according to Ph. Eur. 11th [21]; Table 1). On the other hand, the flow properties of SMEDDS granules with Pharmacoat®s were better (average values of 13.9 and 14.7 %) and classified as good (Table 2). The influence of binder type on the average SMEDDS granule size was also clear, as all povidone-based granules showed median diameter (d_{50}) of 600–800 µm (Table 1), while hypromellose-based granules were smaller (d_{50} values of 300–600 µm; Table 2).
Considering these results, hypromellose would definitely be more favorable for use in wet granulation in terms of better flow properties for further processing. Overall, the addition of the binder exhibited favorable effect on flow properties, and the addition of 1.85 % polymer in GD was determined as an optimal binder amount. Although we were aiming to find substantial differences between SMEDDS granules flow properties, it turned out that they all showed relatively good flow properties and based on our experience with tableting we estimated that all were suitable for production of SMEDDS tablets, carried out later in the study.

1.2. The influence of polymer concentration on SMEDDS granules dissolution rate

Since SMEDDS formulations were designed to improve the solubility of poorly-water soluble drugs in the gastro-intestine, the drug release rate and the amount of the drug released were very important indicators of suitability of this delivery system. Hence, in this part of the research, carvedilol *in vitro* release profile was determined for SMEDDS granules in two media, phosphate buffer pH = 6.8 (Figures 1 and 2) as more discriminative medium and diluted HCl solution with pH = 1.2 (Figure S1) as less discriminative medium. To better distinguish between the influences of low and high binder concentrations, granules with 1.85 and 7.45 % were chosen for *in vitro* dissolution testing, namely: SMEDDS granules with 1.85 % PVP K30 (G_m PVP_{K30} L), PVP K90 (G_m PVP_{K90} L), copovidone (G_m copovidone L), Pharmacoat® 603 (G_m PC_{603} L), Pharmacoat® 615 (G_m PC_{615} L), Methocel™ K100 (G_m Methocel™ L) as well as SMEDDS granules with 7.45 % PVP K30 (G_m PVP_{K30} H), PVP K90 (G_m PVP_{K90} H), copovidone (G_m copovidone H), Pharmacoat® 603 (G_m PC_{603} H), Pharmacoat® 615 (G_m PC_{615} H) and Methocel™ K100 (G_m Methocel™ H) and SMEDDS granules prepared without binder in GD (G_m zero).
In general, carvedilol release was faster at a lower pH medium, as a result of its higher solubility in acidic medium due to the presence of secondary amine [22]. In any case, in the final point of dissolution testing, all binder-based SMEDDS granules exhibited above ~91 % release in both media. Moreover, from G_m PVP_{K30} H, ~96 % of carvedilol was released from medium with pH 1.2 (Figure S1), while ~82 % at medium with pH 6.8 (Figure 2) within the first 5 minutes. Therefore, not only did the total amount of the drug released improve, but also the dissolution rate, especially in comparison to crystalline carvedilol. The release of pure crystalline carvedilol in medium with pH 6.8 was very slow, as only 46 % of the drug was released after 4 hours, which was why this pH was considered as more discriminative.
Drug release was found to be dependent on polymer addition, as less carvedilol was released from binderless granules. Furthermore, the beneficial effect of increasing binder concentration was clearly visible in Figures 1 and 2. For example, during the first 10 minutes, only ~58% of carvedilol was released from G_m Methocel™ L, compared to ~81 % from granules with higher binder concentrations (G_m Methocel™ H). Likewise, both Pharmacoat®s at high polymer concentration exhibited faster dissolution rate, as 9 and 12 % more of

car[illegible]on granules. The same trend was observed with PVP-based granules. Thus, in all cases SMEDDS granules with higher polymer amounts demonstrated faster carvedilol release, compared to the ones with lower polymer amount. This can be explained through improved wettability due to addition of hydrophilic binder and possibly through faster disintegration of granules [23].

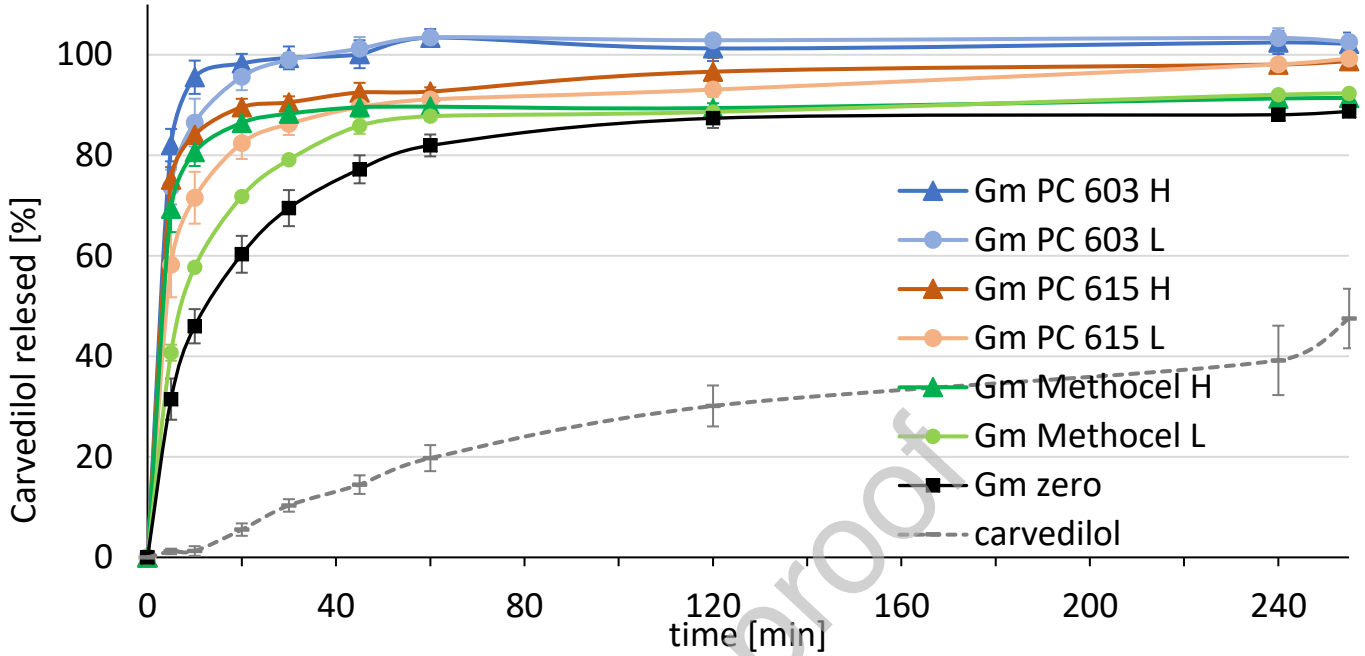

Figure 1. The influence of low (L; 1.85 % w/w) and high (H; 7.45 % w/w) polymer concentration in GD on *in vitro* carvedilol dissolution profile (medium with pH 6.8) of hypromellose-based SMEDDS granules.

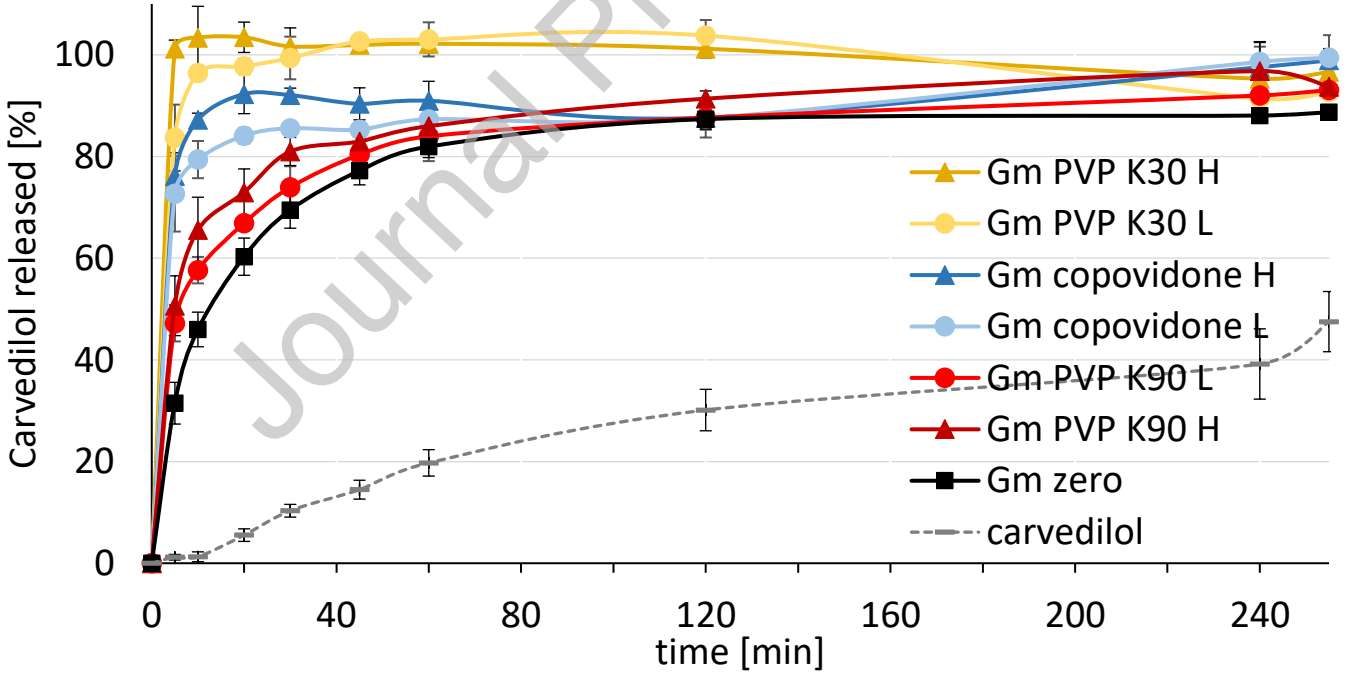

Figure 2. The influence of low (L; 1.85 % w/w) and high (H; 7.45 % w/w) polymer concentration in GD on *in vitro* carvedilol dissolution profile (medium with pH 6.8) of vinylpyrrolidone-(co)polymer-based SMEDDS granules.

The results of this study correlate the molecular weight of the polymer to the dissolution properties of SMEDDS granules and the effect of binder type on these properties are shown in Figures S2 and S3. For PVP-based binders the carvedilol release after 5 minutes was: 84 % from G_m PVP_{K30} L, which was 11 % more than from G_m copovidone L and 17 % more than from G_m PVP_{K90}. Of all binding polymers, PVP K30-based SMEDDS granules proved to have the best dissolution properties, as carvedilol was released the fastest. Copovidone also showed a beneficial effect, although to a lesser extent, contrary to the PVP K90 that slowed down the release in comparison to SMEDDS granules without a binder, at pH of 6.8. Explanation for that could be in the higher molecular weight of the binder and higher degree of polymerization, which slowed down the diffusion of water into the granules and particle's disintegration [24]. Thus, higher molecular weight of binder showed a negative influence on release profile; this proved to be true in the case of lower as well as higher binder concentrations (Figures S2 and S3, respectively).

The same trend could be observed when hypromellose was used as binder. Looking at release profiles from low molecular weight Pharmacoat® 603 SMEDDS granules, 74 % of carvedilol was released in 5 minutes, in comparison to 58 % for medium molecular weight Pharmacoat® 615 and 41 % for granules with high molecular weight Methocel™ K100. Besides influencing the release rate, the polymer type affected the drug release extent as well, since low molecular weight binders reached more than 90 % release sooner (for example, 10 min vs. 2 h, in case of Pharmacoat® subtypes). Again, a reasonable explanation could be in higher molecular weight, and therefore higher viscosity of Pharmacoat® 615, which was probably forming a thicker gel layer around the granules during the dissolution, in that way slowing down the drug release [26,27].

Overall, taking into consideration all the granule's characteristics, we could conclude that SMEDDS granules with higher binder concentration exhibited better flowability and faster carvedilol release.

1.4. The influence of granulation method on SMEDDS granules properties and surface morphology

Before scaling up from manual to automatic HS granulation, it was necessary to choose a suitable formulation, particularly regarding the viscosity of GD as this was considered critical for unobstructed addition to the granulation vessel through the nozzle. Therefore, the viscosity of GDs was measured for each polymer at low and high concentration (1.85 % and 7.45 % w/w) and the results are presented in Figure S4. and Table S3. As expected, the binder concentration was found to positively corelate with viscosity of GD, as it was increasing at higher binder share.

High molecular weight polymers, PVP K90 and Methocel™ K100, had the highest viscosity of 1.58 and 1.72 Pa·s at shear rate of 10 s^{-1} (respectively), indicating possible clogging issues while pumping the liquid to the granulation vessel. In addition to poor loading into carriers' pores reported by Vranikova B. et al. [27], highly viscous liquids tend to form less spherical particles that could impair the flow properties [26]. For these reasons, as well as poorest dissolution properties, PVP K90 and Methocel™ K100 was omitted from further studies. Due to these reasons, we decided to scale up to HS granulator only granules with PVP K30 and both Pharmacoat® subtypes, at 1.85 % and 7.45 % binder.

In the following set of experiments, a laboratory HS granulator was used for preparation of SMEDDS granules with low and high binder concentration in GD, namely: SMEDDS granules with 1.85 % PVP K30 (G_{hs} PVP_{K30} L), 1.85 % Pharmacoat® 603 (G_{hs} PC_{603} L), 1.85 % Pharmacoat® 615 (G_{hs} PC_{615} L), 7.45 % PVP K30 (G_{hs} PVP_{K30} H), 7.45 % Pharmacoat® 603 (G_{hs} PC_{603} H) and 7.45 % Pharmacoat® 615 (G_{hs} PC_{615} H), as well as binderless SMEDDS granules (G_{hs} zero). Produced granules were evaluated in the same way as their manually produced counterparts, to observe the influence of method preparation on granule flow and dissolution properties.

The [illegible] on average, in comparison to the manually prepared granules, apart from binderless SMEDDS granules, that exhibited slight improvement in flow time (7.6 vs 6.3 s/100 g; Table S4). In line with this, HS granulation showed negative impact also on CI, with exception of G_m PVP_{K30} H, in which case CI was slightly improved.

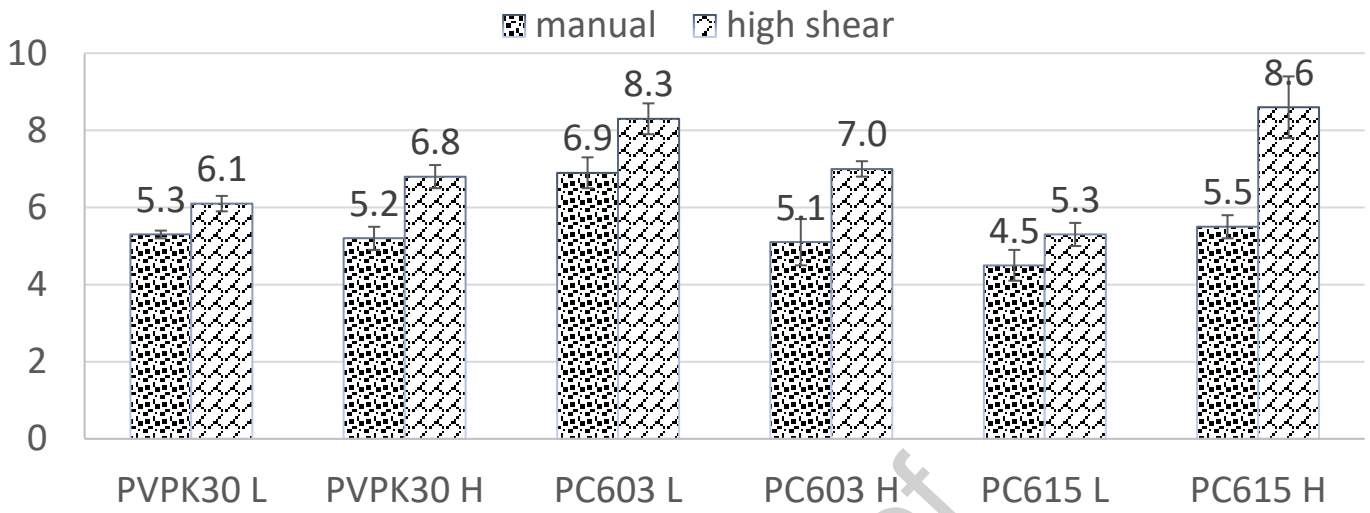

Figure 3. The comparison of flow time (s) between SMEDDS granules produced manually and using HS granulator.

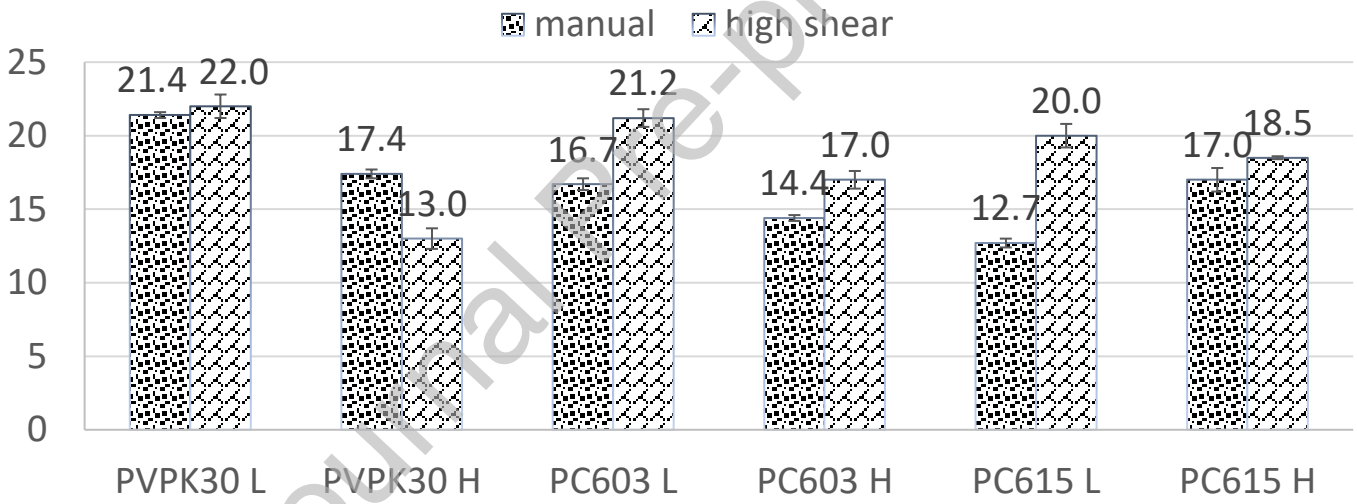

Figure 4. The comparison of CI (%) values between SMEDDS granules produced manually and using HS granulator.

In addition to flow properties, surface morphology of SMEDDS granules was assessed by SEM analysis to observe the influence of preparation method on the particles shape, surface, and lipid-filled pores. Figure 5 shows SEM images of G_m PVP_{K30} H vs. G_{hs} PVP_{K30} H, while SEM images of other SMEDDS granules' counterparts (G_m zero vs G_{hs} zero, G_m PVP_{K30} L vs. G_{hs} PVP_{K30} L, G_m PC_{603} L vs. G_{hs} PC_{603} L, G_m PC_{603} H vs. G_{hs} PC_{603} H, G_m PC_{615} L vs. G_{hs} PC_{615} L, and G_m $PC_{615\,H}$ vs. G_{hs} PC_{615} H) are presented in Figure S5.

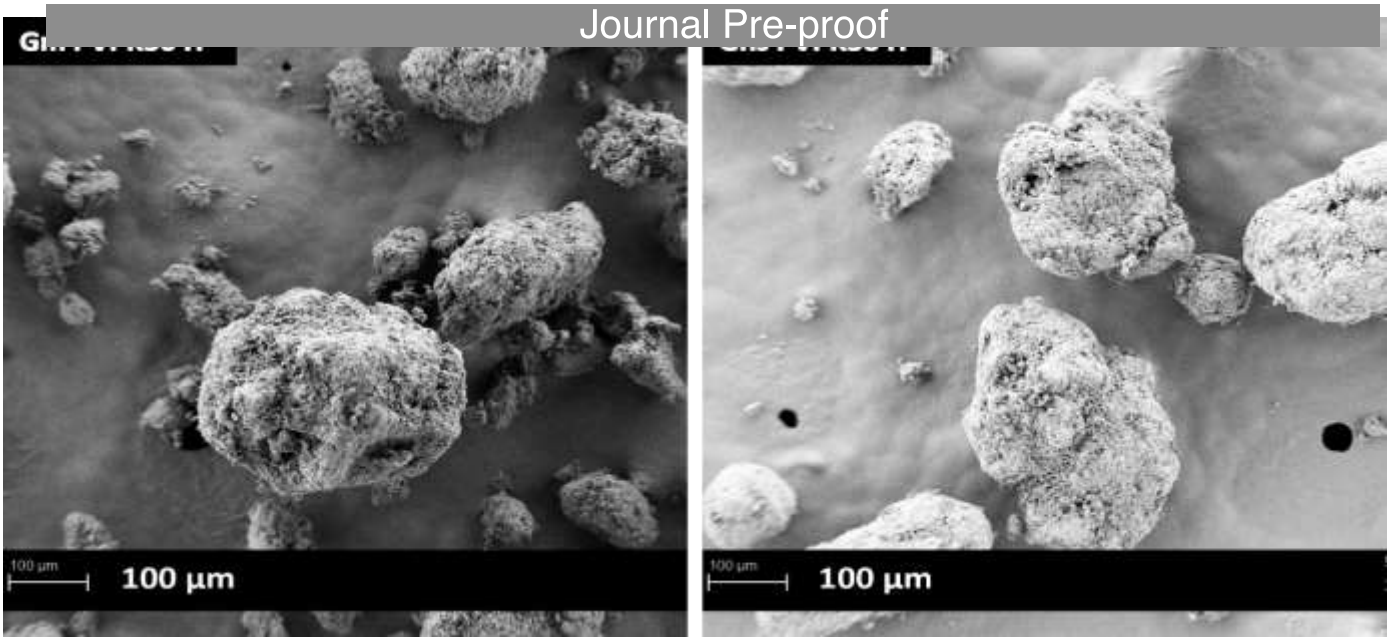

Figure 5. SEM images of G_m PVP_{K30} H (manual granulation) and G_{hs} PVP_{K30} H (HS granulation), under magnification of 250 ×.

In general, SMEDDS granules prepared by HS granulation looked smoother and more spherical in shape, which was in accordance with the literature data [27,28]. A noticeable amount of crushed material can be seen on SEM images of manually produced counterparts, indicating that particles had been partly crushed with the pestle during granulation process. We can assume these pieces subsequently glued to the surface, giving a slightly rougher appearance, contrary to the smoother surface of granules prepared using HS, where this effect can also take place, but seems it was not so pronounced. In some cases (e.g. samples G_{hs} zero and G_{hs} PC_{603} H) also granules produced by HS granulator showed such rougher surface morphology.

In addition to the way of mixing, the difference in SMEDDS granules' surface morphology could also be explained by the difference GD addition. In the case of manual granulation, GD was added onto the mesoporous carrier periodically, opposite to continuous dripping of GD during HS granulation. The former method addition was considered less favorable, as it affected the initial nuclei size and further granule growth, leading to formation of more irregular granules' shape and size [30]. Such occurrence can be seen on SEM image of G_m PC_{603} L with a lot of fragmented or even ungranulated particles with sizes below 100 µm.

Concerning *in vitro* dissolution properties, PVP K30 again proved to be the optimal binding polymer, as G_{hs} PVP_{K30} H exhibited the fastest release profile with ~72 % of carvedilol released in first 5 minutes (Figure 7). Still, the difference in the production method was noticeable as the release was faster from all manually prepared SMEDDS granules. The same phenomenon was also observed with both Pharmacoat® binders, as well as reported within our previous research study. Proposed explanation was that, due to the high shear forces in the granulator, the liquid SMEDDS was pushed deeper into the carriers' pores, slowing down release [15].

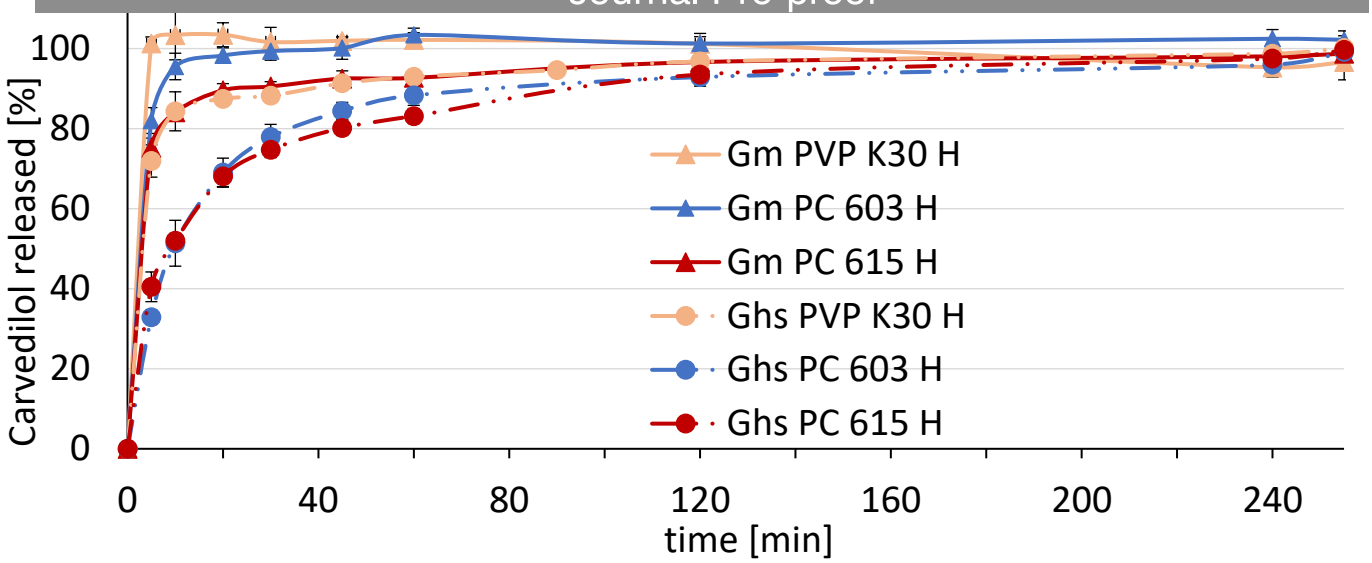

Figure 6. Comparison of *in vitro* carvedilol dissolution profiles (medium with pH 6.8) of SMEDDS granules prepared manually (G_m) vs. HS granulator (G_{hs}), using 7.45 % of different binders in GD.

Likewise, the comparison of release profiles in case of 1.85 % of the polymer in GD followed the same trend: manually produced granules showed a faster dissolution rate, with same binder order (Figure S6).
Contrary to this, the extent of released drug, wasn't influenced by preparation method, as the drug was completely released until the end of testing period in case of SMEDDS granules with high binder concentration (Figure 6), while for granules with low polymer concentration, this value was still > 90 % (Figure S6).

1.5. Carvedilol Physical State in SMEDDS Granules

The DSC analysis was conducted to assure that no crystalline carvedilol precipitated from SMEDDS during the granulation process. As shown on DSC thermograms (Figure 7), crystalline carvedilol had a pronounced endothermic peak with onset at 115.43 °C corresponding with melting temperature of carvedilol.
As seen in Figure 5, no carvedilol melting peaks were detected, implying the absence of crystalline carvedilol and drug precipitation during the granulation. Most likely the presence of binding polymers had beneficial effect on precipitation inhibition since both povidone and hypromellose are known to be effective precipitation inhibitors in supersaturated formulations and used exactly for that purpose [19,31,32].
In some SMEDDS granules (e.g. G_{hs} PVP_{K30} L), a wide peak can be seen in the range up to 100 °C. This was most likely caused by evaporation of water from the sample, as hydrophilic polymers can typically contain higher amounts of loosely bound moisture due to their high hygroscopicity. Additionally, DSC thermograms of pure components and ternary physical mixtures in ratio 1:1:1 (data not shown) were measured. The results showed no issues with compatibility of components, namely, no unexpected results (e.g. missing peaks) or changes in crystalline carvedilol peak in ternary physical mixtures were observed.

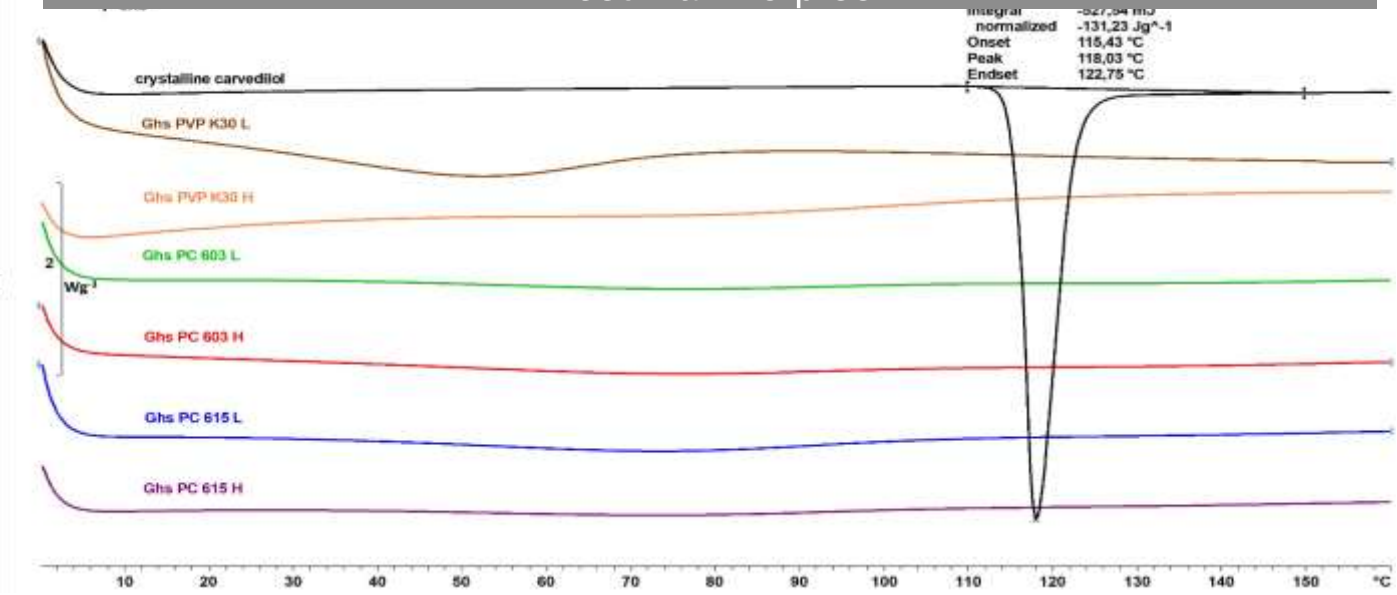

Figure 7: DSC thermograms of pure crystalline carvedilol and produced SMEDDS granules G_{hs} PVP_{K30} L, G_{hs} PVP_{K30} H, G_{hs} PC_{603} L, G_{hs} PC_{603} H, G_{hs} PC_{615} L and G_{hs} PC_{615} H.

2. Development of SMEDDS Orodispersible Tablets Formulation

In our previous study [15] the biggest challenges associated with producing tablets were low hardness and large mass of single dose SMEDDS tablet, therefore the present study aimed to optimize the formulation. The amount of SMEDDS granules used in the tablets presented a particular challenge, considering they contained more than 60 % of liquid. According to our previous research, 50 % of granules in the tablet composition still didn't ensure the appropriate hardness of SMEDDS tablet (e.g. in case of Syloid® 244FP, the maximum achieved hardness was only 34.9 N). So, four different tableting mixtures were prepared, containing 25, 30, 35 and 38 % of SMEDDS granules with target hardness of 100 N being the goal. Ideally, such tablets would also have low friability, fast disintegration time and would keep their self-microemulsifying properties.

Decreasing granule amount in the tablet composition was found to have a positive influence on SMEDDS tablet hardness which was in agreement with our expectations, given the granules' high liquid SMEDDS content. SMEDDS tablets produced from mixtures containing 38 % and 35 % of SMEDDS granules exhibited insufficient tablet maximum hardness of 28 N and 39 N. In case of formulation containing 30 % of granules, adequate hardness couldn't be reached even at high compression forces (maximum hardness ~50 N), in addition to lamination occurring. Finally, the appropriate hardness of ~100 N was achieved with the tablet formulation containing 25 % of granules. Unfortunately, to maintain the adequate dose of carvedilol in single tablet (12.5 mg), the final weight of such tablet was ~854 mg (despite granules high SMEDDS load), which represented a drawback of such a prototype formulation.

Nevertheless, six SMEDDS tablet formulations were developed with optimal amount of 25 % of granules: T-PVP_{K30} L, T-PVP_{K30} H, T-PC_{603} L, T-PC_{603} H, T-PC_{615} L and T-PC_{615} H (to present different SMEDDS tablets, symbol G_{hs} from SMEDDS granules was replaced with symbol T-). Such a broad choice of formulations was expected to better illustrate the influence of binder (sub)types and concentration, by examining the difference in tablets' hardness, disintegration time, friability, self-microemulsifying and *in vitro* dissolution properties. SMEDDS tablets prepared with SMEDDS granules without binder (T-zero) were produced as a reference.

For tablet comparison, all formulations were compressed to similar tablet hardness of around 100 N. The results of SMEDDS tablet's most important properties are presented in Table 3.

Table 3: The characteristics of SMEDDS tablets with 25 % of SMEDDS granules: tablet hardness, friability and disintegration time.

	Hardness [N]	Friability [%]	Disintegration time [min:sec]
T-zero	88.0 ± 5.8	0.47	0:58
T-PVPK30 L	88.6 ± 2.4	0.22	0:52
T-PVPK30 H	103.6 ± 6.6	0.35	1:11
T-PC603 L	88.1 ± 2.5	0.44	1:51
T-PC603 H	97.6 ± 6.7	0.58	0:40
T-PC615 L	72.5 ± 6.1	0.41	3:30
T-PC615 H	62.5 ± 3.7	0.83	1:30

As seen from Table 3, the appropriate hardness of SMEDDS tablets was achieved with PVP K30 and Pharmacoat® 603, used as binders in GD, as well as T-zero. Pharmacoat® 615 was found to be an outlier not only considering the hardness, but friability and disintegration time as well. T-PC_{615} H exhibited the highest friability of 0.83 %, which is still in accordance with Ph. Eur. 11th, but is considerably larger than values of other SMEDDS tablets (0.22-0.58 %). Also, the disintegration time of ~3.5 min for T-PC_{615} H was noticeably longer in comparison to otherwise very fast disintegration of other SMEDDS tablets (0:40-1:51). Due to such a rapid disintegration time, such SMEDDS tablets can be considered as orodispersible, which presents a great advantage for patients having difficulty in swallowing, for example elderly and pediatrics [33,34]. Moreover, the presented results also support the favorable effect of higher binder amount on shorter disintegration time, probably through improved wetting.

2.2. The comparison of self-microemulsifying characteristics of SMEDDS tablets and granules

The self-microemulsifying properties of solid SMEDDS were also evaluated by measuring the average droplet diameter and polydispersity index (PDI) of the obtained dispersion, using photon correlation spectroscopy. The comparison of z-average values between drug-loaded liquid SMEDDS, SMEDDS granules and tablets, measured in dissolution medium with pH 6.8, are presented in Figure 8, while individual peaks, PDI and average droplet size in other two media are presented in Table S5.

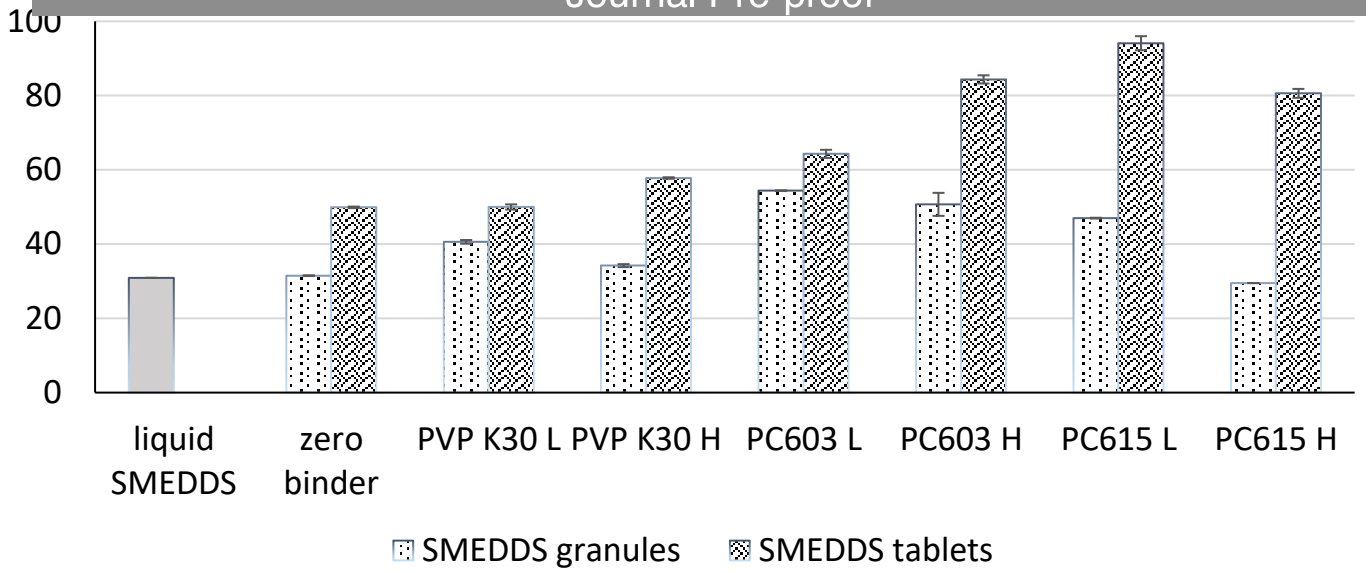

Figure 8: The comparison of average droplet size (z-average diameter) of liquid SMEDDS, SMEDDS granules and SMEDDS tablets, after redispersion in media with pH 6.8.

In addition to obtaining a visually clear dispersion after sample redispergation, which indicates the successful formation of a microemulsion, the analysis also confirmed the self-microemulsifying properties of solid SMEDDS. The results for SMEDDS granules showed the maximum z-average diameter of 54 nm (sample G_{hs} PC_{603} L, in media with pH 6.8), which in general suggests preservation of microemulsifying properties of initial liquid SMEDDS (used as a reference sample). Overall, the droplet size of SMEDDS tablets were somewhat bigger (droplet size increased for ~27 nm on average, in medium with pH 6.8) in comparison to granules. A possible explanation is in the addition of magnesium-stearate, which was used as lubricant during tableting. As reported by Čerpnjak et al, the presence of such hydrophobic molecule negatively influences the thermodynamic stability of oil-water interface, leading to an increase in droplet size [12]. In addition, droplet size increase is linked to irreversible adsorption of hydrophilic surfactants onto the internal carriers' surfaces, which is more pronounced in case of SMEDDS tablets, where SMEDDS is pushed deeper into the pores due to compression process [14,35,36]. However, we can still consider SMEDDS tablets to have acceptable self-microemulsifying properties as the average droplet size (z-average diameter) was still smaller than 100 nm [37]. Again, T-PC_{615} H stood out, with average droplet diameter of 120.9 nm in water medium, which was still acceptable considering some literature sources [6].

The results of this research study confirmed that self-microemulsifying abilities of solid SMEDDS, both in case of granules as well as tablets, were preserved, which was of great importance for gastrointestinal absorption and bioavailability of carvedilol as a poorly water-soluble drug. Hence, to achieve our ultimate goal of improving dissolution properties of SMEDDS tablets, *in vitro* release studies were conducted.

2.3. The comparison of *in vitro* carvedilol release from SMEDDS tablets and granules

A comparison of the dissolution profiles between SMEDDS granules and corresponding tablets is shown in Figures 10 (at high polymer concentration, 7.45 %) and 11 (at low polymer concentration, 1.85 %). Similar as with granules, the addition of binder demonstrated a favorable effect on *in vitro* dissolution properties, as all SMEDDS tablets exhibit faster release profile than T-zero.

Of all SMEDDS tablets, T-PVP_{K30} exhibited the fastest release profile, followed by Pharmacoat® 603 and Pharmacoat® 615. With 62 % of carvedilol released at 5-minute timepoint, PVP K30 indicated its superior

infl[illegible]as more suitable in the comparative study of Morkhade D.M, whose result indicated its superiority over hypromellose for promotion of granules growth in less polar carriers, such as mesoporous Syloid® 244F [30]. In comparison to SMEDDS granules, tableting process slowed down the release of the drug in the most cases (G_{hs} PC_{603} L and G_{hs} PC_{615} L were only exceptions; Figure 9), as dissolution rate was faster for the corresponding granules. Nevertheless, SMEDDS tablets release extent found to be comparable to the granules produced with HS granulation. T-PC_{603} H was the exception, since 10 % less carvedilol was released compared to granules (Figure 10). Presumably, the compaction impaired the dissolution properties of T-PVP_{K30} L, considering higher compression force used than in other formulations. Therefore, the release of carvedilol might be improved by lowering compression force [13,15], in which case an undesirable decrease in tablet hardness is to be expected. Finally, the trend of faster carvedilol release with increasing polymer concentration previously observed with granules, was also expressed within SMEDDS tablets and was pronounced the most at T-PVP_{K30} H, from which 18 % more carvedilol was released in first 5 minutes, compared to T-PVP_{K30} L.

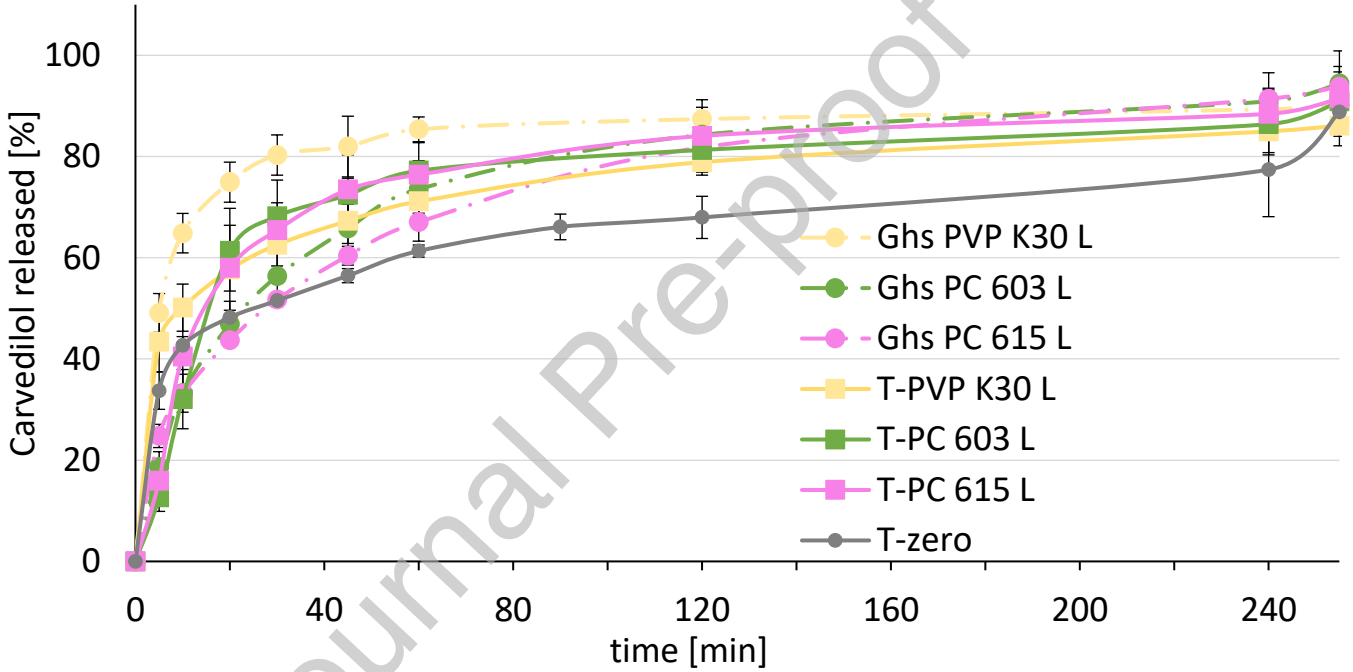

Figure 9. *In vitro* carvedilol dissolution profiles in media with pH 6.8; for SMEDDS granules produced in HS granulator with lower binder concentration (H; 1.85 %) and corresponding SMEDDS tablets, in comparison to SMEDDS tablet without binder (T-zero).

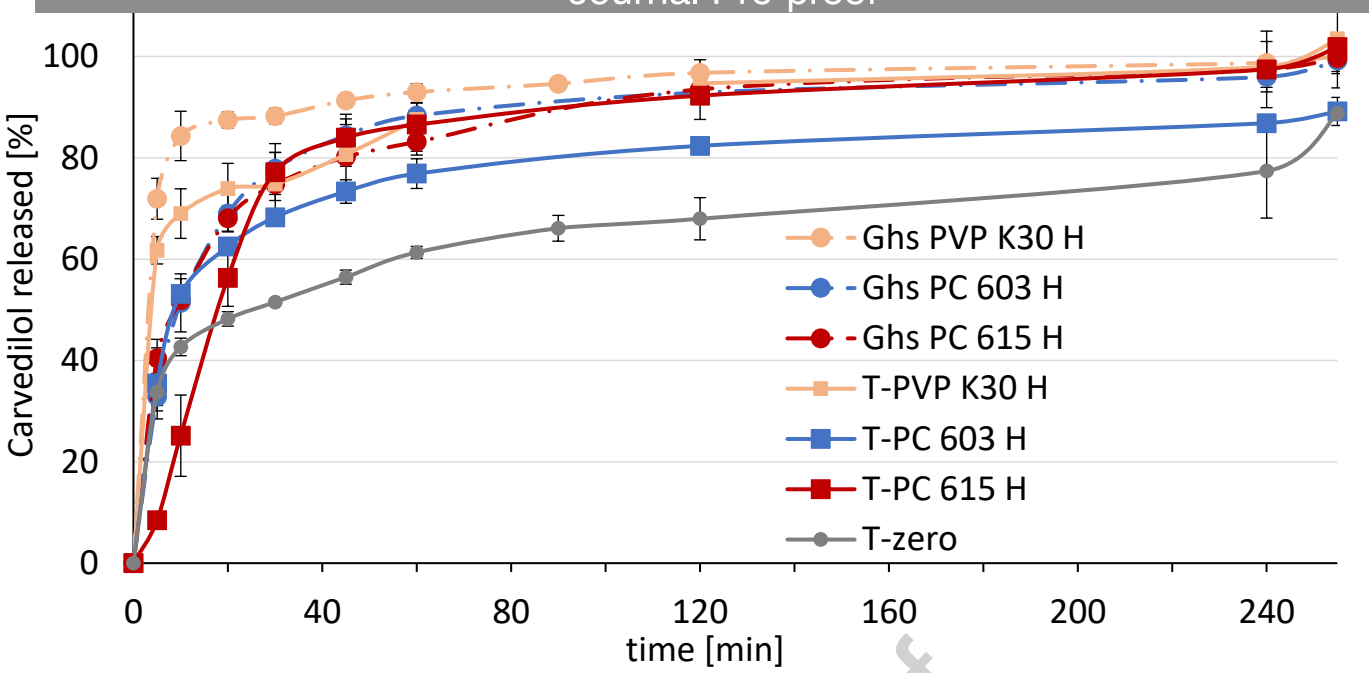

Figure 10: *In vitro* carvedilol dissolution profiles in media with pH 6.8, for SMEDDS granules produced in HS granulator with higher binder concentration (L; 7.45 %) and corresponding SMEDDS tablets, in comparison to SMEDDS tablet without binder (T-zero).

Taking into consideration all of the obtained results, we can say that by the production of SMEDDS granules and SMEDDS tablets, an evident carvedilol dissolution rate improvement was achieved by preserving the self-microemulsifying properties of liquid SMEDDS. PVP K30 was determined to be the best polymeric binder and as such most suitable for further research, as it brought together good flow and dissolution properties of granules, into optimized SMEDDS tablet prototype, as the most desired pharmaceutical dosage form among patients.

Conclusion

The goal of the presented study was to investigate the influence of six different polymers, used as binders for SMEDDS solidification by wet granulation, on relevant technological and biopharmaceutical characteristics of produced granules and tablets. Firstly, the results of SMEDDS granules that were prepared manually showed that the addition of polymeric binder exhibited favorable effect on both flowability and *in vitro* drug release. The incorporation of higher molecular weight binders resulted in slower *in vitro* carvedilol release profile, while high binder concentration was related to faster drug release. The highest release rate was achieved with PVP K30 at 7.45 % binder concentration, as corresponding granules exhibited complete drug release already in first 5 minutes.

Secondly, SMEDDS granulation was successfully scaled up to HS granulator, using low and high concentration (1.85 % and 7.45 %) of the Pharmacoat® binders and PVP K30. HS granulation method found to slow down the drug release rate, probably due to high shear forces pushing the liquid SMEDDS deeper into the carrier pores. Nevertheless, the fastest carvedilol release of ~72 % in first 5 minutes was once again achieved with PVP K30. Such granules were further compressed into tablets, to investigate the impact of granule content, binder type and concentration on SMEDDS tablets' mechanical and dissolution properties.

Incr[illegible]m granule content of 25 % was needed to obtain adequate hardness, thus high final tablet weight remains as challenge. Still, the biggest advantage of final tablet prototype lays in short disintegration time, which was therefore considered as orodispersible. Alternatively, due to the short flow time of SMEDDS granules (< 8.6 s/100 g), a process of filling hard capsules could be employed to produce the final dosage form. Such tablets exhibited slightly slower drug release than corresponding granules, with PVP K30 at 7.45 % concentration standing out as the best polymeric binder candidate for further research.

Acknowledgments

The authors would like to acknowledge Public Scholarship, Development, Disability and Maintenance Fund of Republic of Slovenia for Ad futura scholarship for Nationals of Western Balkans for post-graduate study in the Republic of Slovenia. Also, great thanks to Prof. Dr Odon Planinšek for his assistance in conducting the SEM analysis as well as Matic Šmigoc and Tadej Kobe for their help with the experimental work.

Formatting of Funding Sources

This work was supported by the Slovenian Research Agency.

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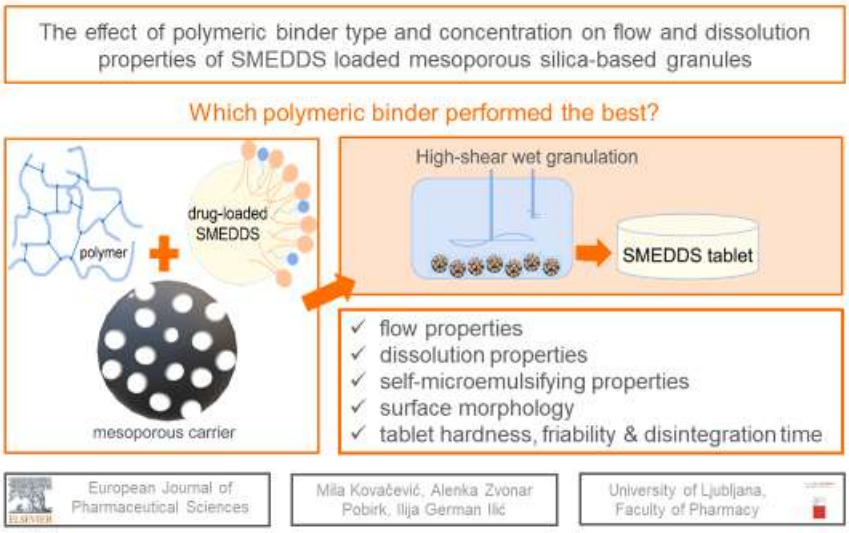

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