Acta Pharm. **62** (2012) 497–513
DOI: 10.2478/v10007-012-0033-y

Original research paper

A study of *in situ* fluid bed melt granulation using response surface methodology

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The objective of this work was to investigate the influence of selected individual variables (binder content, inlet air temperature, and product endpoint temperature) of *in situ* fluid bed melt granulation on the granule particle size distribution and percentage of dissolved carvedilol using a three-factor, five-level circumscribed central composite design. Increased binder content had the effect of increasing the granule particle size and drug dissolution rate. The effect of inlet air temperature and product endpoint temperature was found to be more pronounced in case of granule particle size parameters. Within the studied intervals, the optimal quantity of binder as well as optimal process parameters were identified and validated using response surface methodology. Utilizing these optimal process and formulation parameters, successful scaling up of the fluid bed melt granulation process was carried out. Granule characteristics obtained at pilot scale are comparable to those obtained at laboratory scale.

Keywords: fluid bed melt granulation, carvedilol, central composite design, scale-up

Accepted August 29, 2012

Melt granulation belongs to the group of hot-melt technologies, which represent an alternative to the classical solvent-mediated technological processes of agglomeration. The main advantage of hot-melt processes, including melt granulation, is the absence of solvents, which can be efficiently utilized in enhancing chemical stability of moisture sensitive drugs and also improving their physical properties. Moreover, a drying phase is eliminated, which results in a more economical and environmentally friendly process. There are also some limitations in using melt granulation processes. The major drawback is the required high temperature during the process, which can cause degradation and/or oxidative instability of the ingredients, especially of thermolabile drugs (1, 2).

Equipment used for melt granulation technologies must be modified to promote melting and prevent unwanted solidification of the product on exposed equipment sur-

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faces. Nowadays, high shear and fluid bed granulators are the most suitable equipment for melt granulation of pharmaceutical powders (3). Interest in melt granulation in fluid bed granulators has grown significantly since 2001, when first scientific publications on melt granulation in fluid bed were published (4–6).

Addition of low melting binders to the starting powder mixture can be either in the form of solid particles that melt during the process (*in situ* melt granulation) or in the form of a molten liquid, optionally containing the dispersed drug (spray-on procedure). From the industrial point of view, the melt-in procedure is favoured over the spray-on procedure due to its avoidance of hot-melt flows (4, 7), which renders the procedure simpler for production.

In contrast to extensive studies of wet and dry granulation processes, there is still a lack of knowledge about the predictability and modelling of melt granulation processes (8–10). However, the US Food and Drug Administration (FDA) Quality by Design (QbD) initiative encourages the use of statistical tools for improving the development of high quality pharmaceuticals (11). One of these tools is the experimental design, or design of experiments (DoE), which allows a better understanding of how formulation and process variables can influence product quality by defining the design space. From the experimental results of a response surface design, a polynomial model, describing the relation between a response and considered factors, is built. Afterwards, graphical and/or statistical analysis is carried out to determine the optimal operating conditions in order to obtain the desired formulation properties (12).

In general, once the effect of the formulation and process parameters are investigated thoroughly in the laboratory scale equipment and these parameters are optimized, the next stage is to transfer the process to the pilot scale and ultimately to the commercial production scale. Batch size increase using fluid bed granulation requires a good understanding of equipment functionality and identification of the critical variables that affect the process of agglomeration (13, 14). The majority of numerous scale-up studies focus only on the scaling up of solvent based fluid bed granulation (15–17). However, there is still lack of papers demonstrating the scale-up of melt granulation in a fluid bed granulator.

The present study shows the optimization of the fluid bed melt granulation process using a factorial design. The aim was to evaluate the influence of the formulation and process parameters on the selected responses and to identify optimal values of independent factors within the studied intervals. Further, the second objective of the study was to evaluate the influence of scale-up on the optimized formulation.

EXPERIMENTAL

Materials

Carvedilol (Krka, Slovenia) (d_{v10} of 18.9 μm, d_{v50} of 80.1 μm, and d_{v90} of 190.3 μm measured by the laser diffraction method) was used as a poorly soluble drug, lactose 200 mesh (α-lactose monohydrate, DMV, Germany) and microcrystalline cellulose (MCC, Avicel PH 101, FMC, Germany) were used as fillers, and poloxamer 188 powder (P188,

Lutrol® F68, BASF, Germany) served as meltable binder. The binder sieved fraction of particle size less than 315 μm was used.

Preparation and optimization of granules at laboratory scale

The granules were prepared by *in situ* melt granulation in a laboratory scale fluid bed granulator BX CGD 1 (Brinox process systems, Slovenia) using the process chamber »Tornado« with a specific air distribution plate (18) and computer logging of process parameters. The batch size was 1 kg. All the ingredients, carvedilol (10 %), P188 (between 1.6 and 18.4 %), lactose and MCC at mass ratio 3:2, were placed into the process chamber, and fluidized at an inlet air flow rate of 60 m^3 h^{-1}. Powders were heated at selected inlet air temperatures between 63.2 and 96.8 °C up to the product endpoint temperature, which was varied between 52.3 and 60.7 °C. Immediately after reaching the pre-specified product endpoint temperature, the cooling of the product was started by opening the by-pass airway, setting the fluidizing inlet air temperature to the ambient temperature and increasing the fluidizing air flow rate to 100 m^3 h^{-1}. The process was stopped when the product temperature reached 40 °C.

Design of experiments (DoE)

The above described granule preparation procedure was optimized by a three-factor, five-level circumscribed central composite design (CCCD), with binder content (x_1), inlet air temperature (x_2), and product endpoint temperature (x_3) as independent variables, as shown in Table I. The level of each independent variable was set on the basis of preliminary screening experiments. Experimental design was carried out in two stages, where firstly the experiments of three-factors, two-level full factorial design with triplicate centre points were conducted and then supplemented with additional experiments at a distance of ±α, *i.e.*, 1.682 for three factors, along each axis (12). The Unscrambler® software (version 10.1, CAMO software, Norway) was applied for generation and evaluation of the statistical experimental design. All experiments were performed in randomized order. The mass particle diameters of d_{10}, d_{50}, and d_{90}, corresponding to the 10^{th}, 50^{th} and 90^{th} weight percentiles of the cumulative granulate size distribution, respectively, and D_{5min} and D_{60min}, corresponding to percentiles of dissolved carvedilol after 5 and 60 minutes, respectively, were selected as response variables. CCCD and the response surface methodology were used to determine the influence of a particular independent variable on selected responses. In order to find the relationship able to describe the response variation within the design space, nonlinear quadratic models of the form given below were constructed from a response surface design for three factors (Eq. *1*):

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 + \\ + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{33} x_3^2 \qquad [1]$$

where y is the measured response, β_0 the intercept, β_i the main coefficients, β_{ij} the two-factor interaction coefficients, β_{ijk} the three-factor interaction coefficients, and β_{ii} the quadratic coefficients. Significant terms ($p < 0.10$) according to the analysis of variance (ANOVA) were chosen for final equations. Positive and negative signs represent synergistic and antagonistic effects, respectively. Response surface plots, illustrating the corre-

lation between a fixed response variable and two factors, were also created, where the remaining factor was fixed at the 0 level. The optimal quantity of binder and optimal processing parameters were determined based on response surface functions according to the desired predetermined responses.

Table I. Selected formulation and process variables for the fluid bed melt granulate optimization

Level	Factor x_1: binder content (%)	Factor x_2: inlet air temperature (°C)	Factor x_3: product endpoint temperature (°C)
–1.68	1.6	63.2	52.3
–1	5.0	70.0	54.0
0	10.0	80.0	56.5
1	15.0	90.0	59.0
1.68	18.4	96.8	60.7

Scale-up experiment

The granules were prepared by *in situ* melt granulation in a pilot scale fluid bed granulator Aeromatic 3/2/4 (GEA Pharma Systems, Belgium) equipped with computer logging of process parameters. The batch size was 10 kg. All the ingredients, carvedilol (10 %), P188 (12.5 %), lactose and MCC at mass ratio 3:2, were placed into the process chamber, fluidized at an inlet air flow rate of 180 m^3 h^{-1} and heated at inlet air temperature of 70.0 °C to the product endpoint temperature of 56.5 °C. Immediately after reaching the pre-specified product endpoint temperature, the cooling of the product was started by opening the by-pass airway, setting the fluidizing inlet air temperature to ambient temperature and increasing the fluidizing air flow rate to 300 m^3 h^{-1}. The process was stopped when the product temperature reached 40 °C.

Characterization of the prepared granules

Particle size, shape and flow properties. – Size distribution of the obtained granules compared to the starting materials was determined by sieve analysis, using seven sieves in the range 0.071–1.25 mm (Air Jet Sieve 200 LS-N, Hosokawa Alpine, Germany). Linear interpolation of the cumulative percentage frequency curve was used to determine d_{50}, d_{10}, and d_{90}. Flow properties of the obtained granules and starting materials were evaluated by the Carr index (CI), which was determined using a Stampfvolumeter STAV 2003 (JEL Engelsmann AG, Germany) with a 250 mL glass-measuring cylinder. In order to characterize and estimate the shape of the granules, the aspect ratio (*AR*) and circularity (*C*) were calculated using a Sysmex FPIA-3000 Flow Particle Image Analyzer (Malvern Instruments, UK) and equations *2* and *3*.

$$AR = \frac{F_{max}}{F_{90}} \quad [2]$$

$$C = \frac{4\pi A}{P^2} \quad [3]$$

where F_{max} is the maximum Feret diameter and F_{90} is the Feret diameter perpendicular to F_{max}. P is the perimeter of the 2D graphical representation of granule, while A is its surface.

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

X-ray powder diffraction (XRPD). – X-ray diffractograms were obtained using a Philips PW3040/60X'Pert Pro MPD (Philips Electronic Instruments, USA) with Cu K0 radiation (1.5418 x 10^{-10} m) at 40 kV and 30 mA. The scanning angle ranged from 3.5–32.5° of 2θ; the steps were 0.04° of 2θ, and the counting time was 10 s per step.

Assay. – Carvedilol content in the granulates was determined by suspending the sample in 20 mL of methanol. Sample solution was filtered through a 0.45 μm pore filter (Minisart RC 25, Sartorius, Germany). Drug concentration was assayed using a UV-spectrophotometer (Agilent 8453, Germany) at a wavelength of 285 nm. Standard solutions used to construct the calibration curves were prepared using the same media. All analyses were performed in triplicate.

Dissolution study. – In vitro dissolution studies were performed using a USP type II apparatus (VK 7000, VanKel, U.S.A.), equipped with standard glass vessels and paddles. Samples equivalent to 12.5 mg of carvedilol were placed in a dissolution vessel that contained 900 mL of phosphate buffer solution pH 6.8 at 37 ± 0.5 °C and stirred at 50 rpm. Samples were collected periodically, filtered through a 0.45 μm pore filter (Minisart RC 25, Sartorius, Germany) and replaced with fresh dissolution medium. Carvedilol concentration was determined spectrophotometrically at 285 nm (Agilent 8453, Germany). All dissolution experiments were carried out in triplicate. Linear calibration curve was constructed (Eq. *4*) and used for analytics of dissolution samples.

$$y = 28.214x - 0.0058 \ (R^2 = 0.9998) \quad [4]$$

Carvedilol solubility in phosphate buffer pH 6.8 for pure drug (20 μg mL^{-1}) and granules with P188 to drug ratio 1:3 (89 μg mL^{-1}) was reported (19). Data indicate that moderate excess solubilizing capacity of the dissolution medium was achieved for pure drug. Drug solubilizing capacity further increased with the increase of P188 content in prepared granule samples. Although no true sink conditions were assured over the samples, the authors think that this has somewhat assured discriminatory power of the dissolution method and at least limited physiological relevance (19, 20).

RESULTS AND DISCUSSION

Optimization of melt granulation – DoE analysis

The CCCD design independent levels and the observed responses for 17 experiments including triplicate centre points are shown in Table II.

Table II. Three factor five-level CCCD and responses

Run	Factor			Response ($y_{1–5}$)					*CI* (%)
	x_1	x_2	x_3	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	D_{5min} (%)	D_{60min} (%)	
9	–1	–1	–1	41.3	197.1	567.3	28.9	55.9	19.4
1	1	–1	–1	100.8	444.1	847.5	48.4	92.7	9.2
6	–1	1	–1	38.3	182.3	537.3	27.7	57.1	19.2
10	1	1	–1	105.8	448.7	861.6	47.7	90.8	9.7
2	–1	–1	1	69.3	305.9	723.1	32.4	60.6	14.3
4	1	–1	1	119.3	500.8	912.6	50.3	94.1	8.3
5	–1	1	1	58.7	279.5	632.7	29.8	58.8	16.1
8	1	1	1	87.8	425.5	833.2	48.8	93.1	11.1
3	0	0	0	80.4	371.5	813.5	42.8	80.2	12.0
7	0	0	0	83.9	385.4	821.7	40.9	81.4	11.8
11	0	0	0	82.3	380.2	823.5	40.1	79.6	11.7
14	1.68	0	0	137.5	597.3	1105.9	53.3	99.7	7.5
13	–1.68	0	0	24.2	123.1	337.1	17.4	32.6	22.7
17	0	1.68	0	73.2	355.2	756.5	39.1	77.4	13.1
15	0	–1.68	0	95.0	427.9	872.3	43.9	83.9	10.7
12	0	0	1.68	84.2	384.5	801.2	41.9	81.0	12.1
16	0	0	–1.68	47.2	239.0	494.0	38.9	78.2	17.4

Model functions were calculated from the results of CCCD experiments using the least square method. Regression coefficients for the predictive second-order polynomial model of d_{10} (y_1), d_{50} (y_2), d_{90} (y_3), D_{5min} (y_4), and D_{60min} (y_5) are shown in Table III. The values of the coefficients (β_{1-3}) are related to the effect of these variables on the responses ($y_{1–5}$).

ANOVA was applied to estimate the significance of the model. It can be concluded from the *p*-values in Table III that the proposed models were significant ($p < 0.05$) and valid for all the examined responses. In addition, the high R^2 values of models (Table III) confirm the quality of the models. This means that the found relationships were able to describe response variation in the function of factor variations and therefore described the design space. Three-dimensional (3D) response surface plots are presented in Fig. 1

Table III. Regression coefficients with p*-values for the predictive second-order polynomial models of responses* y_{1-5}

	y_1		y_2		y_3		y_4		y_5	
	coeff.	*p*-value	coeff.	*p*-value	coeff.	*p*-value	coeff.	*p*-value	coeff.	*p*-value
β_0	82.11	–	379.4	–	818.5	–	41.25	–	80.39	–
β_1	21.41	0.0003	88.09	0.0003	67.21	0.0084	8.94	0.0010	15.83	0.0001
β_2	–4.21	0.0290	–9.82	0.1213	–17.01	0.2139	–0.38	0.6234	0.38	0.4726
β_3	3.42	0.0489	22.67	0.0158	5.64	0.6379	1.18	0.1900	1.50	0.0483
β_{12}	–1.61	0.0852	–3.71	0.2674	6.83	0.3669	0.20	0.6628	–0.29	0.3748
β_{13}	–5.99	0.0025	–21.57	0.0042	–26.75	0.0254	–0,33	0.4906	–0.34	0.3094
β_{23}	–5.52	0.0032	–11.44	0.0248	–19.31	0.0579	–0,28	0.5548	–0.26	0.4124
β_{123}	–3.60	0.0109	–8.54	0.0521	–4.07	0.5726	0.08	0.8681	0.49	0.1760
β_{11}	–0.23	0.6975	–7.77	0.0431	–30.86	0.0108	–2.03	0.0102	–4.99	0.0002
β_{22}	0.92	0.1836	3.30	0.2464	1.99	0.7378	–0.96	0.6988	0.14	0.5971
β_{33}	–5.59	0.0019	–24.90	0.0017	–56.98	0.0018	–0.24	0.5416	–0.23	0.3891
Model		0.0071		0.0057		0.0050		0.0379		0.0009
	R^2 = 0.9993		R^2 = 0.9993		R^2 = 0.9982		R^2 = 0.9972		R^2 = 0.9996	

and 2. These types of plots show the effects of two factors on the response at a time. In both figures, the third factor was kept at a zero level. Influence of the selected independent variables on responses, *i.e.*, granule particle size ($y_{1\text{-}3}$) and drug dissolution rate ($y_{4\text{-}5}$), is explained in detail below.

Effect of variables on the particle size of granules. – The results of regression coefficients with *p*-values for the granule particle size parameters (d_{10}, d_{50}, and d_{90}) presented in Table III show that the most influential term ($p < 0.01$) of the response surface quadratic model was the binder content coefficient, β_1. The square factor coefficient of product endpoint temperature, β_{33}, is highly significant in case of the d_{90} value. In addition, coefficients β_{13}, β_{23}, and β_{33} had a significant effect ($p < 0.01$) on granule particle size in case of the d_{10} value, and coefficients β_{13}, and β_{33} in case of the d_{50} value. Granule particle size was found to be mostly influenced by the binder content, showing a positive effect on granule growth, though the influence of a single factor was difficult to interpret owing to the substantial influence of interaction and square factors. In general, the trends observed in Fig. 1a-b, representing the effect of binder content and inlet air temperature or product endpoint temperature on d_{50}, are similar also for d_{10} and d_{90} as responses. In case of d_{10} and d_{50} response parameters significant ($p < 0.01$) interaction was observed between binder content and product endpoint temperature, and in case of d_{90} parameter the observed interaction was significant at $p < 0.05$. On the other side, the interaction between binder content and inlet air temperature was found insignificant ($p > 0.05$) in all three cases. In the case of lower binder content, the granule particle size was increasing with rising product endpoint temperature (Fig. 1b-c). However, in the case of higher binder content the effect of the product endpoint temperature on particle size was less

pronounced. These results suggest that an increase in binder content increases the proportion of available softened or molten binding material during the granulation process, as already reported in the literature (8, 21, 22). It may be hypothesized that each binder particle once softened or molten is able to agglomerate a constant number of primary solid particles by sticking; therefore lower binder content is evidently not sufficient for complete agglomeration and leaves a significant proportion of un-granulated primary particles. Considering the fine particle fraction, represented by the d_{10} parameter, the se-

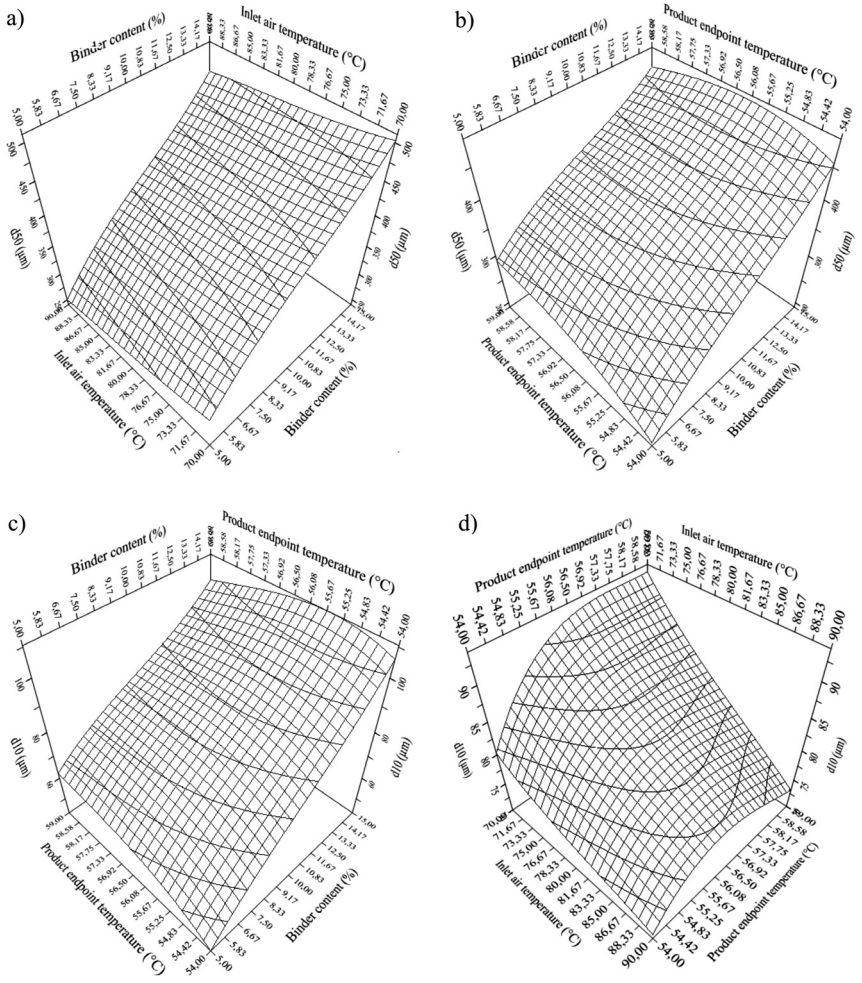

Fig. 1. 3D response surface plots showing the effect of: a) binder content and inlet air temperature and b) binder content and product endpoint temperature on response d_{50}, and the effect of: c) binder content and product endpoint temperature and d) inlet air temperature and product endpoint temperature on response d_{10}.

cond interesting trend in Table III revealed a significant ($p < 0.01$) interaction between inlet air temperature and product endpoint temperature. At lower product endpoint temperature the fraction of fines was increasing with rising the inlet air temperature, as can be seen from Fig. 1d. The effect of increased inlet air temperature on d_{10} is even more pronounced at higher product endpoint temperatures. It may be assumed that the selection of inlet air temperature, at a constant air flow rate, defines the overall granulation time to achieve the selected product endpoint temperature and thereby the total input of heat. Low product endpoint temperature can be compensated by lower inlet air temperature, and *vice versa*, ensuring sufficient heat input as a function of prolonged granulation time and thereby avoiding an excessive fraction of fines. Combination of low inlet air temperature and high product endpoint temperature will prolong granulation time and reduce the fraction of fines most efficiently (Fig. 1d), but at the cost of increased energy consumption per batch.

Effect of variables on the drug dissolution rate. – According to the *p*-values of D_{5min} and D_{60min} responses in Table III, the binder content coefficient, β_1, followed by the square factor coefficient of binder content, β_{11}, are in both cases the most statistically significant terms ($p < 0.01$) of the model. Inlet air temperature and product endpoint temperature did not seem to have a significant influence on the drug dissolution rate. Response surface plots exhibit a nearly linear relationship of binder content with inlet air (Fig. 2a-b) and product endpoint temperature (Fig. 2c-d) in the form of almost straight lines. It is evident from the plots (Fig. 2) that about 30 and 55 % of carvedilol was dissolved after 5 and 60 minutes, respectively, when poloxamer 188 was at the lowest level (5 %, *m/m*) and the increase in percentiles of dissolved drug was almost exclusively binder content dependent. This finding is in accord with the literature (23, 24) reporting that using a polymeric meltable binder with surface active properties had a significant effect on the enhancement of dissolution of poorly soluble drugs in melt granulation processes, where an increase in binder content resulted in higher dissolution rate. On the other hand, the dissolution behaviour was found to be practically independent of the variation of process parameters while keeping the binder content constant at the same time.

Granule flowability. – The Carr index, as an indicator of granule flowability, was calculated, and the values are given in Table II. It was found that the results of granule flowability were in direct correlation with granule particle size. As expected, larger particle size resulted in better flowability of granules, *i.e.*, lower Carr index, as presented in Table II. For example, for all granulates having the d_{50} value above 300 μm the Carr index values were within range 5–15 %, indicating good flow properties.

Table IV. Assay in different particle size fractions

Particle size fraction	Assay (% ± SD)	
	Optimal run – laboratory scale	Optimal run – pilot scale
0–250 μm	100.7 ± 0.9	101.6 ± 0.5
250–710 μm	99.8 ± 0.6	99.4 ± 0.7
710–1250 μm	97.9 ± 0.4	99.1 ± 0.6

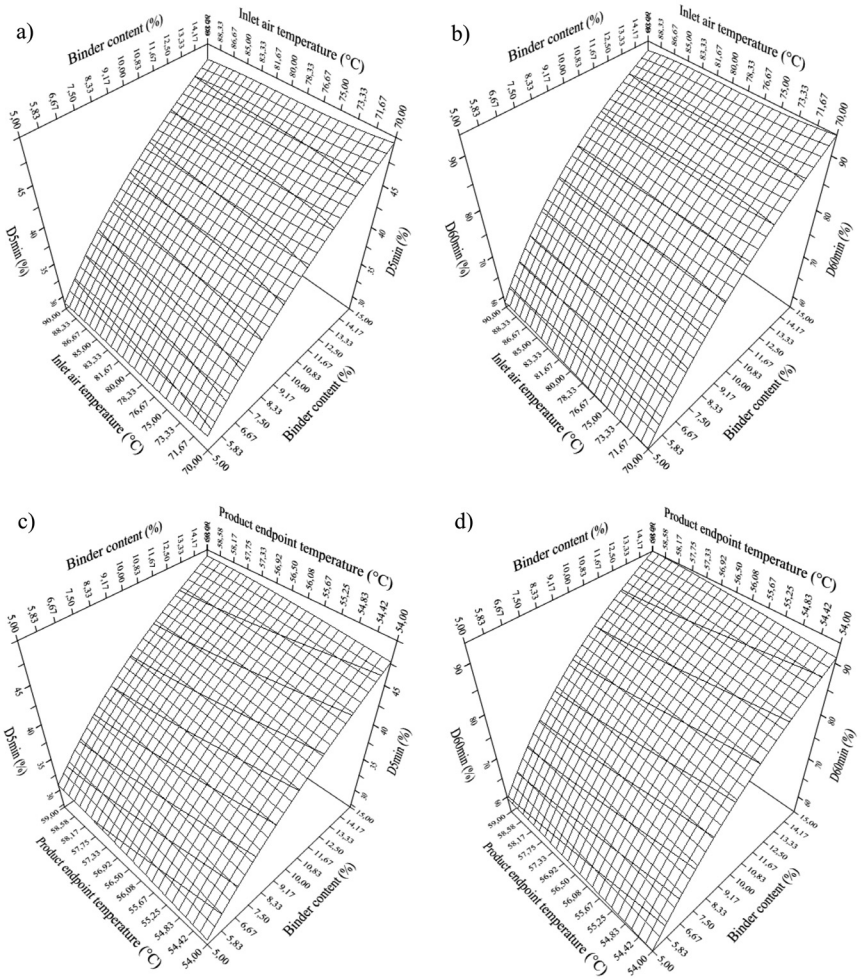

Fig. 2. 3D response surface plots showing the effect of binder content and inlet air temperature on responses: a) D_{5min}, and b) D_{60min} and the effect of binder content and product endpoint temperature on responses c) D_{5min}, and d) D_{60min}.

Assay. – The actual drug content of carvedilol in granules was between 98.4 and 101.8 % of the theoretical drug content, with RSD values below 1 % for all obtained granules (runs 1–17 as listed in Table II), indicating uniform distribution of the drug in granules. This means that the actual drug content in granules can be expected to be in accord with the theoretical value within the design space of this study. We have also analyzed the assay in different particle size fractions for optimal laboratory and pilot scale runs (Table IV). Although the *in situ* hot melt granulation process was used for the preparation of granules, the results showed no significant dependence of the drug assay as a function of particle size fraction.

Optimized granulation experiment

At the end, the optimal quantity of the binder and optimal processing parameters for melt granulation were identified graphically and mathematically using a regression model within the investigated experimental region. It was necessary to find an optimal compromise between the values of selected factors in order to obtain a granulate with the mass median diameter (d_{50}) of approx. 450 μm by minimizing the amount of fines (d_{10} > 100 μm) and the amount of lumps (d_{90} < 900 μm) at the same time, and simultaneously maximizing the carvedilol dissolution rate enhancement (D_{5min} > 45 % and D_{60min} > 85 %). Statistically calculated values describing the optimal values of independent variables were 12.5 % for binder (P188) content, 70 °C for inlet air temperature, and 56.5 °C for product endpoint temperature.

An independent experiment, defined as optimal run, was performed in triplicate to verify the optimal conditions identified in the CCCD experiments. The results are listed in Table V and show good agreement between the calculated (predicted) and experimental (observed) values of the responses. Consequently, this, along with the drug content of 99.4 % and Carr index of 9.5 %, can add further experimental verification to the validity of the established statistical models.

Table V. Optimal values of independent variables, predicted and observed values of response variables

Factor	Optimal value	Response	Predicted value	Observed value	Relative error
x_1	12.5 %	y_1	102.8 μm	107.1 ± 2.1 μm	+4.2 %
x_2	70.0 °C	y_2	449.5 μm	462.8 ± 4.7 μm	+2.9 %
x_3	56.5 °C	y_3	876.3 μm	838.6 ± 7.2 μm	–4.3 %
		y_4	87.1 %	91.8 ± 3.1 %	+5.4 %
		y_5	45.2 %	49.1 ± 2.3 %	+8.6 %

Solid state characterization

To characterize the solid state of carvedilol in the granules, XRPD diffractograms were obtained for pure crystalline carvedilol, lactose, MCC, P188, granules and the corresponding physical mixture (Fig. 3). Diffractograms of granules (Fig. 3f-j) exhibited predominating signals for α-lactose monohydrate (43–53 % in formulations) (Fig. 3b) at 12.5, 16.4, 19–20° and 20.6–21.3° of 2θ. MCC (Fig. 3c) and P188 (Fig. 3d) show broad diffraction lines (at 14.5–18.5°, and 23.05–26.0° of 2θ) and (at 20.5°, and 24.0–25.5° of 2θ), respectively. Pure carvedilol was in crystalline form (Fig. 3a), as demonstrated by the sharp and intense diffraction lines corresponding to form II of the drug (25). XRPD diffractograms of the physical mixture (Fig. 3e) and granules with binder content from 1.6 to 18.4 % (Fig. 3f-j) show the same characteristic diffraction lines (at 5.9, 14.9, 17.6, 18.4, and 24.4° of 2θ) as pure carvedilol polymorph II (Fig. 3a). It can be concluded that there was no evidence of polymorph transformation during the melt granulation process. However,

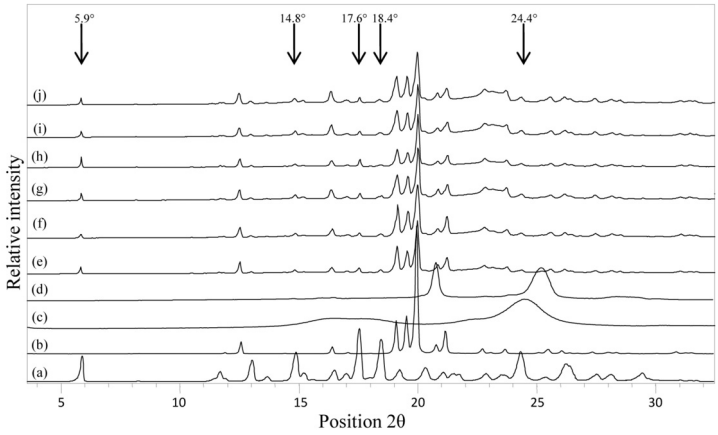

Fig. 3. XRPD data of a) crystalline carvedilol, b) lactose, c) MCC, d) P188, e) physical mixture and granules of f) run 13, g) run 14, h) center point, i) optimal point and j) optimal point – scale-up.

somewhat lower intensities of diffraction lines in the physical mixture and granulates were observed and were attributed to lower drug content due to dilution of carvedilol in the physical mixture and granules, as already observed in a previous study (19).

Scale-up of melt granulation

The influence of scale-up (10× batch size increase) on the optimized granule composition produced at laboratory scale, as determined by CCCD, was investigated using a pilot scale fluid bed granulator. Overall, the goal of this scale-up study was to maintain similar product characteristics, *i.e.*, granule particle size distribution, granule shape and morphology, drug particle properties, content and dissolution rate as obtained for sam-

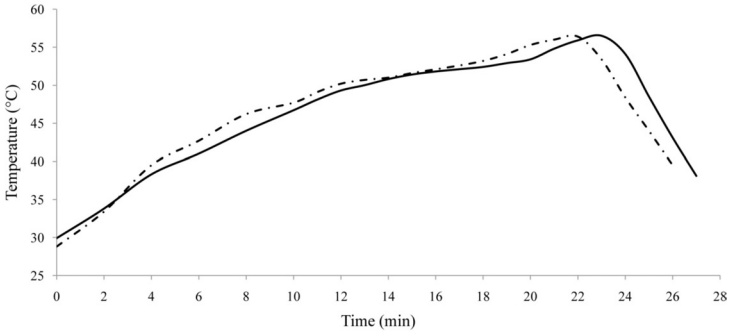

Fig. 4. Comparison of in-line product temperature data of the optimal run – lab scale (dashed line) and the optimal run – pilot scale (solid line).

ples produced by an optimal run at laboratory scale. Therefore, the study was primarily focused on being able to reproduce product attributes across scales. Inlet air temperature, granulation/cooling endpoint temperature, and inlet air flow rate were selected as key scale-up process parameters. Initially, preliminary placebo trials were performed to adjust the inlet air flow rate enabling comparable product temperature *vs.* time evolution as in the lab-scale optimal run while maintaining constant predetermined optimal values for inlet air temperature of 70 °C and for product granulation/cooling endpoint temperature of 56.5/40 °C. Fig. 4 proves that comparable production times and product temperature profiles during the granulation procedure scale-up have been ensured. As can be seen from experimental methods, a threefold increase in the inlet air flow rate was used during scale-up. This can be partially attributed to the distribution-plate area ratio between the pilot and laboratory granulators (2.65:1), as well as to the differences in design features of both distribution plates and in equipment heat losses.

Table VI compares the technological properties for pilot scale granules to those of the optimal laboratory run. The results of granule properties, *i.e.*, particle size, shape, and flowability, obtained in the pilot scale experiment are relatively close to those obtained at the laboratory scale, and therefore confirm that the used process parameters were suitably determined. In addition, SEM micrographs of granules of the optimal run (Fig. 5a) and its scale-up run (Fig. 5b) were utilized to compare their shape and surface morphology characteristics. It is evident that a comparable, relatively spherical and quite porous granule structure was obtained in both cases. Moreover, micrographs of the cross section of granules from both runs (Fig. 5c-d) revealed the presence of a hollow core, indicating that immersion and layering were the dominant agglomeration mechanism in both cases (4, 21).

Table VI. The effect of scale up on technological properties of prepared granules

	Fluid bed granulator	
	Laboratory scale (batch size: 1 kg)	Pilot scale (batch size: 10 kg)
d_{10}	107.1 μm	98.5 μm
d_{50}	462.8 μm	440.7 μm
d_{90}	818.6 μm	783.0 μm
AR	0.85 ± 0.07	0.80 ± 0.08
C	0.81 ± 0.03	0.77 ± 0.05
CI	9.5 %	10.4 %

The *in vitro* dissolution profiles of optimal run granules obtained at laboratory and pilot scales compared to that of pure drug and the corresponding physical mixture are summarized in Fig. 6. The dissolution rate of pure carvedilol was relatively low, with the amount of drug dissolved in 60 min being less than 20 %. Comparison of dissolution profiles of carvedilol granules produced in laboratory and pilot scale granulators indicated that the dissolution behaviour was not influenced by scaling up. The *in vitro* disso-

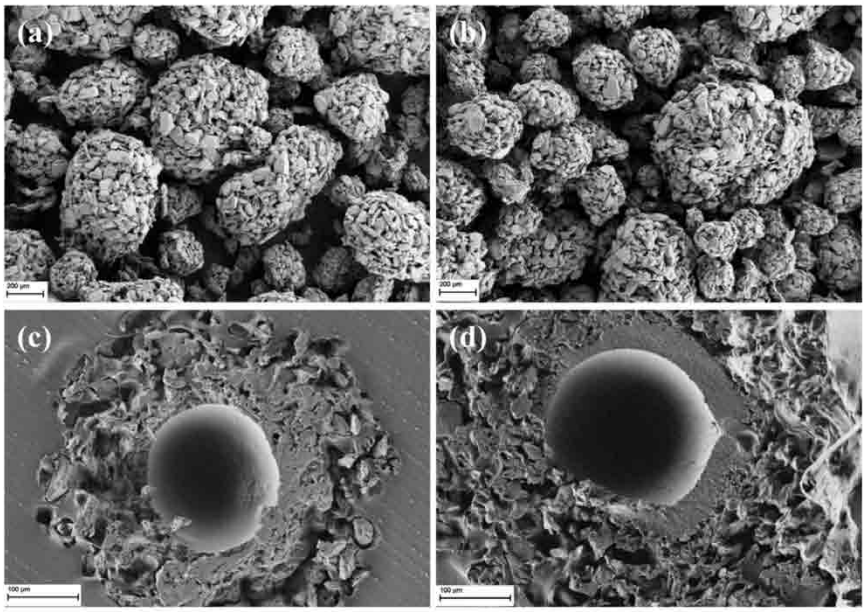

Fig. 5. SEM micrographs of granules of a) optimal run – lab scale and b) optimal run – pilot scale; cross section of a granule of c) optimal run – lab scale and d) optimal run – pilot scale. Magnification of 50× (a–b) and 500× (c–d).

lution rate of prepared granules was significantly higher compared to pure drug and the corresponding physical mixture. The results have confirmed that melt granulation using hydrophilic binders, *e.g.*, poloxamer 188 in this study, is an effective method to improve the dissolution rate of a poorly soluble drug, *e.g.*, carvedilol in this study. Furthermore, XRPD analysis of the optimal run (Fig. 3f) and optimal run-scale up (Fig. 3g) granules indicated a similar diffraction pattern with comparable intensity of the lines, thereby suggesting that scaling up does not show any influence on the crystalline form of carvedilol.

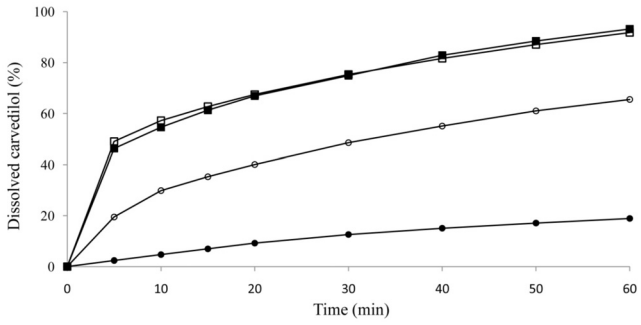

Fig. 6. Dissolution profiles in buffer at pH 6.8 for powders of pure carvediol: ●, physical mixture: ○, granules of optimal run – lab scale: □ and granules of optimal run – pilot scale: ■.

CONCLUSIONS

This study has demonstrated that response surface methodology is an appropriate statistical method to optimize the fluid bed melt granulation process. CCCD was implemented to investigate the effect of binder content, inlet air temperature, and product endpoint temperature on the obtained granule particle size and drug dissolution rate of a poorly soluble drug. Granule particle size was primarily dependent on binder content but also seemed to be affected by the selected process parameters. Drug dissolution rate was significantly influenced by the binder content, while the variation of process parameters did not seem to have a significant influence. An optimization study was employed to identify the optimal quantity of the binder and optimal processing parameters that would allow optimal selected response values to be obtained. Predictability was proven successful, demonstrating the importance and worth of the mathematical model to simplify and increase flexibility in melt granulation. Scale-up of the optimized formulation from a lab to a pilot scale apparatus was successfully performed. The pilot scale experiment resulted in final product properties close to the ones obtained during the optimized run at lab scale.

Acknowledgements. – The authors thank KRKA, d.d., Novo mesto, and Brinox process systems, d.o.o., Slovenia, for supporting this study.

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P O V Z E T E K

Uporaba metodologije odgovornih površin za študij *in situ* granulacije s talinami v zvrtinčenih plasteh

SIMON KUKEC, FRANC VREČER in ROK DREU

V raziskovalnem delu smo z uporabo tri-faktorskega pet-nivojskega središčnega mešanega eksperimentalnega načrta proučevali vpliv izbranih procesnih spremenljivk (delež veziva, temperatura vhodnega zraka in končna temperatura produkta) *in situ* granulacije s talinami na porazdelitev velikosti izdelanih granul in na delež raztopljenega karvedilola. Ugotovili smo, da povečana količina veziva v formulaciji kaže učinek povečanja velikosti izdelanih granul kakor tudi hitrosti raztapljanja karvedilola. Prav tako smo ugotovili, da temperatura vhodnega zraka in končna temperatura produkta izkazujeta izrazit vpliv na parametre velikosti granul. Z metodo odgovornih površin smo znotraj proučevanih intervalov določili in validirali optimalno količino veziva in optimalne procesne parametre. Z uporabo optimalnih formulacijskih in procesnih parametrov smo tehnologijo *in situ* granulacije s talinami uspešno prenesli iz laboratorijskega v večje (pilotno) merilo, pri čemer smo zagotovili primerljivost proučevanih lastnosti granulata.

Ključne besede: granulacija s talinami v zvrtinčenih plasteh, karvedilol, središčni mešani načrt, prenos v večje merilo

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