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Optimization of melt pelletization in a high shear mixer

P. Bukovec[a,*], V. Krošelj[a], S. Turk[a], F. Vrečer[a,b]

[a] KRKA d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
[b] University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

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ABSTRACT

The effects of process conditions and binder content on the process yield and pellet characteristics of two formulations prepared by melt pelletization in a laboratory-type high shear mixer were investigated. The formulations were prepared using Gelucire® 50/13 and Lutrol® F68 as meltable binders. The factors under investigation were impeller speed, mixing time, mixer load, binder concentration, and their reciprocal interactions. Analysis of variance (ANOVA) was used in order to study the significance of above mentioned process variables on the useful yield. Twenty-seven experiments were required for the response surface methodology based on Box–Behnken experimental design (24 combinations with three replications of the centre point) for each formulation.

The control over the process and the quality of the resulting pellets were found to depend on the rheological properties of the binders used. In the case of a low viscosity binder (Gelucire® 50/13), the process was easily controllable whereas in the case of a high viscosity binder (Lutrol® F68), the process was more difficult to control.

The useful yield of the formulation in the case of the low viscosity binder was found to be mostly influenced by the concentration of the binder. On the other hand, different binder concentrations did not affect the useful yield of the formulation prepared by use of the high viscosity binder. In the latter case, mixing time was identified as the variable that mostly influenced the pelletization process.

Finally response surface methodology was applied to find the optimum values of the process variables.

1. Introduction

Thermoplastic pelletization in a high shear mixer 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 the hot-melt processes, including the thermoplastic pelletization, is the absence of solvents, which enables simple and fast formulation of moisture-sensitive active ingredients (Schaefer et al., 1990). Moreover, the drying phase is eliminated and, consequently, the process is more economical and environmentally friendly. Furthermore, the availability of the chemically and physically versatile group of meltable binders ensures flexibility in the design of the pharmaceutical dosage forms.

The main limitation of the hot-melt technologies is the required high temperature which can cause chemical degradation of the ingredients, especially of the active substance. Another disadvantage is their high sensitivity to process variables and changes in the formulation (Schaefer et al., 1990, 1992b, 1993; Voinovich et al., 1999; Heng et al., 2000).

The influence of process variables and formulation changes on the process yield of pelletization has been studied by many authors. The most investigated parameters are mixer load, impeller speed, mixing time (Schaefer et al., 1992b, 1993; Campisi et al., 1999; Voinovich et al., 1999; Heng et al., 2000), temperature of the heating jacket (Schaefer, 1996; Voinovich et al., 1999), chopper action (Schaefer et al., 1992b; Voinovich et al., 1999), binder concentration (Schaefer et al., 1992b; Voinovich et al., 1999), binder particle size (Schaefer et al., 1992b; Schaefer and Mathiesen, 1996b; Voinovich et al., 1999), binder viscosity (Schaefer and Mathiesen, 1996a; Eliasen et al., 1998), apparatus variables (Schaefer et al., 1993; Voinovich et al., 1999), and physical properties of the materials (Schaefer et al., 1992a; Voinovich et al., 1999). The mentioned parameters were studied simultaneously by use of factorial experimental designs (Campisi et al., 1999; Voinovich et al., 1999; Heng et al., 2000).

In our previous studies (Krošelj et al., 2008) it was proven that pellets with very fast release of a low soluble model drug (lansoprazole) can be prepared by thermoplastic pelletization with surface-active low melting point binders.

The aim of the present study was to investigate the influence of individual variables onto the process yield of the thermoplastic pelletization in a high shear mixer using molten surface-active binders.

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[*] Corresponding author. Tel.: +386 7 331 38 12; fax: +386 7 331 32 70.
E-mail address: polona.bukovec@krka.biz (P. Bukovec).

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The two formulations were prepared using the stearyl polyoxyglyceride binder Gelucire® 50/13 and the poloxamer binder Lutrol® F68, which differ in their particle size, melting point, and in the viscosity in their molten phase.

Using statistical methods, the influences of the binder concentration, impeller speed, mixing times and mixer load on the process yield, and the physical properties of the produced pellets were studied.

Within the studied intervals, an optimum quantity of binder was identified as well as optimum process parameters. The aim was to minimize the quantity of residual powder and the formation of lumps while maximizing the amount of pellets of appropriate size.

2. Materials and methods

2.1. Materials

Lansoprazole (Krka, Novo mesto, Slovenia) was used as a poorly soluble active ingredient, magnesium carbonate (Cognis, Düsseldorf, Germany) as a stabilizer, lactose 450 mesh (α-lactose monohydrate; DMV, Veghel, The Netherlands) as a diluent, and Gelucire® 50/13 (Gattefosse, Saint Priest, France) and Lutrol® F68 (BASF, Burgbernheim, Germany) as binders.

Gelucire® 50/13 consists of a mixture of mono-, di- and triesters of glycerol and of mono- and diesters of macrogol with stearic (octadecanoic) acid and has an HLB value of 13. Lutrol® F68 is a hydrophilic block copolymer of ethylene oxide and propylene oxide with an HLB value of 29. While the former was provided in the form of solid beads, Lutrol® F68 was used in the form of small prills.

2.2. Methods

2.2.1. Characterization of starting materials

The melting behavior of the binders was evaluated by a Mettler STAR^e SW 8.01, differential scanning calorimeter (Mettler, Schwarzenbach, Switzerland). Samples of about 4 mg were sealed in 40 μL aluminum pans and scanned between 10 °C and 70 °C at a heating rate of 5 K/min.

The viscosities of the molten binders were measured with a Physica Rheolab MC 100 UM (Germany) at different shear rates and different temperatures.

2.2.2. Pellet preparation

The matrix pellets were prepared by hot-melt pelletization in a ProCept Mi-Pro high shear mixer equipped with a double jacket for heating/cooling and a three-bladed impeller with a mixing vessel capacity of 200–300 g.

The pelletization process and the formulation were optimized on the basis of preliminary trials with placebo mixtures. Amounts of binders, mixing times and temperatures were varied (based on trial and error principle). After approximate composition was determined, a part of the filler was replaced with lansoprazole (10%) and magnesium carbonate (10%), the latter used as an alkaline stabilizer.

All ingredients were mixed manually in a plastic bag and transferred into the mixing vessel of the high shear mixer preheated to 45 °C. The heat required for the softening and melting of the binder came from the mixer wall (the double-jacket wall was heated by a heating liquid to 50 °C in the case of Gelucire® 50/13 and to 55 °C in the case of Lutrol® F68) as well as from the friction as a consequence of particle movement during the process.

The concentration of the two binders, mixing times, impeller speed and mixer load were varied according to the Box–Behnken design with factor levels as shown in Tables 1 and 2 randomly. At the end of the pelletization process, the pellets were cooled down at room temperature on metal plates and sieved through a 2.4 mm sieve to determine the amount of lumps.

2.2.3. Characterization of the prepared pellets

The total yield of the process was measured as the amount of pellets passing through the 2.4 mm sieve, divided by the total mass of starting material. Pellets in the range of 0.500–1.400 mm were selected as the useful fraction.

The size distribution of the so obtained pellets was determined by the vibrating sieve analysis, using seven sieves in the range of 0.250–2.00 mm (Prufsieb Jel 200, Hosokawa, Augsburg, Germany). The shape and surface properties of selected pellet samples were investigated using an optical microscope (Stereomicroscope Olympus SZH10, Tokyo, Japan), equipped with a Sony DXC-107AP camera.

Microphotographs of the pellets were made using a field emission scanning electron microscope, FE-SEM SUPRA 35 VP (Carl Zeiss, Oberkochen, Germany), equipped with energy dispersive spectroscopy Inca 400 (Oxford Instruments, Oxford, UK).

The Box–Behnken experimental design and the response surface methodology were used to determine the influence of particular process parameters and binder concentration on the process yield, the amount of by-products and the size of the final product. A second-order polynomial model obtained by multiple regression analysis for four factors was used to describe the response surface.

Furthermore, optimum values of the selected factors were calculated in order to obtain the maximum product yield by use of the SAS system (version 9.1.3).

3. Results and discussion

3.1. Characterization of starting materials

Molten Gelucire® 50/13 has lower viscosity than Lutrol® F68 at a given temperature (Figs. 1 and 2). As expected, the viscosity of both molten binders is inversely proportional to the temperature. The viscosity is also influenced by mechanical stress which is more pronounced at lower shear forces whereas at higher shear forces the viscosity is less influenced. At temperatures higher than 55 °C in the case of Gelucire® 50/13 and above 60 °C in the case of Lutrol® F68, the effect of the mechanical stress on the viscosity is not substantial any more.

The DSC measurements demonstrate that the two binders also differ in their melting behavior (Fig. 3). While Lutrol® F68 has a relatively narrow melting range at 55 °C ($T_{onset} = 53$ °C), Gelucire® 50/13 has a wider peak at approximately 43 °C ($T_{onset} = 37$ °C) as it is not a simple single-component excipient but is composed of mono-, di-, tri-glycerol esters and macrogol esters with stearinic acid, which cause widening of the melting peaks and, sometimes, even a two-peak melting range (Sutananta et al., 1994).

Table 1
Selected process variables and levels for pellets with Gelucire® 50/13 and Lutrol® F68.

Level	Factor x_1: binder concentration (%)		Factor x_2: impeller speed (rpm)		Factor x_3: mixing time (min)		Factor x_4: mixer load (g)	
	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68
−1	15	18	900	1300	6	3	200	200
0	16	19	1200	1500	9	6	250	250
1	17	20	1500	1700	12	9	300	300

Table 2
Box–Behnken experimental design plan and results for Gelucire® 50/13 and Lutrol® F68.

Run	x_1: binder concentration (%)	x_2: impeller speed (rpm)	x_3: mixing time (min)	x_4: mixer load (g)	Gelucire®50/13 y_1: useful yield (%)	Lutrol® F68 y_1: useful yield (%)
7	0	−1	−1	0	28.9	47.7
8	0	−1	1	0	64	63.2
15	0	1	−1	0	46.7	31.1
1	0	1	1	0	29.3	20.2
3	−1	0	0	−1	47.3	49.3
9	1	0	0	−1	21.9	5.3
20	−1	0	0	1	31.8	55
5	1	0	0	1	32.4	61.4
11	−1	−1	0	0	27.7	55.3
16	1	−1	0	0	61.1	59.6
4	−1	1	0	0	44.8	19
10	1	1	0	0	13.8	47.7
17	0	0	−1	−1	54.4	48.1
23	0	0	−1	1	39.2	42.9
2	0	0	1	−1	32.5	5.9
24	0	0	1	1	58.5	29.8
26	0	−1	0	−1	32.7	68.3
22	0	−1	0	1	31.2	63
18	0	1	0	−1	42.9	44.4
13	0	1	0	1	30.7	65.3
6	−1	0	−1	0	32	69.4
25	1	0	−1	0	21.1	56.6
27	−1	0	1	0	54	74.1
19	1	0	1	0	14	12.3
21	0	0	0	0	62.3	73.7
12	0	0	0	0	51.9	73.7
14	0	0	0	0	61.7	71.5

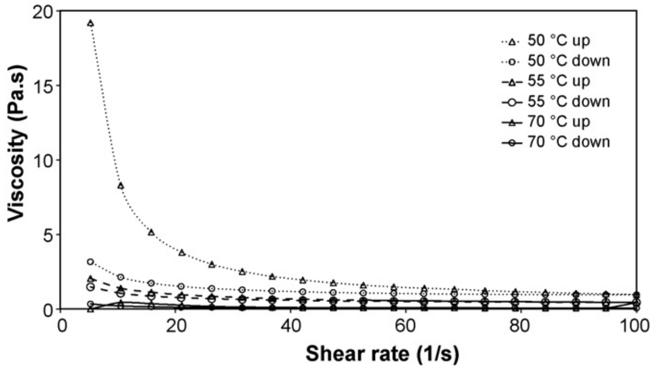

Fig. 1. Effects of temperature and shear stress on the viscosity of Gelucire® 50/13.

3.2. The pelletization process

The double-jacket vessel of a high shear mixer enables heating of material to the temperature at which melt granulation takes place. However, it has to be considered that the heat is not evenly distributed throughout the vessel. In the hot-melt agglomeration process, appropriate temperature setting is very important as this parameter can affect the binder viscosity and, consequently, the pellet size distribution and process yield. This is especially important for poloxamer binder Lutrol® F68 owing to the higher temperature dependence of its viscosity (Fig. 2) (Seo and Schaefer, 2001). The temperature of the heating jacket was set in a way so that the product temperature always reached the T_{onset} of the individual binder. On the other hand, the lowest possible temperature of the product, which still led to the pelletization process, was chosen in order to achieve appropriate stability of lansoprazole during the process.

The melt pelletization process was supervised by granulation graphs, showing the changes of torque and temperature over time. The two phases of the process can be clearly observed; during the first one, i.e. the granulation phase, fast torque growth is observed until the maximum is achieved; during the second one, i.e. the pelletization phase, the torque drops sharply first and then grows steadily (Fig. 4). The granulation graphs proved to be an appropriate tool for determining the starting point of the pelletization faze (torque maximum) and particularly for detecting the destructive phase of the process. Namely, in the

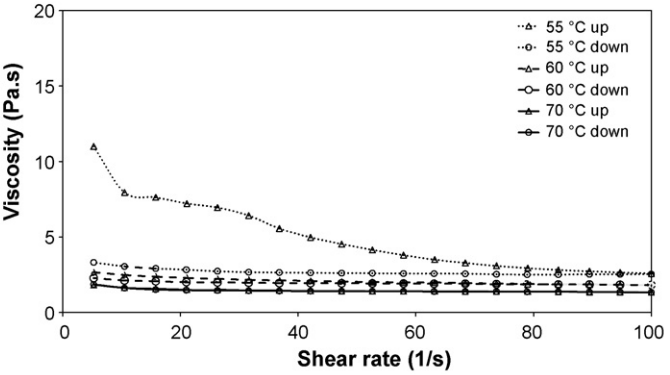

Fig. 2. Effects of temperature and shear stress on the viscosity of Lutrol® F68.

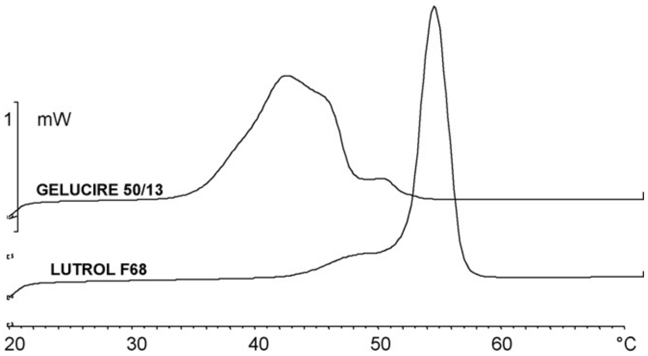

Fig. 3. DSC curves showing melting behaviour of the binders.

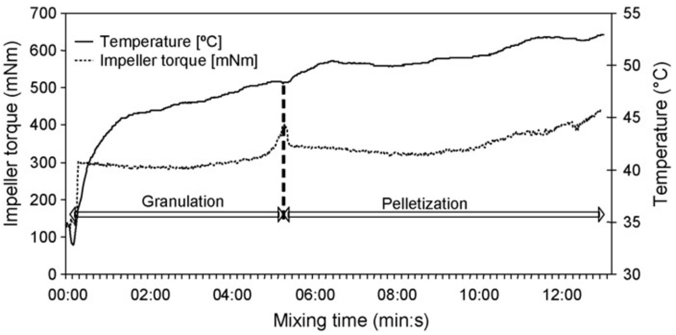

Fig. 4. Example of granulation graph.

case of excessive lump formation, the torque started to fluctuate sharply.

3.3. The influence of selected factors on process yield and their optimization

As already mentioned, the three-level four-factorial Box–Behnken design was used for the planning of experiments. To establish the initial melt pelletization process understanding and for the determination of critical process and formulation variables first a screening design was performed.

Box–Behnken design is often preferred for fitting a second-order response model, since interaction parameters are not completely confounded. Box–Behnken designs are efficient, simple and economic as they reduce the number of experiments needed. The main advantage of the Box–Behnken design lies in the fact that it does not include experiments in which all factors would be at the highest (+1) or at the lowest (−1) level. All combinations predict at least one factor to be at the medium level (0). This is especially important in cases of extreme conditions leading to situations where performance of such experiments is not possible or safe.

Using the response surface analysis based on multiple regression analysis and the analysis of variance (ANOVA), we computed a square response surface model for the useful yield.

A mathematical model explained the main and square effects, and the interactions of factors that affected the useful yield:

$$Y = \beta_0 + \sum_{j=1}^{k} \beta_j X_j + \sum_{j=1}^{k} \beta_{jj} X_j^2 + \sum_{i<} \sum_{j=2}^{k} \beta_{ij} X_i X_j$$

Model functions were calculated from the results of the Box–Behnken experiments using the least square method. The significant regression coefficients for the predictive second-order polynomial model of useful yield (y_1), amount of residual powder (y_2) and lumps (y_3) for pellets with Gelucire® 50/13 and Lutrol® F68, are shown in Tables 3 and 4. Fisher's *F*-test demonstrates high significance for the regression models ($p < 0.1$).

It can be seen from Table 3 that in the case of Gelucire® 50/13 the significant factors for the useful yield were binder concentration (x_1), impeller speed (x_2) and their square factors, mixing time (x_3) and additional square factor of mixer load (x_4^2), were present as well as two mixed factors of binder concentration–impeller speed (x_1x_2) and impeller speed–mixing time (x_2x_3).

In the case of Lutrol® F68 (Table 4), significant factors that influence the useful yield were impeller speed (x_2), mixing time (x_3) and two square factors of mixing time (x_3^2) and mixer load (x_4^2).

The relationship between the dependent and independent variables was further studied using response surface methodology.

As the useful yield, pellets in the size range of 0.500–1.40 mm were chosen because such matrix pellets allow further processing, e.g. coating with film coatings such as enteric coating. The useful yield of the formulation in the case of a low-viscosity binder (Gelucire® 50/13) was found to be mostly influenced by the concentration of the binder although the influence of a single factor was difficult to interpret owing to the substantial influence of interaction and square factors. Two negative interactions between the independent variables were determined—between impeller speed and mixing time and between impeller speed and binder concentration. At a low impeller speed, the useful yield was increasing with rising binder concentration (Fig. 5) up to 16.5 w/w% of the binder. After this point, the yield started to decrease with increasing mixing time. At a medium impeller speed, this point was moved to 16.1 w/w% and at high impeller speed to 15.4 w/w% of the binder. However, at a low impeller speed, it is the mixing time that determines sufficient surface plasticity; namely, the molten binder needs more time to diffuse from the core to the surface of the agglomerates while fast mixing propagates the densification process itself and is not so

Table 3
The significant regression coefficients for the predictive second-order polynomial model of useful yield (y_1), residual powder (y_2) and lumps (y_3) in case of Gelucire® 50/13) are presented. Fisher's *F*-test demonstrates high significance for the regression models ($p < 0.1$).

	y_1: useful yield	y_2: residual powder[a]	y_3: lumps[a]
Intercept	52.24	0.982	1.86
x_1	−6.11	−0.37	1.14
x_2	−3.12	−0.33	1.71
x_3	2.50	−0.21	1.03
x_4	−0.66	−0.22	/
x_1^2	−13.88	0.32	/
x_2^2	−7.40	0.29	/
x_3^2	/	/	/
x_4^2	−7.18	/	/
x_1x_2	−16.10	0.43	/
x_1x_3	/	/	/
x_1x_4	/	/	/
x_2x_3	−13.13	/	/
x_2x_4	/	/	/
x_3x_4	10.30	/	/
Model (*p*-value)	0.0103	0.0001	0.0001

[a] For statistical analysis, transformation of the values for the powder and lump amount were applied using square root and logarithmic transformation, respectively.

Table 4
The significant regression coefficients for the predictive second-order polynomial model of useful yield (y_1), residual powder (y_2) and lumps (y_3) in case of Lutrol® F68 are presented. Fisher's *F*-test demonstrates high significance for the regression models ($p < 0.1$).

	y_1: useful yield	y_2: residual powder[a]	y_3: lumps[a]
Intercept	59.31	1.07	−0.79
x_1	/	−0.58	/
x_2	−10.78	−0.56	0.90
x_3	−7.52	−0.65	1.63
x_4	8.01	0.27	/
x_1^2	/	/	/
x_2^2	/	0.37	/
x_3^2	−14.32	0.68	1.60
x_4^2	−9.64	/	/
x_1x_2	/	/	/
x_1x_3	/	/	/
x_1x_4	/	/	/
x_2x_3	/	/	/
x_2x_4	/	0.64	/
x_3x_4	/	−0.47	/
Model (*p*-value)	0.0588	0.0001	0.0031

Some effects are included in the model to preserve hierarchy.

[a] For statistical analysis, transformation of the values for the powder and lump amount were applied using logarithmic transformation of the values.

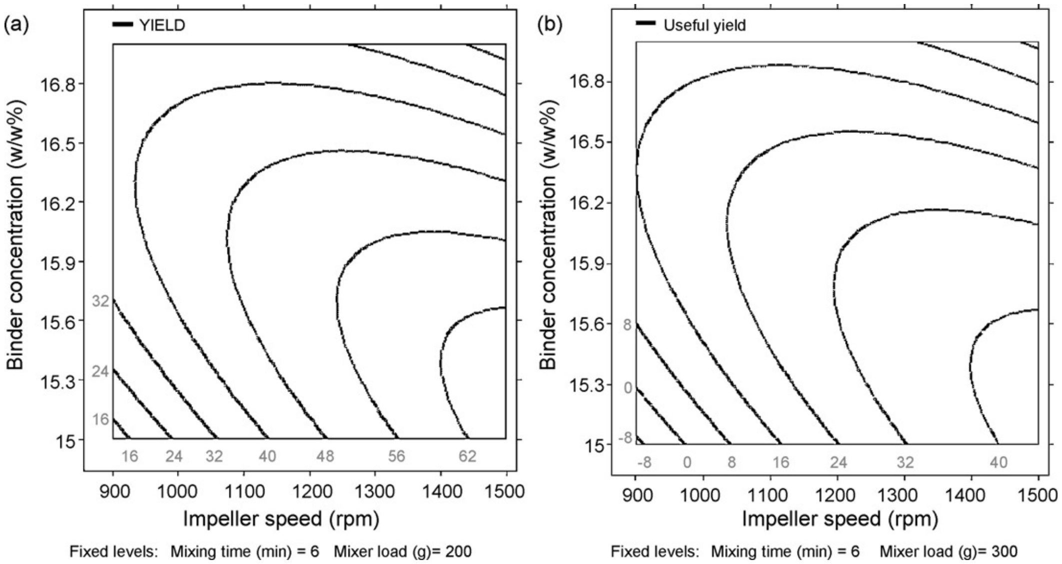

Fig. 5. The influence of binder concentration and impeller speed on the useful yield at low mixing time and (a) low mixer load and (b) high mixer load in case of Gelucire® 50/13.

much influenced by the time needed for the binder to diffuse to the surface. It can be concluded that high impeller speed can be compensated by shorter mixing time, and the other way round (negative interaction). The importance of the binder concentration can be explained by the growth mechanisms, which were examined by photographing the product at different time points (Fig. 6). It was confirmed that the distribution was predominant in the nucleation phase and the steady growth in the consolidation phase.

Although the viscosity of the binder was shown to be too high to achieve a controllable process in case of Lutrol® F68, the mixing time was identified as the variable that mostly influenced the pelletization process; by contrast, the concentration of the binder did not seem to have any influence on the useful yield. This difference, compared to the results obtained by Gelucire® 50/13, is a direct consequence of the predominant mechanism in the nuclear phase of the process, which is immersion in the case of Lutrol® F68. This mechanism is typical for the processes in which high viscosity binders with relatively large particle size are used (Fig. 7). Three factors were found to significantly influence the useful yield. These were impeller speed, mixing time, and mixer load (Fig. 8). No interactions between the factors were noted. By prolonging the mixing time from 3 to 6 min, the useful yield was rising, whereas longer mixing times reduced the useful yield (Fig. 8b). If the mixing time is too short, there is not enough time for melting of the binder. Small solid particles therefore stick to the softened binder only and not to each other. To get particles of appropriate size, optimum mixing time is needed for the product temperature to rise only slightly above the melting temperature of the binder. If the mixing time is too long, the energy input into the system is too high. Consequently, the densification of the agglomerates is accelerated which increases the deformability of the aggregates and also their rapid growth. This phenomenon is even more pronounced at higher impeller speeds and product temperatures.

The hot-melt pelletization process requires optimum energy input into the system to reach equilibrium between the particle coalescence and the comminution of the forming aggregates. At a low energy input, both processes, the coalescence and the comminution, are slow and the equilibrium is difficult to achieve. If the energy input is too high, both processes are too fast and rapid growth of aggregates out of comminuted particles occurs. The optimum energy input can be achieved by careful control of impeller speed and mixing time.

In the case of Lutrol® F68, higher yield was also achieved by decreasing impeller speed. At a higher impeller speed, the shear forces propagated the densification and rearrangement of the internal structure of aggregates after coalescence and the saturation of the molten binder liquid on the surface. Excessive lump formation was observed. This effect was controlled by decreasing the mixing time.

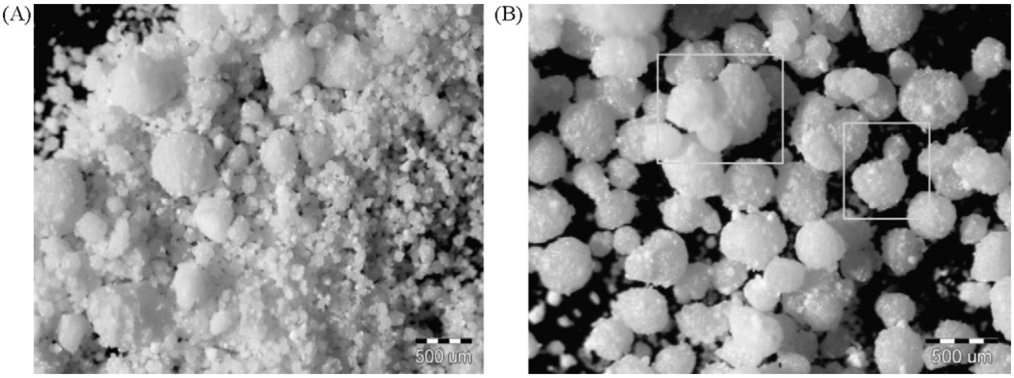

Fig. 6. Distribution of the binder in early granulation phase (a) and growth by coalescence in the pelletization phase (b) in case of Gelucire 50/13®.

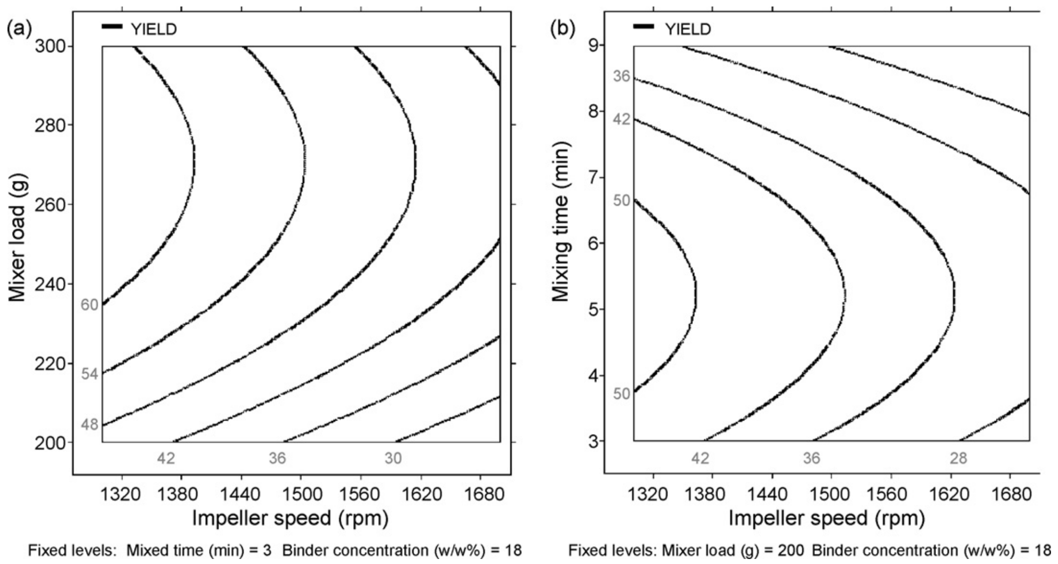

Fig. 7. The influence of (a) impeller speed and mixer load and (b) impeller speed and mixing time on the useful yield in case of Lutrol® F68.

Fig. 8. Immersion as a predominant process in nucleation phase in case of Lutrol® F68.

On the other hand, the sticking of the pelletizing mixture to the vessel walls was more pronounced when Gelucire® 50/13 was used as the binder. Agglomerates that are formed by use of binders with lower viscosities are more deformable and are therefore more prone to sticking than binders with higher viscosities, such as Lutrol® F68, where this effect was not noticed within the selected experimental region.

At the end, the optimum quantity of each binder and optimum processing parameters for pelletization were identified mathematically (regression model) within the investigated experimental region. Our goal was to maximize useful yield by minimizing at the same time the amount of lumps formed during the pelletization process and the amount of residual powder. Statistically calculated values describing the optimum process parameters and binder concentration are shown in Table 5.

Table 5
Predicted values describing optimal process.

Factors	Predicted optimal values	
	Lutrol® F68	Gelucire® 50/13
Impeller speed (rpm)	1300	900
Mixing time (min)	6	12
Mixer load (g)	275	275
Binder concentration (%)	18.2	16.5

Table 6
Predicted and observed values.

Response surface	Predicted values		Observed values	
	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68
Useful yield (%)	68.1 ± 10.6	71.9 ± 18.7	66.0	75.2
Residual powders (%)	0.9 ± 0.3	3.5 ± 0.5	0.8	2.0
Lumps (%)	5.8 ± 0.8	5.3 ± 1.8	8.6	4.8

Independent experiments were performed to verify the optimum conditions identified in the Box–Behnken experiments. The observed values obtained form these additional experiments were in close agreement with the predicted values (Table 6). In both cases (pelletization with Gelucire and Lutrol) useful yield was higher than in the previous Box–Behnken experiments. In the experiment performed with Lutrol® F68, it even exceeded the predicted value. In the case of Gelucire® 50/13, the experimentally obtained values for the useful yield were slightly lower than the predicted ones. In both cases the amount of residual powders was lower than predicted. In the case of Lutrol® F68, also the amount of lumps was lower whereas with Gelucire® 50/13 the amount of lumps formed was slightly higher than predicted.

4. Conclusion

The Box–Behnken experimental design and the response surface methodology allowed both the determination of the influence of particular process parameters and their optimization. The predicted response values, obtained mathematically by regression model, were confirmed also experimentally and the models were successfully validated, regardless of the binder used.

In the case of low viscosity binders such as, macrogolglycerides the pelletization process is easily controllable whereas in the case of high viscosity binders (poloxamers) the process was slightly more difficult to control. In the latter case, this could be improved by higher temperatures of the heating jacket and by use of cool inlet air, which would ensure better control of product temperature and, consequently, of the level of liquid saturation and agglomerate growth. With the repetition of pelletization experiment using the predicted optimal settings for process and formulation parameters the quality of the two models was proved.

The results of the present work show that thermoplastic pelletization in a high shear mixer is a simple and effective alternative to classical pharmaceutical methods. The process itself strongly depends on the thermal and rheological behavior of the binder used and is sensitive to the changes in the process and formulation variables. This drawback can be overcome by identification of critical parameters, their optimization and careful control.

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