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Research paper

Melt pelletization in high shear mixer using a hydrophobic melt binder: influence of some apparatus and process variables

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Abstract

The effects of process conditions and the apparatus variables on the granulometric characteristics of a formulation containing a hydrophobic binder (stearic acid), lactose and paracetamol prepared by melt pelletization process were investigated in a 10-litre high shear mixer. The factors under investigation were: impeller speed, massing time, type of impeller blades and presence of the deflector and their reciprocal interactions. Two granule characteristics were analysed: the percentage of aggregates larger than 3000 μm (Y_1) and the yield of the 2000-μm pellet size fraction (Y_2). In order to estimate simultaneously the above-mentioned factors, a particular experimental design was adopted, that allowed the reduction of the number of trials from 378 to 35 and took into consideration other uncontrolled factors with the aid of a block variable. Using the postulated model, we found the optimal operating conditions to minimize Y_1 and increase Y_2 by selecting the type of impeller, and by using an impeller speed lower than 300 rpm, a massing time of 8-9 min and by not using the deflector. Finally, the validity of the adopted strategy has been proved with an additional check point.

Keywords: Melt pelletization; 10 liter High shear mixer; Paracetamol; Stearic acid; D-optimal design

1. Introduction

The melt agglomeration is a single-step technique that converts fine powders into granules of various sizes. In this process, the agglomeration is promoted through the addition of either a molten binder liquid, a solid binder or a solid which melts during the process. The product temperature is raised to above the binder melting point either by a heating jacket or by the heat of friction during the mixing phase [1]. Though different equipment can be used to accomplish melt granulation, high shear mixers are the equipment of choice for this technology. The influence of the apparatus and process variables on the characteristics of the final pellets were studied by many authors using both water-soluble and water-insoluble melt binders.

The most widely used water-soluble melt binders are the polyethylene glycols. Schaefer, using several formulations containing polyethylene glycols 3000 and 6000 in a 10-litre Baker Perkins vertical granulator, indicated that the granule size and size distribution were strongly influenced by massing time, whereas a high impeller rotation speed favoured a narrow size distribution [2]. Different scales of Pellmix high shear mixer (50 l and 8 l scale) were then used to study the effect of massing time and rotation speed onto mixtures of lactose and PEGs, giving evidence that larger rounded pellets with a narrow size distribution could be obtained at high impeller speeds and with a prolonged massing time [3,4]. The recent work conducted by Heng and coworkers in a 10-l PMA-1 Aeromatic Fielder dealt with the effect of impeller speed, massing time and mixer load, also considering the reciprocal interactions [5]. The results indicated that rapid consolidation and agglomeration growth rates were obtained with increased impeller speeds, and the interaction between mixer load and impeller rotation speed must be considered as a sensitive parameter to achieve the necessary energy input into the system.

The influence due to the type of impeller blades was investigated by Schaefer et al. in 8 l Pellmix [6]. They found that curved impeller blades were more able to promote the formation of smooth and spherical pellets compared to plane blades, due to the higher power input given to the system.

In our previous work, conducted in a 10-l Roto J Zanchetta high shear mixer using PEG 6000 as a binder, a screening between several apparatus and process variables was carried out to evaluate their influence on the agglomerate size growth. This screening permitted isolation of the qualitative and quantitative variables, showing that a change of type of impeller blades, impeller speed and massing time led to a spheronized product rather than a simply granulated one [7].

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On the other hand, several authors employed water-insoluble low melting binders, often with the aim to prepare sustained release dosage forms. In particular, the work by Thomsen et al. [8] must be remembered, dealing with the preparation of matrix pellets containing paracetamol, where microcrystalline wax and glycerol monostearate were used as melt binders in a 8 l Pellmix. That study established the importance of impeller speed and massing time when using curved impeller blade for obtaining the maximum yields of pellets in the range of 500–1400 μm. Zhou et al. [9], who produced a matrix of pellets based on the combination of microcrystalline waxes and a starch derivative in different types of granulators with a volume ranging form 2 to 70 l, noted that the processing (production and formulation) parameters had to be adjusted as a function of the granulator in order to obtain the same pellet quality, due to the different movement of the mass which depends on the impeller shape and size. Furthermore, they found that an increased mixing time and an increased impeller speed induced a larger pellet size and a lower porosity. More recently, Thies and Kleinebudde [10], after melt pelletization experiments conducted in a 10-l P10 Diosna using glycerol monostearate as a binder, indicated that impeller speed was the most important apparatus variable influencing the mean granule size and size distribution. Our recent work, also conducted in a 10-l Roto J Zanchetta, focused on the design of a melt pelletized formulation containing stearic acid as a binder. We found that the yield of the 2000-μm size fraction was very sensitive to small variations of impeller rotation speed and massing time [11].

The purpose of the present work has been to investigate the feasibility of a melt pelletized formulation containing paracetamol, by employing stearic acid as hydrophobic binder and using the 10-l Roto J Zanchetta high shear mixer. Other authors studied the pelletization capability of a mixture of the same drug with stearic acid using calcium hydrogen phosphate as a filler. This study indicated that stearic acid at concentrations of 21.5% v/m does not favour the pelletization process, whereas the combination with glyceryl monostearate and a reduction of the total amount of binder to 19.5% does [12]. This paper is concerned with the evaluation by experimental design of the effects of some apparatus and process variables on the melt pelletization, and considers the reciprocal interactions. Following the previous positive results obtained with the incorporation of theophylline [11], in this study, a mixture of lactose, stearic acid and a water-soluble model drug, paracetamol, has been used.

2. Materials and methods

2.1. Materials

Paracetamol reagent-grade (ACEF, Fiorenzuola D'Arda, Piacenza, Italy), stearic acid reagent-grade (Galeno, Milan, Italy), and monohydrate lactose (Pharmatose 200 mesh, Meggle, Wasserburg, Germany) were used as starting materials. The size distributions of the starting materials were determined by microscopical analysis technique (Olympus BH-2 microscope, equipped with a computer-controlled image analysis system Optomax V, Cambridge, UK). The mean diameter and the standard deviation were found to be 13.91 ± 3.83 μm for paracetamol, 16.00 ± 11.30 μm for lactose, and 204.20 ± 95.78 μm for stearic acid.

The melting range of the stearic acid was estimated by a differential scanning calorimeter (Mod. TA 4000, equipped with a measuring cell DSC 20 Mettler, Greifensee, CH). Samples of about 8 mg were placed in pierced aluminium pans (nominal capacity of 40 μl) and heated from 25 to 100°C at a scanning rate of 10°C/min, under air atmosphere. Stearic acid melted with a peak temperature of 58.3°C.

2.2. Equipment

The granules were prepared in a 10-l laboratory scale Zanchetta Roto J vertical axis high shear mixer equipped with an electrically heated jacket (maximum temperature 100°C), described in a previous work [13]. Three different interchangeable impeller blades were compared. The difference between the impeller blade lies in the inclination angles, the blade area and the geometry. In particular, the impeller A and B are plane and they have a blade area of 189 and 187 cm^2, respectively, resulting from an inclination angle of 30° and 45° (Fig. 1A,B). The impeller C has a blade area of 176 cm^2, and its geometry is different. Two parts can be distinguished: the plane blade with an inclination angle of 60°, the tip with an angle of 30° (Fig. 1C).

The relative swept volumes of the impeller blades and the respective impeller speed used in the trials are shown in Table 1. The effect of the presence of a deflector into the upper part of the bowl has also been considered (Fig. 1Z). The relative swept volume was calculated by dividing the impeller swept volume by the net volume of the bowl. With the deflector on, a reduction of the bowl volume from 10 to 8.4 l must be considered.

2.3. Pellet production

The granulation procedure was standardized on the basis of both the preliminary trials and the methodology already applied in the pelletization of mixtures, the latter being based on the combination of stearic acid and lactose [11]. With respect to this previous work, the range of velocity has been restricted to 200–300 rpm, since in this case a higher impeller rotation speed caused an uncontrolled ball growth.

The temperature of the powders inside the bowl was continuously recorded by a thermo-resistance probe fixed on the bowl lid and dipped in the powder mass.

All components, with the exception of stearic acid, were first mixed at an impeller speed of 50 rpm while heating, until their temperature had reached 55°C. The dry mixing was interrupted to add the stearic acid, and then restarted for 3 min at 100 rpm to obtain a uniform distribution of the

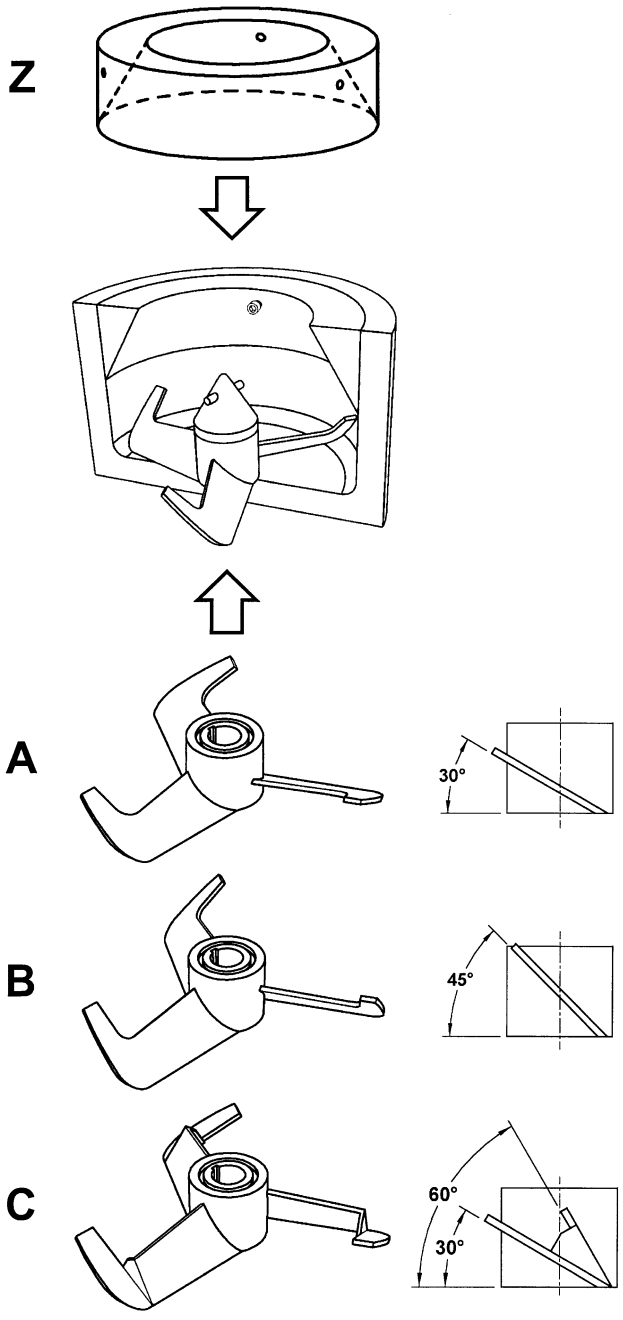

Fig. 1. Schematic drawing of the 10 L Roto J Zanchetta high shear mixer. The three different types of impeller blades characterized by different angles of inclination of the plane blades: (30°, A; 45°, B; 60°, C), and the deflector used in this study (Z).

binder. At this point, the stearic acid reached a molten state (the temperature was around 65°C). During the subsequent massing process, impeller speed, massing time and other qualitative values were varied according to the experimental plan reported in Table 2. The total amount of paracetamol and excipients used was 1 kg. The composition of the mixtures was paracetamol/lactose/stearic acid 60:20:20. At the end of the granulation process the granules were cooled at room temperature by spreading them out in thin layers on trays and then stored in sealed bags.

2.4. Pellet characterization

After 10 days of storage in sealed bags, the pellets were characterized by sieve analysis. A vibrating apparatus (Octagon 200, Endecotts) and a set of sieves (3000, 2000, 1250, 800 and 630 μm) were used for size distribution determinations, calculating the yield of each size fraction. Finally, the content of fines smaller than 630 μm was determined.

2.5. Experimental design

The influence of different process factors on the granulometric characteristic of the final product has been studied by many authors, often with the aid of the experimental designs. In particular, the full factorial designs at two levels [14,15], the asymmetrical factorial design [7], the orthogonal design matrix $L_3$4 [5] and the Doehlert matrix [11] have been used to develop a melt pelletized formulation, or optimize a melt pelletization process. Equally, in this case, to reduce the number of experiments needed to obtain the highest amount of information on product performance, the evaluation of process and apparatus variables and the reciprocal interactions were conducted using an experimental design. In our design, two out of four considered variable factors (X_2, X_3) were quantitative and continuous and they were fixed at definite levels (three levels). The other two factors are qualitative (X_4, X_5); among them, the first one (X_4) is fixed at two levels and X_5 at three levels. For the quantitative factors, the experimental design is 3^2 full factorial and consists of nine experiments (Fig. 2a), whilst for the qualitative factors the design is asymmetrical factorial and consists of six experiments (Fig. 2b).

Theoretically, for considering all the possible combinations between the factors at the different levels, the number of experiments needed was 54 (resulting from 9×6) (Fig. 2c). However, from the preliminary trials we noticed that

Table 1
Relative swept volumes (s^{-1}) of the impeller blades in 10-l (Roto J) high shear mixer

Rpm	Impeller A		Impeller B		Impeller C		Peripheral speed ($m\ s^{-1}$)
200	2.83[a]	2.37	2.80[a]	2.35	2.63[a]	2.21	2.89
250	3.53[a]	2.96	3.50[a]	2.94	3.28[a]	2.76	3.61
300	4.24[a]	3.56	4.20[a]	3.52	3.99[a]	3.32	4.33

[a] Relative swept volume in presence of the deflector.

Table 2
Experimental plan and observed response values

Experiment	Process variables					Percentage yield (w/w) of pellet size fraction					
	X_1 (block)	X_2 (rpm)	X_3 (min)	X_4	X_5	3000 μm (Y_1)	2000 μm (Y_2)	1250 μm	800 μm	630 μm	< 630 μm
1	1	200	8	No	B	4.82	6.87	34.23	34.01	2.07	18.00
2	1	300	8	Yes	A	11.03	40.13	31.14	2.90	1.74	13.05
3	1	200	12	No	A	0	2.57	42.50	40.51	1.60	12.82
4	1	200	10	Yes	C	0	0	40.36	46.15	1.84	11.64
5	1	250	12	Yes	B	24.94	30.30	8.19	6.24	6.33	24.00
6	2	300	8	No	A	0	22.96	58.43	7.60	1.38	9.63
7	2	200	12	Yes	A	8.29	13.03	60.78	9.20	0.62	8.08
8	2	300	12	Yes	B	37.40	12.22	7.96	11.47	10.25	20.70
9	2	200	10	No	B	2.51	3.77	43.47	26.98	1.63	21.64
10	2	250	12	No	C	1.48	1.38	68.20	14.69	1.22	13.02
11[a]	3	200	8	Yes	B	9.13 ± 3.09	8.96 ± 3.51	51.18 ± 5.35	9.32 ± 4.05	3.24 ± 1.80	18.17 ± 4.26
12	3	200	8	No	C	0	0	12.38	65.10	4.42	18.10
13	3	300	8	No	B	25.63	38.99	12.54	5.39	5.67	11.78
14	3	200	12	No	B	4.20	11.43	60.18	8.07	0.95	15.17
15	3	250	10	No	A	6.82	13.09	54.95	11.90	1.03	12.21
16	4	200	8	No	A	2.95	5.47	15.06	56.62	6.07	13.83
17	4	200	12	Yes	C	0	2.18	21.80	53.97	2.52	19.53
18	4	300	12	Yes	A	52.90	30.69	5.86	3.62	2.02	4.91
19	4	300	10	No	C	10.77	24.05	43.92	5.24	1.96	14.06
20	4	250	8	Yes	C	3.52	1.26	54.27	22.53	1.46	16.96
21	5	200	8	Yes	B	3.36	5.18	56.80	14.08	7.36	13.22
22	5	300	8	No	C	2.02	19.62	58.51	10.42	1.46	7.97
23	5	200	12	No	C	0	0	10.48	68.11	3.71	17.70
24	5	300	12	No	B	57.90	33.66	2.40	1.66	1.07	3.30
25	5	300	12	Yes	C	11.55	36.03	33.46	4.42	2.59	11.95
26	6	200	8	Yes	C	0	0	3.29	70.88	8.47	17.36
27	6	300	8	Yes	B	29.05	16.42	15.68	15.84	9.27	13.74
28	6	200	12	Yes	B	5.92	14.32	61.69	3.67	1.21	13.17
29[a]	6	300	12	No	C	20.95 ± 4.47	32.76 ± 4.71	27.99 ± 5.04	3.33 ± 2.70	2.26 ± 1.37	12.71 ± 3.41
30	6	250	10	Yes	A	8.64	17.74	53.30	7.12	1.12	12.07
31	7	200	8	Yes	A	0	4.26	23.18	48.28	3.79	20.49
32	7	300	8	Yes	C	0	23.01	56.09	10.59	5.94	4.37
33	7	300	12	No	A	27.70	37.92	17.33	5.13	3.57	8.35
34	7	300	10	Yes	B	25.58	11.18	11.19	15.18	11.17	25.70
35	7	250	8	No	B	2.88	9.83	36.70	34.64	2.20	13.75

[a] Mean ± SD, $n = 4$.

some additional factors, such as the time related to introduction of changes in the apparatus (change of the impeller type and insertion of the deflector). In fact, for an accurate control of the temperature, it was not possible to carry out more than five experiments per day, due to the time-consuming changes that had to be made to the apparatus and due to the slow warming-up of the bowl which is only laterally jacketed. In order to take into consideration these uncontrolled factors, a block column (X_1) at seven levels was introduced into the experimental matrix. Hence, the final number of experiments necessary was 378 (resulting from $6 \times 9 \times 7$) (Table 3).

Two product variables (Y_i) have been selected, the percentage of aggregates larger than 3000 μm (Y_1) and the yield of the 2000-μm size fraction (Y_2). In fact, the need to reduce the number of large aggregates (having dimensions superior to 3000 μm) has previously been attested in melt granulation experiments carried out using both hydrophilic and hydrophobic binders [11,14]. On the other hand, considering the results of our previous work [11] and on the basis of the remarkably low in vitro drug release rate obtained in the preliminary dissolution tests, the 2000-μm size fraction was found to be the most suited for the desired aim of preparing a potential sustained release formulation.

Therefore, a special polynomial model, with 23 coefficients to estimate, was constructed for the description of the measured responses as function of the process variables (Eq. (1)).

$$Y = b_0 + c_1(x_{1A}) + c_2(x_{1B}) + c_3(x_{1C}) + c_4(x_{1D}) + c_5(x_{1E}) + c_6(x_{1F}) + b_2x_2 + b_3x_3 + b_4x_4 + b_5x_5 + b_{22}x_2^2 + b_{33}x_3^2 + b_{55}x_5^2 + b_{23}x_2x_3 + b_{24}x_2x_4 + b_{25}x_2x_5 + b_{34}x_3x_4 + b_{35}x_3x_5 + b_{45}x_4x_5 + + b_{255}x_2x_5^2 + b_{355}x_3x_5^2 + b_{455}x_4x_5^2 \quad (1)$$

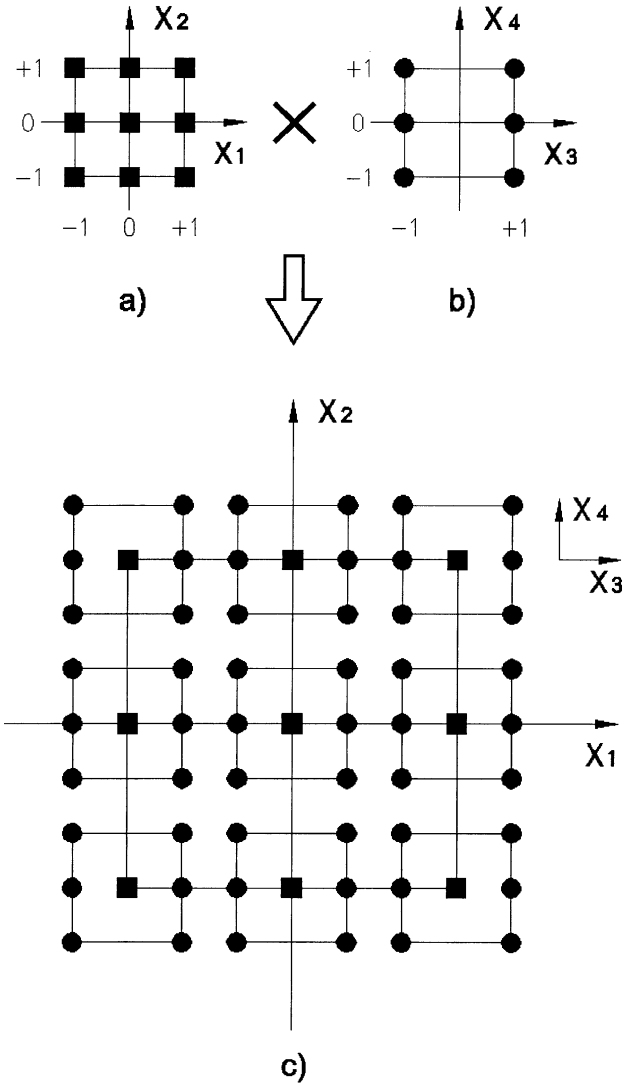

Fig. 2. Spatial distribution of the experimental points ($n = 54$) of four variables. The variables (X_i) are expressed in terms of normalized values.

For all the considered variables a full second-order model has been used, with the only exception of X_4, being fixed at two levels. It must be pointed out that to estimate the effect of the three levels it has been necessary to introduce the square term (X_5^2).

3. Results and discussion

To evaluate the influence of the considered variables on the two measured responses, the mathematical model previously reported (Eq. (1)) was postulated with 23 coefficients to be estimated. Since our matrix consisted of 378 experimental points, we applied the exchange algorithm to reduce the total number of experiments to be carried out. In consideration of the existing limitations (maximum number of experiment per day and fixed quantity of active substance available for the study) the number of experiments was fixed at 35, the highest possible. Another seven experiments were then carried out to test the validity of the postulated mathematical model. In order to select the most suitable matrix (D-optimal design), we compared several matrices in terms of the a priori criteria (Det(M)$1/p$, Trace$(X'X)^{-1}$, and the function of the variance (d_{max})) as described in our previous report [16], whose application into the pharmaceutical field has been widely described [17]. The 'best' design (that with the highest value of a priori criteria) was selected in each case; in our case the first suitable matrix consisted of 25 experiments. The trends in the design criteria are shown in Fig. 3. Fig. 3a shows that the determinant (Det(M)$1/p$) increased with N, but it is clear that on going from 25 to 26 experiments, the information carried by each experiment is considerably increased. The value then continues to increase from $N = 26$ to 35. We concluded that at $N = 35$ each experiment had provided the maximum of information for determining the coefficients. Secondly, Fig. 3b shows the Trace of $(X'X)^{-1}$, that diminishes when going from 32 to 35 experiments. This signifies that the precision of the estimation of the coefficients becomes more homogeneous and the estimations become more independent (orthogonal). Finally, d_{max}, shown in Fig. 3c, also diminished when going from 25 to 35. With the addition of the 35th experiment we observed a further decrease down to a value smaller than 1, which means that the model variance of prediction is equal to experimental variance.

The experimental runs were carried out in a totally random order according to the combined design (shown in Table 2). In addition, the experiments (numbers 11 and 29) were replicated ($n = 3$) in order to have a model independent measure of pure error for testing the model adequacy.

Table 3
Process variables (X_i) with their levels and measured responses (Y_i) for the experimental design

Independent variables	Normalized level	Experimental value
X_1: blocking factor	1-2-3-4-5-6-7	
Quantitative factors		
X_2: impeller speed (rpm)	1	300
	0	250
	−1	200
X_3: massing time (min)	1	12
	0	10
	−1	8
Qualitative factors		
X_4: presence of deflector	1	Yes
	−1	No
X_5: type of impeller blade	1	A
	0	B
	−1	C
Measured responses		
Y_1: percentage of aggregates larger than 3 mm (w/w)		
Y_2: percentage yield (w/w) of pellet, 2000 μm size fraction		

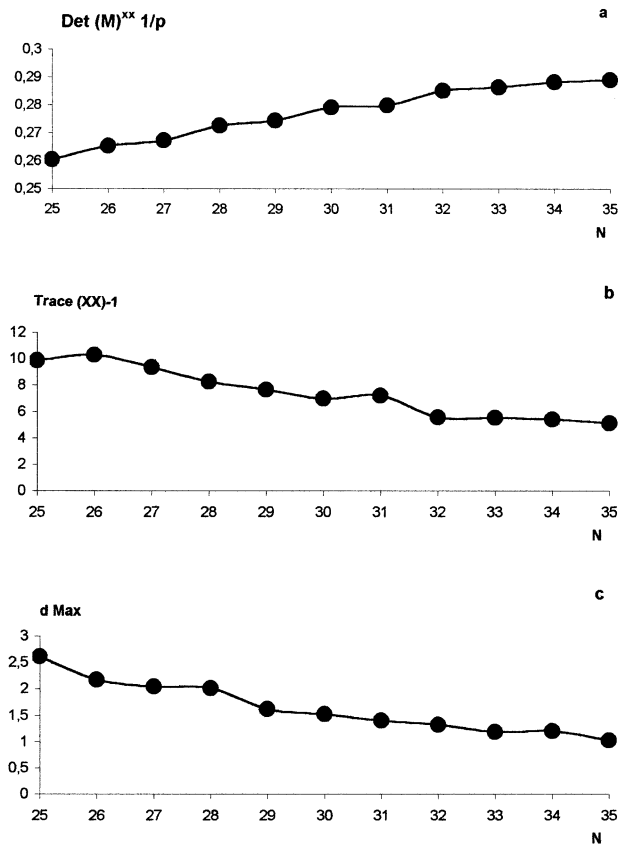

Fig. 3. Properties of the D-optimal designs for melt pelletisation: (a) Det(M)$1/p$; (b) Trace $(X'X)^{-1}$; (c) d_{max}.

Including replicates in the experimental design allows the partition of the residual sum of squares (SS_E) into two components: one due to pure error (SS_{PE}) and another due to lack of fit (SS_{LOF}). A statistical test based on the F ratio can be used for testing the significance of the null hypothesis about zero lack of fit of the model.

For the two considered variable responses the estimated residual variance was $MS_E = 347.945$ and $MS_E = 281.37$ for Y_1 and Y_2, respectively. Using the replicates, the experimental error variance was estimated such as $MS_{PE} = 14.77$ with 6 degrees of freedom (df), $MS_{LOF} = 25.87$ with 12 df for Y_1, and $MS_{PE} = 17.32$ with 6 df, $MS_{LOF} = 31.33$ with 12 df for Y_2. The value of the F statistic was $F = 1.75$ with a P value of < 0.01 for Y_1 and $F = 1.80$ with $P < 0.01$ for Y_2, respectively. In this way, the presence of lack of fit of model (Eq. (1)) was demonstrated. From the analysis of variance table, the R^2 were computed and their values were $R^2 = 0.95$ with an $R_A{}^2 = 0.89$ for Y_1, and $R^2 = 0.93$ with an $R_A{}^2 = 0.84$ for Y_2, respectively.

The estimates of the model coefficients (Eq. (1)) for the two response variables were determined by multiple regression analysis using the NEMRODW program [18] and the results are listed in Table 4.

From the analysis of the model coefficients, listed in Table 4, it was possible to obtain suitable information on the weight of the variables, and their reciprocal interactions. All four variables, both qualitative and quantitative, have been demonstrated to have a certain influence on the two measured responses.

In particular, concerning the effect on the percentage of aggregates larger than 3 mm (Y_1), among all variables, the two quantitative variables, impeller speed (X_2) and massing time (X_3), as well as their reciprocal interaction (X_2X_3), have been shown to be the most important. Moreover, the existence of interactions between the type of impeller (X_5) and the impeller speed (X_2X_5) was noted, as was the massing time (X_3X_5) and the presence of the deflector (X_4X_5). More specifically, into more details, the impeller of type B was found to be the most important in consideration of the significance of the square term (X_5^2) and of its interaction with the impeller speed ($X_2X_5^2$).

Secondly, the percentage yield of 2000-μm size fraction pellets (Y_2) was affected by the impeller speed (X_2, X_2^2), the presence of deflector (X_4) and the type of impeller (X_5). Significant interactions of impeller speed with the type of impeller B ($X_2X_5^2$), impeller speed with the presence of the deflector (X_2X_4), and impeller of type B with the presence of the deflector ($X_4X_5^2$) were noted.

As shown in Table 4, the effect of the blocking factor was estimated, but it did not influence the prediction of the experimental response since it was included in the model [17].

For a simpler analysis of the response behaviour over the whole experimental domain in function of the two qualitative variables, the isoresponse surfaces were drawn and they

Table 4
Estimates and statistical significance of the model coefficients (Eq. (1)) for the two measured response variables

Coefficients	Y_1	Significance (%)[a]	Y_2	Significance (%)[a]
b0	9.03	1.46*	5.51	14.9
c1	6.86	4.51*	4.70	19.7
c2	2.64	44.00	−4.53	22.5
c3	7.48	2.49*	7.71	3.35*
c4	13.74	0.0616***	−0.77	82.8
c5	7.15	4.04*	3.10	40.3
c6	6.55	4.36*	4.24	21.9
b2	15.91	< 0.01***	8.28	< 0.01***
b3	5.95	0.0669***	2.44	13.5
b4	−0.79	54.6	−3.47	2.12*
b5	−4.89	0.0241***	−4.25	0.182**
b22	3.91	8.4	5.41	3.38*
b33	2.40	28.2	3.35	17.3
b55	−13.19	< 0.01***	0.95	63.7
b23	5.63	< 0.01***	0.18	85.3
b24	−0.83	36.6	−2.15	3.94*
b25	−2.40	4.45*	0.66	60.5
b34	−1.49	12.3	1.07	31.0
b35	−3.37	0.736**	1.31	29.9
b45	−2.61	2.16*	−0.32	77.6
b255	−8.26	0.0257***	5.67	0.966**
b355	0.04	98.0	0.30	87.5
b455	2.62	12.8	5.88	0.459**

[a] ***$\alpha < 0.001$; **$\alpha < 0.01$; *$\alpha < 0.05$.

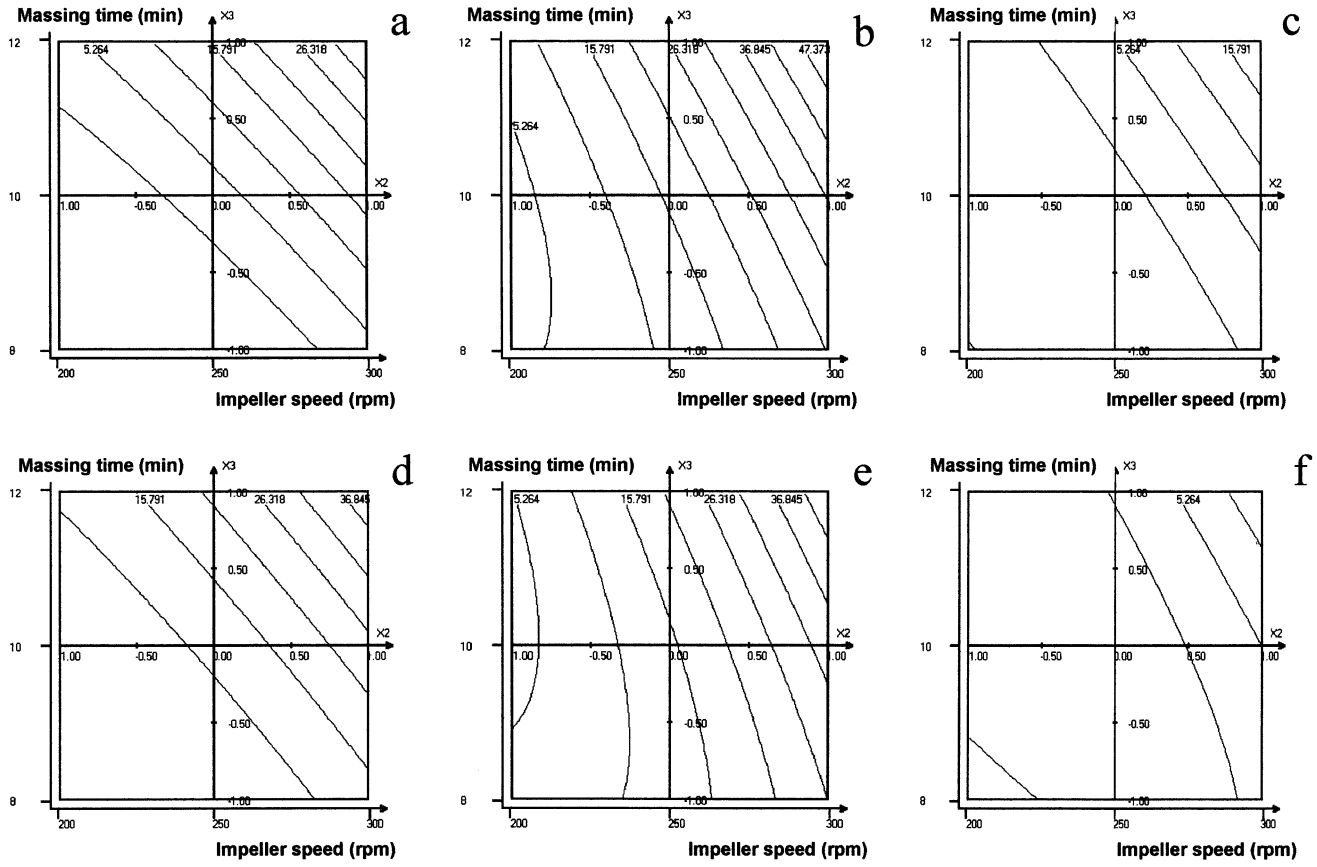

Fig. 4. Isoresponse surfaces for the percentage of aggregates larger than 3000 μm (Y_1) as function of the impeller speed (X_2) and massing time (X_3): without the deflector in the presence of the type of impeller (a) A, (b) B, (c) C; with the deflector in the presence of the type of impeller (d) A, (e) B, (f) C.

are depicted in Figs. 4 and 5 for Y_1 and Y_2, respectively. From the isoresponse surface we found the ideal experimental conditions to achieve our above mentioned aim, consisting in a reduction of Y_1 and an increase of Y_2. In particular, to minimize the variable Y_1 it was necessary not to use the deflector and employ the impeller of type A or C. Since the inclination of the tip of the blade is equal in both types of impeller and this restricted triangular portion has been previously found to be the active zone for the agglomeration process [1], the impellers A and C determine a similar impact of the granulating mass, thus having a similar effect. Moreover, the presence of the same types of impeller were found to be necessary to increase the yield of the 2000-μm size fraction (Fig. 5a,c,d,f).

To verify the above-mentioned findings, another experiment (check point) was carried out with the following conditions: impeller speed of 289 rpm, massing time of 8 min, absence of the deflector and presence of the impeller of type A. This way, the measured responses were found to be 0.85 for Y_1 and 32.12 for Y_2, compared to the values predicted by the model (Eq. (1)) 1.86 ± 3.83 for Y_1 and 30.78 ± 4.20 for Y_2, thus testifying the validity of the adopted strategy. This also indicated that impeller speed regulates the formation of pellets of the 2000-μm size fraction, in agreement with the results of our previous investigation [11], where a variation of only 50 rpm in the impeller speed caused an increase of 30% in the yield of this fraction. In the present work, one strategy to increase the yield of this fraction, using only stearic acid as a binder, could be to operate at an impeller speed of about 290 rpm, stop the process after 8–9 min of massing, recuperate the considered fraction and then restart the agglomeration process.

4. Conclusions

In this work we demonstrated that granulometric characteristics of the final product obtained by melt pelletization, from a mixture containing a hydrophobic binder, in a high shear mixer are influenced by process variables and apparatus variables. To reduce time and cost and taking into consideration other uncontrolled factors through a block variable, a D-optimal design has been applied in this melt pelletization study. This experimental design enabled the number of trials to be reduced from 378 to 35. With only 35 experiments we were able to estimate the 'weight' of the four variables and their reciprocal interactions on the two granulometric characteristics under study: the percentage of aggregates larger than 3000 μm (Y_1) and the yield of the 2000-μm pellet size fraction. In particular, the postulated

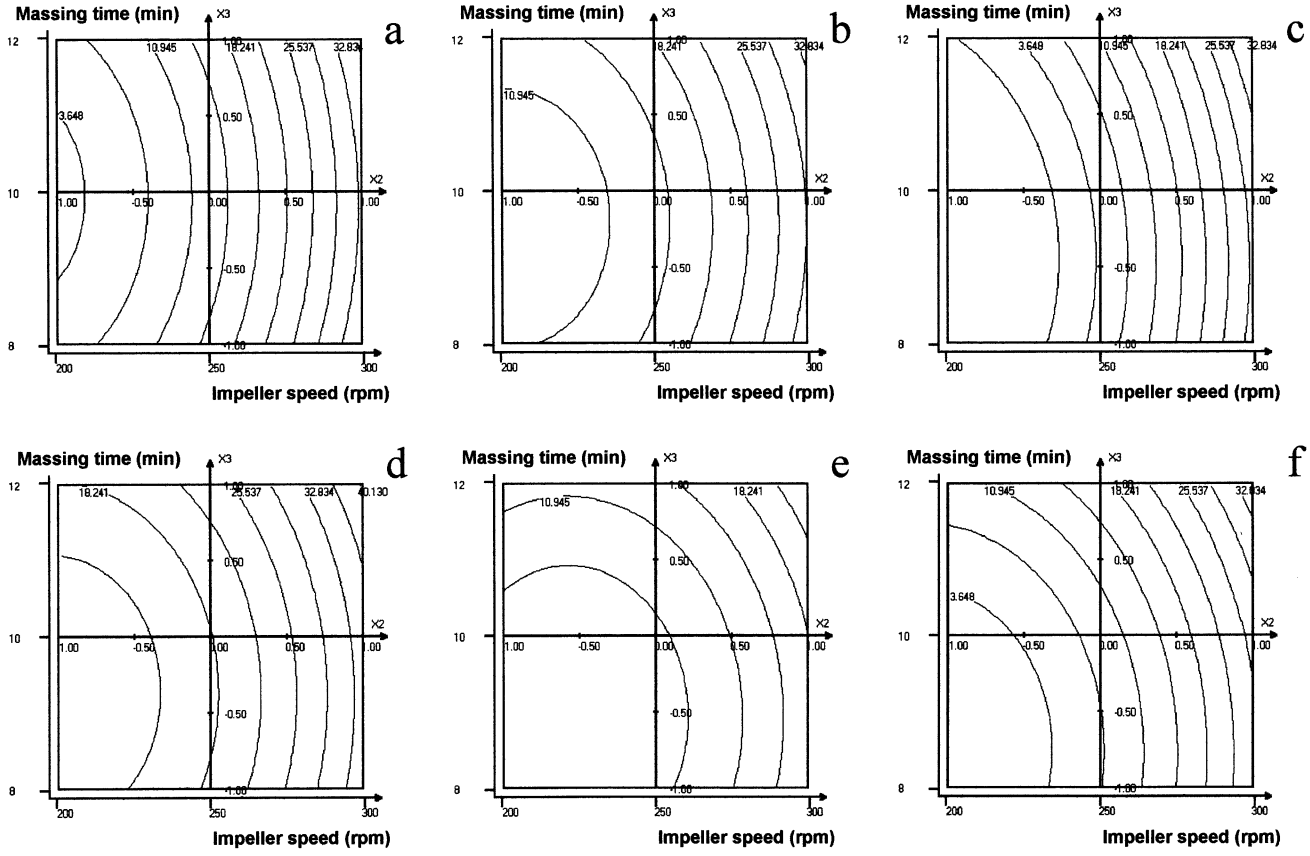

Fig. 5. Isoresponse surfaces for the yield of the 2000-μm pellet size fraction (Y_2) as function of the impeller speed (X_2) and massing time (X_3): without the deflector in the presence of the type of impeller (a) A, (b) B, (c) C; with the deflector in the presence of the type of impeller (d) A, (e) B, (f) C.

model permitted Y_1 to be minimized and Y_2 to be increased by selecting the optimal values for the four considered variables. Going into more detail, the optimal operating condition controlling the process was the presence of impeller of type A or C, an impeller speed lower than 300 rpm, a massing time of 8 min and the absence of the deflector. Finally, the validity of the adopted strategy has been proved with an additional check point.

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