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Screening of high shear mixer melt granulation process variables using an asymmetrical factorial design

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Abstract

The effects of process conditions on the granulometric characteristics of a placebo formulation prepared in a 10 l high shear mixer by single-step melt granulation were studied. The factors under investigation were: binder grade, mixer load, presence of the deflector (all of analysed at two levels), binder concentration, impeller speed, massing time, type of impeller blades (these four at three levels) and jacket temperature (considered at four levels). Two granule characteristics were analysed: the geometric mean diameter and the percentage of particles finer than 315 μm. In order to screen simultaneously the above-mentioned factor levels, an asymmetrical factorial design was adopted, which allowed the reduction in the number of runs from 2592 to 25. Additionally, this technique permitted the selection of the factor levels which have the major 'weight' on the two granule characteristics under study. Two additional trials were performed to attest the screening validity.

Keywords: Factor level screening; Asymmetrical factorial design; Melt granulation; High shear mixer

1. Introduction

The melt granulation is a single-step technique converting fine powders into granules of various size and more or less regular spherical shape. In particular, the powder agglomeration is promoted by the addition of a low melting point binder, which can be a wax, or a mixture of waxes, fats, fatty acids and/or polyethylene glycol. The binder is liquefied by heat generated either by a heating jacket or by friction during the mixing phase (McTaggart et al., 1984; Schaefer et al., 1990).

The melt granulation process in high shear mixers is obviously affected by starting material variations and by several process variables. The influence of different process factors, on the granulometric characteristic of the final product, has been studied by many authors, often by the aid of factorial experimental designs. In particular, the most investigated variables are the following:

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mixer load, impeller speed, massing time (McTaggart et al., 1984; Kinget and Kemel, 1985; Schaefer et al., 1990, 1992a, 1993), temperature of the heating jacket (Kinget and Kemel, 1985; Schaefer and Mathiesen, 1996a), chopper action (Schaefer et al., 1992a); binder concentration (Schaefer et al., 1990, 1992a), binder particle size (Schaefer et al., 1992a; Schaefer and Mathiesen, 1996b), binder viscosity (Schaefer and Mathiesen, 1996c; Eliasen et al., 1998), apparatus variables (Schaefer et al., 1993), physical properties of the materials (Schaefer et al., 1992b; Schaefer 1996a,b).

In the present investigation, an asymmetrical fractional-factorial screening experimental design was employed in order to evaluate the weights of different factor levels on the granulometric characteristics of a placebo formulation obtained by single step melt granulation in a 10 l laboratory scale high shear mixer. The following factors were considered: binder grade, mixer load, presence of a deflector, binder concentration, impeller speed, massing time, type of impeller blades and jacket temperature, each of them analysed at different levels. The granules were composed of lactose, hydroxypropylmethylcellulose and polyethylene glycol (PEG) 6000 as a melting binder. Geometric mean diameter of the granules and percentage of particles having a diameter smaller than 315 μm were the two properties of interest for the placebo granulation. The main purpose of this investigation was to screen simultaneously the effects of the process variables at each assigned level on the two properties.

2. Experimental design

To reduce the number of runs needed to obtain the highest amount of information on product performance, the screening was planned using an experimental design. In particular, an asymmetric plan was employed, since the factors involved were considered at different levels. The factorial arrangement $2^3 3^4 4^1//25$ was used, where 25 represents the number of runs, the tested factors being 8: three factors at two levels, four factors at three levels and one factor at four levels (Table 1).

For generating the asymmetrical factorial arrangement the procedure proposed by Addelman (1962) was applied. The multilevel experimental plan required was obtained from a complete factorial design using some correspondence schemes for collapsing the number of levels and factors. In general, the advantage of this special design technique lies in a large reduction of trials needed. In fact, in this study, though the number of factors and the corresponding levels would yield 2592 ($2^3 \times 3^4 \times 4^1 = 2592$) possible combinations, the total number of runs performed was 25.

Four subsequent steps were needed to design the multilevel experiment. At first, from the complete 5^2 factorial design a 5^6 treatment was ob-

Table 1
The process and product factors, test levels, and experimental responses

Experimental variables	Levels			
	0	1	2	3
A Binder grade	Powder	Flakes		
B Mixer load (kg)	1.5	2		
C Presence of deflector	Yes	No		
D Binder concentration (%) (w/w)	23	24	25	
E Impeller speed (rpm)	300	400	500	
F Massing time (min)	17	21	25	
G Type of impeller blades	α	β	γ	
H Jacket temperature (°C)	65	70	80	90
Y_1 Geometric mean diameter (μm)				
Y_2 Particles finer than 315 (μm) (w/w)				

Table 2
Asymmetrical factorial design ($2^3 3^4 4^1//25$) obtained using Addelman's procedure

Run	x_1	x_7	x_8	x_2	x_3	x_4	x_5	x_6
1	0	0	0	0	0	0	0	0
2	1	0	1	0	1	1	1	1
3	0	1	1	0	2	2	2	2
4	1	1	0	0	1	1	1	1
5	0	0	0	0	0	0	0	0
6	0	0	0	1	1	2	1	0
7	1	0	1	1	2	1	0	0
8	0	1	1	1	1	0	0	1
9	1	1	0	1	0	0	1	2
10	0	0	0	1	0	1	2	1
11	0	0	0	2	2	0	1	1
12	1	0	1	2	1	0	2	0
13	0	1	1	2	0	1	1	0
14	1	1	0	2	0	2	0	1
15	0	0	0	2	1	1	0	2
16	0	0	0	3	1	1	0	2
17	1	0	1	3	0	2	0	1
18	0	1	1	3	0	1	1	0
19	1	1	0	3	1	0	2	0
20	0	0	0	3	2	0	1	1
21	0	0	0	0	0	1	2	1
22	1	0	1	0	0	0	1	2
23	0	1	1	0	1	0	0	1
24	1	1	0	0	2	1	0	0
25	0	0	0	0	1	2	1	0

tained using special column generators, requiring the modulo 5 arithmetic for all calculations, as 5 was the number of factors levels (Kacker et al., 1991). Successively, Addelman's collapsing schemes were adopted to assign: (a) six four-level factors to the five-element array by repeating one of the levels; (b) three two-level factors onto one four-level factor; and (c) four three-level factors to the remaining four-level columns. The final experimental design is represented in Table 2.

Using the 25-run experiment with two-level for three factors, three-level for four factors, and four-level for one factor (Table 3), the 'weight' of each factor level was estimated by means of the least squares method. For each factor the weight of each level is related to the upper level weight, which becomes the 'reference state' among each factor. It should be noticed that the use of an asymmetrical design to compare different factor levels does not give any information about the effect of the factors themselves. The only considerations that can be drawn regard the weight of each level, and hence a comparison between the levels of the factors considered one at a time (Lewis et al., 1999).

3. Materials and methods

3.1. Materials

Lactose (Pharmatose, 200 mesh, Prodotti Gianni-Italy), microcrystalline cellulose (MC-Avicel PH 101), hydroxypropylmethylcellulose (HPMC-Methocel K 100M) and PEG 6000 (Faravelli-Milano, Italy) were used as starting materials.

3.2. Equipment

The granules were prepared in the 10 l laboratory scale Zanchetta Roto J high shear mixer equipped with an electrically heated jacket (maximum temperature 100°C), already described in a previous work (Vojnovic et al., 1993). Three different sets of impeller blades were compared. The plane part inclination angles of the blades were: 60° (α), 30° (β) and 45° (γ) (Fig. 1). The relative swept volumes of the impeller blades at the respective impeller speed used in the trials are shown in Table 4. The relative swept volume was calculated dividing the volume swept by the impeller 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.

A vibrating apparatus (Octagon 200, Endecotts) and a set of sieves (1250, 800, 630, 500, 400, 315 and 250 μm) was used for size distribution determinations.

Photographs of the granules were taken using a scanning electron microscope (SEM) (Jeal JSH 5200, Japan).

3.3. Granulation manufacture

The granulation procedure was standardised on the basis of preliminary trials, and the temperature of the powders inside the bowl were continuously recorded by a thermo-resistance probe fixed on the bowl lid and dipped in the powder mass.

The placebo mixture composed of lactose (66%), microcrystalline cellulose (7%), hydroxypropylmethylcellulose (27%) and PEG 6000 was dry-mixed using an impeller speed of 50 rpm for 10 min. Successively, the mixture was heated up. The temperature and all the other factors (Table 1) were varied according to the experimental plan (Table 3). At the end of the granulation process the granules were cooled at room temperature by spreading them out in thin layers on trays.

3.4. Granule characterisation

The cooled granules were sieved in order to remove lumps larger than 2 mm and stored in well closed bags for 10 days. Thereafter, the geometric mean diameter and the percentage in weight (w/w) of granules finer than 315 μm were evaluated by sieve analysis, as described previously (Vojnovic et al., 1995).

4. Results and discussion

After verifying the feasibility of the experimental plan (Table 3), the 25 trials were run randomly. The experimental results are also reported in Table 3. In the following discussion Y_1 is used for indicating the geometric mean diameter and Y_2 for the percentage of particle finer than 315 μm.

From the experimental results of each response (Y_1 and Y_2) the 'weights' associated to the factor levels were estimated by means of the least square method (Table 5).

Since the upper level of each factor (A2, B2, C2, D3, E3, F3, G3 and H4) was taken as the reference state for the factor itself, the weights associated to upper levels are always equal to zero. Hence, when all the factors are at their highest level, the constants for Y_1 and Y_2, reported in Table 5, are given by the response value.

Table 3
Experimental plan and observed response values

Run	A	B (kg)	C	D (%) (w/w)	E (rpm)	F (min)	G	H (°C)	Y_1 (μm)	Y_2 (%) (w/w)
1	Powder	1.5	Yes	23	300	17	α	65	558	9.34
2	Flakes	1.5	No	24	400	21	β	65	600	12
3	Powder	2	No	25	500	25	γ	65	1035	0.1
4	Flakes	2	Yes	24	400	21	β	65	792	6.73
5	Powder	1.5	Yes	23	300	17	α	65	496	14.78
6	Powder	1.5	Yes	24	500	21	α	70	724	5.21
7	Flakes	1.5	No	25	400	17	α	70	617	15.29
8	Powder	2	No	24	300	17	β	70	488	15.57
9	Flakes	2	Yes	23	300	21	γ	70	564	26.55
10	Powder	1.5	Yes	23	400	25	β	70	551	15.58
11	Powder	1.5	Yes	25	300	21	β	80	716	1.7
12	Flakes	1.5	No	24	300	25	α	80	565	24.26
13	Powder	2	No	23	400	21	α	80	551	10.08
14	Flakes	2	Yes	23	500	17	β	80	627	8.41
15	Powder	1.5	Yes	24	400	17	γ	80	780	7.13
16	Powder	1.5	Yes	24	400	17	γ	90	776	7.96
17	Flakes	1.5	No	23	500	17	β	90	503	24.3
18	Powder	2	No	23	400	21	α	90	522	12.21
19	Flakes	2	Yes	24	300	25	α	90	655	14.32
20	Powder	1.5	Yes	25	300	21	β	90	505	1.95
21	Powder	1.5	Yes	23	400	25	β	65	604	7.05
22	Flakes	1.5	No	23	300	21	γ	65	542	22.12
23	Powder	2	No	24	300	17	β	65	553	9
24	Flakes	2	Yes	25	400	17	α	65	899	2.19
25	Powder	1.5	Yes	24	500	21	α	65	831	0.35

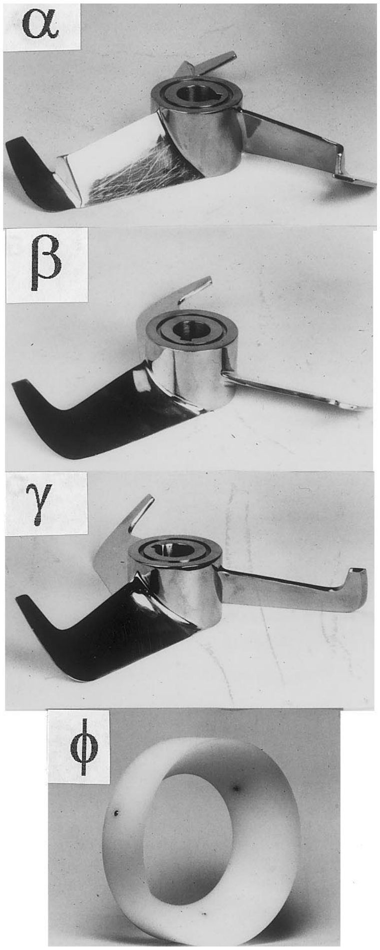

Fig. 1. Three different types of impeller blades characterised by different angles of inclination of the plane blades (60°, α; 30°, β; 45°, γ), deflector (ϕ) used in the screening study.

Table 5
'Weights' associated to each factor level estimated according to the upper level of each factor taken as a reference for Y_1 and Y_2

Factor	Level	'Weight' for Y_1	Y_2
Binder grade	A1	5.55	−7.369
	A2	0	0
Mixer load	B1	−58.85	2.833
	B2	0	0
Presence of deflector	C1	83.15	−5.120
	C2	0	0
Binder concentration	D1	−202.60	10.769
	D2	−78.00	6.007
	D3	0	0
Impeller speed	E1	−179.80	6.285
	E2	−74.80	1.948
	E3	0	0
Massing time	F1	−52.30	−0.865
	F2	−47.30	−2.372
	F3	0	0
Impeller blades	G1	−97.60	−1.969
	G2	−145.50	−2.543
	G3	0	0
Jacket temperature	H1	98.80	−3.782
	H2	−3.40	3.492
	H3	55.60	−1.832
	H4	0	0
	Constant	925.45	11.027

The data processing was carried out using NEMRODW software (Mathieu et al., 1999).

For a better interpretation of the influence of the different variable levels on the two product properties analysed (Y_1 and Y_2) a graph-mode representation can be used (Fig. 2). The level effect graph is the representation of Table 4: the highest level of each factor is omitted since it is taken equal to zero. In the total effect graph, the

Table 4
Relative swept volumes of the impeller blades in 10 l (Roto J) high shear mixer

rpm	Impeller α		Impeller β		Impeller γ		Periph. speed (m s^{-1})
	Rel. swept volume (s^{-1})						
300	3.99*	3.33	4.24*	3.56	4.20*	3.52	4.33
400	5.27*	4.43	5.65*	4.75	5.60*	4.70	5.77
500	6.59*	5.54	7.06*	5.93	6.99*	5.87	7.22

* Relative swept volume in presence of deflector.

highest level of each factor is taken as the level unit measure for each single factor. Therefore, all the highest levels are represented with the same length. This graphical procedure enables the visualisation and allows comparison of both the effects on Y_1 and Y_2 simultaneously. In this way, the factor levels that remarkably influence the final result are pointed out.

As the granulation product is intended for hard gelatine capsule preparation, the geometric mean diameter of particles is to be maximised whereas the percentage of particles finer than 315 μm is to be minimised in order to achieve a homogenous filling of the capsules themselves. Thus, from the graph analysis the levels giving the lowest value of Y_1 and the highest value of Y_2 can be identified. Hence, the following observations have been drawn.

The PEG 6000 grade (used as powder, A1; or as flakes, A2) has only a minor effect on Y_1. On the other hand, the powder form of the binder causes a reduction of Y_2.

A mixer load of 2 kg (B2), rather than one of 1.5 kg (B1), should be used in order to increase Y_1 and reduce Y_2.

The deflector (presence, C1; absence, C2) has a great importance on both final issues Y_1 and Y_2. The presence of the deflector greatly increases Y_1, while it largely decreases Y_2.

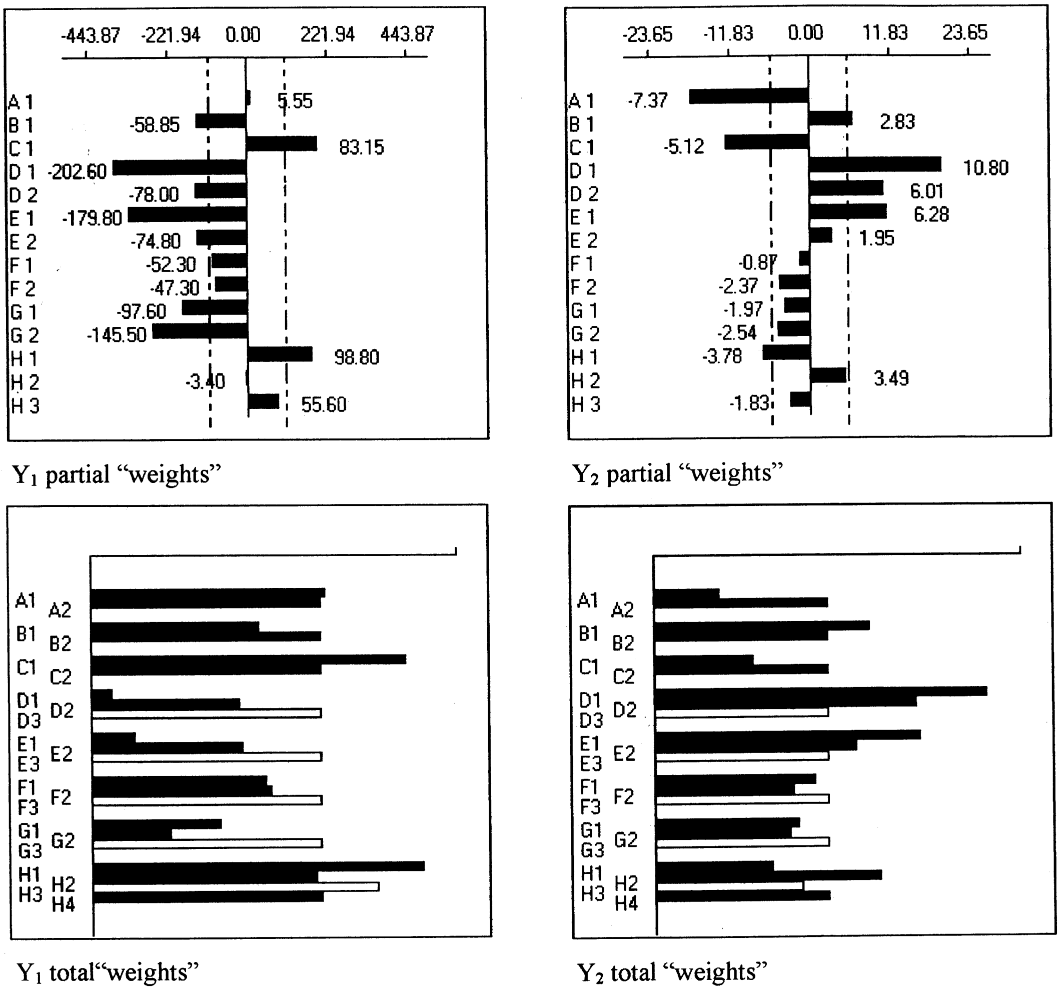

Fig. 2. Graph mode representation of partial and total 'weights' associated to the factor levels.

Table 6
Conditions and experimental results for the validity of the screening

Factor	Levels	
	Exp. 1	Exp. 2
A PEG 6000 grade	Powder	Powder
B Mixer load (kg)	2	2
C Presence of deflector	Yes	Yes
D Binder concentration (% w/w)	25	25
E Impeller speed (rpm)	500	500
F Massing time (min)	25	21
G Type of impeller blades	γ	β
H Jacket temperature (°C)	65	65
Measured responses		
Y_1 = (μm)	1050	740
Y_2 = (%)	0	6.27

The binder concentration levels (23%, D1; 24%, D2; 25%, D3) have a great influence on both responses. It can be observed that the highest value of Y_1 and the lowest value of Y_2 are obtained with 25% of binder.

The three different impeller speed levels tested (300 rpm, E1; 400 rpm, E2; 500 rpm, E3) cause important variations on the final results. An impeller speed of 500 rpm remarkably increases Y_1, while it decreases Y_2.

As to the massing time levels (17 min, F1; 21 min, F2; 25 min, F3), it can be observed that Y_1 is not much influenced by massing times lower than 21 min, while a massing time of 25 min increases its value. On the other hand, a massing time of 21 min is more effective if a reduction of Y_2 is required.

The type of impeller blades (α, G1; β, G2; γ, G3) exerts a great influence mostly over Y_1, where type γ gives Y_1 highest value. Y_2 is not strongly influenced by any of the three impeller types, although with the type β it is possible to obtain the lowest value of Y_2.

Among the four different jacket temperatures tested (65°C, H1; 70°C, H2; 80°C, H3; 90°C, H4), the 65°C one gives the highest values of Y_1 and the lowest Y_2.

Thus, from the global analysis of factor level effects, the melt granulation parameter set that gives higher values for response Y_1 is as follows: binder concentration at 25%, impeller speed at 500 rpm, jacket temperature at 65°C, presence of deflector, and impeller blades type γ; the binder grade either in powder or flakes does not affect Y_1. On the other hand, for lowering Y_2 response, the massing time should be 21 min, with type β impeller blades, while the other variables are taken at the same level as for increasing Y_1. In order to test the screening validity, two additional trials were performed using the variable levels above mentioned. Thus, the operating conditions were chosen considering those levels that led to an increase of Y_1 (experiment 1) and to a decrease of Y_2 (experiment 2). The results are reported on Table 6.

The experimental results confirmed the validity of the screening. The aim of experiment 1 was to increase the geometric mean diameter and in fact it gave a product with Y_1 equal to 1050 μm and Y_2 almost equal to 0%. Additionally, experiment 2, which was expected to yield a product with a low Y_2 value, gave granules with the percentage of particles smaller than 315 μm was 6.27%, while the geometric mean diameter was 740 μm.

Experiments 1 and 2 differ only in massing time and type of the impeller blades. In order to see if the appearance of the agglomerates obtained with the two trials reflected the difference among the conditions of the two experiments, the granulate was analysed by an electron microscope (Fig. 3).

After 25 min massing with impeller blades type γ, regularly shaped, nearly spherical agglomerates were obtained (Fig. 3, experiment 1). While impeller blades type β, after 21 min massing, produced an agglomerate with irregular shape (Fig. 3, experiment 2). The different appearance is due to the different mass movement in the bowl, caused by the different blade inclination angles (impeller type β, 30°; γ, 45°) and relative swept volumes. Type γ has a higher angle of blade plane inclination and thus the mass receives a lower impact force. Additionally, the impeller γ relative swept volume is smaller than the one of impeller β (see Table 4). These two characteristics of impeller blades type γ, lead to a lower fluidification of the mass itself, which yield to a more spherical granulate using 25 min massing time.

5. Conclusions

The granulometric characteristics of the final product obtained by melt granulation in high shear mixer are influenced by several process variables and by the characteristics of the different components.

Usually, the optimisation stage for the production of a granulate is preceded by the screening of the factors that influence the granulate characteristics and that can be varied to obtain the desired final product. During the screening stage, the factors that have a 'real' effect are selected whereas the others are fixed at a convenient value. Thus, the researcher can concentrate on a more detailed examination and optimisation of the selected factors.

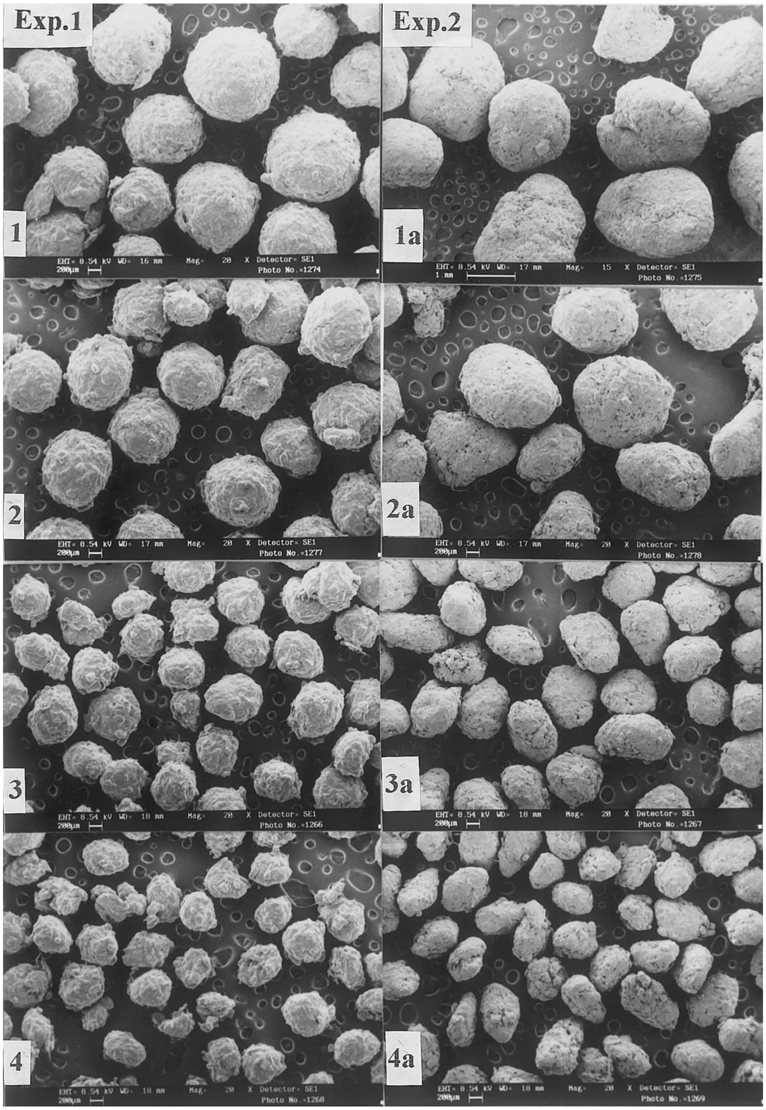

Fig. 3. Scanning electron microscope (SEM) photographs of the granules obtained using the conditions (experiment 1; experiment 2) reported in Table 4. Size fraction: 1250 (1, 1a); 800 (2, 2a); 630 (3, 3a); 500 (4, 4a) μm.

To reduce time and cost employed in the production project, the financial resources used for the screening stage should not take up more than 20–30% of the total cost of the project (Lewis et al., 1999). In the screening of numerous factors at different levels, the use of an asymmetric factorial design allows to reduce the number of runs needed, and thus to reduce both the time employed and the costs of the experiment itself.

In the present work, the number of trials was 25 instead of the 2592 trials required if a complete factorial design method had been used. These 25 trials permitted to estimate the 'weight' of the factor levels on the two granulometric characteristics under study: the geometric mean diameter and the percentage of particles finer than 315 μm. Two additional experimental trials confirmed the validity of the adopted strategy and provided further information on the role of the impeller type in the examined granulation process.

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