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Factorial design in the feasibility of producing Microcel MC 101 pellets by extrusion/spheronization

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Abstract

This study evaluates the effects of certain process variables in the feasibility of producing Microcel MC 101 pellets by the extrusion/spheronization technique. A 2^3 factorial design was realised to demonstrate the influence of the significant factors and their interactions in the experimental response. The selected process variables such as water content, extruder screen size and spheronizer speed were studied, as well as their influences on the properties of particle size distribution and the densities were determined. The results showed that high levels of the three factors increased sphere size, and low levels decreased it. A strong interaction between water content and extruder screen size is observed for the particle size distribution response. Extruder screen size has a significant effect on the bulk density. Water content and spheronizer speed interaction influence the sphere density.

Keywords: Extrusion/spheronization; Factorial design; Microcel MC 101; Moisture content; Extruder screen size; Spheronizer speed

1. Introduction

Among the pelletization techniques available at present (O'Connor and Schwartz, 1989), extrusion/spheronization invented in 1964 by Nakahara (Chariot et al., 1987) and for the first time described in the pharmaceutic field by Reynolds (1970) and by Conine and Hadley (1970) constitutes the methodology of choice in the preparation of spherical particles.

Extrusion/spheronization requires a whole number of sucessive steps: moistening, extrusion, spheronization and drying (Newton, 1990) enabling the transformation of powder mixtures into individualized spherical particles – the pellets.

Several of the past works have been oriented towards the study of technological parameters typical of each step (Woodruff and Nuessle, 1972; Rowe, 1985; Mouton and Gayot, 1988; Elbers et al., 1990). The polyphasic character of this procedure demonstrates that while the set of steps contributes to the transformation of the starting powder mixtures in spheroids, these same steps are also particularly dependent on each other.

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Therefore, the aim of this work was to analyze the eventual interactions among the factors of study over the specifications of spheroids; in order to do so, the experimental plan chosen was factorial analysis (Yates, 1937; Box and Wilson, 1951; Philippe, 1967; Chariot et al., 1987; Ortigosa, 1991; Hasznos et al., 1992).

2. Materials and methods

2.1. Materials

Microcrystalline cellulose Microcel® MC 101 was obtained from Blanver Farmacoquimica Ltda Cotia, SP, Brazil. The solvent was distilled water.

2.2. Methods

2.2.1. Spheroid production

The given conditions which were chosen after preliminary experiments were as follows:

Wet massing (planetary mixer; Kenwood Major, U.K.): rotation speed, 50 rpm; wetting time, 10 min; liquid proportion (% w/w), 56.5 and 60.0; wet massing time, 2 min.

Extrusion (single-screw radial extruder; Pharmex 35T, Glaber Machinenbau, Ettlingen, Germany): extrusion speed, 60 rpm; diameter of die, 0.5 and 0.7 mm.

Spheronization (spheronizer; Sphaeromat SPH 250 MA, Glaber Machinenbau, Ettlingen, Germany): time, 8 min; rotation speed, 1000 rpm; load, 200 g.

Drying (oven; Prolabo E.U., Paris, France): temperature, $50 \pm 1°C$; relative humidity (Sartorius MA 30), $\leq 3\%$.

2.2.2. Testing

2.2.2.1. Particle size distribution.

Sphere size distribution was determined using conventional sieve analysis as described in a previous paper (Barrau et al., 1993) on a Granulotest 150 apparatus (Sea Langrade, Paris, France) containing a set of sieves with apertures of 0.315, 0.400, 0.500, 0.630, 0.800 and 1.000 mm.

Table 1
Experimental design

Level	*S* (spheronization speed)	*W* (water content)	*D* (screen size)
(−)	800 rpm	56.5%	0.5 mm
(+)	1400 rpm	60.0%	0.7 mm

2.2.2.2. Densities.

Tapped density of pellets was measured by using an automatic tapper (Stampsvolumenometer Stav 2003) on a 50 g sample according to the French Pharmacopoeia (1991) method.

Sphere density was determined on a 20 g sample in a Beckman 930 air-comparison pycnometer.

2.2.3. Experimental design

The construction of an experimental design involves the selection of parameters and the choice of responses. The factorial design, as any model, is a simplified representation in analytical form of a given reality. In possession of the chosen factors, a factorial plan 2^3 was conceived randomly. The three factors as well as their levels are shown in Table 1. The levels for each parameter are represented by a (−) sign for the low level, and a (+) sign for the high level.

The matrix of the factorial plan is represented in Table 2. Each line identifies an experiment and each experiment gives a result. Applying the algorithm of Yates (1937) one obtains a polynomial equation (Doornbos, 1981) as follows:

$$Y = a_0 + a_i X_i + a_{ij} X_i X_j + a_{ijk} X_i X_j X_k \quad (1)$$

Table 2
Experimental matrix

Experiment	*X1*	*X2*	*X3*	Result
1	−	−	−	*R1*
2	+	−	−	*R2*
3	−	+	−	*R3*
4	+	+	−	*R4*
5	−	−	+	*R5*
6	+	−	+	*R6*
7	−	+	+	*R7*
8	+	+	+	*R8*

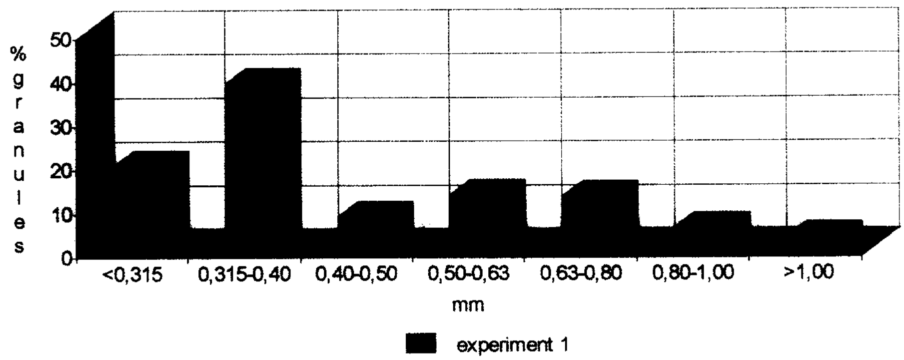
X1 = *S* = spheronization speed; *X2* = *W* = water content; *X3* = *D* = screen size.

Table 3
Sieve analysis

Expt	< 0.315	0.315–0.40	0.40–0.50	0.50–0.63	0.63–0.80	0.80–1.00	> 1.00
1	19.60	38.41	8.04	12.90	12.58	5.32	3.14
2	1.60	23.60	6.20	11.32	15.06	10.88	31.33
3	0	29.88	18.50	25.33	16.76	6.76	2.76
4	0	0.30	1.92	14.98	49.69	10.52	22.58
5	0	13.20	11.60	42.67	31.40	1.00	0.12
6	0	1.00	2.00	10.32	33.57	10.80	42.30
7	0	0	0	0	0	0.06	99.93
8	0	0	0	0	0.12	14.48	85.39

where Y is the response, a_0 denotes the mean value, a_i is the main effects coefficient, a_{ij} and a_{ijk} represent coefficients of interaction effects (first and second order) and X_i, X_j, and X_k are parameters.

This equation enables the study of the effects



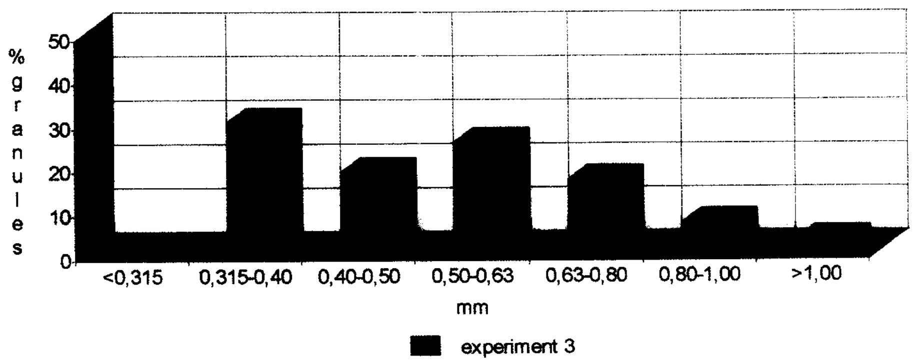
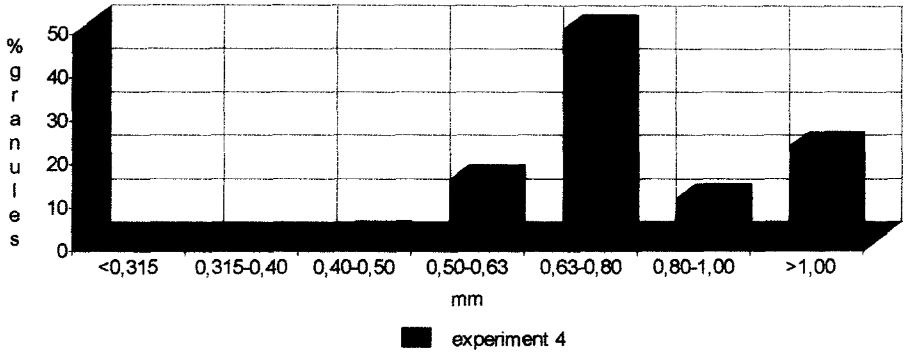


Fig. 1. Particle size distribution of some experiments. Expt 1: spheronization speed = low level; water content = low level; screen size = low level. Expt 3: spheronization speed = low level; water content = high level; screen size = low level. Expt 4: spheronization speed = high level; water content = high level; screen size = low level. Expt 8: spheronization speed = high level; water content = high level; screen size = high level.



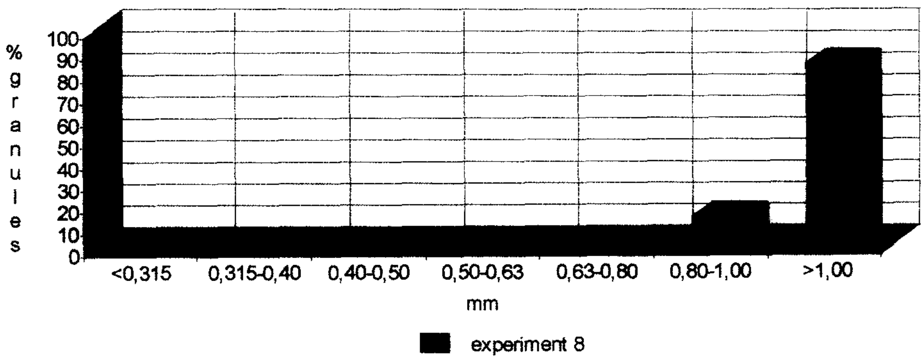


Fig. 1 (continued).

of each factor and their eventual interactions over the responses taken into consideration. The effect of a factor or an interaction is considered significant as long as it is superior to the experimental error (Philippe, 1967; Ortigosa, 1991), which leads us to reduced polynomial equations. In this study, there are seven chosen responses for the particle size distribution (as described above for the sieves overtures), and two for the densities.

3. Results and discussion

3.1. Particle size distribution

The Table 3 lists the results of the particle size distribution for the eight experiments. A global analysis of the results demonstrates that the particle size distribution does not follow a Gaussian curve (Fig. 1, Expts 1, 3, 4 and 8). Two groups can be distinguished among the observed experimental conditions:

The first group, concerning Expts 1–6, presents a clear dispersion in its granulometry. Two distinct elements can be observed in this group. Concerning Expts 1, 2, 3 and 5, the percentage of particles with sizes inferior to 0.50 mm surpasses 20% of the yield; this can be related to the low level of at least two of the three factors studied. On the other hand, Expts 4 and 6 present a percentage of granules of size greater than 1.00 mm, at least equal to 20% of the population. These latter two results can be related to the presence of two factors at high level. Relating to Expts 4 and 5, as pointed by Briquet (1985), Galmen (1985) and Cuiné (1987), the size of spheroids should be close to that of the screen orifices. Under such conditions, these two experiments offer the best yields (66.6 and 85.7%) within the fractions 0.40–0.80 mm, which comprise the limits of the two screens.

The second group represents Expts 7 and 8. For each of them, the percentage of spheres measuring over 1.00 mm corresponds to at least 85% of the population. In the particular case of Expt 7, the chosen conditions offer an optimal yield of spheres with size superior to 1.00 mm, although for the selected screen (0.7 mm) this response surpasses the expected size. This may mean excessive particle agglomeration due to the high level of factors such as water content and extruder screen size.

Due to the complexity of the overall observations, treatment according to a mathematical model was carried out. This was done in order to determine the role played by each of the factors studied. Seven reduced polynomial equations were established from the seven given granulometric responses.

$$Y_{(<0.315)} = 2.65 - 2.25S - 2.65W + 2.25SW - 2.65D + 2.25SD + 2.65WD - 2.25SWD \quad (2)$$

$$Y_{(0.315-0.40)} = 13.30 - 7.07S - 5.75W - 9.75D + 4.02SD \quad (3)$$

$$Y_{(0.40-0.50)} = 6.03 - 3.50S \quad (4)$$

$$Y_{(0.50-0.63)} = 14.69 - 5.53S - 8.63WD \quad (5)$$

$$Y_{(0.63-0.80)} = 19.90 + 4.71S - 12.96WD \quad (6)$$

$$Y_{(0.80-1.00)} = 7.48 + 4.19S + 1.86SD \quad (7)$$

$$Y_{(>1.00)} = 35.94 + 9.46S + 16.72W + 20.99D + 19.00WD \quad (8)$$

Except for Eq. 2, corresponding to dust fractions (non-significant) for which the results do not follow any mathematical model, the responses for the remaining polynomial equations will be under the influence of the three factors and their interactions.

Screen size factor (D): Whenever the response is placed in a fraction directly related to the screen overture, the screen size factor will not have any influence. However, the interaction of this factor with 'moisture content' is significant (Eq. 5 and 6). On the other hand, when the response is placed in an area exterior to that of the screen, screen size factor will become significant but of opposite sign (Eq. 3 and 8).

Water content (W) and spheronizer speed (S): The influence of the water content factor is similar to that observed for the screen size factor. In sieve fractions inferior to 0.40 mm moisture content and spheronizer speed have negative effects (Eq. 3) while for fractions larger than 1.00 mm, these are positive (Eq. 8).

In order to appreciate the effect of the 0.5 mm diameter screen, it was decided to bring together the sieve fractions 0.40–0.50 and 0.50–0.63 mm (Eq. 4 and 5) to which one of the limits is the same of that of the diameter screen. The reduced polynomial equation then obtained is:

$$Y_{(0.40-0.63)} = 20.72 - 9.04S - 11.11WD \quad (9)$$

When comparing this equation to that of the 0.7 mm diameter screen (Eq. 6), it is noticeable that in both cases the effect of the main factor S is significant, but with opposite sign. It seems then that in the defined experimental domain the variation of spheronizer speed modifies the particle size distribution yield. With the 0.7 mm screen, any increase of this factor will provoke growth of the yield response in the 0.63–0.80 mm fraction. As for the smaller orifice screen (0.50 mm) the effects in the 0.40–0.63 mm fraction will be translated into lower yields.

In both polynomial equations the interaction WD, of negative sign, is important and sensibly identical (12.96 and 11.11). It is convenient, though, to analyze it so as to observe the influence of both factors over the experimental response. Mean values for $W(-)D(-)$, $W(+)D(-)$, $W(-)D(+)$ and $W(+)D(+)$ are reported on an interaction diagram for the 0.40–0.63 mm fraction (Fig. 2a) and 0.63–0.80 mm fraction (Fig. 2b).

For each of the screens, the results are symmetric and the best responses are obtained either when W is at a high level and D at a low level (30.4 and 33.2%), or when the opposite occurs

(33.3 and 32.5%). If both factors are at a high level, the yields will be worthless.

When D is kept constant (0.5 or 0.7 mm) the effect of variation in W is translated into inverse responses: whereas for the 0.7 mm screen (Fig. 2b), the increase in W will lead to a growth of response (32.5 to 33.2%), the 0.5 mm screen (Fig. 2a) will result in a decrease (33.3 to 30.4%). At the same time, when W is kept constant (56.5 or 60.0%) the responses will be similar to the former ones. For example, for $W(-)$, if D is at a high level $(+)$, the responses will increase (from 19.2 to 33.3% for the 0.40–0.63 mm fraction and from 13.8 to 32.5% for the 0.63–0.80 mm fraction).

The strong interaction between water content and screen size suggests that the state of aggregation of Microcel particles is related to the strength borne by moist mass during extrusion. The total strength is supported by the solid particles and by interstitial pressure, which is here represented by hydrostatic pressure (Arquie and Morel, 1988). If there is less water, cohesion among the particles will require smaller strength. However, a maximum of spheres of the same size can be obtained by balancing the moisture content with a small size orifice screen, or by decreasing the amount of water with a larger size orifice screen.

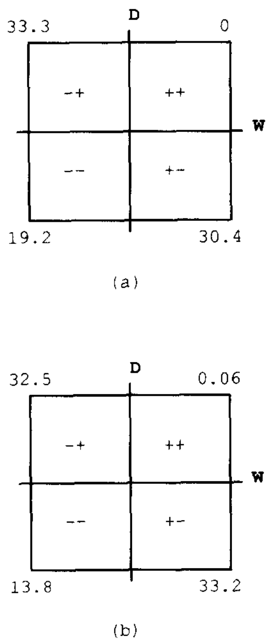


Fig. 2. Interaction diagram of moisture content (W)×screen size (D) in the particle size distribution. (a) 0.40–0.63 mm; (b) 0.63–0.80 mm.

Table 4
Tapped and sphere density

Expt	Density (g/ml)	
	Tapped	Sphere
1	0.943	1.416
2	0.943	1.485
3	0.893	1.484
4	0.952	1.492
5	0.877	1.417
6	0.926	1.475
7	0.893	1.472
8	0.877	1.483

3.2. Densities

Values of the densities are reported in Table 4.

For each density, the mathematical model response is given by the following reduced polynominal equations:

$$Y_{\text{tapped}} = 0.913 - 0.020D \quad (10)$$

$$Y_{\text{spheres}} = 1.465 + 0.018S + 0.017W - 0.014SW \quad (11)$$

Bulk density is indicative of the packing properties of spheres and is greatly dependent on the diameter of pellets (Ghebre-Sellassie et al., 1989; Metha, 1989). It seems that here the screen size becomes an influential factor on tapped density – any decrease leads to an increase in the response. These results can then be related to those previously obtained in the particle size distribution.

Sphere density indicates the importance of compactness of substances; the influence of spheroid size is less relevant. Eq. 11 demonstrates a significant interaction SW, of negative sign, where the effect of each factor is identical (0.018 and 0.017).

The analysis of this interaction (Fig. 3) indicates that for a given amount of water, the in-

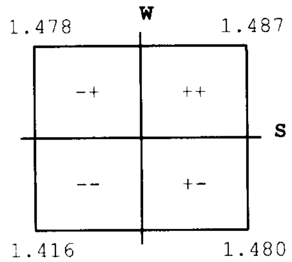


Fig. 3. Interaction diagram of spheronizer speed (S)×moisture content (W) in the sphere density.

crease in spheronizer speed is translated into an increase in sphere density (from 1.416 to 1.480). At the same time, for a given speed, the increased moisture content will provide the same effect (from 1.416 to 1.478). Finally, when the two factors are at a low level, the density will decrease (1.416).

In the process of extrusion/spheronization several phenomena occur successively: during wet granulation the raw material is agglomerated with the help of a liquid by capillary forces. During extrusion a product of high density is manufactured (the extrudate) which is also agglomerated by capillary forces and solid bridges; and finally, in the spheronization step, mechanical forces contribute to creating cohesion and forming spherical particles. Under such conditions the values of sphere density are dependent on the interaction of moisture content and spheronizer speed factors.

The application of experimentation plans allows one to simultaneously control, with a maximum of information and a minimum of experiments, all technical variables extremely complex when facing the technology of extrusion/spheronization in which several steps interfere in the production of pellets.

From the significance of main effects and their interactions found in this work, it was possible to define the influence of the factors within the defined experimental domain. Thus, the factorial experimentation here developed constitutes a preliminary investigation for future optimization studies.

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