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DESIGN AND OPTIMIZATION OF THEOPHYLLINE PELLETS OBTAINED BY WET SPHERONIZATION IN A HIGH-SHEAR MIXER.

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ABSTRACT

The pelletization of lactose, cellulose, polivinylpirrolidone and theophylline was carried out in a 10 l high-shear mixer. The effect of impeller speed and the amount of binding solution was investigated on the characteristics of the pellets (percentage of pellets possessing a diameter in the interval 800 to 1250 μm and porous structure). Numerous experiments were performed using the experimental design methodology, in particular a Doehlert and simplex matrix combination.

INTRODUCTION

Pellets for pharmaceutical application are defined as spherical granules of 0.5 to 2.0 mm average size. It is experimentally known that narrow granule size distributions can be produced by wet granulation in a high-shear mixers. The major advantage of this pelletization technique over others (e.g. extrusion and spheronization) is that dense pellets can be produced within a short processing time.

Holm (1) examined the applicability of a 90 l modified high-shear mixer for pelletization of dicalcium phosphate in the presence of 15% w/w Kollidon VA 64, lactose and Avicel PH 101 with water as binder.

Wehrlè et al. (2) developed active pellets of 20% anhydrous theophylline, 30% lactose and 50% Avicel PH 101 with 15% hydroalcoholic solution of hydroxypropylmethylcellulose as binder, using a Stephan UMC 5 high-speed granulator.

In our previous work (3) we examined the wet pelletization of lactose, cellulose and paracetamol with water as binder in a Zanchetta Roto J 10 l high-shear mixer. The effect of process variables on the characteristic of pellets was studied by a surface response design.

One interesting quality is the number of distinct levels taken by each of the variables: figure 1a shows that the first variable (X_1) is at 5 levels and the second (X_2) is at 3 levels. Some experiments may lead to the allocation to one or two variables of as few levels as possible. Others, on the contrary, may take it obligatory for the variables to have as many levels as there are experiments. We used a rotated Doehlert matrix to achieve this last property : figure 1b indicates that the first and the second variable are both at 7 levels.

The aim of present investigation is to examine the wet pelletization of theophylline, lactose, Avicel, PVP with isopropanol alchool as binder, always in the Zanchetta Roto J 10 l high-shear mixer.

A particular combination of Doehlert and simplex matrix (4,5) let us to study the effect of process variables on the characteristics of pellets (yield of 800-1250 μm fraction and its porous structure-total porousness, average diameter of the pores and porosimetric profile).

MATERIALS AND METHOD

Materials

Lactose (Meggle Germany), microcrystalline cellulose (Avicel PH 101, Faravelli Italy), anhydrous theophylline and PVP (Gianni, Italy), isopropanol alchool (Carlo Erba, Italy) were used as starting materials.

Instruments

Zanchetta Roto J granulator, set of sieves (200, 250, 315, 400, 500, 630, 800, 1250, 2000 μm) connected to a vibrating apparatus (Octagon 2000, Endecotts), multi-pycnometer (Quantochrome) with helium as gas, and mercury porosimeter (Mod. 225, Carlo Erba Instruments, Milano, Italy) with intrusion pressure of mercury from 0 to 2000 atm, were employed.

Preparation of Theophilline Pellets

A 1 kg batch containing lactose (32%), microcrystalline cellulose (15%), PVP (3%) and theophylline (50%) was mixed using the impeller at 120 rpm for 10 min. The granulating liquid was isopropanol. The binder solution was added by spraying at a flow rate of 50 to 70 ml/min, pressure of 4.0 bar and atomized by a pneumatic nozzle of 0.3 mm in diameter. The pellets were dried in a oven at 60°C for 4 h.

Characterization of the Pellets

The particle size distribution was accomplished by determining the percentage in weight (%w/w) of each pellet fraction. A particular relevance was given to the percentage of fines which, if high, indicates a rather friable product.

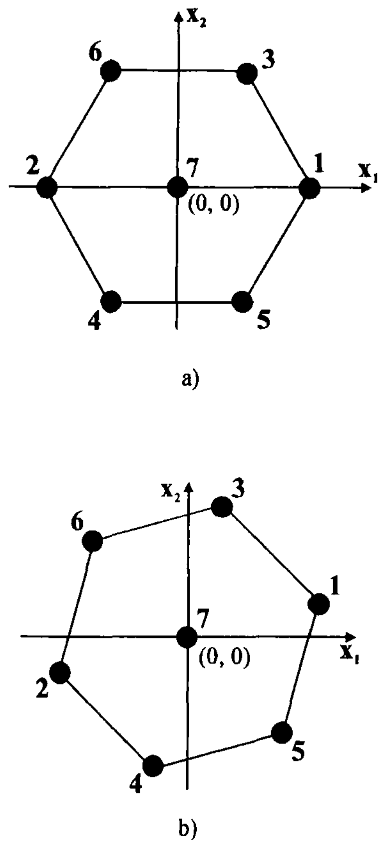

FIGURE 1
Doehlert experimental design: a) classic, b) rotated

Experimental Design

We chose an experimental matrix proposed by Doehlert to compare the effects of process variables on the pellet characteristics. This experimental design consists of seven experiments and is represented in Figure 1.

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TABLE 1
Levels of process variables

Process variable	Normalized level	Experimental value
X_1: amount of binding solution (%)	-1 0 +1	26 30 34
X_2: impeller speed (rpm)	-1 0 +1	300 400 500

In the preliminary investigation, the percentage of pellets possessing a size distribution within the range of 800 to 1250 μm was chosen as the quality criterion. This was due to similar previous results obtained employing 50 l granulator and aiming at verifying the feasibility of the scaling up.

The experimental design and matrix are given in Figure 2 and Table 2.

The overall strategy adopted was developed employing a program NEMROD (6,7).

RESULTS AND DISCUSSION

The results obtained in the first set of experiments are reported in Table 3.

On the basis of these parameters experiment number 7 appears to be the best point of the design because of the high yield of the 800-1250 μm fraction and the low percentage of fines.

In order to increase the yield of the fraction taken into consideration, we followed the strategy of translating the point number 7 using the simplex methodology, thus obtaining two new points, number 8 and 9 (Figure 2).

Point number 9 showed an increase in the yield of the 800-1250 μm fraction and a lower percentage of fines.

Thereafter we designed four other test points (10,11,12,13) around the point number 9, obtaining a new Doehlert matrix. However we observed no improvements in the pellet characteristics taken into consideration (Table 4).

Therefore, according to this strategy, points number 7 and 9 resulted the best ones (Figure 3).

In order to see whether the variation of the impeller speed during pelletization provokes not only an increase of the yield but also a modification in physical chemical characteristics of the pellets, we determined the porousness and the average diameter of the pores (Table 5 and Figure 4).

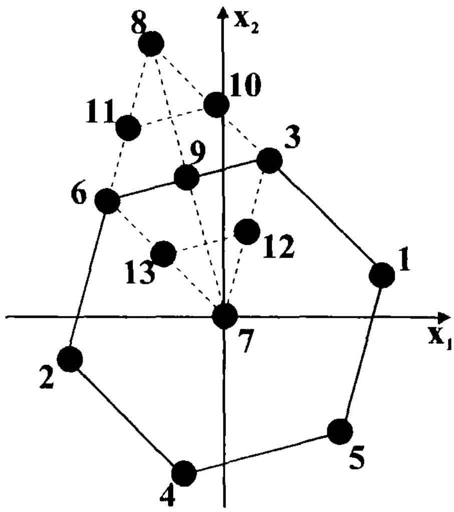

FIGURE 2
"Doehlert and simplex" experimental design

TABLE 2
"Doehlert and simplex" experimental design

N°	X_1	X_2	%	rpm
1	0.966	0.259	34	426
2	-0.966	-0.259	26	373
3	0.259	0.966	31	500
4	-0.259	-0.966	28	300
5	0.707	-0.707	32	326
6	-0.707	0.707	27	473
7	0.000	0.000	30	400
8	-0.448	1.673	28	567
9	-0.224	0.836	29	483
10	-0.094	1.319	29	531
11	-0.577	1.190	27	519
12	0.129	0.483	30	423
13	-0.353	0.353	28	435

TABLE 3
Experimental results for points 1-7

EXPERIMENT NUMBER	FRACTION (%W/W)								% of fines
	>2000 µm	1250 2000 µm	800 1250 µm	630 800 µm	500 630 µm	400 500 µm	315 400 µm	250 315 µm	
1	Spheroid not formed								
2	/	1.98	7.61	32.49	14.80	6.13	2.94	5.75	28.26
3	35.12	24.46	15.51	8.23	6.36	5.38	2.64	1.62	0.60
4	/	1.81	4.66	28.12	18.16	6.68	2.35	6.02	32.20
5	/	4.43	22.65	35.00	7.51	2.58	1.79	4.15	21.89
6	/	7.80	51.34	8.62	2.33	1.68	2.24	4.76	21.20
7	/	8.31	65.09	14.69	2.96	0.90	0.38	0.78	6.89

TABLE 4
Experimental results for points 8-13

EXPERIMENT NUMBER	FRACTION (%W/W)								% of fines
	>2000 µm	1250 2000 µm	800 1250 µm	630 800 µm	500 630 µm	400 500 µm	315 400 µm	250 315 µm	
8	44.41	48.40	6.30	0.35	/	/	/	/	0.54
9	0.36	8.16	72.37	9.97	2.00	0.83	/	/	6.31
10	0.89	44.33	45.65	4.66	1.33	1.08	0.41	/	2.43
11	1.29	5.48	40.80	8.56	3.52	4.95	4.96	7.98	22.46
12	30.05	25.47	20.03	11.49	4.28	3.07	2.98	1.06	1.57
13	1.09	12.41	56.89	6.66	1.59	1.36	1.93	3.82	14.25

Through the study of the porograms we observed that the average diameter of the pores and the percentage of porousness is higher as the impeller speed increases during spheronization.

These results obtained employing a high speed mixer are in disagreement with those obtained using the process of extrusion-spheronization (8).

Furthermore experiences 7 and 9 differ in the percentage of granulating liquid (30% and 29% w/w respectively) and this indicates a tendency for the porosity to decrease as the granulating liquid content increases. This is in agreement with studies of influence on porousness of percentage of water content of extrudate in extrusion-spheronization process (9,10).

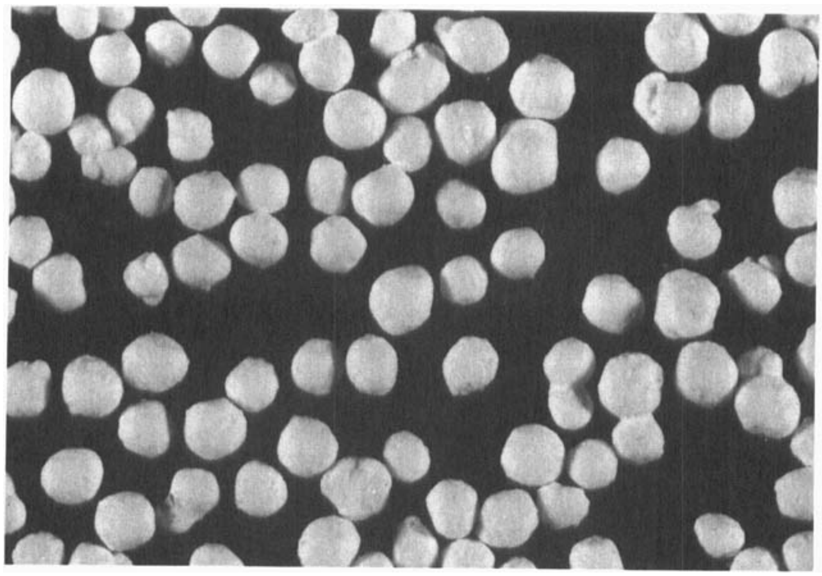

FIGURE 3
Typical pellets shape of the 800-1250 μm fraction corresponding to point number 9. Magnification 10X

TABLE 5
Porosimetric characteristics depending on the spheronization speed

Speed of spheronization (rpm)	Porousness (%)	Average diameter of the pores (nm)
400	15.8	520
483	32.0	634

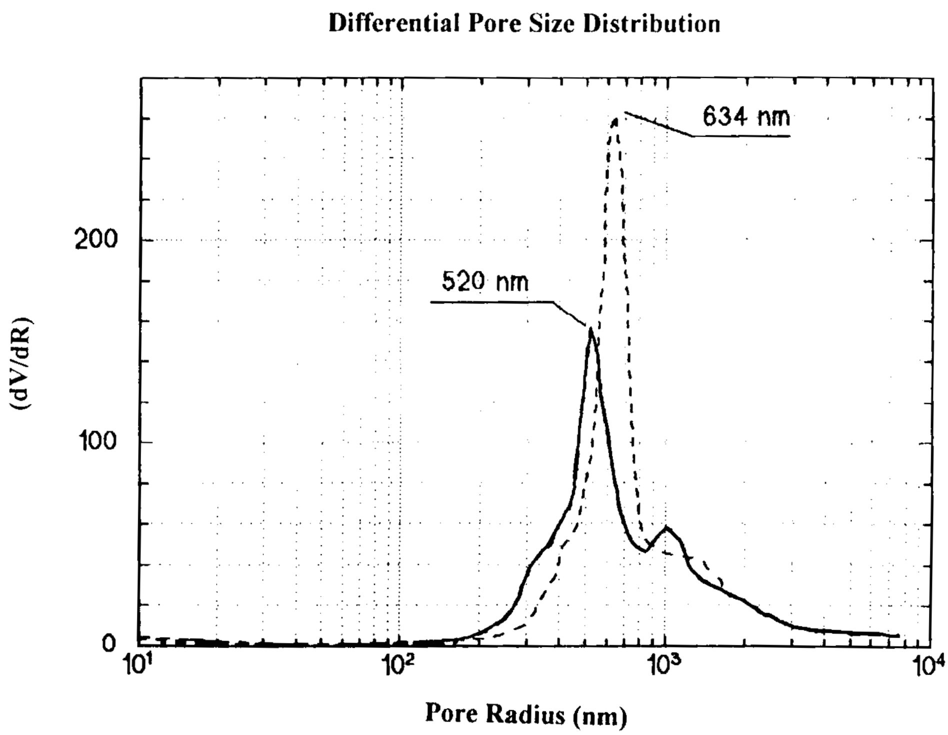

FIGURE 4
Evolution of the porosimetric distribution depending on the spheronization speed
(—— exp 7, 400 rpm; ---- exp 9, 483 rpm)

CONCLUSION

This work indicates that it is possible to produce active pellets with a Roto granulator using a simple procedure.

In order to optimize the process variables of theophilline pelletization in a laboratory scale high-shear mixer we demonstrated the value of combination of two different types of matrices (Doehlert and simplex). With this strategy the number of experiments were significantly reduced and optimized pellets with high yield and good porosity were obtained.

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