Drug Development and Industrial Pharmacy, 24(4), 353–358 (1998)

RESEARCH PAPER

Optimization of the Processing of Matrix Pellets Based on the Combination of Waxes and Starch Using Experimental Design

F. Zhou,[1] C. Vervaet,[1] D. L. Massart,[2] B. Massart,[3] and J. P. Remon[1,*]

[1]*Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium*
[2]*Pharmaceutical Institute, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium*
[3]*Department of Chemistry, University of Bergen, Allegt. 41, N-5007 Bergen, Norway*

ABSTRACT

An experimental design was used in order to optimize the one-step production process of matrix pellets based on the combination of waxes and starch. The parameters tested were the impeller speed (x_1) and the mixing time (x_2). Ibuprofen and theophylline were used as model drugs at a concentration of 60 and 70% (w/w), respectively. The 0.8–1.25 mm yield fraction of the matrix pellets was evaluated as the response factor Y. A quadratic equation was fitted to the experimental data and used to predict the response factor Y of the theophylline and the ibuprofen. The contour plots of both formulations revealed a flat and therefore rugged region from the upper left to the lower right of the domain investigated. The energy input into the system during the production process controlled the pellet growth, the impeller speed having a greater impact on the energy input compared to the mixing time.

*To whom correspondence should be addressed.

INTRODUCTION

Experimental designs have been widely used in the optimization of different processes. In the field of granulation experimental designs have been used to determine the critical parameters of the wet granulation process (1–8) and to study the production process of pellets by means of rotary granulators (9) and by extrusion/spheronization (10–15). Schaefer et al. used experimental designs extensively to determine the critical processing and formulation variables of the melt granulation technique for the production of pellets in a high-shear granulator using polyethylene glycols as binders (16–26). In the present study an experimental design was applied for the optimization of two critical processing parameters, impeller speed and mixing time, of the manufacturing process of sustained-release matrix pellets based on the combination of microcrystalline waxes and starches.

MATERIALS AND METHODS

Materials

Ibuprofen (Knoll Pharmaceuticals, Nottingham, UK) and theophylline monohydrate (Ludeco N.V., Brussels, Belgium) were used as model drugs. Lunacera M® (melting range: 68–72°C) and Lunacera P® (melting range: 58–62°C) (Füller GmbH, Luneburg, Germany), both microcrystalline waxes, were used as hydrophobic binders. Waxy maltodextrin (dextrose equivalent [DE] value = 10) (Eridania-Béghin Say-Cerestar, Vilvoorde, Belgium) was used as a filler.

Equipment

The PP1 Processor (Aeromatic Fielder, Eastleigh, Hants, UK), equipped with a 7.5-liter pelletizing bowl with a Teflon lining, a two-blade impeller, and a heated jacket, was used as a high-shear granulator. The impeller speed was variable between 300 and 1500 rpm. No chopper was present.

Formulations

Ibuprofen pellets were formulated with 60% (w/w) ibuprofen, 17.5% (w/w) Lunacera M, 7.5% (w/w) Lunacera P, and 15% (w/w) waxy maltodextrin. The theophylline pellets contained 70% (w/w) theophylline monohydrate, 21% (w/w) Lunacera M, and 9% (w/w) waxy maltodextrin.

Production Process

The hydrophobic binder was added as a solid phase and mixed with the drug and the waxy maltodextrin. The mixture was then heated and mixed until the hydrophobic binder was melted and homogeneously dispersed throughout the mass. The mass was cooled to a preset product temperature range (50–53°C and 55–58°C for formulations containing ibuprofen and theophylline, respectively), followed by a mixing phase during a preset time interval (mixing time) at a constant impeller speed to allow the formulation of matrix pellets. The batch size was 1.5 kg in all cases.

Evaluation of the Matrix Pellets

The particle size distribution of the pellets was determined by sieving a 100-g pellet sample for 5 min at an amplitude of 2 mm on a sieve shaker (VE1000, Retsch, Germany) using a nest of sieves. The fraction remaining on each sieve was determined and expressed as a percentage of the total weight. All results were the mean of three determinations.

Statistical Evaluation

Two process variables were studied: x_1, the impeller speed and x_2, the mixing time. The batch size, the jacket temperature, and the product temperature were kept constant. The response variable (Y) was the pellet yield of the 0.8–1.25 mm sieve fraction.

For theophylline pellets the original aim was to carry out the experiments according to a 3 × 3 orthogonal array (experiments 1–9) describing a rectangular domain between $x_1 = 0$ (500 rpm) and 1 (625 rpm) and $x_2 = 0$ (18 min) and 1 (28 min). Because it was impossible to obtain pellets at the extreme levels of $x_1 = 1$ and $x_2 = 1$ (experiment 9), two additional experiments (experiments 10 and 11) were carried out with the following coordinates: $x_1 = 1/x_2 = 0.25$ and $x_1 = 0.8/x_2 = 1$. To be able to better predict the production process, three other experiments (experiments 12–14) were performed. A schematic view of the experimental points is given in Fig. 1.

For ibuprofen pellets, the full orthogonal array (experiments 1–9) was obtained with extreme levels of $x_1 = -1$ (550 rpm) and 1 (650 rpm) and of $x_2 = -1$ (20 min) and 1 (32 min). Four additional tests (experiments 10–13) were run to be able to compare the predicted values of the statistical model with the experimental

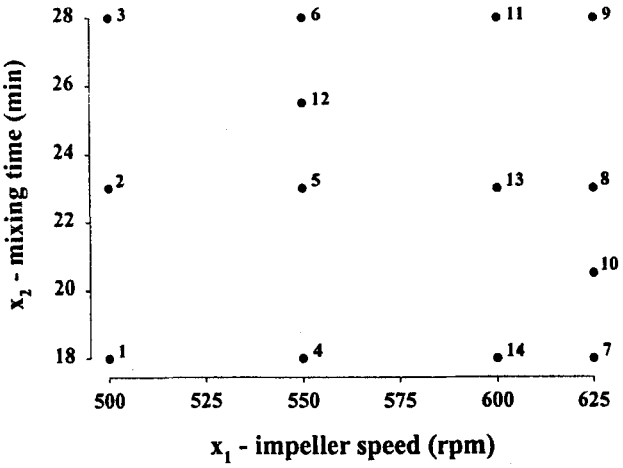

Figure 1. Schematic view of the experimental points for theophylline.

values. A schematic view of the experimental points is given in Fig. 2.

In both cases the experimental data were fitted using the following quadratic equation:

$$Y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2 + b_{11}x_1^2 + b_{22}x_2^2$$

where Y is the response variable (percent in 0.8–1.25 mm sieve fraction); x_1 is impeller speed; x_2 is mixing time; b_0 is a constant; and b_1, b_2, b_{12}, b_{11}, b_{22} are coefficients.

At first the full equation was used and the b coefficients were tested for significance at a level of $\alpha = 0.05$. The term corresponding to the least significant coefficient among the nonsignificant ones was then deleted from the equation. Subsequently, a new model was calculated and the significance testing procedure was used in the same way on this equation as described above. This was done until all coefficients were significant at a level of $\alpha = 0.05$. All calculations were carried out in Matlab (The Mathworks, MA).

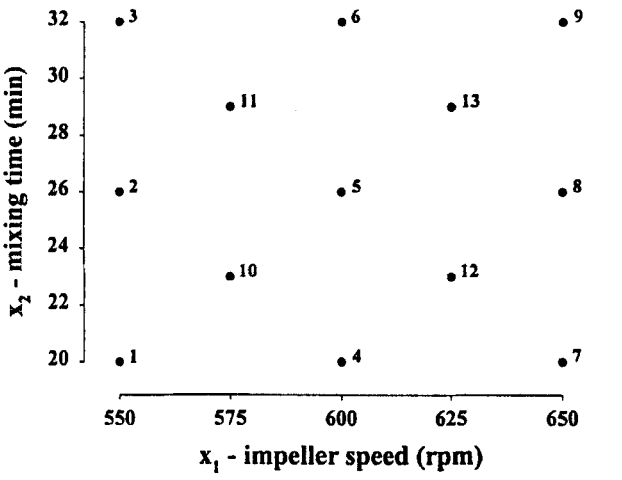

Figure 2. Schematic view of the experimental points for ibuprofen.

RESULTS AND DISCUSSION

The development of sustained-release matrix pellets based on the combination of microcrystalline waxes and starches using a one-step production process was previously described by Zhou et al. (27). The final particle size distribution of those matrix pellets was affected by the impeller speed of the high-shear granulator and the mixing time used during the production process (28). Therefore those two parameters were included into an experimental design for optimization of the production process of matrix pellets, using theophylline and ibuprofen as model drugs. The range of x_1 (impeller speed) and x_2 (mixing time) used in the experimental design was determined during a preliminary study. Below the investigated area no agglomeration of individual particles occurred, whereas exceeding the investigated domain resulted in a too rapid granule growth, yielding only large agglomerates.

The yield fraction (0.8–1.25 mm) of the experimental points is given in Tables 1 and 2 for theophylline and ibuprofen pellets, respectively. Using these experimental points a quadratic equation was fitted to the data. The b coefficients (level of significance: $\alpha = 0.05$) are listed in Table 3.

For ibuprofen, only b_0, b_{11}, and b_{12} were significant ($\alpha = 0.05$). The term $b_{11}x_1^2$ describes the fact that with an increase of x_1 the response factor Y first increased and then decreased; the term $b_{12}x_1x_2$ describes the fact that the highest value along x_1 depended on the value of x_2. Using these quadratic equations, contour plots for theophylline and ibuprofen were drawn in Figs. 3 and 4, respectively. As shown by the contour plots both cases yielded similar results in the sense that a central zone was obtained with the higher values diagonally over the domain investigated. In the flat and therefore rugged region from the upper left to the lower right the response factor Y was higher for the theophylline matrix pellets compared to the matrix pellets loaded with ibuprofen. This is in accordance with previous results (28) in which formulations containing theophylline resulted in a more narrow particle size distribution compared to pellets containing ibuprofen.

Table 1

Process Parameters and Yield Fraction (0.8–1.25 mm) of the Experimental Points for Theophylline

Experiment Number	x_1 Impeller Speed (rpm)	x_2 Mixing Time (min)	Y Yield Fraction 0.8–1.25 mm
1	500	18	28.7
2	500	23	35.5
3	500	28	43.1
4	550	18	46.6
5[a]	550	23	76.8
6	550	28	72.2
7	625	18	61.2
8	625	23	32.9
9	625	28	[b]
10[c]	625	20.5	56.7
11[c]	600	28	24.6
12[c]	550	25.5	80.2
13[c]	600	23	80.2
14[c]	600	18	64.1

[a]Experiment no. 5 (n = 3); Y = 76.8 ± 2.6%.
[b]No pellets were obtained due to fusion of individual pellets.
[c]Additional experiments.

Table 2

Process Parameters and Yield Fraction (0.8–1.25 mm) of the Experimental Points for Ibuprofen

Experiment Number	x_1 Impeller Speed (rpm)	x_2 Mixing Time (min)	Y Yield Fraction 0.8–1.25 mm
1	550	20	28.0
2	550	26	39.7
3	550	32	60.6
4	600	20	41.9
5[a]	600	26	74.5
6	600	32	73.7
7	650	20	70.0
8	650	26	17.2
9	650	32	0.0
10[b]	575	23	52.7
11[b]	575	29	75.3
12[b]	625	23	71.0
13[b]	625	29	18.7

[a]Center experiment (n = 3), Y = 74.5 ± 0.4%.

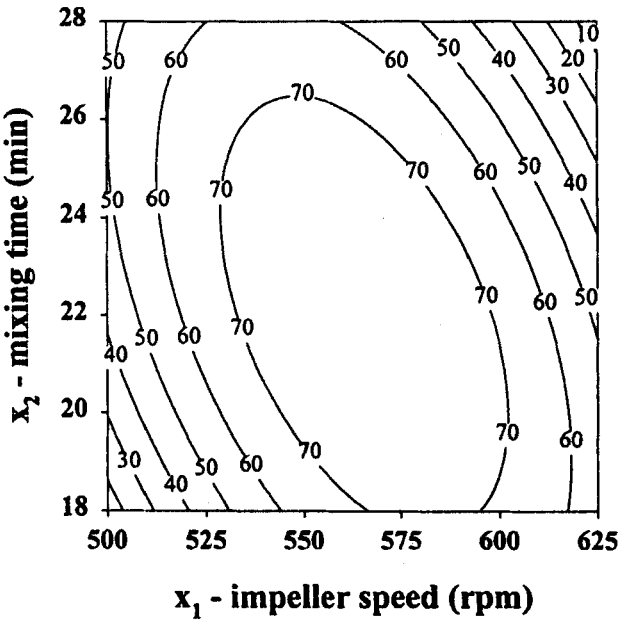

Figure 3. Contour plot for the evaluation of the response factor Y (0.8–1.25 mm yield fraction) for theophylline.

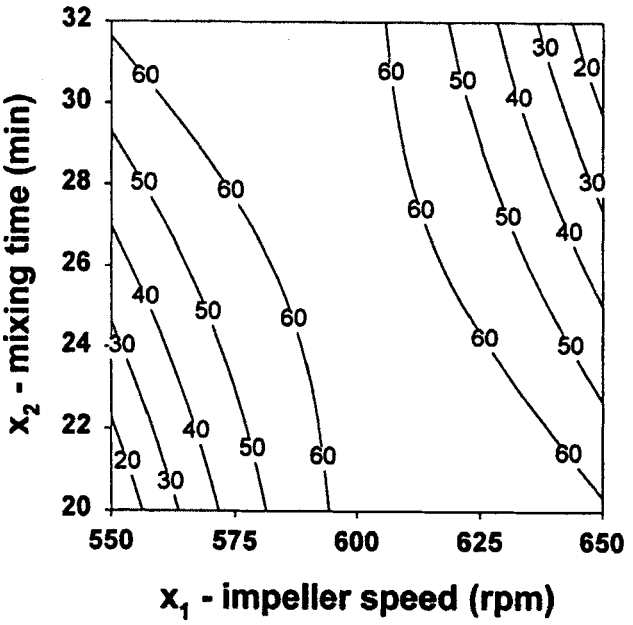

Figure 4. Contour plot for the evaluation of the response factor Y (0.8–1.25 mm yield fraction) for ibuprofen.

Table 3

b Coefficients of the Quadratic Equation ($Y = b_0 + b_1x_1 + b_2x_2 + b_1b_2x_1x_2 + b_{11}x_1^2 + b_{22}x_2^2$) for Theophylline and Ibuprofen; Significance was Determined at a Level of $\alpha = 0.05$; Y: Yield Fraction (0.8–1.25 mm); x_1: Impeller Speed; x_2: Mixing Time

b Coefficients	b_0	b_1	b_2	b_1b_2	b_{11}	b_{22}
Theophylline	14.64983	176.8763	91.39368	-83.3993	-136.951	-59.4046
Ibuprofen	63.36	[a]	[a]	-25.65	-27.45	[a]

[a] *b* Coefficients not significant.

Both contour plots showed the importance of the energy input into the mass. An increased energy input resulted in fusion of the individual particles giving an increase of response factor *Y*. An excess high energy input induced the fusion of the pellets into larger particles (above 2 mm). Increasing the impeller speed from 500 to 575 rpm resulted in an increase of the response factor *Y* for theophylline matrix pellets from 30.5 to 77.4% at a mixing time of 20 min, whereas it dropped to 53.8% at 625 rpm using the same mixing time. Increasing the energy input by extending the mixing time had a less pronounced effect on the response factor *Y*. Tables 4 and 5 give an overview of the experimental data and the data calculated by means of the quadratic equations for theophylline and ibuprofen pellets, respectively. In both cases the quadratic model allowed the main features to be described. However it did not describe the experimental results as well as one would hope. Because the true model is probably sigmoid, the quadratic models underestimate the response values of the central zone and overestimate them when the values drop steeply in the high x_1–x_2 zone. One way of avoiding this problem could be to model the mean diameter of the granules as response value instead of the sieve fraction.

Table 4

Experimental and Calculated (by Means of Quadratic Equation) Yield Fraction (0.8–1.25 mm) for Theophylline

Experiment Number	*Y* Experimental	*Y* Calculated	Deviation
1	28.7	14.6	-14.1
2	35.5	45.5	10.0
3	43.1	46.6	3.5
4	46.6	63.5	16.9
5	76.8	77.6	0.8
6	72.2	62.1	-10.1
7	61.2	54.6	-6.6
8	32.9	43.7	10.8
10	56.7	52.9	-3.8
11	24.6	33.8	9.2
12	80.2	73.6	-6.6
13	80.2	66.0	-14.2
14	64.1	68.5	4.4

Table 5

Experimental and Calculated (by Means of Quadratic Equation) Yield Fraction (0.8–1.25 mm) for Ibuprofen

Experiment Number	*Y* Experimental	*Y* Calculated	Deviation
1	28.0	10.3	-17.7
2	39.7	35.9	-3.8
3	60.6	61.6	1.0
4	41.9	63.4	21.5
5	74.5	63.4	-11.1
6	73.7	63.4	-10.3
7	70.0	61.6	-8.4
8	17.2	35.9	18.7
9	0.0	10.3	10.3
10	52.7	50.1	-2.6
11	75.3	62.9	-12.4
12	71.0	62.9	-8.1
13	18.7	50.1	31.4

ACKNOWLEDGMENTS

The authors wish to thank Eridania-Béghin Say-Cerestar (Vilvoorde, Belgium) for the generous supply of the starch derivatives. Special thanks to Niro-Fielder Ltd. (Eastleigh, UK) for providing the PP1-Processor. C. Vervaet is a research assistant of the National Fund of Scientific Research (Brussels, Belgium).

REFERENCES

1. P. Timmins, A. M. Delargy, J. R. Howard, and E. A. Rowlands, Drug Dev. Ind. Pharm., 17, 531 (1991).
2. P. Wehrlé, P. Nobelis, A. Cuiné, and A. Stamm, S.T.P. Pharma Prat., 2, 38 (1992).
3. P. Wehrlé, P. Nobelis, A. Cuiné, and A. Stamm, S.T.P. Pharma Prat., 2, 173 (1992).
4. P. Wehrlé, P. Nobelis, A. Cuiné, and A. Stamm, Drug Dev. Ind. Pharm., 19, 1637 (1993).
5. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., 20, 1035 (1994).
6. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., 21, 823 (1995).
7. C. Vervaet, H. Vermeersch, M. S. Khotz, D. L. Massart, and J. P. Remon, Int. J. Pharm., 106, 157 (1994).
8. S. Bouckaert, D. L. Massart, B. Massart, and J. P. Remon, Drug Dev. Ind. Pharm., 22, 321 (1996).
9. B. Gajdos, Drugs Made Ger., 27, 30 (1984).
10. H. J. Malinowski and W. E. Smith, J. Pharm. Sci., 63, 284 (1974).
11. H. J. Malinowski and W. E. Smith, J. Pharm. Sci., 64, 1688 (1975).
12. M. Chariot, J. Francès, G. A. Lewis, D. Mathieu, R. Phan Tan Luu, and H. N. E. Stevens, Drug Dev. Ind. Pharm., 13, 1639 (1987).
13. L. Hasznos, I. Langer, and M. Gyarmathy, Drug Dev. Ind. Pharm., 18, 409 (1992).
14. C. C. Ku, Y. M. Joshi, J. S. Bergum, and N. B. Jain, Drug Dev. Ind. Pharm., 19, 1505 (1993).
15. L. Baert, H. Vermeersch, J. P. Remon, J. Smeyers-Verbeke, and D. L. Massart, Int. J. Pharm., 96, 225 (1993).
16. T. Schaefer, Int. J. Pharm., 132, 221 (1996).
17. T. Schaefer, Int. J. Pharm., 139, 149 (1996).
18. T. Schaefer and C. Mathiesen, Int. J. Pharm., 134, 105 (1996).
19. T. Schaefer and C. Mathiesen, Int. J. Pharm., 139, 125 (1996)
20. T. Schaefer and C. Mathiesen, Int. J. Pharm., 139, 139 (1996).
21. T. Schaefer, P. Holm, and H. G. Kristensen, Acta Pharm. Nord., 4, 133 (1992).
22. T. Schaefer, P. Holm, and H. G. Kristensen, Acta Pharm. Nord., 4, 141 (1992).
23. T. Schaefer, P. Holm, and H. G. Kristensen, Acta Pharm. Nord., 4, 245 (1992).
24. T. Schaefer, B. Taagegaard, L. J. Thomsen, and H. G. Kristensen, Eur. J. Pharm. Sci., 1, 125 (1993).
25. T. Schaefer, B. Taagegaard, L. J. Thomsen, and H. G. Kristensen, Eur. J. Pharm. Sci., 1, 133 (1993).
26. L. J. Thomsen, T. Schaefer, J. M. Sonnergaard, and H. G. Kristensen, Drug Dev. Ind. Pharm., 19, 1867 (1993).
27. F. Zhou, C. Vervaet, and J. P. Remon, Int. J. Pharm., 133, 155 (1996).
28. F. Zhou, C. Vervaet, and J. P. Remon, Int. J. Pharm., 147, 23 (1997).