International Journal of Pharmaceutics, 96 (1993) 225–229

IJP 03230

Study of parameters important in the spheronisation process

L. Baert [a], H. Vermeersch [a], J.P. Remon [a], J. Smeyers-Verbeke [b] and D.L. Massart [b]

[a] *Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, 9000 Gent (Belgium) and*
[b] *Pharmaceutical Institute, Free University of Brussels (VUB), Laarbeeklaan 103, 1090 Brussel (Belgium)*

(Received 16 December 1992)
(Accepted 19 February 1993)

Key words: Spheronisation; Parameter analysis; Quality; Pareto analysis

Summary

An experimental design was used to determine the influence of parameters that are important in the extrusion-spheronisation process. The parameters tested were water content of binary mixtures of Avicel PH 101®/water, spheroniser speed and spheronisation time. They appeared to have a significant influence on the quality of the spheres. By using a Pareto analysis, optimal parameter settings for water content, spheroniser speed and spheronising time were obtained.

Introduction

Several authors have reported on the application of experimental design for the extrusion-spheronisation process (Malinowski and Smith, 1975; Chariot et al., 1987; Hasznos et al., 1992). In these studies factors that have been included in the experimental designs are: rate of extrusion, water content, screen size, spheroniser speed, spheronisation time and spheroniser load. All the factors were tested at two levels. In this work, water content, spheroniser speed and spheronisation time were tested at three levels at least. The spheres were evaluated according to two criteria: yield of spheres between 710 and 1400 μm and roundness of the spheres (E value). Mathematical modeling was performed using stepwise multiple regression and a Pareto analysis was carried out to determine the optimal conditions.

Correspondence to: J.P. Remon, Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium.

Materials and Methods

Materials

Microcrystalline cellulose (Avicel PH 101®, FMC, Wallingstown, Little Island, Cork, Ireland) was used as pellet forming agent and demineralised water was used as the granulating fluid.

Composition of the mixtures and granulation procedure

Three different mixtures of microcrystalline cellulose/water were used: 425:575, 475:525 and 525:475 w/w.

The microcrystalline cellulose was granulated with water for 2 min at 60 rpm using a planetary mixer (Kenwood Chef, Hampshire, U.K.) with a K-shaped mixing arm.

Extrusion procedure

After granulation, the mixtures were extruded in an instrumented gravity feed extruder (Extruder 40, GB Caleva Ltd, Dorset, U.K.) as described by Baert et al. (1991). The rotational speed of the axes was 30 rpm.

Spheronisation

200 g of the extrudate were spheronised on a friction plate with cross-hatch geometry in a spheroniser (Spheroniser Model 15, Caleva Ltd, Dorset, U.K.) for different time periods and at different speeds. The time periods tested were 1, 5, 10, 20 and 30 min and the speeds were 500, 750 and 1000 rpm. Next the spheres were dried in a fluidized bed (Aeromatic AG, Aeromatic Ltd, Basel, Switzerland) for 20 min at 50°C.

Evaluation of the spheres

The spheres were evaluated based on two criteria: yield of spheres between 710 and 1400 μm and roundness of the spheres.

Sieve analysis A 100 g sample was sieved using 2000, 1400, 1000, 710, 500 and 250 μm sieves. The sieves were placed on a vibrating shaker (Retostat, Germany) for 5 min at the maximum speed (position 270). The yield of spheres between 710 and 1400 μm was calculated and expressed as a percentage of the total weight.

Roundness Photographs were taken of a 710–1000 μm sieve fraction and the largest (R_1) and the smallest diameter (R_2) of 10 individual spheres were determined. For each sphere the $E(R_1/R_2)$ value was calculated.

Evaluation of the results

A computer program for multiple regression (SPSS/PC+ Statistics T.M. 4.0 for the IBM PC/XT/AT and PS/2 (SPSS Inc., Chicago, IL, U.S.A.)) was used to determine the parameters influencing the yield of spheres between 710 and 1400 μm and the E value and to construct the mathematical models describing the functional relation between the yield of spheres between 710 and 1400 μm or the E value and the parameters that were significantly important. The stepwise regression procedure was applied throughout. A Pareto analysis (Smilde et al., 1986; Keller and Massart, 1990) was performed to determine the conditions giving an optimal yield and E value.

TABLE 1

Evaluation of parameters for the spheronisation of a 425 Avicel PH 101® : 575 water mixture

Spheronisation speed (rpm)	Spheronisation time (min)	Yield between 710–1400 μm (%)	E value ± SD
500	1	87.56	2.045 ± 0.236
500	5	90.91	1.351 ± 0.136
500	10	92.26	1.239 ± 0.110
500	20	95.45	1.065 ± 0.051
500	30	99.57	1.046 ± 0.020
750	1	87.27	1.230 ± 0.200
750	5	90.22	1.045 ± 0.035
750	10	91.11	1.038 ± 0.032
750	20	94.48	1.023 ± 0.029
750	30	95.08	1.035 ± 0.013
1000	1	79.00	1.170 ± 0.111
1000	5	82.59	1.079 ± 0.078
1000	10	82.61	1.058 ± 0.051
1000	20	86.43	1.027 ± 0.026
1000	30	86.69	1.030 ± 0.022
Replicates			
500	1	88.34	1.830 ± 0.149
500	1	88.80	1.913 ± 0.174
500	1	88.96	1.872 ± 0.162
500	30	98.25	1.027 ± 0.024
500	30	99.28	1.052 ± 0.024
500	30	97.58	1.042 ± 0.022

Results

Three different formulations with an Avicel PH 101®/water ratio of 425:575, 475:525 and 525 : 475 (w/w), respectively, yielding good, medium and poor quality spheres (Baert et al., 1992) when spheronised for 10 min at a speed of 750 rpm were selected for the experiments. The spheronisation speed was 500, 750 and 1000 rpm and the spheronisation time was 1, 5, 10, 20 and 30 min. The results for the different experiments can be found in Tables 1–3. The parameters having a significant influence on the yield between 710 and 1400 μm or on the E value were evaluated (Tables 4–6) for each of the formula-

TABLE 2

Evaluation of parameters for the spheronisation of a 475 Avicel PH 101®: 525 water mixture

Spheronisation speed (rpm)	Spheronisation time (min)	Yield between 710–1400 μm (%)	E value ± SD
500	1	92.76	1.740 ± 0.247
500	5	89.47	1.647 ± 0.460
500	10	87.34	1.270 ± 0.210
500	20	84.14	1.146 ± 0.140
500	30	76.78	1.103 ± 0.090
750	1	78.18	1.388 ± 0.215
750	5	79.54	1.104 ± 0.084
750	10	79.49	1.062 ± 0.045
750	20	76.20	1.024 ± 0.028
750	30	79.34	1.078 ± 0.032
1000	1	57.36	1.147 ± 0.180
1000	5	56.53	1.108 ± 0.141
1000	10	49.69	1.048 ± 0.025
1000	20	40.03	1.038 ± 0.026
1000	30	44.88	1.024 ± 0.016
Replicates			
750	10	78.33	1.048 ± 0.036
750	10	82.17	1.048 ± 0.036
750	10	78.30	1.047 ± 0.033
1000	20	43.26	1.038 ± 0.019
1000	20	40.67	1.052 ± 0.050
1000	30	44.49	1.023 ± 0.017
1000	30	44.80	1.021 ± 0.016

TABLE 3

Evaluation of parameters for the spheronisation of a 525 Avicel PH 101®: 475 water mixture

Spheronisation speed (rpm)	Spheronisation time (min)	Yield between 710–1400 μm (%)	E value ± SD
500	1	87.90	2.080 ± 0.241
500	5	83.40	2.060 ± 0.299
500	10	77.50	1.790 ± 0.250
500	20	64.30	1.630 ± 0.372
500	30	67.58	1.615 ± 0.193
750	1	73.20	1.438 ± 0.232
750	5	67.80	1.270 ± 0.132
750	10	60.60	1.202 ± 0.155
750	20	66.93	1.080 ± 0.065
750	30	65.71	1.042 ± 0.028
1000	1	41.50	1.130 ± 0.058
1000	5	43.60	1.158 ± 0.129
1000	10	41.50	1.095 ± 0.053
1000	20	43.84	1.051 ± 0.035
1000	30	40.34	1.037 ± 0.022
Replicates			
750	30	64.65	1.048 ± 0.037
750	30	66.26	1.065 ± 0.036
750	30	62.85	1.060 ± 0.037

tions. A model including the proportion of Avicel PH 101® as a variable was also constructed (Table 7).

For each of the three formulations the square of the speed was the most important parameter with respect to the yield between 710 and 1400 μm. For the 425 Avicel PH 101®: 575 water formulation this parameter was less important than for the other two formulations as was concluded from the cumulative proportion of the variation explained (%) (Tables 4–6). The influence of spheronisation time is more important for the formulation with the highest amount of water (425 Avicel PH 101®: 575 water) than for those containing less water (425 Avicel PH 101®: 525 water and 525 Avicel PH 101®: 475 water). Moreover, the effect is negative for the former formulation and positive for the latter two.

For the 525 Avicel PH 101®: 475 water formulation, the effect of time was dependent on the speed as was concluded from the interaction term, time × speed. Taking the model constructed for all the mixtures into consideration, the effect of speed was dependent on the formulation as can be observed from the interaction term 'proportion Avicel × speed' which explains about 64% of the variation observed in the yield (Table 7). This confirms the different degree of importance of speed mentioned previously.

Evaluating the E values, a transformation using $\log(E-1)$ instead of E was required in order

TABLE 4

Factors having a significant influence on log(E − 1) and on the yield between 710 and 1400 μm (S%) for a 425 Avicel PH 101®: 575 water mixture with the cumulative proportion of the variation explained (%) by the different factors

S%		Log(E − 1)	
(1) Speed^2	57.33%	(1) time × speed	53.49%
(2) Time	91.10%		

$Y_{(S\%)} = 93.512 - 0.00001328 \times \text{speed}^2 + 0.29764 \times \text{time}$
$Y_{(\log(E-1))} = -0.69275 - 3.96620E - 5 \times \text{time} \times \text{speed}$

TABLE 5

Factors having a significant influence on log(E − 1) and on the yield between 710 and 1400 μm (S%) for a 475 Avicel PH 101®:525 water mixture with the cumulative proportion of the variation explained (%) by the different factors

S%		Log(E − 1)	
(1) Speed^2	86.07%	(1) time × speed	54.70%
(2) Time	91.10%	(2) speed	71.35%

$Y_{(S\%)} = 105.9989 - 0.00004952 \times \text{speed}^2 - 0.34858 \times \text{time}$

$Y_{(\log(E-1))} = 0.06825 - 3.11761E-5 \times \text{time} \times \text{speed} - 9.34286E-5 \times \text{speed}$

TABLE 6

Factors having a significant influence on log(E − 1) and on the yield between 710 and 1400 μm (S%) for a 525 Avicel PH 101®:475 water mixture with the cumulative proportion of the variation explained (%) by the different factors

S%		Log(E − 1)	
(1) Speed^2	83.90%	(1) speed	67.42%
(2) Time	88.80%	(2) time × speed	90.62%
(3) Time × speed	93.70%		

$Y_{(S\%)} = 102.1260 - 0.00005985 \times \text{speed}^2 - 1.51170 \times \text{time} + 0.001586\text{time} \times \text{speed}$

$Y_{(\log(E-1))} = 0.82789 - 1.60695E-3 \times \text{speed} - 2.91242E-5 \times \text{time} \times \text{speed}$

TABLE 7

Factors having a significant influence on log(E − 1) and on the yield between 710 and 1400 μm (S%) for binary mixtures of Avicel PH 101®/water with the cumulative proportion of the variation explained (%) by the different factors

S%		Log(E − 1)	
(1) Proportion Avicel × speed	63.68%	(1) speed	35.52%
(2) Speed	84.26%	(2) time	66.02%
		(3) proportion Avicel	77.86%
		(4) time^2	82.60%

$Y_{(S\%)} = 114.1881 - 0.000377 \times \text{proportion Avicel} \times \text{speed} + 0.12595\ \text{speed}$

$Y_{(\log(E-1))} = -0.29760 - 1.46153E-3 \times \text{speed} + 4.438506E-6 \times \text{proportion Avicel} - 0.06719 \times \text{time} + 1.313077\ \text{time}^2$

to obtain normally distributed residuals. The importance of speed increased with decreasing amount of water (Tables 4–6). For each of the three formulations the effect of time was dependent on the speed but was less pronounced for the 525 Avicel PH 101®:475 water formulation. On examination of the model for all the mixtures, the speed was found to be the most important factor followed by the time factor, (proportion of Avicel)^2 and time^2 (Table 7).

Mathematical models were constructed relating, respectively, the yield between 710 and 1400 μm and log(E − 1) to the significant parameters discussed earlier (Tables 4–7).

For the individual mixtures more than 90% of the variation was explained for the yield whereas for log(E − 1) value the % variation explained depended on the formulation ranging from 53.49 to 90.62% for decreasing amounts of water.

The replicate measurements mentioned in Tables 1–3 were used to perform a lack of fit test. There was always a significant lack of fit ($p \leqq 0.05$, F-test) except for the E value of the 525 Avicel PH 101®:475 water mixture.

For the model constructed with all three mixtures together, 84.26% of the variation of the yield between 710 and 1400 μm and 82.60% of the variation of the log(E − 1) value were explained. These models were used to predict the value for the yield between 710 and 1400 μm and the E value. A Pareto analysis was conducted using steps of 1 min, 50 rpm and 25 Avicel PH 101® in a range of 1–30 min, 500–1000 rpm and 425–525 Avicel PH 101®. The Pareto analysis revealed five optimal parameter settings as indicated in Table 8. Suboptimal spheres with an E

TABLE 8

Optimal parameter settings, resulting yield between 710 and 1400 μm and E values obtained by Pareto analysis

Proportion Avicel PH 101®	Time (min)	Speed (rpm)	S%	E
425	26	700	90.08	1.04
425	22	650	91.80	1.05
425	29	600	93.52	1.06
425	29	550	95.24	1.07
425	26	500	96.97	1.08

value smaller than 1.20 and a yield between 710 and 1400 μm larger than 90% were obtained for mixtures containing 425 Avicel PH 101® or 450 Avicel PH 101® using a rotational speed between 500 and 700 rpm or between 500 and 550 rpm, respectively, and a spheronisation time of 3–30 or 9–30 min, respectively.

Discussion

The aim of this study was to reveal the parameters which influenced the quality of spheres and to construct mathematical models describing the relation between the quality of the spheres and these important parameters.

The quality of the spheres was evaluated using two criteria: the sphere yield between 710 and 1400 μm and the roundness of the spheres expressed by the E value (Baert et al., 1992). Spheres of equal size are required during the manufacturing process in order to be able to fill hard gelatin capsules in a reproducible way (Reynolds, 1970) and to control the drug delivery rate from the spheres. The yield is important in order to reduce drug loss to a minimum. The roundness of the spheres is important for coating spheres and for improving the flowability (Chapman et al., 1988; Lövgren and Lundberg, 1989). The roundness as well as the yield between 710 and 1400 μm was influenced by the amount of water and the spheronisation speed. The greater the amount of water used or the lower the spheronisation speed, the higher was the yield of spheres between 710 and 1400 μm. The roundness of the spheres was also influenced by the spheronisation time. A longer spheronisation time yielded rounder spheres.

When the different formulations were considered individually (Tables 4–6), it was observed that, with respect to the roundness and the yield of spheres between 710 and 1400 μm, the speed became more important and the time less important with decreasing amounts of water in the mixture. Nevertheless, the lack of fit indicated that a significant proportion of the variation in both variables could not be explained by the parameters considered here.

Possible important factors that were not considered are the temperature and the relative humidity during the experiments.

Since two criteria had to be optimized, i.e., it was necessary to maximize the sieve fraction and minimize the E value, a multicriterion decision analysis was performed. With the Pareto analysis, five optimal parameter settings were detected as indicated in Table 8. These settings will result in an optimal compromise between yield and roundness of the spheres.

References

Baert, L., Fanara, D., De Baets, P. and Remon, J.P., Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces. *J. Pharm. Pharmacol.*, 43 (1991) 745–749.

Baert, L., Fanara, D., Remon, J.P. and Massart, D., Correlation of extrusion forces and sphere quality. *J. Pharm. Pharmacol.*, 44 (1992) 676–678.

Chapman, S.R., Rowe, R.C. and Newton, J.M., Characterization of the sphericity of particles by the one plane critical stability. *J. Pharm. Pharmacol.*, 40 (1988) 503–505.

Chariot, M., Francès, J., Lewis, G.A., Mathieu, D., Phan Tan Luu, R. and Stevens, H.N.E., A factorial approach to process variables of extrusion – spheronisation of wet powder masses. *Drug Dev. Ind. Pharm.*, 13 (1987) 1639–1649.

Hasznos, L., Langer, I. and Gyarmathy, M., Some factors influencing pellet characteristics made by an extrusion/spheronisation process: I. Effects on size characteristics and moisture content decrease of pellets. *Drug Dev. Ind. Pharm.*, 18 (1992) 409–437.

Keller, H.R. and Massart, D.L., Program for Pareto-optimality in multicriteria problems. *Trends Anal. Chem.*, 9 (1990) 251–253.

Lövgren, K. and Lundberg, P.J., Determination of sphericity of pellets prepared by extrusion/spheronization and the impact of some process parameters. *Proc. 8th Pharmaceutical Technology Conference*, Monte Carlo, 1989, pp. 308–325.

Malinowski, H.J. and Smith, W.E., Use of a factorial design to evaluate granulations prepared by spheronization. *J. Pharm. Sci.*, 64 (1975) 1688–1692.

Reynolds, A.D., A new technique for the production of spherical particles. *Manuf. Chem. Aerosol News*, 41 (1970) 40–44.

Smilde, A.K., Knevelman, A. and Coenegracht, P.M.J., Introduction of multicriteria decision making in optimization procedures for high-performance liquid separations. *J. Chromatogr.*, 369 (1986) 1–10.