Drug Development and Industrial Pharmacy, 24(11), 1073–1076 (1998)

COMMUNICATION

Effect of the Formulation Parameters on the Characteristics of Pellets

R. Fekete, R. Zelkó, S. Marton, and I. Rácz

Pharmaceutical Institute of the Semmelweis University of Medicine, Budapest

ABSTRACT

Pelletization is increasingly applied currently for the preparation of solid oral controlled-release dosage forms. The production of the particles, which are regular in shape and size, can be achieved with the application of the proper polymer auxiliary materials and new pharmaceutical technological methods (extrusion, spheronization). Regularity in shape and size, attained by the optimization of several production parameters, can promote the coating procedure. Under optimal conditions, particles were prepared for coating in a high-shear mixer, which is used to produce uniform particles. The effect of the rotating speed of the applied chopper and the amount of microcrystalline cellulose in the composition on the physical characteristics of the pellets was modeled by a second-order polynomial equation fitted to the data gathered by a face-centered central composite statistical design.

INTRODUCTION

In the development of reservoir-type modified-release products, the use of pellets has become predominant since it provides an efficient method of maximizing reproducibility and minimizing the risk of dose dumping. Since the multiparticulates spread uniformly throughout the gastrointestinal tract, high local drug concentrations can be avoided (1).

Pellets have a minimum surface/volume ratio and an ideal shape for coating. Coated pellets offer a practical method to control the site and rate of drug dissolution in the gastrointestinal tract (2–5).

The commonly applied pelletization technique, extrusion/spheronization, requires special equipment and a number of successive steps: moistening, extrusion, spheronization, and drying (6,7). The polyphasic character of extrusion/spheronization demonstrates that the steps contributing to the transformation of the starting powder mixtures in spheroids are particularly dependent on each other (8).

The aim of the present study was to formulate pellets in one step with STEPHAN UMC 5 electronic apparatus and to examine the formulation factors that may influence the physical properties of the prepared pellets.

EXPERIMENTAL

Materials

Salicylic acid (Sigma-Aldrich Ltd., Budapest), Avicel PH 101 (Ph. Eur., Fluka, Germany), α-D-lactose monohydrate (Ph. Hg. VII., Hungaropharma, Budapest), and Amylum solani (Ph. Hg. VII., Hungaropharma, Budapest) were used.

Methods

Preparation of Pellets

The pelletization was carried out in a Stephan UMC 5 electronic apparatus (Stephan Mashinen GmbH, Wien) equipped with different choppers. Three various compositions, containing Avicel PH 101, lactose, and amylum solani as well as the salicylic acid, were prepared. The granulation liquid (i.e., the distilled water) was atomized at a 160 ml/min rate under 20-bar vacuum pressure.

Examination of the Particle Size Distribution of Pellets

The prepared and dried pellets were fractionated using a vibrating sieve (Retsch AS 200 control, Retsch Verder GmbH, Germany) for 5 min with 2.5-mm amplitudes without intervals and sieving aids. The sieve fractions were 1250–2000 μm, 800–1250 μm, 315–800 μm, 160–315 μm, and 63–160 μm.

Determination of the Sphericity Factor of the Pellets

The shape of the pellets was examined with a light microscope (Zeiss, Germany) at 16× magnification. Major and minor axes of 12 particles of each composition were measured. The sphericity factor, the ratio of the minor and major axes of pellets, was determined as a mean value of 12 measurements.

Statistical Experimental Design

A two-factor, three-level, face-centered central composite design (9) was applied to construct a second-order polynomial model describing the effect of formulation factors (revolution number, Avicel PH101 content) on the pellet characteristics (the percentage of the particles of 800–1250 μm, sphericity factor). The two factors, as well as their levels, are shown in Table 1. The levels for each parameter are represented by a minus (−) sign for the lower level, a plus (+) sign for the higher level, and by a zero (0) for the base level.

Table 1

Experimental Design with Factors and Their Levels

Levels	x_1 Rotating Number (rpm)	x_2 Microcrystalline Cellulose (% w/w)
Lower (−)	600	40
Base (0)	900	60
Higher (+)	1200	80

TableCurve 3D (Jandel Scientific) software was applied for the multiple regression analysis. The expected form of the polynomial equation is as follows:

$$y = b_0 + b_1 x_1 + b_2 x_2 + b_{11} x_1^2 + b_{22} x_2^2 + b_{12} x_1 x_2 \quad (1)$$

where y is the response, the x's are the factors, and the b parameters denote the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction (b_{12}) effects.

RESULTS AND DISCUSSION

The resultant equations (Eqs. 2 and 3), obtained after a significance test at the 95% confidence level, represent the effect of formulation factors x_1 and x_2 on the percentage of particles of 800–1250 μm (y_1) and the sphericity factor y_2.

$$y_1 = 20.39 + 0.17x_1 - 1.25x_2 - 1.50 \cdot 10^{-4}x_1^2 + 7.35 \cdot 10^{-3}x_2^2 + 7.05 \cdot 10^{-4}x_1x_2 \quad (2)$$

$$y_2 = 0.75 + 1.29 \cdot 10^{-3}x_1 - 1.33 \cdot 10^{-2}x_2 - 9.07 \cdot 10^{-7}x_1^2 + 9.58 \cdot 10^{-5}x_2^{-2} + 3.33 \cdot 10^{-6}x_1x_2 \quad (3)$$

The positive signs of the coefficients refer to an increasing effect, whereas the negative signs indicate a decreasing effect on the corresponding response.

Figure 1 illustrates the effect of the independent variables on the percentage of pellets that are 800–1250 μm, while Fig. 2 represents the influence of the same variables on the sphericity of the pellets. The profiles of the three-dimensional response surfaces are similar to each other, showing an optimum at the examined 900 rpm rotating number in both of the responses. The formed surfaces were more influenced

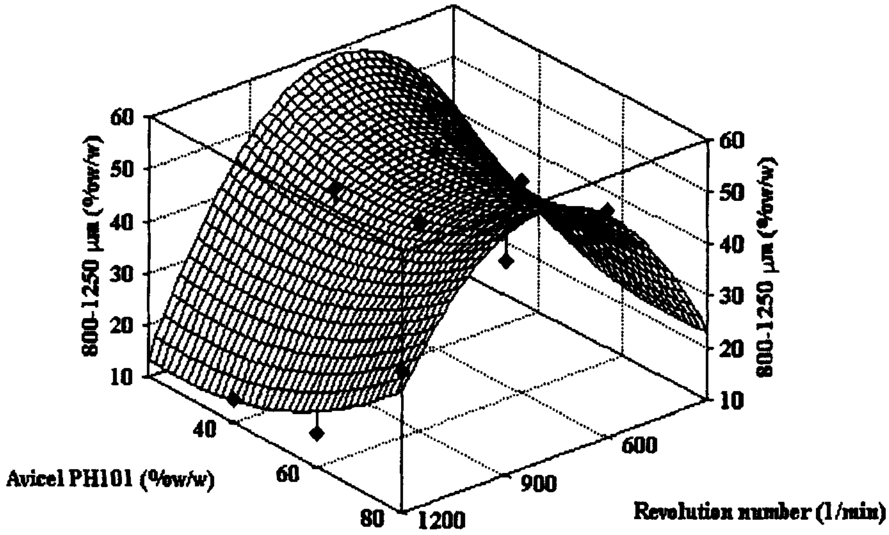

Figure 1. The effect of independent variables of the formulation on the percentage of particles of optimal size.

by the rotating number than by the Avicel PH101 content within the selected range.

In the range 600–900 rpm rotating numbers, the amount of the particles that are 800–1250 μm refers to the main effect (b_1 = 0.17), which increases the amount of the particles of optimal size (y_1). In the range 900–1200 rpm rotating numbers, this main effect is less dominant due to the quadratic effect (b_{11} = $-1.50 \cdot 10^{-4}$) of the same factor. The last effect can be explained by the increasing shear forces applied to the mass and caused by the increased rotating number of the chopper. On the other hand, the higher rotating number not only increased the amount of the particles of optimal particle size, but improved the sphericity of the pellets (y_2) as well. The effect of the rotating number on the sphericity of the pellets is more dominant

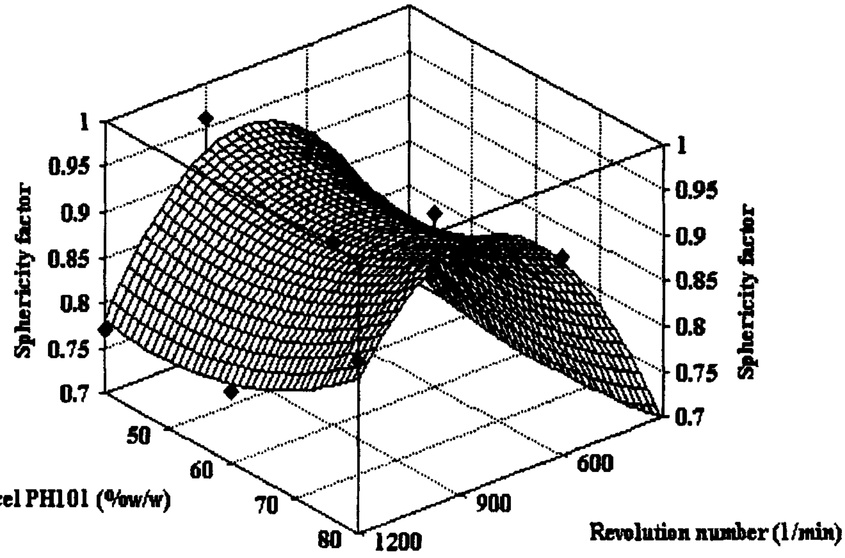

Figure 2. The effect of independent variables of the formulation on the sphericity factor of pellets.

Table 2

Randomized Matrix of the Two-Factor, Three-Level Face-Centered Central Composite Factorial Design

Trial	x_1(rpm)	x_2 (% w/w)	$y_1 \pm$ SD (% w/w) (n = 3)	$y_2 \pm$ SD (n = 12)
1	+	0	16.47 ± 4.27	0.78 ± 0.01
2	−	−	47.76 ± 2.81	0.88 ± 0.02
3	0	−	47.97 ± 2.49	0.96 ± 0.04
4	−	+	53.50 ± 0.83	0.92 + 0.01
5	0	0	50.12 ± 2.30	0.90 ± 0.01
6	+	−	14.49 ± 0.32	0.77 ± 0.01
7	0	+	51.26 ± 4.78	0.95 ± 0.02
8	+	+	37.15 ± 3.96	0.89 ± 0.02
9	−	0	50.66 ± 1.98	0.89 ± 0.02

than is the Avicel PH101 content. Although it was previously reported that the microcrystalline cellulose improved the sphericity of the pellets (10), here it was found that the Avicel PH101 content slightly decreased it. The negative coefficient value ($b_2 = -1.33 \cdot 10^{-2}$) of the Avicel PH101 content refers to the main decreasing effect.

Table 2 summarizes the estimated physical characteristics of the prepared pellets.

CONCLUSIONS

A nonlinear model was selected to describe the effect of the rotating number (r = 0.9779) of the applied Stephan UMC 5 apparatus and that of the Avicel PH101 content (r = 0.9493) of the compositions on the examined physical characteristics of pellets. During the formulation of the examined compositions, the determination of the optimal rotating number of the applied equipment has great importance as regards not only the particle size, but also the sphericity of the pellets.

REFERENCES

1. R. Bodmeier, Eur. J. Pharm. Biopharm., 43, 1 (1997).
2. I. Rácz, *Drug Formulation*, John Wiley and Sons, New York, 1989, p. 362.
3. J. J. Sousa, A. Sousa, F. Podczek, and J. M. Newton, Int. J. Pharm., 144, 159 (1996).
4. N. Follonier and E. Doelker, S.T.P. Pharma Sci., 2, 141 (1992).
5. S. Marton, E. Bihari, Á. Orbán, D. Greskovits, and I. Rácz, in Proceedings of the 1st World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, APGI/APV, Châtenay Malabry-Mainz, 1995, p. 357.
6. J. M. Newton, S.T.P. Pharma Sci., 6, 396 (1990).
7. D. Sonaglio, B. Bataille, C. Ortigosa, and M. Jacob, Int. J. Pharm., 115, 53 (1995).
8. L. Hasznos, I. Langer, and M. Gyarmathy, Drug Dev. Ind. Pharm., 18, 409 (1992).
9. R. M. Franz, J. E. Browne, and A. R. Lewis, in *Pharmaceutical Dosage Forms. Disperse Systems* (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), Marcel Dekker, New York, 1988, p. 427.
10. P. Holm, Pharm. Tech. Eur., 8, 38 (1996).