AAPS PharmSciTech

AAPS PharmSciTech 2000; 1(4) article 35
(http://www.pharmscitech.com/)

Optimization of the Pelletization Process in a Fluid-Bed Rotor Granulator Using Experimental Design

Submitted: July 28, 2000; Accepted: November 28, 2000

Evdokia S. Korakianiti, Dimitrios M. Rekkas, Paraskevas P. Dallas, Nikolaos H. Choulis

Division of Pharmaceutical Technology, School of Pharmacy, University of Athens, Panepistimiopolis, Zografou, Athens 157 71, Greece

ABSTRACT This study examined the effect of rotor speed, amount of water sprayed, and atomizing air pressure on the geometric mean diameter and geometric standard deviation of pellets produced in a fluid-bed rotor granulator using a 2^3 factorial design and an optimization technique.

Pellets were prepared by wet granulation. Equal amounts of microcrystalline cellulose, α-lactose monohydrate, and distilled water were used as the granulation liquid. The size and the size distribution of the pellets were determined by sieve analysis.

The size of the pellets was found to be dependent on the amount of water added, while an increase in rotor speed decreased their size. Both factors were found to be statistically significant ($P < .05$). The effect of atomizing air pressure on pellet size was not statistically significant. None of the 3 factors significantly affected the geometric standard deviation of the pellets.

The rotor speed and the amount of water sprayed were further selected in order to construct a mathematical model that correlates these factors with the geometric mean diameter of the pellets. For this purpose, the optimization technique 3^2 was used. The derived equation described the relationship between the selected factors and the size of the pellets. As a result, the experimental design techniques applied were found to be suitable in optimizing the pelletization process carried out in a fluid-bed rotor granulator.

KEYWORDS: Pellets, Fluid-bed rotor granulator, Optimization, Factorial design

***Corrseponding Author:** Dimitrios M. Rekkas; Division of Pharmaceutical Technology, School of Pharmacy, University of Athens, Panepistimiopolis, Zografou, Athens 157 71, Greece; Telephone: (301) 727-4023; Fax: (301) 727-4027; E-mail: rekkas@pharm.uoa.gr

INTRODUCTION

Pellets as drug delivery systems offer not only technological advantages, such as better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing, but also therapeutic advantages. Therapeutic advantages include less irritation of the gastrointestinal tract, a lowered risk of side effects associated with dose dumping, and a uniform distribution in the gastrointestinal tract resulting in a reduction of peak plasma fluctuations. The reduction of the variation in gastric emptying rates and the overall transit times is also a major advantage [1].

Pellets can be produced in many different ways [2]; extrusion-spheronization, a 3-step process that has been studied extensively, is used most often. Alternative techniques for producing pellets are the single pot methods, where pellets are produced, dried, and coated in the same equipment. They are 1-step processes that take place in one machine, such as a high-sheer mixer or a rotary processor. Using one machine for the whole process ensure batch- to-batch reproducibility and reduction of production time and cost, and enables automation of the process [3].

In this study, pellets were produced using a fluid-bed rotor granulator [4]. The following techniques can be applied using this equipment: solution/suspension layering, spray congealing, spray drying of a solution or a suspension, and wet granulation, where the binder liquid is sprayed onto the powder mass so that the particles are granulated and spheronized at the same time. The wet granulation method was employed in this study.

Pelletization by means of wet granulation in a fluid-bed rotary processor is a multivariable process in which several factors affect the final characteristics of the pellets produced. Therefore, the application of experimental design techniques, such as factorial design and optimization, could be useful tools for the identification and correlation of significant factors that affect the process. They provide valid information while using only a limited number of structured experiments.

The objective of this study was to determine the effect of rotor speed, amount of water sprayed, and atomizing air pressure on the size (geometric mean diameter) and size distribution (geometric standard deviation) of the pellets prepared by the above-mentioned wet granulation method, using a 2^3 factorial design and an optimization technique.

MATERIALS AND METHODS

Materials

Starting materials were α-lactose monohydrate (Pharmatose® 150 M, DMV, Veghel, The Netherlands, lot 23813) and microcrystalline cellulose (Avicel® PH 101, FMC, lot 6814C, Brussels, Belgium). All materials were of Ph. Eur. grade. Deionized water was used as the granulation liquid.

Preparation of pellets

The pellets were prepared in a fluid-bed rotor granulator (Glatt GPCG3, Glatt GmbH, Binzen, Germany) using the wet granulation technique. Equal amounts of microcrystalline cellulose and lactose were adequately mixed. One kg of the powder mixture was loaded into the product chamber of the machine. After a fluidization time of 3 minutes, a preweighed amount of water (**Table 1**) was sprayed through an atomizing nozzle (1.2 mm diameter) into the powder at a rate of 30 mL per minute with the aid of a peristaltic pump (Siemens, RexV/110, model 501R, Germany). The inlet air temperature was kept constant at 27 ± 1°C and the process airflow at 0.3-0.5 bar. Once all the water was sprayed, the pellets were dried for 15 minutes at 40°C.

Evaluation of pellets

The size of the pellets was determined by sieve analysis (Endecotts, Octagon Digital CE, London, UK). Based on these results, the geometric mean diameter on a weight basis (d_g) and the geometric SD (σ_g) were computed using a log-probability plot. As d_g was regarded the particle size equivalent to 50% of the probability scale, and as σ_g the quotient of the ratio 16% oversize/50% size [5].

Experimental design and analysis

Factorial design [6,7] is an experimental technique by which factors involved in a process can be identified and their relative importance assessed. It is thus a means of separating those factors that are important from those that are not and identifying the interactions, if any, between the factors chosen. Thus the construction of a factorial design involves the selection of parameters and the choice of responses.

A 2^3 factorial design was used to determine the effect of the rotor speed, the amount of water sprayed, and the atomizing air pressure on the geometric mean diameter and geometric SD of the pellets. The factors and the levels studied are shown in **Table 1**. The matrix of the factorial design is shown in **Table 2**.

Table 1. Factors and Levels Used in the 2^3 Factorial Design

Factor	Low Level	High Level
A: Rotor speed (rpm)	1000	1400
B: Amount of water (ml)	1250	1750
C: Atomizing air pressure (bar)	1.5	3

Table 2. Matrix of the 2^3 Factorial Design. Geometric Mean Diameter (d_g) and Geometric Standard Deviation (σ_g) of the Produced Pellets*

Experiment	Factor A	Factor B	Factor C	d_g (μm)	σ_g
(1)	-	-	-	1150.7	224.2
(a)	+	-	-	303.0	42.4
(b)	-	+	-	1054.5	222.8
(ab)	+	+	-	507.2	116.0
(c)	-	-	+	326.7	56.0
(ac)	+	-	+	463.5	97.6
(bc)	-	+	+	792.9	135.6
(abc)	+	+	+	1252.7	208.4

*Factor A indicates rotor speed (rpm); Factor B, amount of water (mL); Factor C, atomizing air pressure (bar); -, low level; +, high level.

The different formulations consisted of all possible combinations of all factors at all levels and were conducted in a fully randomized order. The results for the geometric mean diameter and the geometric SD were evaluated by analysis of variance (ANOVA) using a commercial software package (Statgraphics Plus 4®, Manugistics, Inc, Rockville, MD).

RESULTS AND DISCUSSION

The results for the geometric mean diameter and the geometric SD of the pellets produced are listed in **Table 2**. Based on these data, the main effects of the factors under study and their interactions were calculated and statistically evaluated by ANOVA (**Table 3**). **Table 3** shows that an increase in the amount of water sprayed results in an increase in pellet diameter. The ANOVA results (**Table 3**) confirm that the effect is statistically significant ($P < .05$). As expected [8], the size of the pellets is highly dependent on the amount of water added. Many studies have shown the importance of the amount of the moistening liquid in controlling the size of the pellets produced [9-14]. An increase in the amount of moistening liquid increases the wet surface available for agglomeration between the particles. According to Heng et al [10], the amount of moistening liquid should reach a minimum level so that pellets of a suitable size can be obtained. On the other hand, if too much moistening liquid is added, the pellets produced will show a skewed size distribution. Vertommen et al [9] observed that wet massing of cohesive powders like microcrystalline cellulose, which consolidate during the process, is highly sensitive to the added amount of binding solution.

Table 3 also shows that pellet size is significantly affected ($P < .05$) by the speed of the rotor plate. Although this finding is in agreement with previous reports [8,15,16], not all the reports agree on whether the relationship between the 2 factors is proportional. More specifically, Hasznos et al [16] and Vertommen et al [9] found that pellet size increased with an increase in spheronizer speed, while Helen et al [15] reported the opposite. In the present study an increase in rotor speed was found to decrease the size of the pellets produced. Strong centrifugal forces may cause size reduction of the already formed pellets due to attrition or breakage. A possible explanation for the contradictory results regarding the effect of the rotor speed on pellet size could be that each study used a different method and/or equipment for the production of the pellets.

The effect of atomizing air pressure on pellet size was not statistically significant ($P < .05$), as seen in **Table 3**. In fluidized bed granulation, particle growth follows a nucleative process. Powder particles, when wetted, form nuclei that are held together by liquid bonds. The formation of these nuclei is influenced by the size of the droplets sprayed. Larger droplets form larger nuclei because they are able to bind more particles. The size of the droplets sprayed can be changed by varying the atomizing air pressure. According to Merkku and Yliruusi [12], an increase of the atomizing air pressure decreases the size of the droplets and consequently the size of the granules produced. However, these findings do not seem to apply in fluid bed pelletization. Wan et al [17] investigated the effect of atomizing air pressure on spheroid size and found that the size of the droplets sprayed does not seem to have a significant effect on spheroid size. This could be because the centrifugal forces that act in a rotary processor are stronger than those in a fluid-bed granulator, and thus their effect on pellet size is predominant and masks the effect of the size of the droplet.

Table 3. Effects and Interactions of the Selected Factors on the Geometric Mean Diameter and Standard Deviation of the Pellets*

	Geometric Mean Diameter		Geometric Standard Deviation	
Factors	Main Effect or Interaction	*P*-value	Main Effect or Interaction	*P*-value
A	-199.6	0.018**	-43.5	0.156
B	340.9	0.011**	65.6	0.105
C	-44.9	0.079	-26.9	0.245
AB	155.8	0.023**	26.5	0.248
AC	497.9	0.007**	100.7	0.069
BC	286.8	0.012**	29.6	0.225

*A indicates rotor speed (rpm); B, amount of water (mL); C, atomizing air pressure (bar).; **Statistically significant ($P < .05$)

As shown in **Table 3**, all the interactions between the selected factors were found to be statistically significant ($P < .05$). This means, for example, that the magnitude of the effect of the rotor speed on geometric mean diameter of the pellets is strongly affected by the amount of water sprayed (AB interaction) or the atomizing air pressure (AC interaction). As can be seen in **Figure 1**, a change in rotor speed influences the mean geometric diameter of the pellets to a greater extent when the amount of water sprayed is set at high level compared with its effect at a low level.

The geometric SD was used to evaluate the size distribution of the pellets; the results are depicted in **Table 3**. It can be seen that an increase of the rotor speed results in pellets of a narrower size distribution, but this effect was not found to be statistically significant. Helen et al [15] and Holm et al [8] reported that an increase of the spheronization speed decreases the size distribution of the pellets. **Table 3** also shows that when the amount of water sprayed is increased, the size distribution of the pellets is also increased, while an increase of the atomizing air pressure decreases the size distribution. Neither effect was found to be statistically significant ($P < .05$).

Because the geometric SD of the pellets was not statistically significantly affected by the selected factors, the study further focused only on pellet size. Therefore, the factors that were found to significantly affect pellet size (ie, the rotor speed and the amount of water sprayed) were further selected in order to construct a mathematical model that correlates these factors with the geometric mean diameter of the pellets. The optimization technique 3^2 was used for this purpose[6]. The factors and their levels are shown in **Table 4**.

The atomizing pressure was kept constant at 3 bar. The results were further analyzed with multiple regression analysis using a commercially available package (Statgraphics Plus 2.11®, Manugistics, Inc). The polynomial equation obtained correlates the rotor speed (X1) and the amount of water (X2) with the geometric mean diameter (Y).

$$Y = 2.8375 + 0.0006\ X_1^2 - 0.0016\ X_2^2 - 4.5616\ X_1 + 2.6347\ X_2 + 0.0027\ X_1 X_2$$

$$R^2 = 0.998,\ SE = 22.681,\ P < .05 \qquad (1)$$

The surface plot for Equation 1 is shown in **Figure 1**. To assess the reliability of Equation 1, 2 additional experiments were conducted by varying the 2 independent variables (rotor speed, X_1, and amount of water, X_2) and estimating the dependent variable (geometric mean diameter, Y). The levels of the factors and the estimated and experimental values are shown in **Table 5**. It can be concluded that there is a good agreement between the estimated and the observed values.

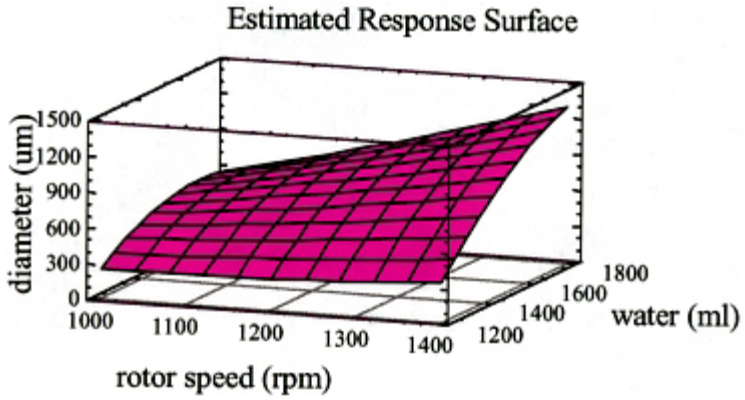

Figure 1. Surface plot for the effect of rotor speed and amount of water on the geometric mean diameter of the pellets.

Table 4. Factors and Their Levels Selected for the Optimization Technique

Factors	Levels		
	Low	Intermediate	High
Rotor speed (rpm)	1000	1200	1400
Amount of water (ml)	1250	1500	1750

Table 5. Comparison Between the Estimated and the Experimental Values of the Geometric Standard Deviation of the Pellets

Formulation	Estimated	Experimental
Rotor speed (X1): 1100 rpm, Amount of water (X2): 1625 mL	710.8	850.2
Rotor speed (X1): 1300rpm, Amount of water (X2): 1375mL	646.8	674.2

CONCLUSIONS

Rotor speed and amount of water were found to significantly affect the geometric mean diameter of the pellets. Interactions between these factors were also found to be statistically significant. These findings suggest that those factors should be considered during pelletization, as far as their geometric mean diameter is concerned. However, the factors did not significantly affect the geometric SD of the pellets.

Furthermore, the correlation of rotor speed, amount of water sprayed, and geometric mean diameter can be adequately described by Equation 1.

Finally, experimental design techniques such as factorial design and optimization proved to be useful for the identification and correlation of the significant factors that affect pellet size.

ACKNOWLEDGEMENTS

This work was supported by grant YPER97 from the Greek Secretariat of Research and Technology and has been presented at the 4th Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V/Association de Pharmacie Galenique Industrielle (APV/APGI) World Meeting (Berlin, 2000).

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