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Note

The influence of operational variables on mean size and size distribution of spheroids produced by rotary spheronization using teardrop studs

C.V. Liew, L. Gu, P.W.S. Heng *

Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore

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Abstract

The rotary processor can be used for single step spheroid production directly from powder with multiple formulation and process variables involved. In this study, a frictional base plate with teardrop studs was used. Four selected independent variables, base plate rotational speed during liquid addition (*A*), spray rate of water (*B*), total amount of water added (*C*) and base plate rotational speed during the tumbling stage (*D*), were put into an orthogonal design with three levels for each variable. Mean spheroid size and size distribution were used as the response variables to evaluate the effect of these independent variables. The variables *C* and *D* were identified as more important among the four variables and should be at optimal levels for producing good quality spheroids. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Rotary processor; Spheronization; Orthogonal design

The rotary processor can be used for single step spheroid production directly from powder (Parikh et al., 1997). The wet spheronization technique in the rotary processor is a valuable alternative to the more commonly used multiple step extrusion–spheronization process. The spheronization process in rotary processor can be divided into three stages: liquid addition stage, tumbling stage and drying stage (Liew et al., 1998). More recently introduced teardrop studs were reported to be advantageous and reduced material adhesion to the frictional base plate. Thus, it is necessary to re-assess the process of spheroid production using the teardrop studs.

Rotary processing is a multivariable process and, consequently, it is important to identify and control the critical formulation and process conditions. Optimization by means of experimental design is a powerful, efficient, and systematic tool for shortening experimental time in technological processes. Orthogonal design is useful for optimizing multivariable processes (Heng et al., 2000). This study was carried out to evaluate the influence of four independent variables on mean spheroid size and size distribution with the aim of

* Corresponding author. Tel.: +65-6874-2930; fax: +65-6775-2265

E-mail address: phapaulh@nus.edu.sg (P.W.S. Heng).

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optimizing conditions for producing spheroids with a size range suitable for further coating.

Spheroids were prepared from a binary mixture of microcrystalline cellulose (MCC; Avicel® PH-101, Asahi Chemical, Japan) and lactose monohydrate (Pharmatose® 200M, De Melkindustrie Veghel, The Netherlands) in a ratio of 1:3. Distilled water was used as the moistening liquid. The multisystem fluidized-bed MP-1 (Aeromatic-Fielder, UK) with a Roto-processor insert was used. The wall of the inner product chamber was polytetrafluoroethylene (PTFE) tape lined and the rotating frictional base plate had teardrop shaped protuberances. The formulation and process parameters used were presented in Table 1.

Base plate rotational speed during liquid addition (*A*), spray rate of water (*B*), total amount of water added (*C*) and base plate rotational speed during the tumbling stage (*D*), were the four independent parameters used in this design. Orthogonal array L_3^4 was employed with four variables and three levels for each variable (Tables 2 and 3). Analysis of variance and multiple regression were applied to assess the effects of the individual variables. Statistical software SPSS (version 10.0) was used to calculate multiple regression equations. Data obtained from the orthogonal design were first transformed to index values within 0–1 using the following equation:

$$X_s = \frac{X_i - X_{min}}{X_{max} - X_{min}}$$

where X_s is the standardized value, X_i is the actual value being transformed, and X_{max} and X_{min} are the maximum and minimum values of each column, respectively.

The size fraction larger than 2.8 mm, defined as lumps, was removed before the product was subdivided by a riffler (PT, Retsch, Germany). A nest of sieves (British standard, Endecotts, UK) of aperture sizes giving a $\sqrt{2}$ progression within the range of 250–2800 μm was used for sizing the spheroids. The spheroid size distributions were in good agreement with the log-normal distribution. Consequently, the mean spheroid size (Dgw) and geometric standard deviation (Sg) of size distribution were calculated using the equations described by Heng et al. (1999).

K values were calculated for a quantitative evaluation of the effects of a single variable. For each

Table 1
Formulation and process conditions for the preparation of spheroids using the rotary processor

Formulation	Quantity (%)
Microcrystalline cellulose	25
Lactose	75
Processing conditions	
Batch size (kg)	0.6
Inlet air temperature during liquid addition and tumbling stages (°C)	30
Inlet air temperature during drying stage (°C)	60
Tumbling time (min)	20
Gap air pressure (bar)	1.5
Atomizing air pressure (bar)	1.2
Spray nozzle diameter (mm)	0.8
Spray rate	As in the orthogonal design (Tables 2 and 3)
Speed of rotating plate	As in the orthogonal design (Tables 2 and 3)
Water content	As in the orthogonal design (Tables 2 and 3)

Table 2
Selected process variables and levels

	A (rpm)	*B* (ml/min)	*C* (%)	*D* (rpm)
Level −1	523	24	37.5	313
Level 0	730	30	40.0	523
Level +1	1045	36	42.5	730

Table 3
Orthogonal design—matrix $L_3{}^4$

Run number	*A*	*B*	*C*	*D*
1	−1	−1	+1	0
2	0	−1	−1	−1
3	+1	−1	0	+1
4	−1	0	0	−1
5	0	0	+1	+1
6	+1	0	−1	0
7	−1	+1	−1	+1
8	0	+1	0	0
9	+1	+1	+1	−1

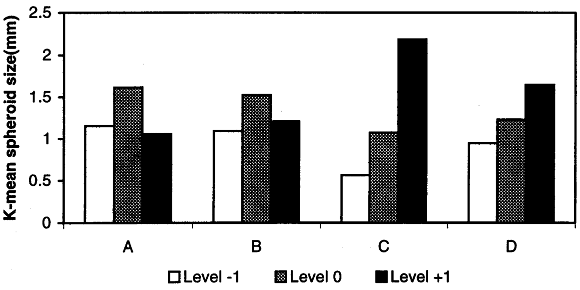

Fig. 1. Effect of the four variables on mean spheroid size.

spheroid characteristic, K was the average of the corresponding responses of a certain variable at the same level. Figs. 1 and 2 showed the effects of each variable on mean spheroid size and size distribution.

In the rotary processor, spheroids are formed directly from a powder mix by an agglomeration–spheronization process. During the liquid addition phase of spheroid production, the moistening liquid was sprayed onto the powder mass moving on the rotating frictional base plate. The powder mass became increasingly moistened as it moved repeatedly across the path of the spray nozzle. Besides supplying the energy input for effecting agglomeration–spheronization, the base plate rotational speed during liquid addition also influenced the uniformity of liquid distribution in the powder mass.

Due to the mixing action effected by the tumbling motion of the powder mass, the moisture tends to equilibrate from the wet region to the less wet region. The moisture added to the powder mass effects the formation of bonds between the powder particles. The presence of surface moisture increases surface plasticity. It aids the deformation and coalescence of particles during collision. Consequently, the moistened particles agglomerate and consolidate to form spheroids. After the liquid addition phase, spheroid continue to grow rapidly as the rotational movement of the base plate enhances the tumbling motion of the wetted mass during the tumbling stage and supplies energy to the system to allow the wetted mass to be subjected to further agglomeration (Wan et al., 1994).

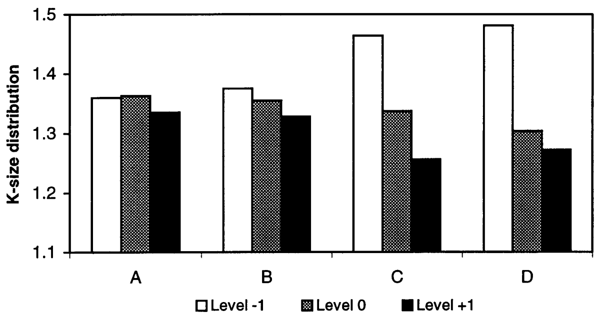

Fig. 2. Effect of the four variables on size distribution of spheroids.

As can be seen from Figs. 1 and 2, the higher amount of water added (C) and higher level of base plate rotational speed during the tumbling stage (D) resulted in a larger mean spheroid size and more uniformly sized spheroids, i.e. smaller Sg value. Higher level of base plate rotational speed supplied more energy to the system to produce spheroids with larger mean size. Low tumbling speed may not supply sufficient energy for uniform mixing and growth. For runs where low amount of water was used, the available surface moisture may not be enough for effecting spheroid growth. Localized over-wetting also occurred as it was more difficult to achieve uniform liquid distribution with a small amount of water. From previous research results, it was observed that there was a linear relationship between spheroid size and liquid spray rate (Wan et al., 1995). However, in this study a larger spheroid size was obtained using a medium base plate rotational speed during liquid addition (A) and medium spray rate (B). For this run the influence of spray rate was overshadowed by the effect of variables C and D. The combination of high water level (C) and high base plate rotational speed during tumbling stage (D) augmented the agglomeration process (run 5 of Table 3 and Fig. 1).

A multiple regression was employed to construct models for spheroid size and size distribution.

$$\mathrm{Dgw} = 0.589{*}C + 0.255{*}D + 0.04171{*}B - 0.035{*}A - 0.107 \ (R^2 = 0.826,\ F = 4.743,\ P = 0.08);\ \mathrm{Sg} = -0.475{*}C - 0.478{*}D$$

Table 4
T-test for the four variables

	Dgw		Sg	
	t	Sig.	*t*	Sig.
(Intercept)	−0.669	0.540	8.349	0.001
A	−0.236	0.825	−0.557	0.607
B	0.282	0.792	−1.022	0.365
C	3.983	0.016	−4.597	0.010
D	1.724	0.160	−4.623	0.010

$-0.106^*B-0.0577^*A+0.933$ ($R^2=0.916$, $F=10.965$, $P=0.02$). The t-test result for the four variables was present in Table 4. It was found that the variables C and D played more important roles in optimizing the process. This finding is in agreement with our previous findings indicating that it is important to ensure that a suitable speed is chosen at appropriate times as the base plate rotational speed has different effects during the course of run (Liew et al., 2000).

Therefore, it can be concluded that among the four variables, the influence of the amount of water added (C) and base plate rotational speed during tumbling stage (D) were found to be more critical. For process optimization, these two variables should be at optimal levels.

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