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Optimization of spheroid production by centrifugal rotary processing

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Abstract

The reproducibility in the preparation of spheroids from powder mixture by centrifugal rotary processing based on a large number of production runs was investigated. Optimization of the process conditions by varying the amount of moistening liquid and spray rate was carried out. The quality of the spheroids produced was evaluated using three criteria, namely the percent yield between 0.85 and 1.18 mm, the geometric weight mean diameter and the geometric standard deviation of the spheroids. From the response surfaces and contour plots, it is apparent that the optimized region of percent yield of spheroids was at an amount of moistening liquid between 38–42% and spray rate between 35–43 ml/min. The release kinetics of the spheroids containing a highly water-soluble drug, chlorpheniramine maleate or a less water-soluble drug, paracetamol, fitted the square-root of time equation, thereby following an inert matrix release mechanism.

Keywords: Spheroids; Centrifugal rotary processing; Optimization; Moistening liquid; Spray rate; Release kinetics

One of the more recent methods for the production of pharmaceutical pellets is rotary processing (Béchard and Leroux, 1992; Maejima et al., 1992; Iyer et al., 1993; Maganti and Çelik, 1994; Wan et al., 1993, 1995; Nesbitt, 1994; Vecchio et al., 1994). There is, however, a limited amount of work published relating to the reproducibility of this process in producing quality pellets within a narrow size distribution based on a large number of production runs. The objective of this study is to examine the feasibility of producing spheroids from powder mixture using the centrifugal rotary processor and to optimize the process conditions by two variables, amount of moistening liquid, 30–45% and spray rates, 20–59 ml/min, employing response surfaces and contour plots. The release kinetics of the core spheroids containing

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a highly water-soluble drug, chlorpheniramine maleate or a less water-soluble drug, paracetamol were also investigated.

Chlorpheniramine maleate (BP grade) and paracetamol (BP grade) were used as model drugs with lactose monohydrate (Pharmatose 200M, DMV, The Netherlands) and microcrystalline cellulose (MCC; Emcocel 50M, Mendell, USA.) as excipients for the preparation of core spheroids.

The core spheroids consisted of microcrystalline cellulose, lactose and drug in the ratio by weight of 12:37:1, respectively. Microcrystalline cellulose and lactose were first mixed and then transferred to the rotary processor (Niro-Aeromatic, MP-1 with rotoprocessor, Switzerland). Chlorpheniramine maleate was dissolved in the granulating liquid, water, whereas paracetamol, due to its relatively lower solubility in water, was added dry to the microcrystalline cellulose and to the lactose before mixing in the cone mixer.

Several variations in spheroid preparation process parameters were evaluated (Table 1). The size distribution of spheroids were determined by sieving (Endecotts EVS1, UK). Dissolution studies were carried out in 1 l of de-aerated distilled water at 37 ± 0.5°C using the paddle method (Method II, USP XXII; Hanson Research, 72-RL, USA) at a stirring speed of 50 rpm. The amount of chlorpheniramine maleate or paracetamol was determined sphectrophotometrically at 262 nm or 242 nm, respectively. For the inter-spheroid drug variation study, a total of 20 accurately weighed spheroids were added to 3 ml of distilled water and agitated in a shaker bath at 37°C for 24 h. The drug content was determined spectrophotometrically.

The percent yield between 0.85 and 1.18 mm, the geometric weight mean diameter and the geometric standard deviation of the spheroids were used separately as the response variables in the mathematical modeling, based upon a total of 87 batch runs of spheroids containing chlorpheniramine maleate. The regression polynomial was calculated using the statistical software SPSS (Version 6.0), then the results were used to approximate the response surfaces and contour plots using the PC-based software Mathematica (Wolfram Research, Version 2.2).

The models generated to fit the various data were as follows:

$$\text{Percent yield} = -1496.17 + 37.672x_1 + 16.914x_2 - 0.00399x_1x_2^2 - 0.0000558x_1^3x_2 - 0.0000849x_1^4 - 0.00000463x_2^4 \quad (r^2 = 0.8173) \qquad (1)$$

Geometric weight mean diameter

$$= 3.501 + 0.0295x_1 - 0.141x_2 + 0.00000594x_1x_2^2 + 0.00000157x_1^3x_2 - 0.00000104x_1^4 + 0.00000016x_2^4 \quad (r^2 = 0.8183) \qquad (2)$$

Geometric standard deviation

$$= -0.0634 + 0.0729x_1 + 0.00293x_2 - 0.0000287x_1x_2^2 + 0.000000555x_1^3x_2$$

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

Formulation	Quantity (%)
Chlorpheniramine maleate or paracetamol	2
Microcrystalline cellulose	24
Lactose	74
Processing conditions	
Batch size (kg)	1
Inlet air temperature during core formation stage (°C)	30
Inlet air temperature during drying stage (°C)	60
Gap air pressure (bar)	0.5
Atomizing air pressure (bar)	1.2–1.5
Spray nozzle diameter (mm)	1
Speed of rotating plate (rpm)	480 × 2 min 1150 × 8 min 480 to end of process
Spraying rate (ml/min)	28 to 59
Volume of moistening liquid (ml)	300 to 450
Base plate diameter (cm)	
Area of a stud on base plate (mm²)	30
Height of studs on base plate (mm)	36
Distance between studs on base plate (mm)	1.25
Studs arranged in a cross-hatched pattern	2

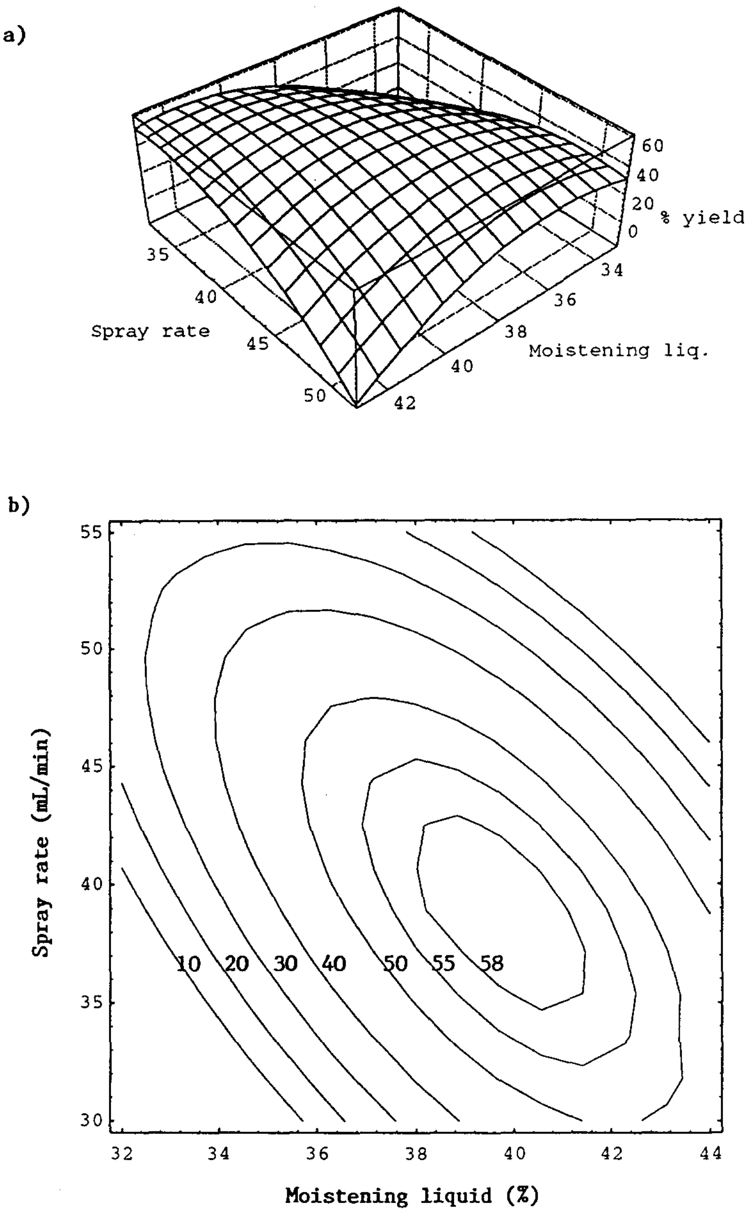

Fig. 1. Estimated response surface (a) and contour plot (b) illustrating the relationship between the percent yield of spheroids, amount of moistening liquid and spray rate.

$$- 0.000000643x_1^4 + 0.000000134x_2^4$$
$$(r^2 = 0.7518) \qquad (3)$$

where x_1:amount of moistening liquid (%)
x_2:spray rate (ml/min)

The response surface and corresponding contour plot (Fig. 1) illustrate the relationship between the percent yield of spheroids, amount of moistening liquid and spray rate over the experimental region. At low spray rate, the percent yield remained low, regardless of a change in the

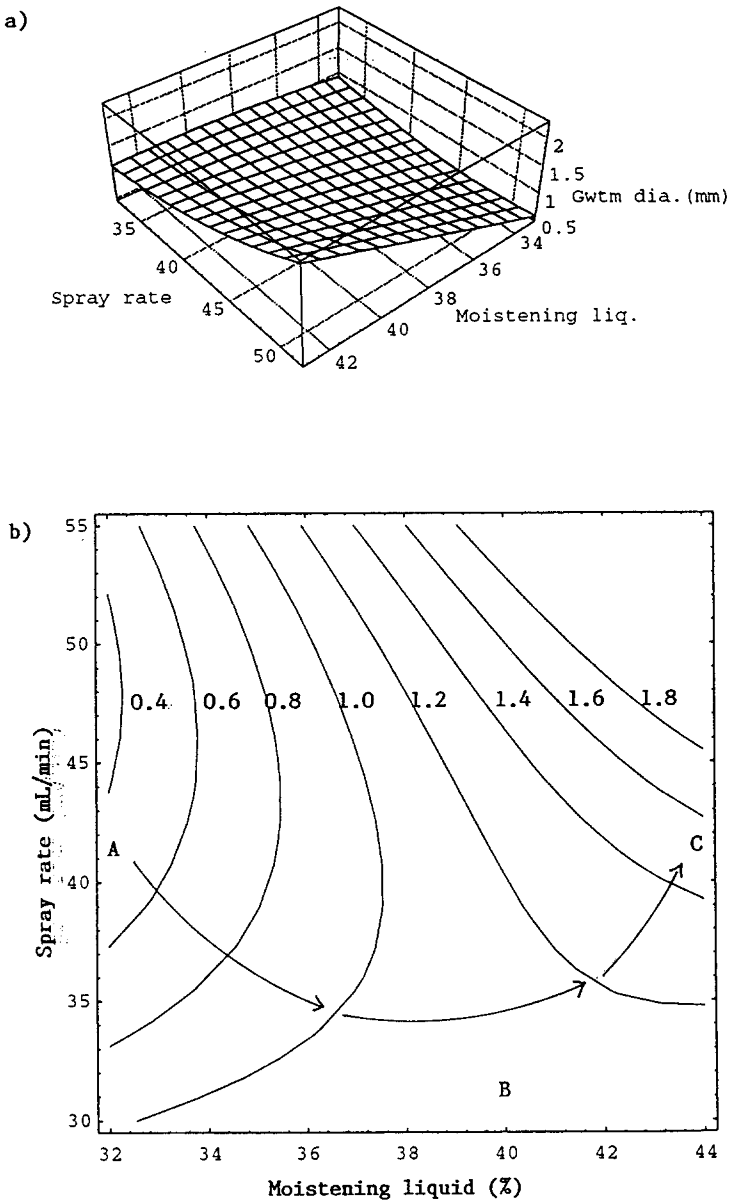

Fig. 2. Estimated response surface (a) and contour plot (b) illustrating the relationship between the geometric weight mean diameter of spheroids, amount of moistening liquid and spray rate.

amount of moistening liquid. The maximum yield of 58% and more, occurred in the region where the amount of moistening liquid was between a narrow and defined range of 38–42% and spray rate was between 35 and 43 ml/min. At a high spray rate, greater than 55 ml/min, the percent yield was found to be very low for amount of moistening liquid from 32 to 44% studied.

The response surface and corresponding contour plot (Fig. 2) illustrate the relationship between geometric weight mean diameter of spheroids, amount of moistening liquid and spray

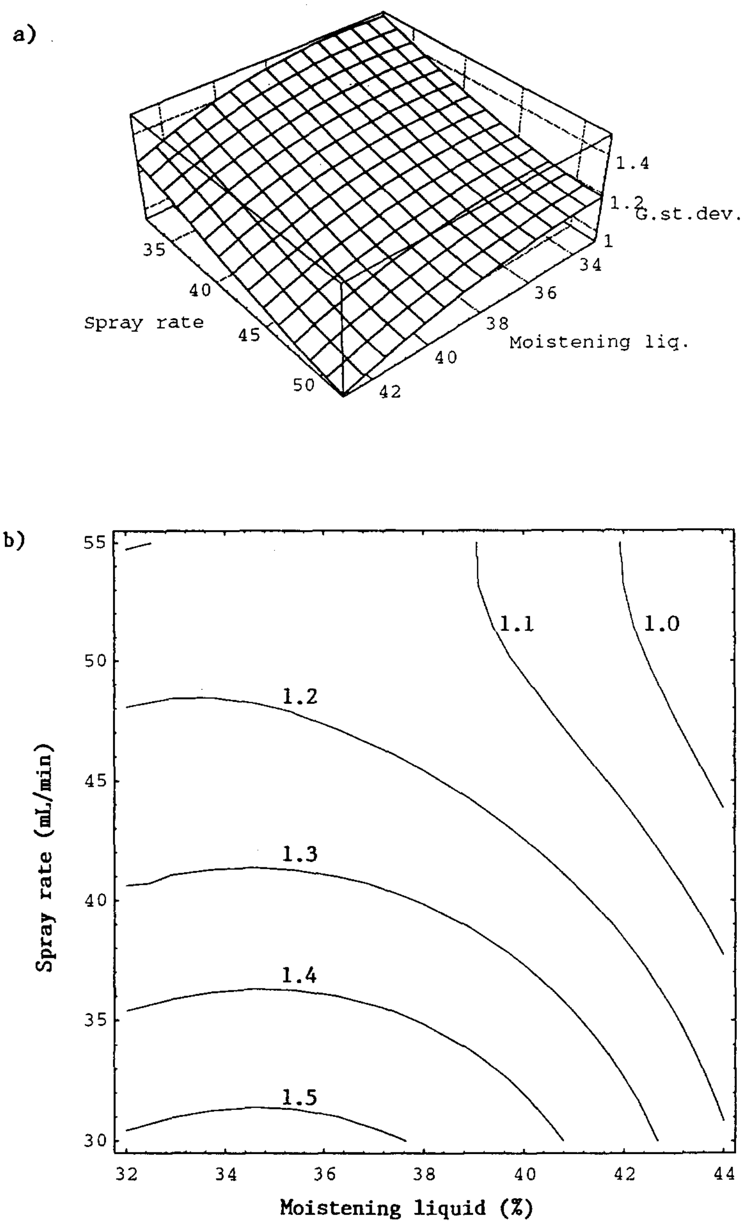

Fig. 3. Estimated response surface (a) and contour plot (b) illustrating the relationship between the geometric standard deviation of spheroids, amount of moistening liquid and spray rate.

rate. Interestingly, the contour plot demonstrates the existence of a 'stable path' for spheroid growth (ABC, Fig. 2b). It can be seen that in order to achieve pellet growth from 0.4 to 1 mm, it is best that the spray rate be decreased from 45 to 35 ml/min, as the amount of moistening liquid is increased from 32 to 38% (AB, Fig. 2b). If the desired spheroid size is from 1 to 1.6 mm, the spray rate needs to be increased as the amount of the moistening liquid is also increased (BC, Fig. 2b). When the amount of moistening liquid was low (less than 36%), an increase in spray rate from 32 to 53 ml/min only produced spheroids having geometric weight mean diameter mostly less than 0.8 mm. The spheroids with geometric weight mean diameter ranging from 0.8 to 1.4 mm were obtainable from amount of moistening liquid varying between 36 to 44% with suitable adjustment of the spray rate. These results demonstrated the importance of amount of moistening liquid in the production of spheroids by centrifugal rotary processing. A minimum amount of water level must be achieved, regardless of the spray rate, before spheroids of suitable size range and yield can be obtained. On the other hand, if amount of moistening liquid is increased indiscriminately, a stage will be reached whereby spheroids with skewed size distribution will result.

The geometric standard deviation for the size distribution of all the batches of spheroids studied, varied from 1.04 to 1.61. However, for majority of the spheroids, the geometric standard deviation ranged between 1.10 to 1.39. The response surface and corresponding contour plot (Fig. 3) illustrate the relationship between the geometric standard deviation of spheroids, amount of moistening liquid and spray rate over the experimental region. In general, at any fixed amount of moistening liquid studied, geometric standard deviation decreased with an increase in spray rate. While at any fixed spray rate, the geometric standard deviation also decreased with an increase in amount of moistening liquid. Within the region of maximum spheroid yield, where amount of moistening liquid was between 38 and 42% and spray rate was between 35 and 43 ml/min, the geometric standard deviation varied from 1.2 to 1.4. Larger geometric standard deviation values (more than 1.5) were found at water level less than 38% and spray rate below 35 ml/min. This was because at low amount of moistening liquid and low spray rate, the amount of moisture available for spheroid formation was only partially sufficient, thus a wider size distribution consisting of formed spheroids and powder particles were obtained.

The results of inter-spheroid drug variation study showed that the average percentage of chlorpheniramine maleate in individually assayed spheroid was 99.1% while that of paracetamol was 100.9%. The standard deviation value for paracetamol (1.79) was marginally higher than chlorpheniramine maleate (1.63) and the t-test result suggested that there was no significant difference in the mean values.

The drug release from chlorpheniramine maleate or paracetamol core spheroids was very fast. The dissolution $T_{50\%}$ values were about 3 min for both types of spheroids and more than 94% of drug was released by 30 min. The drug release kinetics of the spheroids were best described by the square-root of time equation. From a log–log plot of drug released versus time, the slopes for those with chlorpheniramine maleate or paracetamol were 0.43 or 0.46, respectively. These being about 0.5 further support that the drug release followed an inert matrix drug release mechanism.

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