Preparation and evaluation of highly drug-loaded fine globular granules using a multi-functional rotor processor

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Abstract

The manufacture of highly drug-loaded fine globular granules eventually applied for orally disintegrating tablets has been investigated using a unique multi-functional rotor processor with acetaminophen, which was used as a model drug substance. Experimental design and statistical analysis were used to evaluate potential relationships between three key operating parameters (i.e., the binder flow rate, atomization pressure and rotating speed) and a series of associated micromeritics (i.e., granule mean size, proportion of fine particles (106–212 μm), flowability, roundness and water content). The results of multiple linear regression analysis revealed several trends, including (1) the binder flow rate and atomization pressure had significant positive and negative effects on the granule mean size value, Carr's flowability index, granular roundness and water content, respectively; (2) the proportion of fine particles was positively affected by the product of interaction between the binder flow rate and atomization pressure; and (3) the granular roundness was negatively and positively affected by the product of interactions between the binder flow rate and the atomization pressure, and the binder flow rate and rotating speed, respectively. The results of this study led to the identification of optimal operating conditions for the preparation of granules, and could therefore be used to provide important information for the development of processes for the manufacture of highly drug-loaded fine globular granules.

Keywords: Fine globular granules; highly drug loading; fluidized-bed rotogranulation.

Abbreviations: GX, Granurex; d_{50}, granule mean size; SEM, scanning electron microscope; ODTs, orally disintegrating tablets**.**

1. Introduction

Orally disintegrating tablets (ODTs) are solid dosage forms that are placed in the mouth, rapidly disintegrate/dissolve when in contact with the saliva and then easily swallowed without the need for water. Recently, a great deal of interest has been directed towards incorporating multiparticulate drug delivery system in ODT formulations [1)]. The multiparticulate drug delivery system comprises of functional granules with sustained release, delayed release, and taste-masking properties. One of the easiest ways of introducing specific functionalities to granules involves the application of a film coating, where a functional polymer layer is used to cover the drug-loaded core particles. This particular technique is especially useful when the core particles are spherical, because it is then possible to apply a uniform coating to the particles [2)]. Furthermore, in cases where the particle size is less than 200 μm, improvements in the taste and texture of the powders can also be expected. However, in the case of even smaller particles (i.e., <100 μm), it can become increasingly difficult to apply a uniform coating because of the aggregation of the smaller particles resulting from static electrical charges. Therefore, the development of manufacturing processes capable of producing spherical particles with a narrow particle size distribution range of about 100–200 μm is therefore very important.

Layering and wet granulation are two of the most commonly used methods for the manufacture of drug-loaded spherical particles. In the layering technique, the surfaces of commercially available spherical core particles are covered with a layer of drug substance using a

fluidized bed or centrifugal granulator, and this technique has been used extensively in the pharmaceutical industry [3,4]. However, one of the main issues associated with the manufacture of high drug content particles using the layering technique is the long operating times required for the manufacturing process. For example, Tanai reported a layering technique for the preparation of spherical particles containing 10% ethenzamide by spraying a drug-containing binder suspension [4]. However, this process required more than 80 min to reach completion, which suggested that the large-scale manufacture of spherical particles containing large amounts of drug in this way would require extensive and time-consuming operating processes. Furthermore, as the loading of drug increases, so too does the particle size of the product, which would result in the feeling of an undesired texture in the mouths of patients receiving drugs formulated in this way.

The wet granulation method involves the agglomeration of individual powdered materials using a binder solution. In contrast to the layering method, wet granulation does not require lengthy operating times, even when the loading of the drug is increased. Despite the benefits of this method, there have been very few reports in the literature pertaining to the preparation of fine spherical granules using the wet granulation technique. Hamashita et al. reported the successful preparation of spherical granules containing 39.9% ibuprofen over a short operating time using a fluidized-bed rotogranulation technique [5]. In this particular study, the resulting particles were about 270 μm in size, and the application of any additional processes such as film coating with a functional polymer could potentially lead to an increase in the particle size, which would result in the feeling of an undesired

texture in mouth of any patient receiving this formulation. With this in mind, it is therefore difficult to manufacture highly drug-loaded fine particles with a narrow particle size distribution. Furthermore, there have been no reports in the literature, to the best of our knowledge, concerning the manufacture of drug-loaded fine globular granules containing more than 40% of the loaded drug with a particle size of less than 200 μm. We recently used a unique multi-functional rotor processor known as the "Granurex® (GX)" to successfully prepare fine globular granules containing only excipients, such as lactose monohydrate and corn starch, with a narrow size distribution of less than 200 μm [6]. Following on from this work, we also found a relationship between the operating conditions for the GX and the physicochemical properties of granules using multivariate data analysis [7]. Taken together, these results suggest that the GX system could be used to develop a manufacturing process for the preparation of highly drug-loaded fine globular granules with a particle size of less than 200 μm.

With this in mind, we conducted a study to investigate the manufacture of highly drug-loaded fine globular granules using GX. Acetaminophen was selected as a model drug in the current study, with the aim of preparing 50% acetaminophen-loaded formulations. Experimental design and statistical analysis were also used to investigate the relationships between specific operating parameters and the physicochemical properties of the granules generated during the manufacturing process. Finally, the optimized processing conditions were determined for the manufacture of highly acetaminophen-loaded fine globular granules.

2. Materials and methods

2.1. Materials

Acetaminophen with the particle mean size of 14.0 μm, which is listed in the 16th edition of the Japanese Pharmacopoeia (JP16) as an active pharmaceutical ingredient, was kindly provided by Iwaki Seiyaku Co., Ltd. (Shizuoka, Japan). Lactose monohydrate (Pharmatose®, type: 200M, DFE Pharma, Co., Ltd., Vaghel, The Netherlands) and microcrystalline cellulose (Ceolus®, type: PH-101, Asahi Kasei, Co., Ltd., Tokyo, Japan), which are both listed in JP16, were used as fillers. Hydroxypropyl cellulose (HPC-L®, Nippon Soda Co., Ltd., Tokyo, Japan), which is also listed in JP16, was used as a binder.

2.2. Equipment

The granulation experiments were performed in a centrifugal rotating disc processor (Granurex® GX-20, Freund, Tokyo, Japan), which was described in detail in our previous paper [7].

2.3. Granulation

Acetaminophen, lactose monohydrate and microcrystalline cellulose were dried for 12 h at 50°C in an oven, and then sieved through a 297 μm sieve. Three-hundred grams of dried acetaminophen, 200 g of dried lactose monohydrate and 100 g of dried microcrystalline cellulose were loaded into the chamber of the processor. The airflow rates at the inlet and the slit were adjusted

to 200 L/min, and the powders were mixed at 200 rpm for 3 min. Binder liquid containing 5% (w/w) HPC-L was then sprayed into the chamber of the processor, with a total solution mass of 280 g being sprayed. The airflow rate through the slit was then manually increased to 280 L/min in a stepwise manner to coincide with the increase in the bed weight that occurred as a consequence of the binder liquid being sprayed into the chamber. Following the complete addition of the binder liquid to the chamber of the processer, a stream of air (80°C) was passed over the particles to dry them. This drying process was continued until the particles reached a specified end product temperature, which was defined as being equal to the sum of the product temperature and a ΔT of 10°C.

2.4. Experimental Design

A three-factorial central composite design was used to analyze the relationships between the operating parameters of the manufacturing processes and the powder properties of the granules. The binder flow rate (X_1), atomization pressure (X_2), and rotating speed (X_3) were selected as independent variables. Several preliminary trials were conducted prior to applying the experiment design. These trials allowed suitable operating conditions to be determined for the preparation of the granules and the levels of these factors were then decided. Seventeen experiments containing three center-point batches were conducted, and the normalized factor levels of the independent variables and the conditions for each batch are listed in **Table 1**.

2.5. Characterization of Final Product Properties

2.5.1. Particle Size Distribution

The yield of the final product (% w/w) was calculated by dividing the mass of the collected granules by that of the all dry ingredients. The appropriate size distribution was obtained by the sieve analysis of approximately 10 g of the granules using testing sieves (Tokyo Screen Co., Ltd., Tokyo, Japan) of different sizes (i.e., 45 to 1000 μm). These data were used to determine granule mean size (d_{50}). The relative width of the particle size distribution (R_w) was calculated by the following equation; $R_{w} = \{(d_{90} - d_{10}) / d_{50}\} \times 100$, where d_{10}, d_{50}, and d_{90} are 10%, 50%, and 90% of the accumulated particle size under a screen, respectively.

2.5.2. Image Analysis

The diameters and shapes of the granules were determined by the image analysis of the size fractions in the range of 106–212 μm using version 5.5 of the WinROOF image analysis software (MITANI Co., Ltd., Tokyo, Japan). Approximately 40 granules were randomly selected for this analysis. The shapes of the granules were defined by their roundness (P_t/P_r), where P_t is the theoretical perimeter of a perfectly spherical granule of the same area as the real particle, and P_r is the real perimeter of the granule.

2.5.3. Scanning Electron Microscopy

The surface structures of the granules with sizes in the range of 106–212 μm were morphologically assessed using a JEOL JSM--5200LV scanning electron microscope (SEM) (JEOL, Tokyo, Japan). The samples were placed on double-sided adhesive tape, which had been previously applied to an aluminum stub. Excess sample materials were manually removed, and the samples were sputter coated with a mixture of platinum and palladium under an atmosphere of argon prior to being imaged.

2.5.4. Carr's flowability index

The flow properties of the granules were determined using Carr's method [8]. The following four tests were performed: (1) compressibility, (2) angle of repose, (3) angle of spatula, and (4) uniformity coefficient. The uniformity coefficient was obtained by sieve analysis of the granules. Other indices were measured using the Powder characteristics tester (Powder Tester, Hosokawa Micron Co., Ltd., Osaka, Japan).

To determine the compressibility of the granules, the bulk density was first examined using a 100 mL cylinder. The cylinder container was filled with an accurately weighed sample of the granules, and the top of the sample was leveled off. The density was calculated as the ratio of the mass to the volume of the sample, which is known as the "bulk density". The tapped density was also determined using a similar method, but the volume was calculated after the strokes had been performed for 3 min. The compressibility was calculated using the bulk and tapped density values

according to the following equation: Compressibility (%) = {(tapped density–bulk density) / tapped density} × 100.

The angle of repose was measured with a protractor using a heap of granules, which was formed by dropping a sample of granules through a funnel.

The angle of spatula was measured using a protractor and a steel spatula with a 5 × 7/8 in. blade. The spatula was inserted into the bottom of a carefully built heap. The spatula was then withdrawn vertically, and the angle of the heap formed by the spatula was measured as the angle of spatula.

The uniformity coefficient was measured as the numerical value arrived at by dividing the width of the sieve opening that allowed 60% of the sample to pass through the sieve by the width of the sieve opening that allowed 10% of the sample to pass through.

The flowability index was then calculated using the point scores out of 100 as described previously [8]. As a score standard, the point “90-100” represents “excellent” flowability, “80-89” represents “good”, “70-79” represents “fair”, “60-69” represents “passable”, “40-59” represents “poor”, “20-39” represents “very poor”, and “0-19” represents “very, very poor”.

2.5.5. Water content

To determine the water content, samples were withdrawn from the granules that had been treated with 280 g of binder solution and dried in an oven at 70°C for 24 h. The water content was

then calculated on a dry mass basis according to the following equation: water content (%) = {(amount of withdrawn sample (g) – amount of dried sample (g)) / amount of dried sample (g)} × 100.

2.5.6. Drug content

Final product granules were put in 200 mL diluted water, and dissolved for 2 h at 37 °C. After the acetaminophen was completely dissolved, the solution was withdrawn and samples were filtered through a membrane filter (0.45 μm). The amount of acetaminophen released into the medium was quantitatively determined as a proportion of the total acetaminophen contained in a tablet by UV spectroscopy (wavelength: 243 nm; UV-mini 1240, Shimadzu Corp., Tokyo, Japan). The standard deviation of the amount of acetaminophen was taken as an index of drug content uniformity.

2.5.7. Friability

Final product granules which passed through a 1000 μm sieve and then did not pass through 75 μm sieve were sampled and rotated with a constant frequency of 5 rpm for 20 min using a shaker (SA-31, Yamato Scientific, Co., Ltd., Tokyo, Japan). The total weight of the granules which did not pass through 75 μm sieve was recorded after rotation, and the friability was expressed as the percentage loss.

2.6. Statistical Analysis

Multiple linear regression analysis and optimization were performed using JMP 9 (SAS Institute Japan Ltd., Tokyo, Japan). Linear regression analysis was performed on the data for each characteristic as a function of the three process parameters and their interactions. The relationships linking the main factors and their interactions with the results were determined, and subsequently presented as quadratic equations of the general form:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_0$$

where b_1, b_2, b_3, b_{12}, b_{13}, b_{23}, b_{11}, b_{22}, and b_{33} are the coefficients of each term and b_0 is a constant term. Given that the coefficients were calculated using the coded values (**Table 1**), the different terms could be compared directly. The response surfaces were constructed using Maple 13 (Waterloo Maple Inc., Waterloo, ON, Canada).

3. Results and Discussion

3.1. Characterization of Final Product Properties and Multiple Regression Analysis

Table 2 shows results pertaining to the characterization of the 17 experiments. Especially, the results of the center-point batches 15, 16, and 17 were almost similar, which indicated a good level of reproducibility. The obtained data were statistically analyzed to obtain the corresponding linear regressions. The significance of each operational factor and their effect on the properties of the

granules were determined (**Table 3 and 4**). Each table shows the coefficients, the *p*-values obtained using the *t*-test to assess the significance of each term, and the R^2 values (i.e., the coefficients of determination that were doubly adjusted with degrees of freedom), which provide an indication of the fit of each liner regression equation.

3.1.1. Granule mean size (d_{50})

The yield and R_w of the final products were in the range of 71.4–89.4% and 0.96–2.63, respectively. The granule mean size (d_{50}) was determined to be in the range of 96–342 μm (**Table 2**). As shown in **Table 3**, the d_{50} increased with an increase in the liquid binder flow rate (X_1) (P=0.003) or a decrease in the atomization pressure (X_2) (P=0.016). A similar tendency was also observed in our previous study using a drug-free formulation, where the d_{50} was determined to be significantly affected by both of these parameters [7]. Given that an increase in the binder flow rate or a reduction in the atomization pressure leads to an increase in the size of the droplets derived from the binder solution, it is possible that the droplet size of the liquid binder solution could have a significant impact on the d_{50} of the granules in the presence or absence of a drug substance. Based on these results, the liquid binder flow rate and atomization pressure were also identified as critical process parameters because they could have a significant impact on the granule mean size of the highly drug-loaded granules during the granulating process with the GX system.

3.1.2. The proportion of fine particles (106–212 μm)

Multiple regression analysis revealed that none of the main process parameter had a significant effect on the proportion of fine particles (106–212 μm) (**Table 3**). However, the proportion of fine particles (106–212 μm) was positively affected by the product of interaction between the binder flow rate and the atomization pressure (X_1X_2) (P=0.006). As shown in **Fig. 1A**, the proportion of fine particles (106–212 μm) increased as the binder flow rate (X_1) and atomization pressure (X_2) were increased or reduced simultaneously. A similar tendency was also observed in our previous study using the drug-free formulation [6]. These parameters also affected droplet size of the binder solution and allowed granules to grow to a moderate size, as mentioned above, with the particle size distribution becoming much narrower, resulting in an increase in the proportion of fine highly drug-loaded granules increases.

3.1.3. Carr's flowability index

The compressibility, angle of repose, angle of spatula, and uniformity coefficient values of the particles were determined using Carr's flowability index. The results revealed that the Carr's flowability index of the current particles was in the range of 75.0–85.0 points, which represents a "fair-good" flow (**Table 2**). According to multiple regression analysis, the binder flow rate (X_1) had a significant positive effect (P<0.001) on the Carr's flowability index of the particles, whereas the atomization pressure (X_2) had a significant negative effect (P=0.008) (**Table 3**). In addition, the

Carr's flowability index of the particles was negatively affected by the product of interaction between the binder flow rate and the atomization pressure (X_1X_2) (P=0.017). As shown in **Fig. 1B**, the Carr's flowability index increased when the binder flow rate (X_1) was increased and the atomization pressure (X_2) was reduced simultaneously. As mentioned above, these parameters were involved in determining the granule mean size, which suggested that the flowability of the granules would improve as the granule mean size increased.

3.1.4. Roundness and water content of granules

The roundness and water content results for the granules were in the range of 0.81–0.86 and 2.8–26.7%, respectively (**Table 2**). As shown in **Table 4**, the granular roundness increased as the liquid binder flow rate (X_1) (P<0.001) increased or the atomization pressure (X_2) (P=0.001) or rotating speed (X_3) (P=0.008) decreased. Among these three operating parameters, the liquid binder flow rate (X_1) was found to have the largest effect on the roundness. A similar tendency to this was observed in our previous study of GX, where an increase in the binder flow rate led to significant improvements in the granular roundness properties [7]. Taken together, these results led to the identification of the liquid binder flow rate as a critical process parameter during the preparation of highly drug-loaded granules by GX. Although the rotating speed (X_3) had been found to have no effect on the granular roundness during our previous study involving a drug-free formulation [7], the results of the current study were inconsistent with this finding because the rotating speed was found

to have a negative effect on the granule roundness. Furthermore, previous results from the literature revealed similar contradictorily results. For example, certain studies in fluid bed rotogranulation reported that changes in the rotating speed improved granule roundness [9,10], whereas separate studies reported the opposite trend [11,12]. These inconsistencies could be attributed to differences in the physicochemical properties of the raw materials, especially the powder density. In fact, the raw material used in the current study was lighter than that used in the previous study, which only involved an excipient formulation. These results therefore suggest that the lighter (i.e., less dense) raw materials used in the current experiment would have adhered more readily to the walls of the equipment as the rotating speed increased because of the centrifugal force. In contrast, a reduction in the rotating speed would have caused the raw materials to be much more effectively granulated on the rotor, which would have led to an increase in the granular roundness. In addition, since acetaminophen has been considered to have high adhesive property, this property might also be involved in this effect. Taken together, these results clearly indicate that the powder density and adhesive properties of the starting materials should be carefully considered when using a rotogranulation process for the preparation of granules with high roundness.

With regard to their interactions, the product of interaction between binder flow rate and atomization pressure (X_1X_2) (P<0.001) were found to have a significant negative effect on the granular roundness, whereas the product of interaction between binder flow rate and rotating speed (X_1X_3) (P=0.001) were found to have a significant positive effect. As shown in **Fig. 1C**, the granular

roundness increased as the binder flow rate increased and the atomization pressure was reduced simultaneously. Furthermore, the granular roundness increased as the binder flow rate (X_1) and rotating speed (X_3) increased simultaneously (**Fig. 1D)**. Interestingly, the rotating speed (X_3) had a significant positive effect on the granular roundness as the binder flow rate (X_1) increased, even though this variable had a significant negative effect when it was considered as an independent variable. This phenomenon can be derived from microcrystalline cellulose particles, which generally become round in shape when they are wetted. When raw materials such as microcrystalline cellulose are not completely wetted, the roundness of their particles therefore increases with a reduction in rotating speed (X_3) because the materials are effectively prevented from adhering to the wall of the mixing chamber. In contrast, an increase in binder flow rate (X_1) would allow the raw material to be sufficiently wetted and the material density would therefore increase, which would result in an increase in roundness as the rotating speed (X_3) increased. Korakianiti et al. demonstrated that the final product properties of the granules could be affected by the rotating speed used for fluid bed rotogranulation, although the precise nature of the properties would be dependent on the formulation and manufacturing methods used during the granulation process [13)]. Taken together, the results of our current and previous studies of the GX system demonstrate that the final product properties could be affected by the rotating speed, although the extent of these effects would be dependent on the formulation and the manufacturing methods used during the granulation process.

As shown in **Table 4**, the water content increased as the liquid binder flow rate (X_1)

(P<0.001) increased or the atomization pressure (X_2) (P=0.006) or rotating speed (X_3) (P=0.002) decreased. This result was consistent with that observed for the granular roundness. Furthermore, the results of multivariate data analysis from our previous study using a drug-free formulation revealed that the roundness correlated with the water content in a positive manner [7], which suggested that the water content of granules could be one of the critical material attributes in terms of its impact on the granular roundness.

3.2. Process optimization

After generating polynomial equations relating to the dependent and independent variables, we proceeded to optimize the operational conditions using the following criteria:

(1) Particle size distribution: the proportion of fine particles (106–212 μm) > 50%

(2) The granules must possess a Carr's index > 80 points

(3) The roundness must be greater than 0.75

The optimization process was carried out using the version 9 of the JMP software. The optimized operating conditions were obtained as follows: X_1=9.4 g/ min, X_2=0.14 MPa, X_3=400 rpm (**Table 5**). An additional experiment was then conducted according to the predicted optimal operational conditions to verify their accuracy. **Table 5** provides a comparison of the final product properties obtained from the experiment and those predicted by the statistical model. The maximum deviation observed was 2.5%, which indicated that the model was suitable for predicting the granular

properties. It is noteworthy that the experimentally determined characteristic values were compliant with the desired product criteria. In addition, when determining the drug content and friability of final product granules, assumed for subsequent coating process, they showed 53.3% of acetaminophen content and only 0.01% friability, suggesting that final products showed good drug content uniformity and had high granule hardness applicable for coating. Furthermore, as shown in **Fig. 2A and 2B**, highly drug-loaded fine globular granules with a narrow size distribution were obtained from the optimal batch, therefore demonstrating the success of the optimization procedure.

4. Conclusions

The manufacture of fine globular granules containing a large amounts of drug (i.e., 50%) has been investigated using a unique multi-functional rotor processor GX, and experimental design and statistical analysis were used to examined the relationships between several operating parameters (i.e., the binder flow rate, atomization pressure, and rotating speed) and the physicochemical properties of the granules (i.e., the d_{50} value, proportion of fine particles in the range of 106–212 μm, Carr's index, roundness and water content). This work therefore represents the first reported example of the successful optimization of a manufacturing procedure for the preparation of fine globular granules with a drug content greater than 50%. Furthermore, the results of multiple regression analysis revealed deeper insight in the process, such as the binder flow rate and atomization pressure had significant positive and negative effects on the d_{50} value, Carr's flowability index, granular

roundness and water contents, respectively. In addition, the proportion of fine particles (106–212 μm) was positively affected by the product of interaction between the binder flow rate and the atomization pressure, and granular roundness was negatively and positively affected by the product of interactions between the binder flow rate and the atomization pressure, and the binder flow rate and rotating speed, respectively. Taken together, the results of this study could provide important information for the manufacture of highly drug-loaded fine globular granules which can be eventually applied for ODTs.

Acknowledgments

We are extremely grateful to the Freund Corporation for providing the Granurex® for this study. The authors would also like to thank the following companies: Iwaki Seiyaku Co., Ltd., DFE Pharm Co., Ltd., Asahi Kasei, Co., Ltd., and Nippon Soda Co., Ltd. for kindly providing the reagents used in this study.

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Table 1. Experimental design.

Batch no.	X_1:Flow rate		X_2:Atomization pressure		X_3:Rotating speed	
	Level	g/min	Level	MPa	Level	rpm
1	-1	6.8	-1	0.12	-1	240
2	1	9.2	-1	0.12	-1	240
3	-1	6.8	1	0.18	-1	240
4	1	9.2	1	0.18	-1	240
5	-1	6.8	-1	0.12	1	360
6	1	9.2	-1	0.12	1	360
7	-1	6.8	1	0.18	1	360
8	1	9.2	1	0.18	1	360
9	-1.68	6.0	0	0.15	0	300
10	1.68	10	0	0.15	0	300
11	0	8.0	-1.68	0.10	0	300
12	0	8.0	1.68	0.20	0	300
13	0	8.0	0	0.15	-1.68	200
14	0	8.0	0	0.15	1.68	400
15	0	8.0	0	0.15	0	300
16	0	8.0	0	0.15	0	300
17	0	8.0	0	0.15	0	300

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Table 2. Results for the characterization of the granules.

Batch no.	Yield (%)	R_w	d_{50} (µm)	106–212 µm (%)	Carr's index (point)	Roundness (-)	Water content (%)
1	88.4	1.14	139	56.4	77.0	0.83	13.0
2	71.4	0.96	342	13.2	84.0	0.87	26.7
3	86.6	1.29	99	40.2	76.5	0.84	9.0
4	74.4	1.29	164	53.5	80.0	0.83	18.4
5	89.4	1.12	164	51.4	77.0	0.81	7.7
6	83.9	1.30	224	41.9	84.0	0.87	19.9
7	89.3	1.24	111	46.9	76.5	0.82	7.1
8	86.6	1.20	142	59.0	77.0	0.84	15.9
9	79.9	1.27	96	38.2	75.0	0.81	2.8
10	71.8	1.29	221	43.9	85.0	0.86	24.3
11	86.5	2.63	150	45.9	79.0	0.85	14.9
12	86.5	1.56	124	45.9	77.0	0.84	11.5
13	83.1	1.57	183	50.7	77.0	0.85	18.3
14	88.9	1.44	158	55.9	77.0	0.84	11.0
15	86.6	1.36	169	54.2	78.5	0.84	15.8
16	87.5	1.16	140	58.3	77.0	0.84	12.4
17	89.0	1.24	160	56.3	78.5	0.84	16.1

Table 3. Statistical analyses of the granule mean size, proportion of fine particles (106–212 μm) and Carr's index properties of the granules.

Term	d_{50}		106–212 μm		Carr's index	
	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value
X_1	41.1	0.003	-1.25	0.535	2.52	<0.001
X_2	-28.5	0.016	2.62	0.212	-1.11	0.008
X_3	-10.5	0.284	3.21	0.137	-0.215	0.501
X_1X_2	-20.9	0.124	9.76	0.006	-1.25	0.017
X_1X_3	-22.1	0.106	4.06	0.152	-0.375	0.379
X_2X_3	10.4	0.413	-1.44	0.587	-0.375	0.379
X_1^2	4.14	0.682	-5.36	0.035	0.796	0.044
X_2^2	-3.05	0.762	-3.74	0.111	0.128	0.705
X_3^2	8.15	0.428	-1.26	0.558	-0.206	0.544
Constant	156	<0.001	56.3	<0.001	78.0	<0.001
	R^2 = 0.663		R^2 = 0.580		R^2 = 0.855	

Table 4. Statistical analyses of the roundness and water content properties.

Term	Roundness		Water content	
	Coefficient	*p*-value	Coefficient	*p*-value
X_1	0.0141	<0.001	5.82	<0.001
X_2	-0.00481	0.001	-1.64	0.006
X_3	-0.00338	0.008	-2.08	0.002
X_1X_2	-0.0113	0.000	-0.956	0.134
X_1X_3	0.00625	0.001	-0.269	0.649
X_2X_3	0.00125	0.343	0.994	0.122
X_1^2	-0.00223	0.060	-0.225	0.639
X_2^2	0.00111	0.302	-0.350	0.470
X_3^2	0.00111	0.302	0.135	0.778
Constant	0.840	<0.001	14.8	<0.001
	R^2 = 0.960		R^2 = 0.933	

Table 5. Process optimization and validation of the statistical model.

Process parameters: Flow rate (X_1) = 9.4 g/min, Atomization pressure (X_2) = 0.14 MPa, Rotating speed (X_3) = 400 rpm			
	Predicted	Experimental	Deviation (%)
106–212 μm (%)	52.6	51.3	-2.5
Carr's index (point)	82	82	0
Roundness (-)	0.87	0.86	-1.1
Drug content (%)	—	53.3	—
Friability (%)	—	0.01	—

Figure legends

Fig. 1. Response surface plots of the proportion of fine particles (106–212 μm) (A), Carr's index (B) and granular roundness (C) as a function of binder flow rate (X_1) and atomization pressure (X_2) , and granular roundness (D) as a function of binder flow rate (X_1) and rotating speed (X_3).

The remaining parameters were held at specific levels that ensured a maximum response.

Fig. 2. Granular morphology (A) and particle size distribution (B) in the optimized run.

(A) Magnification of ×350 with a scale bar of 50 μm.