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COMMUNICATION

Granulation of Aspirin Sustained-Release Formulation with Hydroxypropylmethylcellulose as Rate-Controlling Agent

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ABSTRACT

Wet granulation using a high-speed mixer was studied with hydroxypropylmethylcellulose (HPMC) as a rate-controlling polymer and aspirin as a model drug. i) High and low HPMC viscosity both produce granulations with high density; high HPMC content gives small density. ii) At low levels, HPMC viscosity and HPMC content contribute separately and negatively to geometric median diameter; at high levels, the synergistic interaction of these two factors contributes most. iii) At very high viscosity range, the yield does not change as HPMC content increases; at other ranges of HPMC viscosity, yield decreases as HPMC content increases. At any HPMC content level, an HPMC viscosity region gives maximum yield. (iv) Using the optimization statistics methodology, an optimal region of HPMC content and HPMC viscosity was found. Within this region, expected granulations will be produced.

INTRODUCTION

Although HPMC hydrogel matrix tablets could be made by direct compression technique, to ensure good content uniformity and avoid flowability-related intertablet weight variation problems, wet granulation may be a preferred processing route in routine commercial production. In the previous report (1) the influence of formulation factor on drug release was studied. The purpose of this work is to study the effects of viscosity and content of HPMC in formulation on granule properties.

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MATERIALS

Metolose 90SH 4000SR, 15000SR, and 100000SR (Shin - Etsu Chemical Co., Tokyo, Japan) were used as rate-controlling materials, aspirin (Chinese Pharmacopoeia grade) as model active exponent, and corn starch (Chinese Pharmacopoeia grade) as diluent.

METHODS

Experiment Design

The optimization technique such as response surface methodology aids in researching the effects of control factors on the final product characteristics. In this study, variables related to equipment and wetting agent were fixed at certain levels, and HPMC content and viscosity in formulation were further investigated using response surface methodology.

Granulation Preparation

Three viscosity grades of HPMC (4830, 15300, and 105000 cps) were added to formulation at levels of 5, 8, 10, 12, and 15%. The total amount of 60 g of aspirin, corn starch, and HPMC was mixed using a high-speed mixer at the impeller speed of 200 rpm for 5 min. After the powder was well mixed, 90% ethanol was added and the preparation was mixed for another 5 min at 400 rpm. Then the wet granules were dried in a hot-air oven until the moisture content was less than 3%.

Granulation Evaluation

Granule particle size was determined using standard sieves. Aeratic or tapped bulk density was evaluated using the graduated cylinder method. Repose angle was measured by determining the angle between the surface of a pile of powder and the horizontal plane. The percentage of dry granules between #26 to #60 mesh size portion was taken as yield.

Statistical Analysis

The controlling factors selected for the study were HPMC viscosity (x, transformed) and HPMC content (y, transformed). The levels of controlling factors were transformed using the following equation (2):

$$T = \frac{A - (\text{Max} + \text{Min})/2}{(\text{Max} - \text{Min})/2} \qquad (1)$$

where T is the transformed value, A is the actual value of the factor being transformed, and *Max* and *Min* are the maximum and minimum values in the range of the factor being transformed. The response variables are the tapped density, repose angle, geometric median diameter, and the yield of granules between #26 and #60 (250–710 μm). Polynomial regression program was used to relate the controlling factors to the response variables. Based on the best-fit regression model, response surface plots and contour plots were constructed to analyze each factor that would optimize the response variables.

RESULTS AND DISCUSSION

Because HPMC absorbs water, swells, and dissolves to form viscous solution, 90% ethanol is a suitable wetting solution to granulate powders containing HPMC. But as the content of HPMC in the formulation increases, more wetting solution is required to wet the powder. Therefore, in this study, the wetting solution is used at a constant ratio of wetting solution to HPMC (5 ml/16 mg). The controlling factor levels and the results of the response variables are summarized in Table 1.

Repose angle of all 15 batches of granulations were relatively constant at 37.2–40.8°, except for batch 3 having the smallest (35.9°) and batch 5 having the largest (43.0°) angles. These values indicated that all of the granulation possessed good flowability. The narrow range of the repose angle suggested that it is not necessary to subject this item to regression analysis.

Analysis of the Granulation Bulk Density

High granulation density is necessary for filling the die in manufacturing tablets. Aerated and tapped bulk density represent two kinds of packing arrangements in a granule bed. The effects of controlling factors to these two densities would be similar. Therefore, we use tapped bulk density as a representative to perform regression analysis. The polynomial equation follows:

$$D_T = -0.0150x - 0.0221y + 0.0718x^2 + 0.5052 \qquad (2)$$

$$N = 15 \quad R^2 = 0.3658 \quad F(3,11) = 5.07$$

where D_T is the tapped bulk density of granule, all other symbols are the same as stated for Eq. (1).

Table 1

The Levels of Controlling Factors and the Experimental Results

No.	HPMC Visco. *X*	HPMC Cont. *Y*	Bulk Density (g/ml)		Repose Angle	L^a	Yield (%)
			Aerated	Tapped			
1	-1	-1	0.48	0.59	37.2	406	76.0
2	-1	-0.4	0.48	0.61	40.8	275	77.3
3	-1	0	0.46	0.56	35.9	280	74.7
4	-1	0.4	0.48	0.61	40.8	122	15.3
5	-1	1	0.44	0.59	43.0	138	19.3
6	0	-1	0.48	0.60	38.4	409	86.0
7	0	-0.4	0.44	0.57	38.4	409	88.7
8	0	0	0.44	0.56	38.4	365	79.3
9	0	0.4	0.42	0.55	39.6	365	82.7
10	0	1	0.42	0.53	37.2	360	78.7
11	1	-1	0.49	0.61	38.4	270	66.7
12	1	-0.4	0.45	0.57	37.2	354	74.7
13	1	0	0.44	0.55	40.8	359	74.7
14	1	0.4	0.43	0.53	39.6	399	68.0
15	1	1	0.43	0.55	39.6	421	64.0

[a]*L* = Geometric median diameter.

Although the correlation coefficient is very small, the Student's *t*-test shows that coefficients for all of the components at the right side of Eq. (2) are very significant ($p < 0.05$). This suggests that this equation is reliable. Based on this equation, the predicted tapped bulk density surface is constructed. Fig. 1 illustrates the three-dimensional predicted surface and contour plot.

The negative coefficients for x in Eq. (2) indicate that HPMC viscosity contributes negatively to the granule density; the term of x^2 is responsible for the curvature in surface plot. In the contour plot, points on the same line represent the same predicted density. It is apparent that high and low HPMC viscosity both produce granulations with high densities. The negative coefficient for

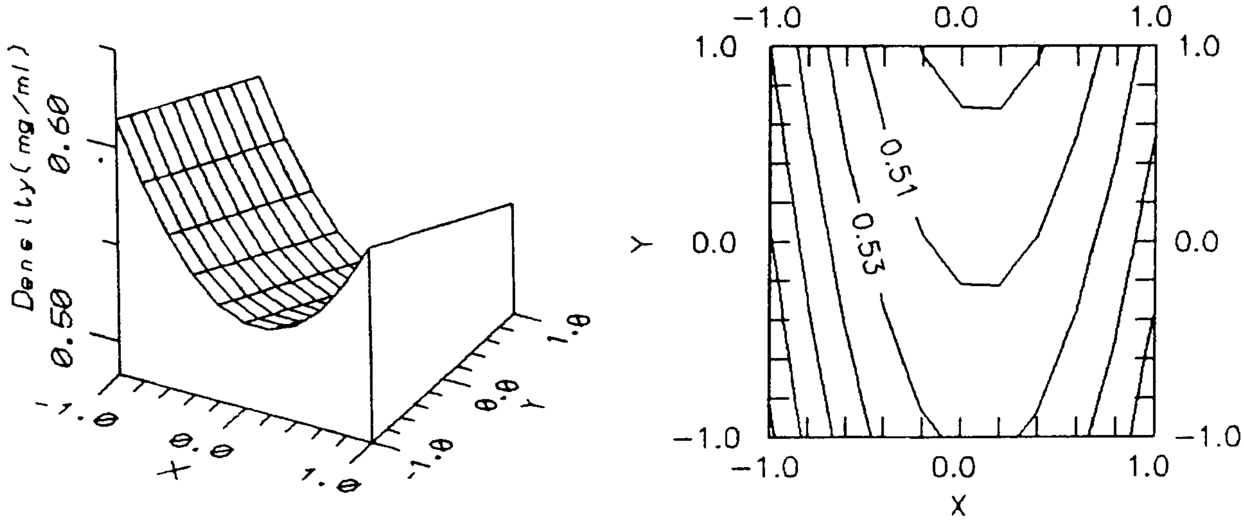

Figure 1. Response surfaces and contour plots of tapped bulk density of aspirin sustained-release formulation.

y in Eq. (2) indicates that HPMC content contributes negatively to the granule density. This could be visualized from its contour plot. This is in accordance with the visual result during the granulation process. During the granulation procedure, the more HPMC contained in powder, the more water is required, and subsequently, the bigger and more irregular the wet particle is. This phenomena could be explained by the swelling character of HPMC. Powder agglomerates quickly when it contacts with wetting agent due to the high viscosity of HPMC, but flaws appear at the same time because of the swelling of HPMC. After drying, some aggregates break into small particles with small flaws; this is why high HPMC content gives small density.

Analysis of Granulation Geometric Median Diameter

Another aim of granulation is to enlarge the particles and to improve their flowability. Therefore, the geometric median diameter is evaluated. The polynomial equation is

$$L = 58.200x - 32.586y - 79.200x^2 + 107.371xy + 381.600 \quad (3)$$

$$N = 15 \quad R^2 = 0.8654 \quad F(4,10) = 30.013$$

where L is the geometric median diameter of granulation, other symbols are the same in earlier equations. Student's t-test shows that coefficients for all of the components at the right side of Eq. (3) are very significant ($p < 0.05$).

Based this equation, response surface and contour plot are constructed as shown in Fig. 2. The signs of the coefficients of x and y in Eq. (3) indicate that HPMC viscosity increases, whereas HPMC content decreases the geometric median diameter. The term x^2 is responsible for the curvature in x direction. The large positive coefficient for interaction, term xy, suggests great synergistic effects between HPMC viscosity and HPMC content. From the contour plot, we can visualize that at low HPMC viscosity, geometric median diameter decreases as HPMC content level increases. This could be explained by HPMC swelling characteristics, but at the high HPMC viscosity region, it increases as HPMC content increases. On the other hand, at low HPMC content level, there is a maximum geometric median diameter (about 400 μm) in the HPMC viscosity range studied, but at high HPMC content level, there is a steady increase in geometric median diameter with the increase of HPMC viscosity. We can therefore conclude that at low levels, HPMC viscosity and HPMC content contribute separately to geometric median diameter; at high levels, the interaction of these two factors contributes most.

Analysis of Yield of Granules Between #26 and #60 Mesh

A narrow range of granule distribution is often expected in term of granule flowability; here, the portion

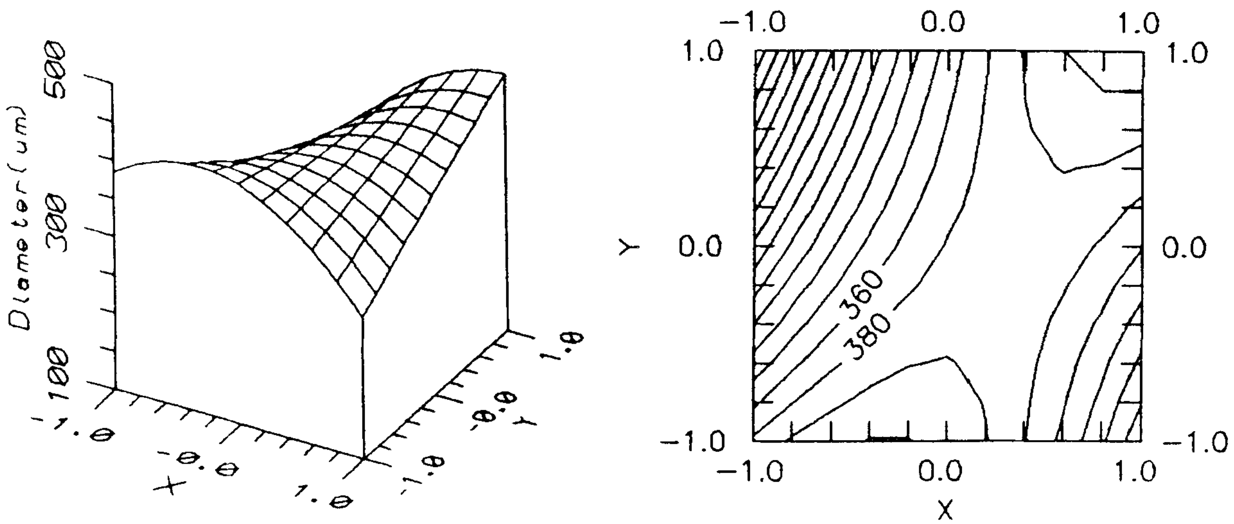

Figure 2. Response surfaces and contour plots of geometric median diameter of aspirin sustained-release formulation.

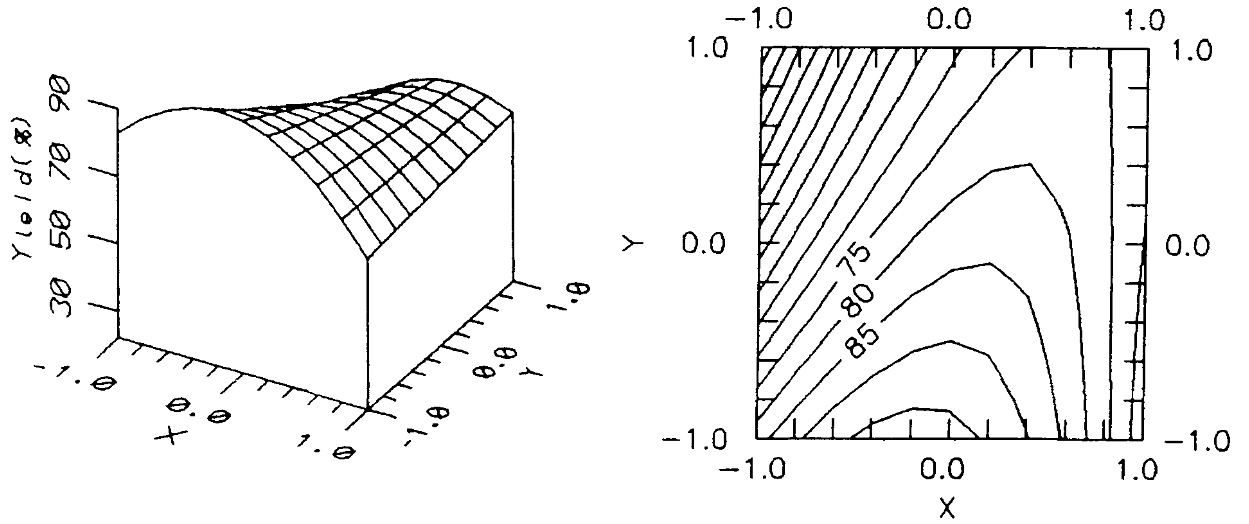

Figure 3. Response surfaces and contour plots of yield of granules between 26 and 60 mesh.

of granules falling between #26 and #60 mesh was collected. The yields of this part of the granules were analyzed and the following equation was obtained:

$$p_y = 8.550x - 13.876y - 22.010x^2 + 16.405xy + 83.080 \quad (4)$$

$$N = 15 \quad R^2 = 0.5467 \quad F(4,10) = 7.150$$

where p_y is the yield of the granule between #26 and #60 mesh, other symbols are the same as stated. Student's t-test shows all term's on the right side of Eq. (4) are very significant ($p < 0.05$)

Based on this equation, response surface and contour plots are constructed (Fig. 3). At very high viscosity range, the yield does not change, although HPMC content increases three times; at other ranges of HPMC viscosity, yield decreases as HPMC content increases. At any HPMC content level, there is an HPMC viscosity that gives maximum yield.

Analysis of Optimal Combination of Control Factors

Based on the above analysis, expected large geometric median diameter and high yield will be obtained at

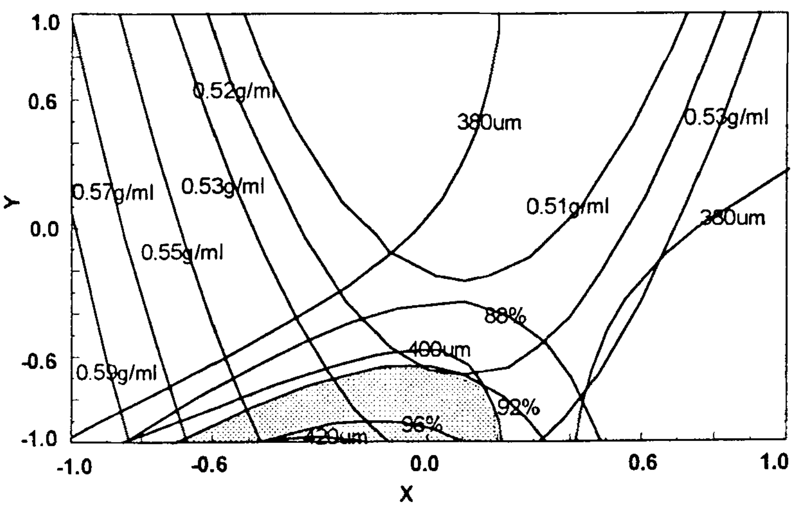

Figure 4. Superimposed contour plot of bulk density, geometric median diameter, and yield.

low HPMC content level and a moderate HPMC viscosity level. With the expected geometric median diameter and yield, we can superimpose these two contour plots and find the optimum region of *x* and *y* combination. In this study, if we chose 400 μm as the minimum expected geometric median diameter, and 92% as the minimum expected yield; we superimposed the contour plots and recognized the optimum *x* and *y* combination as the shaded region in Fig. 4. In this region, the tapped bulk density of granule was 0.52–0.57 g/ml. If we shrink the range of the expected tapped bulk density, we can obtain a more narrow *x* and *y* region by superimposing the contour plots of geometric median diameter, yield and tapped bulk density.

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