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BEAD MANUFACTURE BY EXTRUSION/SPHERONIZATION - A STATISTICAL DESIGN FOR PROCESS OPTIMIZATION

Cathy C. Ku[1], Yatindra M. Joshi[2], James S. Bergum[1] and Nemi B. Jain[1]

[1] Pharmaceutical Research Institute
Bristol-Myers Squibb Company
New Brunswick, NJ 08903

[2] Gensia Pharmaceuticals, Inc.
San Diego, Ca 92121

ABSTRACT

Our recent experience in developing bead formulations for a hydrophilic drug using an extrusion/spheronization technique highlighted several critical processing factors. It was observed that the yield of beads of desired size fraction was significantly affected by water level, water temperature, extrusion speed, spheronization speed, and spheronization time. To further elucidate the roles of these factors, a split-plot factorial design was used to evaluate their effects on the yield of desired size beads, and to determine the optimal levels to maximize the yield. Several 18 kg batches of beads were manufactured using a predetermined level of each factor. The finished beads were sieved using #14 and #20 mesh screens and the yields of beads between #14-20 mesh screen were determined. It was observed that the temperature of water used at the granulation stage significantly affected the bead formation. Using room temperature water for granulation, the significant factors were water level, extruder speed, spheronization speed, spheronization dwell time, and the interactions of water level with extruder speed and spheronization speed with dwell time. Whereas using 50°C water, significant factors were water level, extruder speed, spheronization speed, and the interaction of water level with spheronization speed. The best fitting regression model describing the relationship between the found yields and the factors was used to find the levels of each factor that would optimize the yield. Two scale-up batches at 100 kg each were manufactured using the optimal process conditions to verify the room temperature model. The yields from the two scale-up batches were within 0.4% of the predicted yield using the regression model.

INTRODUCTION

The use of a bead (or pellet, spheroid) type dosage form has been well accepted in the pharmaceutical industry in recent years. Several techniques have been developed for manufacturing beads. These include extrusion/spheronization, loading drug onto sugar beads from a solution or suspension using fluid bed or pan coating systems, and loading drug by powder layering using a pan or a rotogranulator (1-2). Among these techniques, extrusion/ spheronization is extensively used for a wide range of drug loading. It was first developed by Nakahara in 1964 (3). The characterization and processing of beads prepared by extrusion/ spheronization were studied by several authors (4-14). Some used statistical models to optimize the process variables for bead manufacturing. Malinowski and Smith evaluated the effects of water level, extruder speed, screen size, spheronizer speed and spheronizer dwell time on the granules using a 2^5 full factorial design (12). It was found that water level and spheronizer speed had significant main effects on the granulation properties in addition to the interactions of several factors. Chariot et al used a half factorial design to study the effects of extrusion rate, extrusion screen size, spheronization load, speed and time on the yield of the desired size beads (13). They found that screen size, spheronizer speed, the interactions of spheronizer time and load, spheronizer time and speed were significant factors. Hasznos et al evaluated the influence of water level, extrusion rate, spheronization time, speed and load on bead size distribution by multilinear regression analysis (14). They found that water level, spheronizer speed, spheronizer time and the first order interactions of the three factors exerted the most influence.

The size distribution of beads manufactured by extrusion/spheronization technique depends on the selections of excipients, equipment and processing conditions. Uniform size beads are most desired since they assure further coating, dissolution and encapsulation uniformity. The amount of water used for wet-massing of the solid components is critical for imparting desired cohesiveness, plasticity and lubricity to the wet-mass. These attributes of the wet-mass play an important role in assuring control of the size distribution of the beads formed by the extrusion/spheronization process (15). In addition to the amount of water used, it is conceivable that the temperature of the water will also be an important factor. The studies reported to date in the literature have not addressed the effect of water temperature. In the present study, a split-plot factorial study was used to evaluate the effect of water level, water temperature, extruder speed, spheronization speed and spheronization time on the quality and yield of the beads for an experimental formulation. In addition, a response surface technique was used to identify the optimal level for the factors studied.

MATERIALS AND METHODS

1. Materials

A hydrophilic drug was formulated into a bead type dosage form. The beads contained 27% active, 43% microcrystalline cellulose (FMC Corp., PA, USA), 20% lactose hydrous (B.V. Hollandsche Melksuikerfabrick, Uitgeest, Holland), and 10% citric acid (Haarman & Reimer Corp. IN, USA). Microcrystalline cellulose and lactose hydrous functioned as the processing aids. Citric acid was added as the stabilizer to provide a micro-acidic environment for the active. The batch size for the optimization study was 18 kg and was increased to 100 kg for the confirmation scale-up batches.

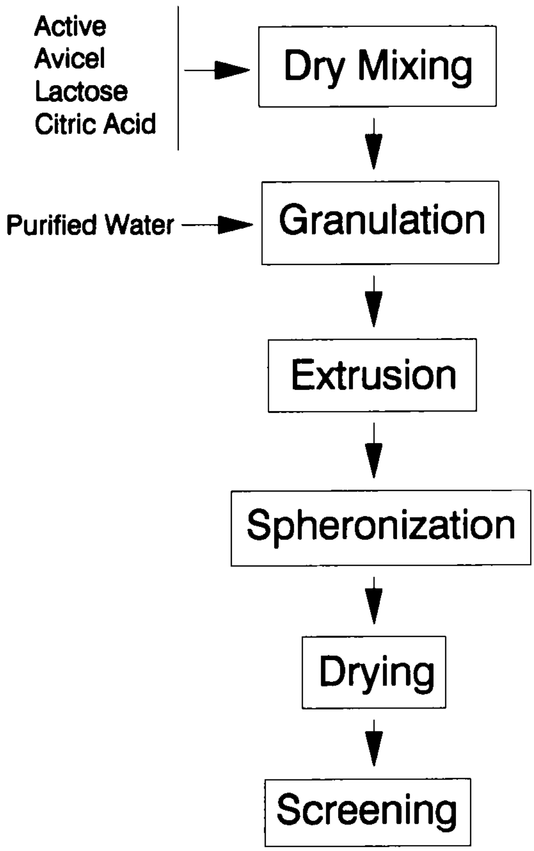

FIGURE 1
The Flow Chart of the Manufacture Process of the Beads

Ten optimization batches, each 18 kg in size, were prepared using either room temperature (22 ± 2°C) or 50°C (50 ± 2°C) water for granulation. The manufacturing process is shown in the flow chart in Figure 1. The first step involved dry-mixing of all ingredients to form a uniform blend in a high shear mixer/granulator (Collette, model Gral 75). Granulation was achieved by adding water at the prescribed water level to the powder blend with both plow and chopper set at high speed for 7 minutes. The entire amount of water was added within the first 4 minutes of granulation. After granulation, the wet-mass was split into six sub-batches. Each sub-batch was placed into the feed chamber of an extruder (Nica, model E-140) and processed at the prescribed extrusion rate. The extrudate was spheronized into beads using a spheronizer (G. B. Caleva, model 15) at the prescribed rotational speed and dwell time. The wet beads from each sub-batch were dried separately in a fluid bed dryer (Glatt, model GPCG5). The dried beads from each sub-batch were hand-screened to collect the #14 to #20 mesh size portion.

TABLE 1
The Processing Parameters and Levels Evaluated in the Optimization Study

Factors	Levels Studied
Water Added in Granulation (WL)	360, 390, 420 g/kg (*)
Water Temperature (WT)	Room Temperature (22 ± 2°C) 50°C (50 ± 2°C)
Extruder Speed (ES)	1.5 Setting 3.0 Setting
Spheronizer Speed (SS)	450, 650, 850 rpm
Spheronizer Dwell Time (ST)	90, 180 seconds

(*) Amount of Water per Dry Powder Weight

2. Statistical Design and Analysis

The processing factors and levels selected for the study are given in Table I. In order to find the optimal level of each factor, a split-plot factorial design was used with granulation batches as the whole plot and the spheronization sub-batches as the split-plot (16). This design allowed for estimation of linear effects for all factors and quadratic effects for water level and spheronizer speed. These two factors were studied at quadratic level due to the consideration that they might not exert a linear effect at the range studied. The interaction between extruder speed and dwell time was partially confounded with batch. In other words, the effect of extruder speed by dwell time interaction could not be completely separated from the effect of batch. All other two-way interactions were not confounded with each other or batches. By using a split-plot arrangement, information about the factors and their interactions was obtained with fewer granulation batches, thus reducing the time and effort.

The study design for room temperature water and 50°C water is given in Tables 2 and 3, respectively. The manufacturing order was randomized to eliminate any systematic bias in the study. The yield of beads between #14 and #20 mesh screen of each sub-batch was used as the response variable in the statistical modeling. SAS software was used for the statistical analysis. Based on the best-fitting regression model, contour plots were used to select the level of each factor that would optimize the yield. These levels were then used in a confirmation study using larger scale batches.

3. Confirmation Scale-up Batches

Two scale-up batches at 100 kg size were prepared using the optimal processing conditions determined by the optimization study for room temperature water. The manufacturing process was similar to that of the optimization batches except a larger mixer/granulator (Collette, model Gral 300) and a larger drier (Glatt, model WSG 30) were used.

TABLE 2
Statistical Design for Batches Prepared Using Room Temperature Water

Batch No	Water Level (WL)	Extruder Speed (ES)	Spheronizer Speed (SS)	Spheronizer Dwell Time (ST)
1	360 g/kg	1.5	450 rpm	90 s
		1.5	650 rpm	180 s
		1.5	850 rpm	180 s
		3.0	450 rpm	180 s
		3.0	650 rpm	90 s
		3.0	850 rpm	90 s
2	360 g/kg	1.5	450 rpm	180 s
		1.5	650 rpm	90 s
		1.5	850 rpm	90 s
		3.0	450 rpm	90 s
		3.0	650 rpm	180 s
		3.0	850 rpm	180 s
3	390 g/kg	1.5	450 rpm	90 s
		1.5	650 rpm	180 s
		1.5	850 rpm	180 s
		3.0	450 rpm	180 s
		3.0	650 rpm	90 s
		3.0	850 rpm	90 s
4	390 g/kg	1.5	450 rpm	180 s
		1.5	650 rpm	90 s
		1.5	850 rpm	90 s
		3.0	450 rpm	90 s
		3.0	650 rpm	180 s
		3.0	850 rpm	180 s
5	420 g/kg	1.5	450 rpm	90 s
		1.5	650 rpm	180 s
		1.5	850 rpm	180 s
		3.0	450 rpm	180 s
		3.0	650 rpm	90 s
		3.0	850 rpm	90 s
6	420 g/kg	1.5	450 rpm	180 s
		1.5	650 rpm	90 s
		1.5	850 rpm	90 s
		3.0	450 rpm	90 s
		3.0	650 rpm	180 s
		3.0	850 rpm	180 s

TABLE 3
Statistical Design for Batches Prepared Using 50°C Water

Batch No	Water Level (WL)	Extruder Speed (ES)	Spheronizer Speed (SS)	Spheronizer Dwell Time (ST)
7	360 g/kg	1.5	450 rpm	90 s
		1.5	650 rpm	180 s
		1.5	850 rpm	180 s
		3.0	450 rpm	180 s
		3.0	650 rpm	90 s
		3.0	850 rpm	90 s
8	360 g/kg	1.5	450 rpm	180 s
		1.5	650 rpm	90 s
		1.5	850 rpm	90 s
		3.0	450 rpm	90 s
		3.0	650 rpm	180 s
		3.0	850 rpm	180 s
9	390 g/kg	1.5	450 rpm	90 s
		1.5	650 rpm	180 s
		1.5	850 rpm	180 s
		3.0	450 rpm	180 s
		3.0	650 rpm	90 s
		3.0	850 rpm	90 s
10	390 g/kg	1.5	450 rpm	180 s
		1.5	650 rpm	90 s
		1.5	850 rpm	90 s
		3.0	450 rpm	90 s
		3.0	650 rpm	180 s
		3.0	850 rpm	180 s

4. Bead Evaluation

The beads were evaluated for sphericity and surface smoothness using an optical microscope (AO Spencer) at 75X magnification. Although these observations were only qualitative, they were considered adequate for comparison of surface characteristics of beads prepared using various factor levels.

RESULTS AND DISCUSSION

The yields of beads between #14-20 mesh screen from all sub-batches are given in Tables 4 and 5. All but two sub-batches were successfully manufactured. The sub-batches that failed

TABLE 4
The Percent Yields of Size #14-20 Beads Prepared Using Room Temperature Water

Water Level (g/kg)	Spheronizer Dwell Time (s)	Spheronizer Speed (rpm)					
		450		650		850	
		Extruder Speed		Extruder Speed		Extruder Speed	
		1.5	3.0	1.5	3.0	1.5	3.0
420	90	78.3	86.7	84.7	87.3	66.4	65.7
	180	80.4	85.4	88.5	88.6	43.6	31.8
390	90	78.0	82.1	82.0	86.0	78.7	82.2
	180	75.5	81.5	85.0	90.9	76.1	81.7
360	90	73.9	81.7	79.1	NA	77.7	86.2
	180	69.7	NA	78.9	87.4	77.1	80.5

NA: not available

TABLE 5
The Percent Yields of Size #14-20 Beads Prepared Using 50°C Water

Water Level (g/kg)	Spheronizer Dwell Time (s)	Spheronizer Speed (rpm)					
		450		650		850	
		Extruder Speed		Extruder Speed		Extruder Speed	
		1.5	3.0	1.5	3.0	1.5	3.0
390	90	75.5	88.5	86.2	87.2	81.3	83.4
	180	82.8	85.2	86.2	91.4	74.5	62.7
360	90	74.8	80.7	84.7	84.0	80.2	85.1
	180	78.2	79.8	78.4	89.4	77.8	84.7

contained the lowest amount of room temperature water (360 g/kg) at the high extrusion rate. The extruder stalled due to insufficient lubricity provided by water. The subsequent statistical analysis was performed without these two points. All other batches produced spherical beads with smooth surface as observed under the microscope. The yields of beads between #14-20 varied between 31.8 to 91.4%.

The data for each temperature was analyzed separately. When room temperature water was used, the combination of high water level (420 g/kg), high spheronization speed (850 rpm), and high dwell time (180 s) gave much lower yields, i.e. 43.6 and 31.8%. At this high level of water and high spheronization speed combination, the extrudates agglomerated while being spheronized inside the spheronizer chamber, thus resulting in excess of oversize beads after long spheronization time. The low yields associated with these two points interfered with fitting a model to the overall data. Therefore they were not included when fitting the response surface. As a result, the response surface should not be used to predict yields in the region where water level, spheronizer speed and dwell time are high. The 62.7% result in the 50°C temperature data was also excluded for the same reason. Excluding these points from the analysis affected the balanced structure of the original design but still allowed the same full model to be fitted to the data. The following full models were used to fit the data.

Equation 1 - the full model for room temperature water

$$\text{Yield (\#14-20 mesh beads)} = \beta_0 + \beta_1{\bullet}WL + \beta_2{\bullet}WL^2 + \beta_3{\bullet}SS + \beta_4{\bullet}SS^2 + \beta_5{\bullet}ES + \beta_6{\bullet}ST + \beta_7{\bullet}WL{\bullet}SS + \beta_8{\bullet}WL{\bullet}ES + \beta_9{\bullet}WL{\bullet}ST + \beta_{10}{\bullet}SS{\bullet}ES + \beta_{11}{\bullet}SS{\bullet}ST + \beta_{12}{\bullet}ES{\bullet}ST$$

Equation 2 - the full model for 50°C water

$$\text{Yield (\#14-20 mesh beads)} = \beta_0 + \beta_1{\bullet}WL + \beta_2{\bullet}SS + \beta_3{\bullet}SS^2 + \beta_4{\bullet}ES + \beta_5{\bullet}ST + \beta_6{\bullet}WL{\bullet}SS + \beta_7{\bullet}WL{\bullet}ES + \beta_8{\bullet}WL{\bullet}ST + \beta_9{\bullet}SS{\bullet}ES + \beta_{10}{\bullet}SS{\bullet}ST + \beta_{11}{\bullet}ES{\bullet}ST$$

where β_0 - β_{12} : coefficients
WL : water level
SS : spheronizer speed
ES : extruder speed
ST : spheronizer dwell time

The term "WL^2" was not present in Equation 2 because only two levels of water were tested at 50°C water temperature. Thus, only a linear term could be fitted to the water level.

The "best" sub-model was found by pooling nonsignificant terms (p-values > 0.10) with the error. Highest order terms were eliminated first. All lower order terms that were a factor of a significant term were left in the model. The sub-models for room temperature and 50°C are given below:

Equation 3 - the final model for room temperature water

$$\text{Yield (\#14-20 mesh beads)} = -470.59 + 1.97\ WL - 0.00196\ WL^2 + 0.545\ SS - 0.000198\ SS^2 + 23.586\ ES - 0.471\ ST - 0.000755\ WL \bullet SS - 0.0516\ WL \bullet ES + 0.00121\ WL \bullet ST$$

Equation 4 - the final model for 50°C water

$$\text{Yield (\#14-20 mesh beads)} = -123.350 + 0.396\ WL + 0.345\ SS - 0.000123\ SS^2 + 3.468\ ES - 0.000489\ WL \bullet SS$$

All of the individual terms in the above models were significant (p-values ≤ 0.10). Note that water level, spheronization speed, extruder speed, and the interaction of water level with spheronization speed were significant factors at both water temperatures. In addition, spheronization time, interactions of water level with extruder speed and water level with spheronization time were also significant factors at room temperature.

Based upon Equations 3 and 4, the predicted yield surfaces were constructed. Figure 2 illustrates the three-dimensional predicted surface for the predicted yield using room temperature water, high extruder speed and short spheronization time. The surface gave the predicted yield for each combination of water level and spheronizer speed over the experimental region. Contours of the surface are given in Figure 3. Points on the same line represented the same predicted yield. At high spheronizer speed, the yields decreased as water level was increased. Whereas at low spheronization speed, the yields stayed nearly the same independent of the water level. The maximum yield of 90% occurred in the region where water level was between 360 and 385 g/kg and spheronizer speed was between 650 and 750 rpm. When high spheronization time was used as opposed to the short spheronization time used in Figure 3, the maximum yield of around 90% also occurred at the same region. However, better bead quality in terms of sphericity was obtained. After taking into consideration both the yield and quality of beads, the combination of medium water level, high extruder speed, medium spheronization speed and high spheronization time was deemed the optimal condition for batches using room temperature water.

The predicted surface for the 50°C water at high extruder speed is shown in Figure 4. Note that this plot applied to both spheronization dwell times since the time was not a contributing factor in Equation 4. The corresponding contour plot is shown in Figure 5. At high spheronizer speed, the yields stayed the same as water level varied; while at low spheronizer speed, the yields increased as water level increased. Three-dimensional surfaces for the other water temperature/extruder speed/spheronization time combinations were constructed and were similar to the ones shown in Figures 2 and 4, therefore they are not shown in this paper.

A separate analysis was conducted to study the effect of temperature by using only 360 and 390 g/kg water levels at both temperatures. It was observed that the temperature significantly affected the bead size. At both water levels, much larger beads were formed at the high temperature. In addition, significantly higher yields (p-value = 0.01) were observed at the higher temperature for both water levels. Water provides the lubricity in the wet-mass necessary for the extrusion and spheronization. In addition, it aids the cohesiveness and plasticity of the wet-mass. The warmer water is believed to further enhance these attributes of the wet-mass and thus it improves the yield of the desired size beads.

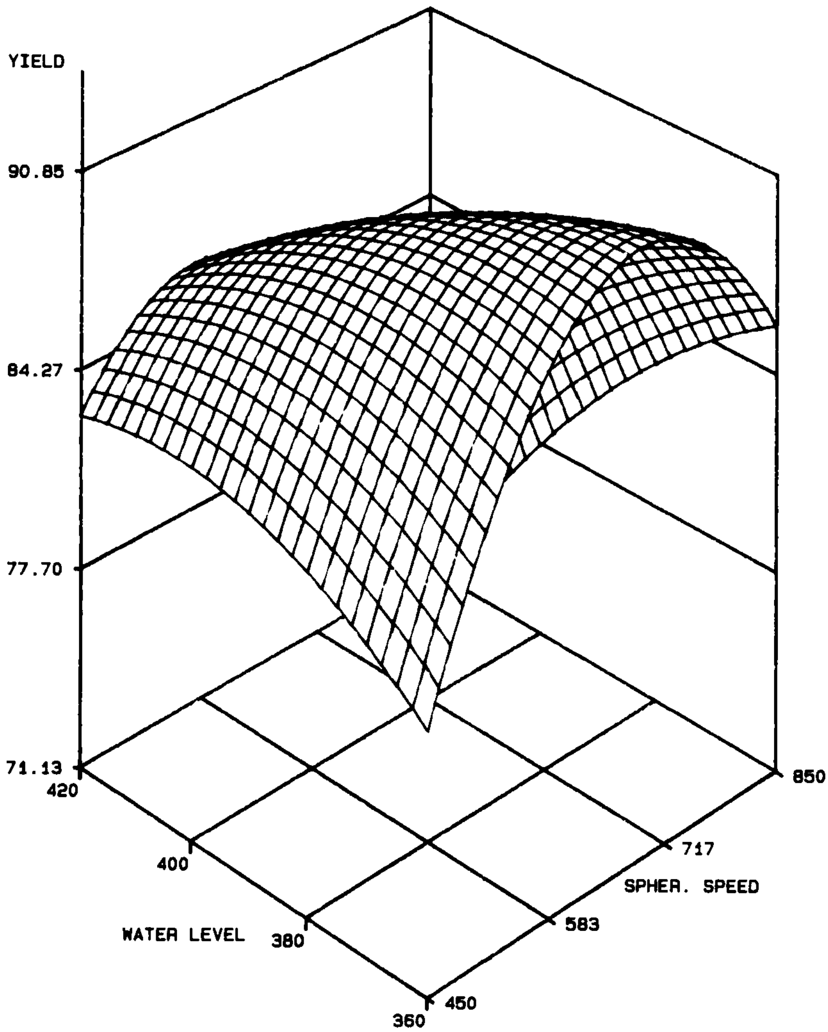

FIGURE 2
The Predicted Surface for Yields of #14-20 Mesh Beads Prepared Using Room Temperature Water, High Extruder Speed, and Short Spheronizer Time

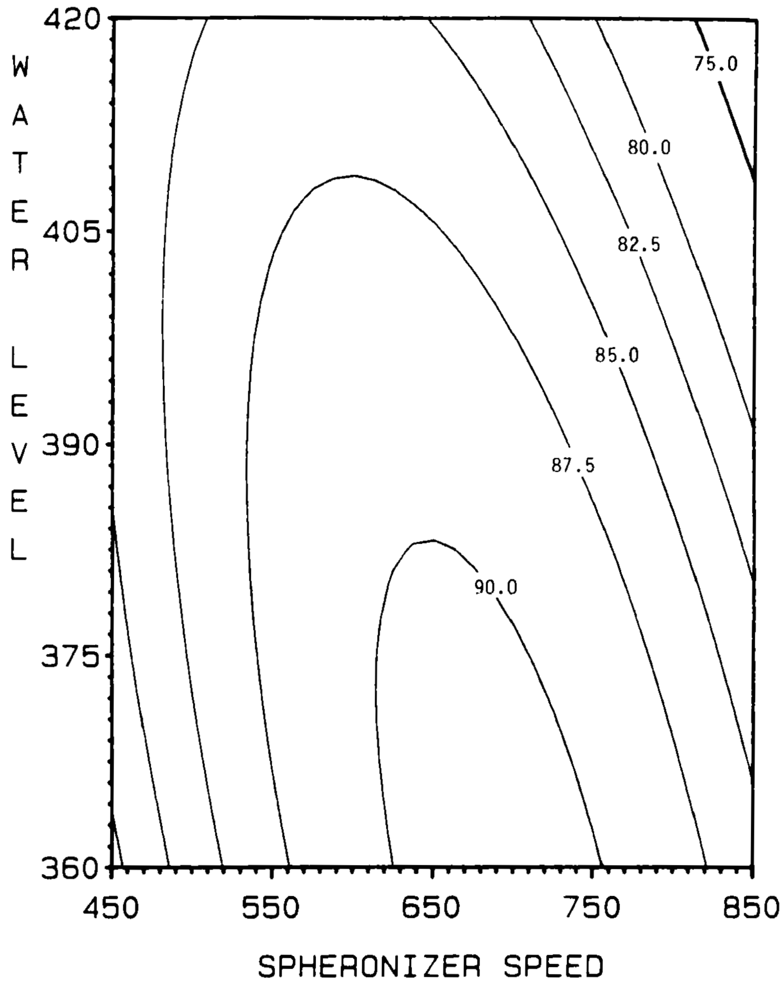

FIGURE 3
The Contour Plot for Yields of #14-20 Mesh Beads Prepared Using Room Temperature Water, High Extruder Speed, and Short Spheronizer Time

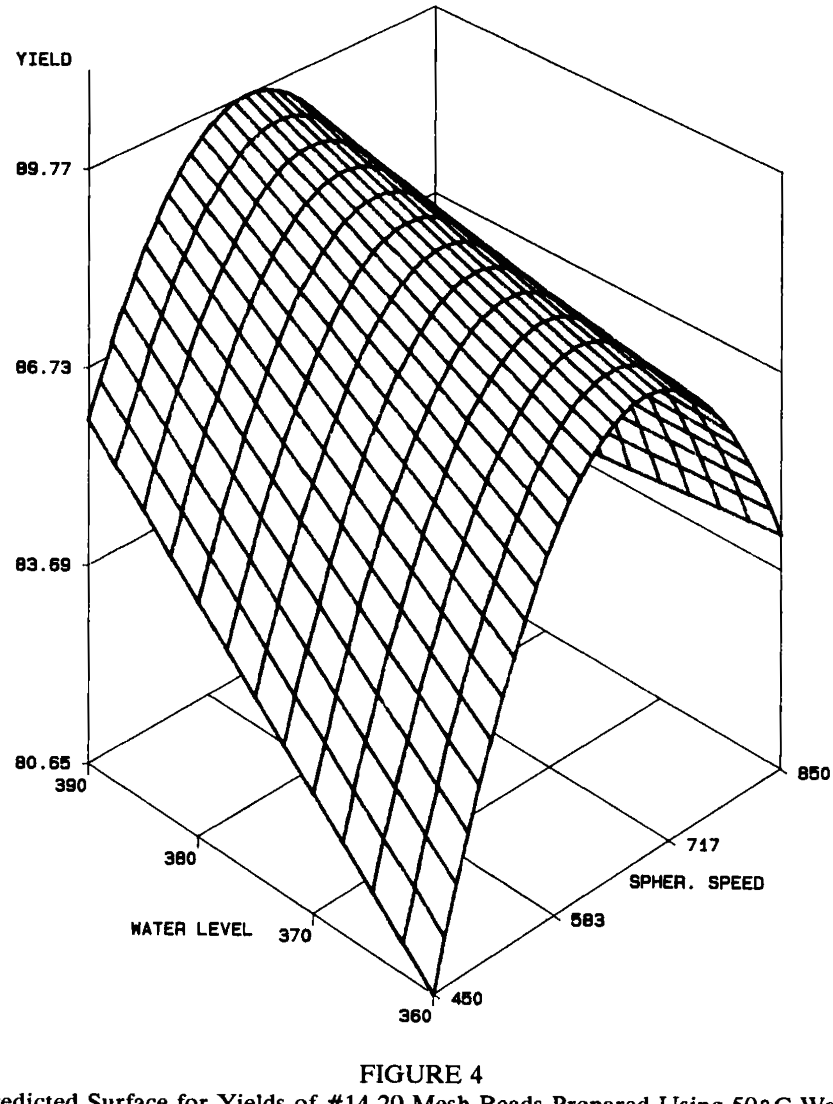

FIGURE 4
The Predicted Surface for Yields of #14-20 Mesh Beads Prepared Using 50°C Water and High Extruder Speed

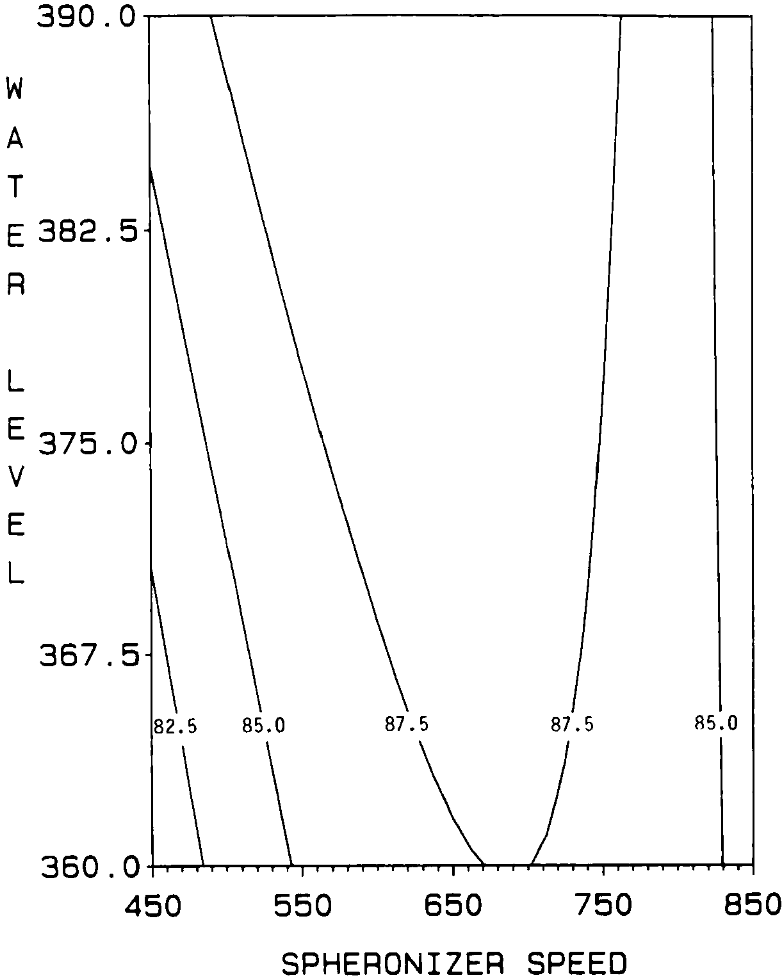

FIGURE 5
The Contour Plot for Yields of #14-20 Mesh Beads Prepared Using 50°C Water and High Extruder Speed

TABLE 6
The Processing Conditions for the 100 kg Scale-up Batches

Processing Parameters	Level
Water Added During Granulation	390 g/kg
Water Temperature	Room Temperature
Extruder Speed	3.0 Setting
Spheronizer Speed	650 rpm
Spheronizer Dwell Time	180 s

TABLE 7
The Predicted Yields versus the Experimental Yields of the Scale-up Batches

	Predicted Yield (%)	Actual Yield (%)
Batch 1	89.6	89.2
Batch 2	89.6	89.9

Similar studies were carried out by other researchers to examine the effects of various processing factors (4-14). In Chariot et al's study, the extrusion speed did not exert significant effect on the yield of desired size beads using a Fuji Paudal extruder model EXDS60 (13). In our study where a Nica extruder model E-140 was used, the extruder speed was a significant factor at both temperatures.

The amount of water used for wet-massing is reported in the literature to have the most pronounced effect on the quality of the beads (8-10, 12, 14). Moreover, the spheronization speed and spheronization dwell time have also been shown to be important factors in determining the yield (8, 11-14). The results from the present study are, in general, in agreement with what is reported in the literature. In addition, the present study also demonstrates the significance of the temperature of water used for wet-massing. It is a common practice in the industry to hold the distilled water at temperatures greater than 80°C to prevent microbial growth. Therefore, controlling the water temperature at the wet-massing stage is important in order to assure batch to batch reproducibility.

In view of the sensitivity of yield to various processing factors, it was of interest to evaluate the feasibility of scale-up and the applicability of optimized levels to scale-up batches. Two scale-up batches of 100 kg size were manufactured to verify the room temperature model. The optimal processing conditions for the scale-up batches, shown in

Table 6, were chosen based on the optimization study. The yields were predicted using Equation 3. The actual yield and the predicated yield are shown in Table 7. The predicted and experimental values are in agreement. This supports the validity of the results of the optimization study.

CONCLUSIONS

A split-plot factorial design was applied to optimize the levels of process variables for bead manufacture using an extrusion/spheronization technique. Among the factors studied, water level, water temperature, extrusion speed, spheronization speed, and spheronization time significantly affected the bead formation. In addition, the interactions of water level with extrusion speed, spheronization speed and spheronization time were also significant. Statistical models were constructed for room temperature water and 50°C water, respectively. Two scale-up batches were manufactured to confirm the room temperature model. The predicted and the experimental values were in agreement.

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