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A FACTORIAL APPROACH TO HIGH DOSE PRODUCT DEVELOPMENT BY AN EXTRUSION/SPHERONIZATION PROCESS

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ABSTRACT

Extrusion/spheronization technology has been used for preparing high drug-loaded pellets. Typical formulations include 40-60% microcrystalline cellulose (MCC) to impart the plastic characteristics required for this process. Studies have suggested that pellets containing greater than 80% drug are difficult to process and require special grades of MCC. Most of these studies focused on either the process or formulation aspects of the product and failed to explore the interactions of process and product. Statistical experimental designs are well suited for exploring both process and product variables and their interactions with each other. This study addresses pelletization of a high dose drug with low density. A Nica® radial (basket-type) extruder was used in extrudate preparation, followed by spheronization on a serrated plate spheronizer. A Plackett-Burman screening design was employed to investigate product and process parameters affecting final pellet drug content, density and roundness. MCC type and concentration, water concentration, spheronizer speed and residence time and extruder screen size were found to be statistically significant in imparting desirable attributes to the final product. Wet mixing time, extruder feed rate and extrusion rate did not significantly affect pellet properties.

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INTRODUCTION

The objective of the present study was to obtain high drug-loaded pellets, sufficiently densified to fill a 500 mg dose into a '0' elongated capsule. Pellets were further required to be sufficiently round and smooth for subsequent controlled release coating. Extrusion-spheronization was chosen to achieve this objective.

The major steps involved dry blending, wet mixing, extrusion of wet granulations into short cylinders and spheronization of the extrudate using a spinning, serrated plate [1, 2]. The effects on final product characteristics of process or formulations variables have been studied by various investigators [3-8]. While microcrystalline cellulose (MCC) has been used to spheronize pellets effectively, MCC products containing sodium carboxymethylcellulose are found to be particularly useful in preparing high dose pellets [9, 10].

Most work on extrusion-spheronization technology reported in the literature has been completed using twin screw or ram extruders. In the present study, pellets were manufactured using a Nica extruder and spheronizer. The Nica extruder is a radial, basket-type extruder and differs significantly from other extruders. It has a much shorter compression zone resulting in low heat buildup, low product holdup and shorter exposure to high pressure gradients.

This study was designed to address eight formulation and process variables in one set of experiments such that the relative importance of each to final the product properties could be directly measured. Factorial designs are especially useful in multiple variable experiments. In the present case, a twelve run fractional factorial (Plackett-Burman) screening design was chosen to identify critical variables affecting final product characteristics.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel RC-581 or Avicel RC-591, FMC Corporation, Philadelphia, PA) was used as a spheronizing aid. The test drug is zwitterionic (isolectric point ~5.5) and was supplied as a fine powder with a mean particle diameter of 10 to 15 microns. It is poorly soluble in water and common alcohols.

Preliminary Experimentation

Initial studies were conducted to establish viable ranges for experimental variables. A simple formulation consisting of drug, MCC and water was selected for study. At 80% to 90% drug levels, acceptable pellets could not be formed. MCC with small amounts of sodium carboxymethylcellulose (Avicel RC-591 or Avicel RC-581) produced acceptable pellets. Also, sufficient densification resulted allowing the 500 mg dose to be encapsulated at only 75% drug concentration. This was used as the minimum drug concentration for subsequent studies.

Process variables examined included all controllable equipment parameters. For the extruder, the orifice plate (screen) can be changed to produce extrudates of different diameters. The extruder itself has two independently variable drives: the feeder drive, which forces material into the extrusion zone; and the extruder drive, which forces material through the extrusion plate. Varying these speeds was reported by the manufacturer to result in different extrusion pressures, and thus pellet densification. The spheronizer rotational speed is controllable and was selected as an experimental variable. Finally, the length of time spent in the spheronizer was also varied.

Water is a critical variable in this process. It acts as a binder during wet massing, a lubricant during extrusion and a plasticizer during spheronization. In preliminary formulations, the effective water concentration was found to be a function of the Avicel concentration. High water levels with low Avicel concentrations resulted in severely overwetted masses that could not be extruded or spheronized. The converse, with high Avicel and low water, produced dry masses which could not be extruded. Since the intent of this study was to vary the type and concentration of Avicel as widely as functionally possible, the water concentration was held at a constant ratio to Avicel.

Variables and the level of each tested in the screening study are listed in Table 1.

Experimental design

Fractional factorial screening designs aid in isolating the few critical factors from many possible variables that affect desired final product characteristics. Discrete critical variables, such as screen size or Avicel type, can then be fixed at optimum levels. Continuous critical variables, such as machine speed or ingredient concentrations, may be further investigated using response surface methodology.

Table 1. Screening Design Variables

Variable	Low	High
Avicel type	RC581	RC591
Avicel Concentration	75%	85%
Screen Size	0.8 mm	1.2 mm
Extruder Speed	30 rpm	110 rpm
Feeder Speed	40 rpm	190 rpm
Plate Rotational Speed	500 rpm	1000 rpm
Residence Time	1 min.	10 min.
Mixing Time	3 min.	8 min.

Of equal importance at the screening stage, variables which are found to exhibit no significant effects on final product properties can be fixed at convenient levels and eliminated from further consideration.

In the present case, a twelve run Plackett-Burman screening design consisting of eight factors at two levels (2^8*3/64) was selected using PC-based software (Statgraphics, STSC, Inc., MD). This design allows separation of the main effect of each variable from other main effects; however, two factor interactions are not separable. Statistical analysis of data from this design allows rank ordering of the test variables regardless of whether they are process, formulation, discrete or continuous. The magnitude of each variable on each resulting product property can be estimated independently of all other tested variables.

Pellet Manufacturing

The formulation and operating variables for each batch as established by the Plackett-Burman design are presented in Table 2. The batch size of each formulation was 0.5 Kg. Avicel and the test drug were blended in a planetary mixer (Hobart N-50, Hobart corporation). Deionized water was added to the mixtures and wet mixing was continued for the prescribed time. Wet granulations were immediately extruded (Nica model E-140 extruder, Niro-Aeromatic Inc., Columbia, MD) under designed conditions. The resulting extrudate was spheronized (Nica model S-320 spheronizer, Niro-Aeromatic Inc., Columbia, MD), also at designed rotational speeds and times. After spheronization, all batches were dried in a fluid bed dryer (GPCG-1, Glatt Air Techniques Inc., Ramsey, NJ) at 45^{o} C for 15 minutes. The order of manufacture was randomized.

Table 2. Plackett-Burman Fractional Factorial Design with Actual Run Conditions Substituted

Run	Avicel type (RC-)	Avicel Conc (%)	Screen size (mm)	Extruder (rpm)	Feeder (rpm)	Plate rotational speed (rpm)	Residence time (minutes)	Mixing time (min.)
1	591	25	0.8	110	40	500	1	8
2	591	25	1.2	30	190	1000	1	8
3	581	25	1.2	110	40	1000	10	3
4	591	15	0.8	30	190	1000	10	3
5	581	25	1.2	30	190	500	1	3
6	581	15	0.8	30	40	500	1	3
7	591	15	1.2	110	40	1000	1	3
8	581	15	0.8	110	190	1000	1	8
9	591	15	1.2	30	40	500	10	8
10	591	25	0.8	110	190	500	10	3
11	581	25	0.8	30	40	1000	10	8
12	581	15	1.2	110	190	500	10	8

Pellet Evaluation

Pellet particle size was reported as the fraction of the batch in the 18 to 20 mesh sieve fraction using U.S. standard sieves. Bulk and tap densities were evaluated using a standard graduated cylinder method. Since shape differences were very distinct (cylinder, dumb-bell and spherical), pellet shape was evaluated by assigning a rank score based on visual inspection ('1.0' being very spherical and '12.0' being a cylinder). Two independent observers evaluated and ranked all samples. Rankings generally agreed, and when different, rank scores were averaged.

RESULTS AND DISCUSSION

The results from the screening design were entered into the Statgraphics program and are shown in Table 3. Appropriate statistical analysis of these results separates the main variable effects from one another. This allows conclusions to be drawn about each individual variable under study and its effects on each response measured, without regard to the levels of the other variables.

P statistics generated from ANOVA of the pellet size data are presented in Table 4, along with the estimated size of the effect on size of changing that variable . The

Table 3. Plackett-Burman Response Values

Run	Tap density (g/cc)	% Retained (Mesh 14/20)	Shape Rank*
1	0.819	9.5	12
2	0.885	91.5	6
3	0.877	82.0	2
4	0.910	14.0	4
5	0.787	97.5	11
6	0.788	5.0	10
7	0.855	69.0	5
8	0.813	1.0	6
9	0.840	65.0	7
10	0.855	39.5	11
11	0.892	55.0	5
12	0.806	58.0	7

* best = 2
worst = 12

Table 4. Influence of Test Variables on Pellet Size

Rank	Factor	Estimated change in 14-20 mesh fraction(%)	Significance (p)
1	Screen size	56.5	0.0062
2	Avicel concentration	27.2	0.0452
3	Extruder speed	- 11.5	0.2551
4	Residence time (Spheronizer)	6.7	0.4835
5	Rotational speed (Spheronizer)	6.3	0.5035
6	Feeder speed	2.7	0.7694
7	Wet massing time	- 4.5	0.6265
8	Avicel type	- 1.7	0.8538

estimated effect indicates the mean relative change in fraction of beads found in the 14 to 20 mesh size fraction as the experimental variable is changed from the lower to the higher end of its respective range listed in Table 1. For example, changing from the 0.8 mm screen to the 1.2 mm screen results in an average increase of 56.5% of the beads in the 14-20 mesh size fraction. This average screen size effect is estimated independent of all other test variable levels. Table 4 indicates that both screen size and Avicel concentration significantly ($p<.05$) increase the fraction of

Table 5. Influence of Test Variables on Pellet Density

Rank	Factor	Estimated effect on density (g/cc)	Significance (p)
1	Rotational speed (Spheronizer)	0.056	0.0019
2	Residence time (Spheronizer)	0.039	0.0057
3	Avicel type	0.034	0.0086
4	Avicel concentration	0.017	0.0510
5	Extruder speed	0.013	0.0994
6	Screen size	- 0.005	0.4769
7	Wet massing time	- 0.003	0.6436
8	Feeder speed	- 0.003	0.6816

pellets in the desirable particle size range. None of the other test variables significantly influence particle size distribution.

Table 5 lists comparable data for the pellet density response. Avicel concentration, spheronizer speed and the residence time in the spheronizer all significantly increase density. Avicel concentration is very near the significant level and probably should not be ignored. Maximizing these three or four variables should yield pellets of maximum density. The data suggest that for this formulation and extruder type, density is relatively independent of extrusion conditions. It had been anticipated that processing effects that would increase resistance during extrusion, such as a smaller screen size or increased feeder speed, would significantly increase pellet density. This is not supported by the data.

Table 6 lists data for the pellet shape response. In ranking the shape, the most spherical pellets were ranked first and the least spherical, last. Negative numbers in the estimated effect column reflect a tendency towards lower (better) shape scores. Process conditions in the spheronizer predominate, with rotational speed determining the quality of the pellet shape. Increasing Avicel concentration resulted in significantly less spherical pellets.

In summary, spheronizer speed and the length of time in the spheronizer control pellet shape and density. Maximizing the spheronizer speed and time would be expected to consistently yield better pellets. Earlier reports[8] found that prolonged spheronization times resulted in surface drying and pellet cracking, neither of which

Table 6. Influence of Test Variables on Pellet Shape

Rank	Factor	Estimated effect on rank score	Significance (p)
1	Rotational speed (Spheronizer)	- 5.1	0.0004
2	Residence time (Spheronizer)	- 2.4	0.0034
3	Screen size	- 1.6	0.0115
4	Avicel concentration	1.3	0.0219
5	Feeder speed	0.6	0.1328
6	Avicel type	0.6	0.1328
7	Wet massing time	0.3	0.4531
8	Extruder speed	0.1	0.7917

was apparent in the current study. Pellet shape appears to be dependent on the moisture modulating capability of each formulation as well as the spheronization conditions. These variables should be optimized for each formulation of interest.

Pellet size was determined by the extruder screen size. Also, increasing screen size improved the shape score. The 1.2 mm screen consistently produced more pellets in the desired particle size range than did the 0.8 mm screen. Avicel RC-591 produced more dense pellets than did RC-581 ($p<0.01$). The RC-591 grade is recommended in this formulation.

Overall, wet massing time, feeder speed and extruder speed did not have significant effects on any of the responses studied. These variables can be fixed at convenient levels, within the ranges studied, for future work.

Increasing Avicel concentration increases the fraction of beads in the desired size range. Conversely, increasing Avicel concentration adversely affects shape scores. This is consistent with prior reports [10] in which Avicel (RC grades) concentration was varied from 10% to 80% of the formulation. Shape may be further improved by optimizing the Avicel/water ratio at any added Avicel concentration.

CONCLUSIONS

Using extrusion and spheronization conditions appropriate to specific formulations, high drug-loaded pellets suitable for subsequent coating were

obtained. Control of Avicel type and concentration, extruder screen size, spheronizer speed and spheronizer residence time are critical for producing acceptable pellets. Wet massing time, extruder speed and feed rate did not significantly affect pellet characteristics. A statistical screening design aided in properly characterizing both formulation and process parameters, and revealed that, for every response measured, product characteristics are determined by both formulation composition and process conditions.

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