Physico-Mechanical Characterization of the Extrusion-Spheronization Process. Part II: Rheological Determinants for Successful Extrusion and Spheronization

Rajen D. Shah,[1,2] Mohan Kabadi,[3] David G. Pope,[2] and Larry L. Augsburger[1,4]

Received September 21, 1994; accepted December 7, 1994

Spheres are widely used as the basis for the design of multiparticulate drug delivery systems. Although the extrusion and spheronization processes are frequently used to produce such spheres, there is a lack of basic understanding of these processes and of the requisite properties of excipients and formulations. It is hypothesized that the rheological or mechanical properties of the wet mass may address the requirements of both extrusion and spheronization. The fact that certain formulations can be extruded, yet not be successfully spheronized, suggests that the two processes depend on different formulation attributes, and that there are different rheological criteria that must be met for each process to be successful. As a preliminary test of these hypotheses, methods were developed to measure the rheological behavior and mechanical properties (plastic yield value, tensile strength, yield loci) of the wet mass and/or extrudate for a model formulation system (microcrystalline cellulose, lactose, hydroxypropylmethylcellulose). The finished spheres were characterized in terms of particle size, bulk density, individual bead crushing strength, and sphericity. A Box-Behnken experimental design was employed by which the independent formulation variables could be related to the dependent rheological/mechanical properties and finished pellet characteristics. It was observed that there was a critical range of rheological/mechanical variables within which pellets having desirable criteria such as yield of 18/25 mesh cut >60%, a shape factor >0.85, etc., can be prepared. Screen pressure was shown to be the most critical variable affecting the yield of 18/25 mesh cut, while the yield value and tensile strength markedly influenced the shape factor. Thus, for the formulations studied, it was possible to define a "window" of rheological/mechanical properties within which both extrusion and spheronization can be successfully carried out.

KEY WORDS: extrusion; spheronization; marumerization; wet mass rheology; yield value; tensile strength; yield loci; response surfaces; experimental design.

INTRODUCTION

Despite the popularity of spheres as a multiparticulate drug delivery system, and of extrusion and spheronization as a means of producing such spheres, there is a lack of basic understanding of these processes and of the requisite properties of materials and formulations. Most reports have ignored material properties and have, instead, focused on the optimization of process variables, e.g. spheronizer speed, load and spheronization time (1–6). Since the wet mass undergoing extrusion and spheronization experiences different kinds of stresses, it is apparent that the rheological or mechanical properties of the wet mass may address the requirements of both processes.

Few studies have ever considered the rheological properties of wet masses that make them suitable for extrusion and spheronization. Harrison *et al.* (7) studied the stress-strain relationships of wet masses by means of ram extrusion rheometry. Short compression and forced flow stages, and a predominant steady-state flow were reported to be essential for producing high quality extrudate. However, none of the existing rheological models could be fitted to their data. Apparently, one of the underlying assumptions, i.e., that the velocity at the wall of the die is zero, is invalid (8). Thus, no parameter independent of the extrusion rate could be identified. Despite this limitation, these investigators later considered the yield value and shear thinning properties of lactose-microcrystalline cellulose mixtures; however, the possible relationship of the yield value to successful extrusion and spheronization was not explored (9).

Microcrystalline cellulose (MCC) has come to be regarded as an essential component for successful extrusion and spheronization, possibly by favorably altering the rheological properties of the wet mass (1,10–15). However, such statements are subjective and have not been supported by definitive rheological studies. It also has been proposed that MCC contributes to the tensile strength of the wet mass through "autohesion," i.e., the mutual interdiffusion of free cellulose polymer chains (16); however, no actual measurements of tensile strength were reported.

In the spheronization process, the initial breakdown of the extrudate to smaller pieces is likely a function of its tensile properties, while subsequent rounding of the pieces must be dependent on the yield properties of the material. Successful extrusion also must at least in part be dependent on the yield properties of the wet mass. The fact that certain formulations can be extruded, yet not be successfully spheronized (11), suggests that the two processes depend on different formulation attributes. It is hypothesized that there are different rheological criteria that must be met for each process to be successful. Thus, the specific objectives of this study are to characterize the wet mass and/or extrudate in terms of its yield properties and tensile strength, and to utilize an experimental design approach to determine if there is a rheological "window" within which both extrusion and spheronization can be carried out satisfactorily.

MATERIALS AND METHODS

Rheological Yield Value

A Haake Rotovisco (model RV20, Fisons Instruments, Saddle Brook, NJ 07662) in a plate-plate configuration (model PK100 sensor with PQ2 plate) was used to obtain rheograms of the wet masses. Very low rates of shear were

[1] Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland 21201.
[2] Present address: Technical R&D, Sandoz Research Institute, 59 Route 10, East Hanover, New Jersey 07936.
[3] Present address: Hoffman-La Roche, Inc., 340 Kingsland Street, Nutley, New Jersey 07110.
[4] To whom correspondence should be addressed.

0724-8741/95/0400-0496$07.50/0

employed (up to 0.1 sec^{-1}). These low shear rates alleviate the problem of slippage and are most likely to generate data relevant to the extrusion/spheronization process (9).

As with any other wet mass testing technique, sample preparation is very critical. The wet mass was placed between two sheets of wax paper and was lightly tamped with a tablet punch of 0.75″ diameter. The sample was then inserted between the plates and was again compressed between the plates of the Rotovisco to form a disc of 1.65 mm thickness. This thickness was kept constant for all tests. The excess material was scraped off from the edges with a spatula. The sample was allowed to equilibrate for 5 min before starting the run. The temperature of the sample was maintained at 25°C (±1) during the test.

The supplied software was programmed to increase the rate of shear from 0 to 0.08 sec^{-1} over 5 min. A typical rheogram is as shown in Figure 1. None of the existing rheological models (viz., Ostwald, Casson, Herschel-Bulkley etc.) could be fitted to the rheogram. However, the rheogram does show a characteristic yield point (Fig. 1). Rheograms were obtained in triplicate for each sample.

Tensile Strength

A horizontally split-die system with cavity diameter of 0.5″ was designed and fabricated from Plexiglas® for a direct "extension" test (Fig. 3). A ram extruder was fabricated to force the wet mass into the split-die in a uniform and reproducible manner. The barrel of the ram extruder was made of Delron® and the piston of aluminum. The die cavity was tapered towards the split to ensure tensile failure in that plane. To achieve proper alignment of the two pieces of the die, the bottom piece was provided with a recess which fitted into the cavity of the top piece such that very little tolerance was allowed. Four alignment screws prevented cocking. The lip area of the split-die was coated with Teflon spray (Elmers), and a vent was provided for any water that may seep into the lip area during extrusion. With these latter two measures any potential interference by the seepage of water was avoided.

Initially, 10 g of material was placed in the barrel of the ram extruder, and a 2 kg load was applied manually to it for 5 min. This was followed by a sequence of placing an additional 10 g of material in the barrel and a manual application of 5 kg load for 5 min. The sequence was repeated until the entire barrel was filled. After filling the barrel, the Instron universal physical testing machine (model 4501, Instron Corp., Canton, MA 02021) was used in the compression mode to extrude the wet mass into the die (one end of which is open). A 200 lb (889.6 N) capacity strain gage load cell was used to monitor force as a piston was driven at a constant rate of 25.4 mm/min up to a total piston displacement of 29 cm (Fig. 2). During this extrusion step the two pieces of the split-die were held together with spring clamps.

For tensile strength measurement, the split-die was placed between the platens of the Instron in the tension mode. The upper and lower die pieces were linked to the upper and lower platens, respectively, and the clamps were removed. A 10 N capacity load cell was used to measure the force required to lift the top piece off the bottom piece of the split-die in the vertical direction (axially) at a constant strain rate of 0.75 mm/min (Fig. 3). The Instron also enabled the measurement of the strain simultaneously with the developing stress during extension. A representative tension profile from the strip chart recorder is shown in Figure 4. The difference between the maximum force at tensile failure and the

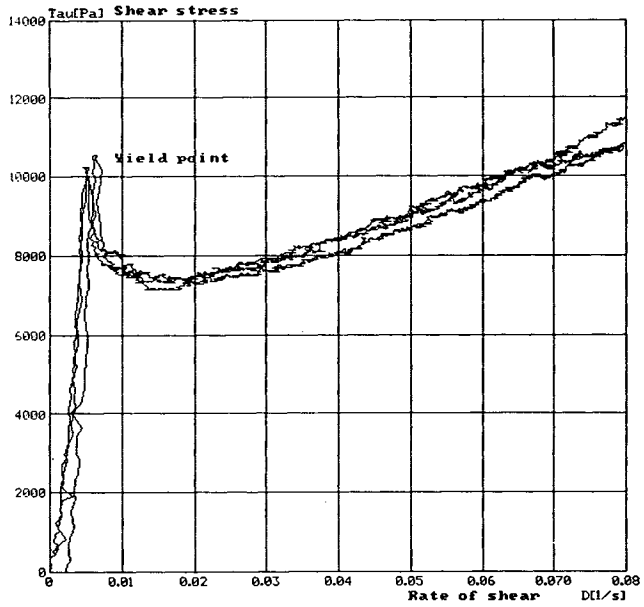

Fig. 1. Representative rheogram of the wet mass (Run# L).

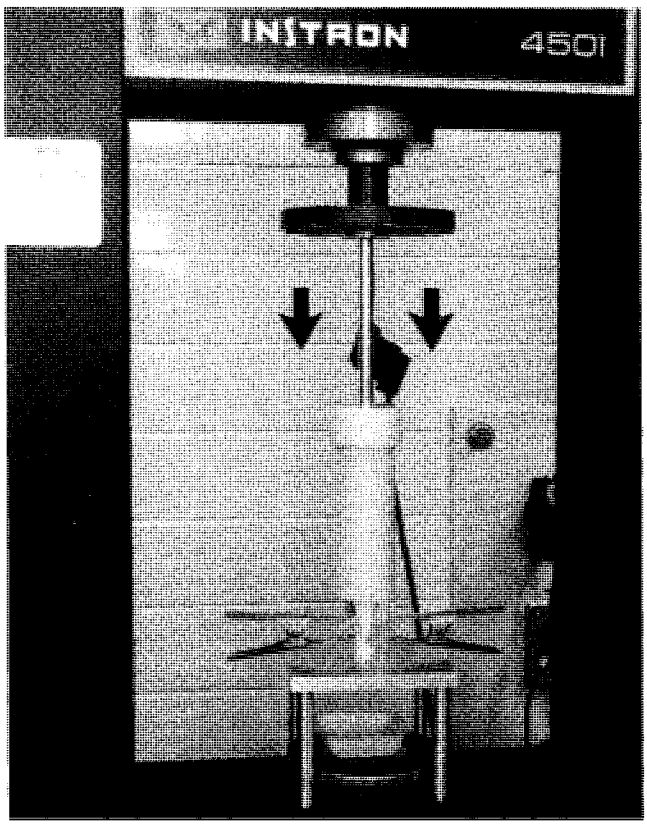

Fig. 2. Instron setup in the compression mode to extrude the wet mass into the die.

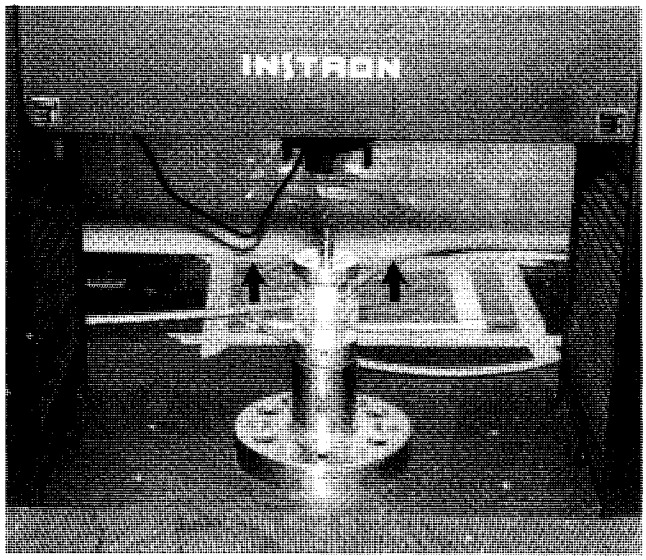

Fig. 3. Instron setup to measure the tensile strength of the wet mass using a specially designed split-die.

weight of the top piece was divided by the apparent area of the cross section of the wet mass and was reported as its tensile strength in N/m^2. The test was repeated three times for each sample and the mean and standard deviation were reported.

Yield Locus

A split level automatic rotational shear tester RO-200 (Siloproject B.V., Sterksel, Netherlands) was used to obtain yield loci of the wet masses (refer to acknowledgment). The RO-200 shear tester cell is split into two levels. The bottom level is rotated at a constant rate, and the top level is held stationary with a torque arm which, in turn, measures the shearing stress. The various normal loads are placed on the loading lid and the corresponding shear stresses are measured.

Samples of comparable density are essential for shear testing. To that end, a standard consolidation procedure was followed in which 50 g of material were filled into the shear cell and was consolidated under a vertical stress of 50 g/cm^2.

After complete consolidation, the sample is unloaded by reversing the direction of rotation until the shear stress becomes zero (17). This step was followed by application of various normal loads (not greater than the consolidation load) and the measurement of the corresponding shear strengths. The consolidation step was repeated between the tests with various normal loads.

A plot of shear strength vs. normal load produces the yield locus, a representative example of which is shown in Figure 5. Coulomb's linear model fitted the data well ($r^2 > 0.98$) (17). The $\tan^{-1}$ of the slope of the line is the angle of internal friction. The Y-intercept is the cohesion parameter.

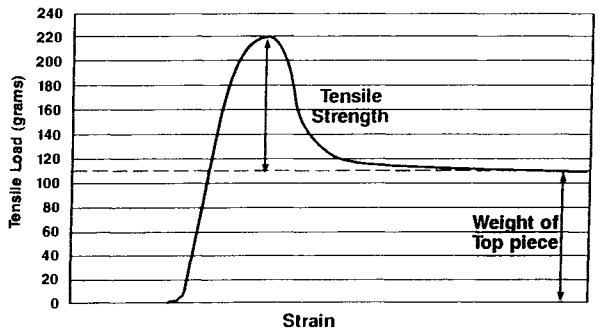

Fig. 4. Representative tension profile of the wet mass (Run# A).

Extrusion/Spheronization

The pellets were prepared using the extrusion/spheronization process as described earlier (Extruder–EXDS-60, Spheronizer–QJ 230, Luwa Corp., Charlotte, NC 28297) (18). The process variables were kept constant, and the screen pressure and screen temperature were recorded using the previously described instrumentation (18).

A sample of the extrudate during the extrusion of each of the fifteen runs was collected very carefully so as to avoid collision with other extrudate or with any of the machine parts. Thus, the extrudate is assumed to be breaking under its own weight. Under these conditions the weight of the extrudate can be used as an indicator of relative tensile strength (19). From the collected samples two extrudates were weighed at a time. This was done in order to measure a larger magnitude of the weight and to reduce the variability in the data. Ten such readings were collected, and the mean and relative standard deviation were reported.

Pellet Testing

The particle size distribution of the pellets was determined by sieve analysis as described earlier (18). The % of pellets falling within the 18/25 mesh cut was used as a parameter reflecting the practical yield of pellets in a range narrow enough for further processing (18). For the measurement of other pellet properties such as bulk density, crushing strength, shape factor and friability, a narrower 18/20 mesh cut was used to reduce variability. Bulk density was measured as previously described (18).

The crushing strength of individual pellets was measured using a vertically mounted motor-driven mechanical slide assembly (Unislide model B4009P20J, Velmex Inc.,

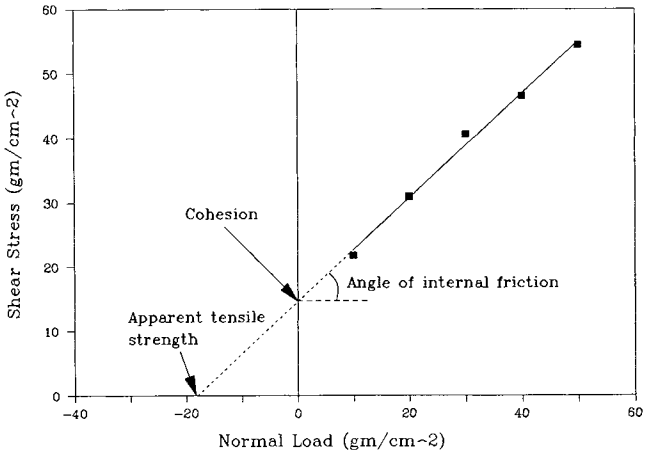

Fig. 5. Representative yield locus obtained using the RO-200 shear cell (Run# A).

Table 1. Statistically Planned Experiments with Box-Behnken design

Run #	MCC Level (ratio of MCC to lactose) (%)	Water Level (%)	HPMC Level (%)
A*	50	46	1.5
B	30	38	1.5
C	70	54	1.5
D*	50	54	0.0
E	50	46	1.5
F	50	46	1.5
G*	50	38	3.0
H*	70	38	1.5
I	30	46	3.0
J*	50	38	0.0
K*	30	54	1.5
L	30	46	0.0
M*	50	54	3.0
N	70	46	0.0
O	70	46	3.0

* Yield loci obtained for these experiments.

Bloomfield, NY 14350) and a piezoelectric load cell (model 9712A6, Kistler Instruments Inc., Amherst, NY 14120). Originally configured as a capsule plug hardness tester (20), the system was modified to measure pellet crushing strength by installing a flat faced cylindrical platen with a diameter of 5 mm. The platen was driven (1.1 mm/sec) against individual pellets. The charge output from the load cell generated during crushing of the pellets was amplified (amplifier model 5004 SN, Kistler Instrument Corp., Amherst, NY 14120) and converted to voltage which was then measured on a strip chart recorder (model 2107-2290-XX, Gould Inc., Cleveland, OH 44101). The mean and standard deviation of 25 readings were reported for each run.

A two dimensional shape factor was measured using a semi-automatic system consisting of an optical microscope (model 65685, Carl Zeiss Inc., Thornwood, NY 10594) and an interactive image analysis system IBAS (Kontron Elektronik GmbH, Eching, West Germany). The IBAS system was programmed to calculate the shape factor according to the following formula:

$$\text{Shape factor} = \frac{(\text{perimeter})^2}{(4\pi \cdot \text{area})}$$

This shape factor was calculated for 250 pellets of each of the fifteen runs, and the mean and standard deviation were reported. A value of "1" indicates a perfect circle (sphere), and any value less than that reflects a deviation from circular shape.

The friability of pellets was measured by a method similar to that described by Malinowski and Smith (4). A 10 g sample of pellets along with 200 5-mm diameter glass spheres were tumbled in a friabilator (model 10801, Van-Kel Industries, Inc., Edison, NJ 08820) for 30 minutes. After tumbling (25 rpm), the glass spheres were separated out and the pellets were sieved through a nest of 18/20/pan sieves. The weight of the fines collected in the pan was divided by the total initial weight (10 g) of the pellets and was reported as % friability.

Experimental Design

A model system of lactose (anhydrous lactose, Lot no. ONA18-147, Sheffield Products, P.O. Box 630, Norwich, NY 13815), MCC (Avicel PH101, Lot no. 1018, Drum 1530, FMC

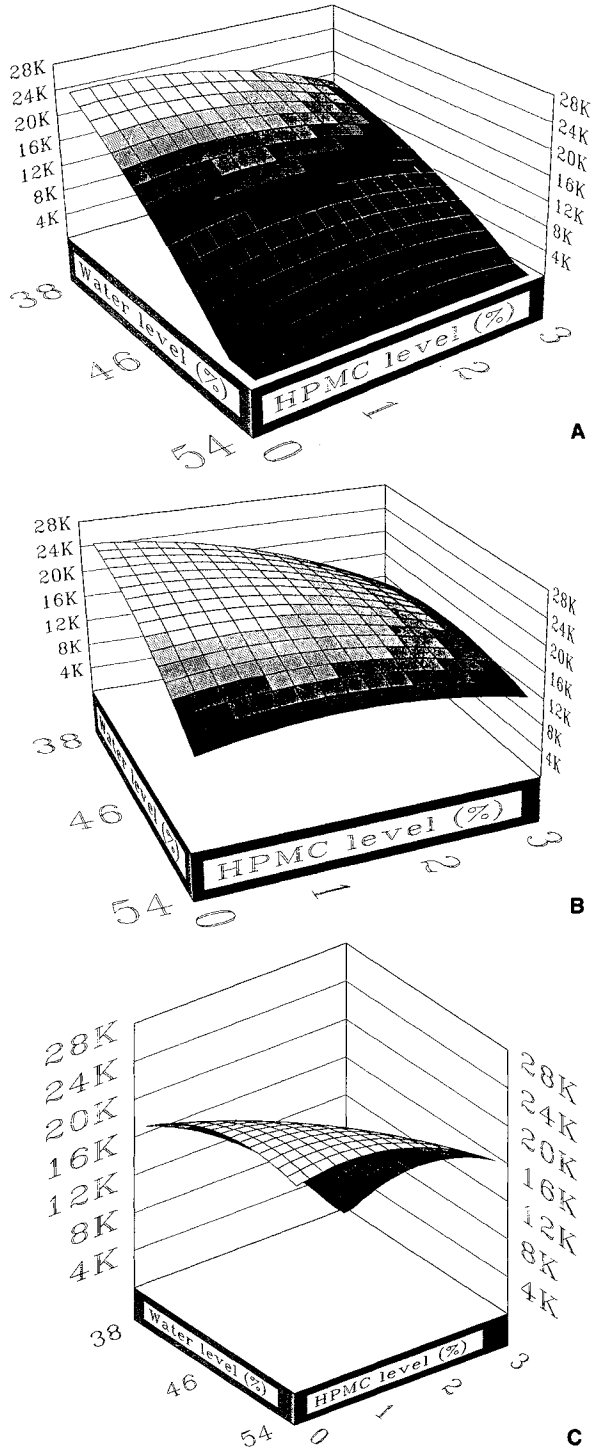

Fig. 6. Response surfaces of rheological yield value (Pa), (the Z-axis represents the response). 6A at 30% MCC, 6B at 50% MCC, and 6C at 70% MCC.

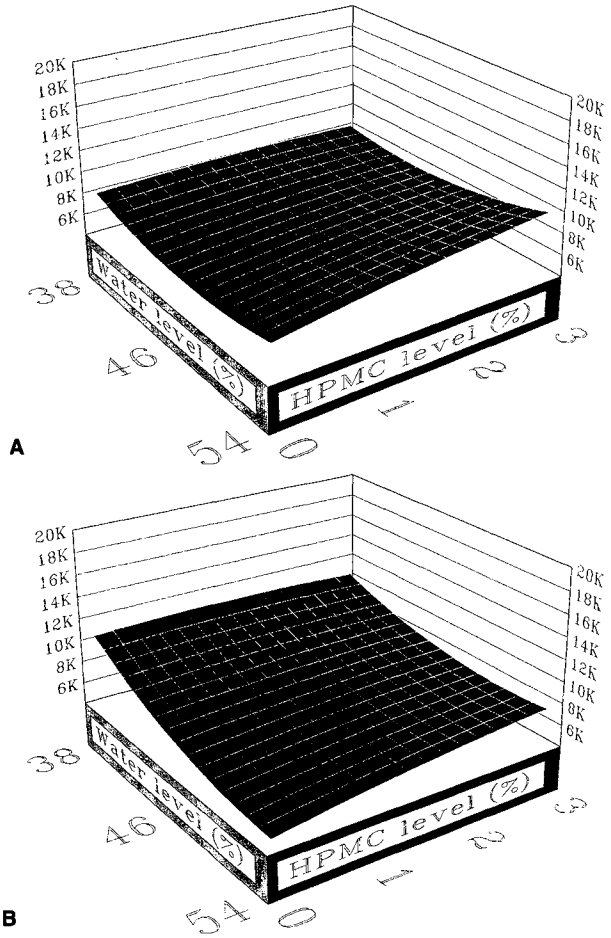

Fig. 7. Response surfaces of tensile strength (N/m^2), measured using the split-die system. 7A at 30% MCC and 7B at 50% MCC.

Corp., Newark, DE 19711) and hydroxypropylmethylcellulose [HPMC] (Pharmacoat grade 606, Lot no. 63-311, Shin-Etsu Chemical Co. Ltd, Tokyo, Japan) was used for this study. All wet masses were prepared in a planetary mixer (model A-200DT, Hobart Corp., Troy, OH 43276). The dry powders were first mixed for 2 min. The granulating liquid (water or binder solution) was added to the dry powder blend and wet massing was continued for 2 min. MCC and lactose were used as supplied. A 15% w/w solution of HPMC in water was prepared. Calculated amounts of this solution were used in the experiments.

X-STAT® (John Wiley & Sons, Inc., New York, NY) software was used to design experiments to study three formulation variables, viz., MCC (ratio of MCC to lactose), water and HPMC (binder) at different levels.

Preliminary experiments were performed to determine the appropriate range of the variables under study, which were found to be MCC level, 30 to 70%; water level, 38 to 54% (as % of total solids); HPMC level, 0 to 3% (also as % of total solids).

A central composite "Box-Behnken" design, was chosen for this study which requires fifteen experiments (Table 1). The yield value and tensile strength were measured for each of the fifteen experiments. Yield loci were obtained only for seven selected experiments.

A quadratic model was fitted to most variables studied, except for screen force and screen temperature where a linear model was sufficient with $r^2 > 90\%$. The regression equation was in turn used to generate response surfaces using the Perspective Junior™ (Three D Graphics, Palisades, CA 90272) software. A table of residuals was generated to check for any systematic deviation from the fit. Also, an analysis of variance (ANOVA) was performed on each of the dependent variables to quantify the usefulness of their regression equation (21).

RESULTS AND DISCUSSION

Rheological Yield Value

A typical rheogram (Fig. 1) shows that the wet mass system under study exhibited Non-newtonian plastic behavior with a characteristic yield value. It also revealed shear-thinning behavior as indicated by decreasing apparent viscosity with time. This observation is similar to that by Fielden *et al.* (9); however, there is an order of magnitude disagreement with their reported yield values. This discrepancy may be explained by the differences in methodology employed (ram extrusion vs. plate-plate rheometry). Within the experimental design the yield values showed an excellent reproducibility with %RSD < 2.5 in all cases.

Yield values generally decreased with increasing water levels (Fig. 6), except at 70% MCC and low water levels where the yield values decreased, especially at high binder

Table 2. Yield Locus Parameter Values

Run #	Cohesion (g/cm^2)	Angle of Internal Friction (°)	Apparent Tensile Strength (g/cm^2)	Unconfined Compressive Strength (g/cm^2)	Major Principle Compressive Stress (g/cm^2)	Relative Flow Index
A	14.6	39.0	18.0	61.1	165	2.71
D	18.4	29.1	33.1	61.2	134	2.20
G	16.9	29.3	30.2	57.9	127	2.19
H	12.9	30.6	21.8	46.3	122	2.63
J	15.6	31.7	25.2	55.8	133	2.39
K	34.1	15.9	119.7	90.3	114	1.26
M	12.1	35.0	17.3	46.5	140	3.02

levels (Fig. 6c). In this region of low water levels and high binder levels at a MCC level of 70%, there may be competition between HPMC and MCC for water. Since HPMC is a hydrophilic colloid undergoing a higher degree of hydration, association of water is greater with HPMC. As a result MCC is in a relatively drier, less cohesive state, which may explain the drop in yield value. At 30% MCC and 50–54% water levels, the regression equation actually predicts negative values (Fig. 6a). Since no physical significance can be attached to negative yield values, they have been forced to zero in this case. However, the low or negative yield values indicate that the wet mass system has reached a state beyond saturation (beyond the capillary state of granulation and into the suspension or droplet state (22)).

Tensile Strength

Tensile strength values increased with decreasing water levels (Fig. 7). This observation is contrary to the theoretical models, which predict tensile strength to increase with increasing water levels (23). A possible explanation suggested by Kristensen *et al.* (23) is that greater particle-particle contact and bonding are introduced during compression in the ram extruder. These interactions are expected to be greatest for the lower water level samples because they require greater extrusion forces.

Yield Locus

As is shown in Figure 5, the wet masses under study are cohesive bodies. For a stress condition below the yield locus there is elastic deformation. Unlimited plastic deformation will occur for all stress conditions on the yield locus. Stresses above the yield locus are not possible. This type of interpretation can help predict flow properties under any given condition.

The yield loci parameters of seven selected experiments are as shown in Table 2. Run# H was repeated twice and showed acceptable reproducibility with %RSD < 10 for all parameters. The data indicated that the system of wet masses was cohesive, as shown by the significant Y-intercepts. Although yield loci parameters were not capable of discriminating most formulation variables, since the parameter values did not show significant differences, they could detect over-wet granulations, such as Run# K. Compared to other samples, Run# K showed a higher cohesion value, and lower angle of internal friction value and relative flow index.

Extrusion/Spheronization

During extrusion, screen pressure and screen temperature were monitored, and a linear model was found to fit both sets of data well. The screen pressure response surfaces for the three levels of MCC were parallel to each other with 70% MCC the exhibiting highest extrusion pressures (Fig. 8). Screen temperature data showed a high degree of correlation (r^2 = 0.984) with screen pressure.

During the course of the experiment, it was found that run# H could not be practically extruded. The extruder is equipped with a slip clutch assembly which is set to a certain threshold torque beyond which it begins to slip. Thus, it acts as a safety mechanism and protects the motor from getting overloaded. With run# H, the slip clutch began to slip and extrusion had to be stopped. However, it was possible to record screen pressure and screen temperature during the short interval of time that extrusion was ongoing. Based on these data (screen pressure = 16470 kPa and screen temperature = 23°C) an upper threshold for successful extrusion can be proposed at 15000 kPa and 21.5°C. However, the utility of this threshold may be restricted to the levels of the process variables used in this study and also possibly to

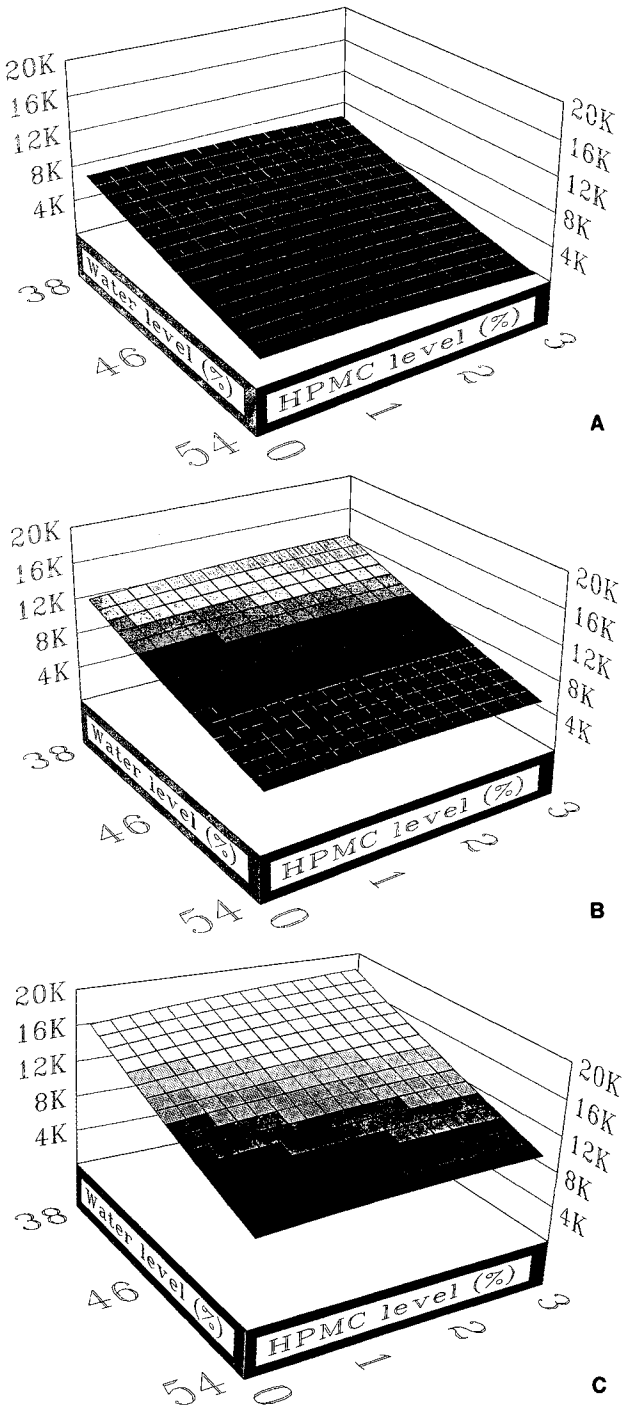

Fig. 8. Response surfaces of screen pressure (kPa). 8A at 30% MCC, 8B at 50% MCC, and 8C at 70% MCC.

MCC based systems. Within these restrictions, if the above upper thresholds are exceeded, then extrusion would be unsuccessful. Thus, objective measures of extrudability of formulations are now available. In the past, this problem had been addressed purely by subjective judgment (11,14,15,24–26).

With extruders that are not equipped with such safety mechanisms as slip clutch assemblies, damage to screens during extrusion of difficult formulations has been reported (27).

In general, the weight of the extrudates increased with increasing water levels (Fig. 9). This observation is in agreement with the predictions of theoretical models. Although relatively crude this method of analysis avoids the compression that occurs in sample preparation for the split-die assembly which forces particles to interact, thereby leading to unrealistically high values. It was observed that higher pressures in the screw extruder (EXDS-60) led to lower tensile strength based on extrudate weight. However, higher ram extrusion pressures used to load the split-die led to high tensile strength due to increased compression of the wet mass. Although both the EXDS-60 extruder and the ram extruder obviously apply pressure to the wet mass, the compression that occurs in the EXDS-60 is under comparatively less confined conditions. This could possibly explain the dif-

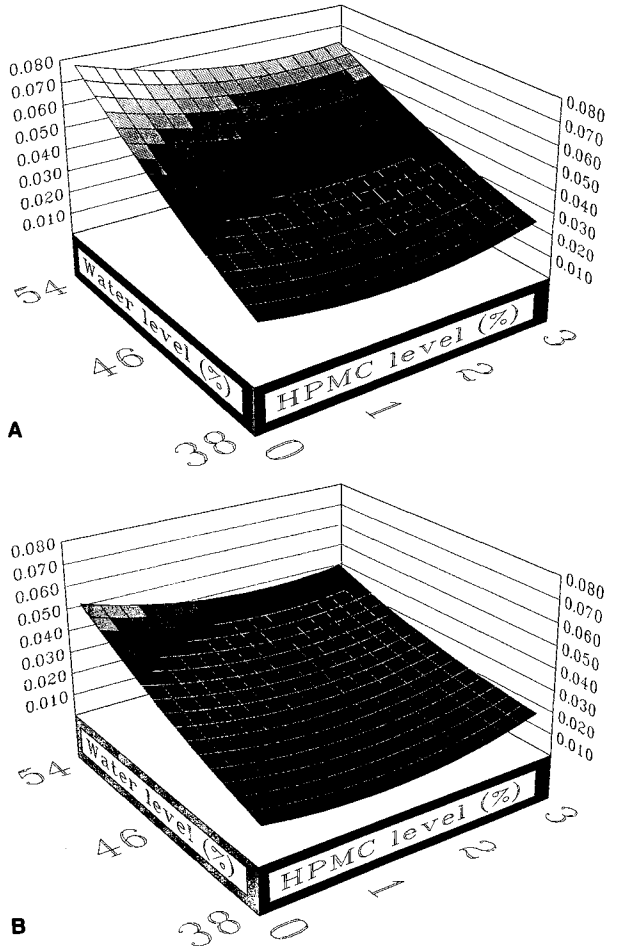

Fig. 9. Response surfaces of weight of extrudate (g). 9A at 30% MCC, and 9B at 70% MCC.

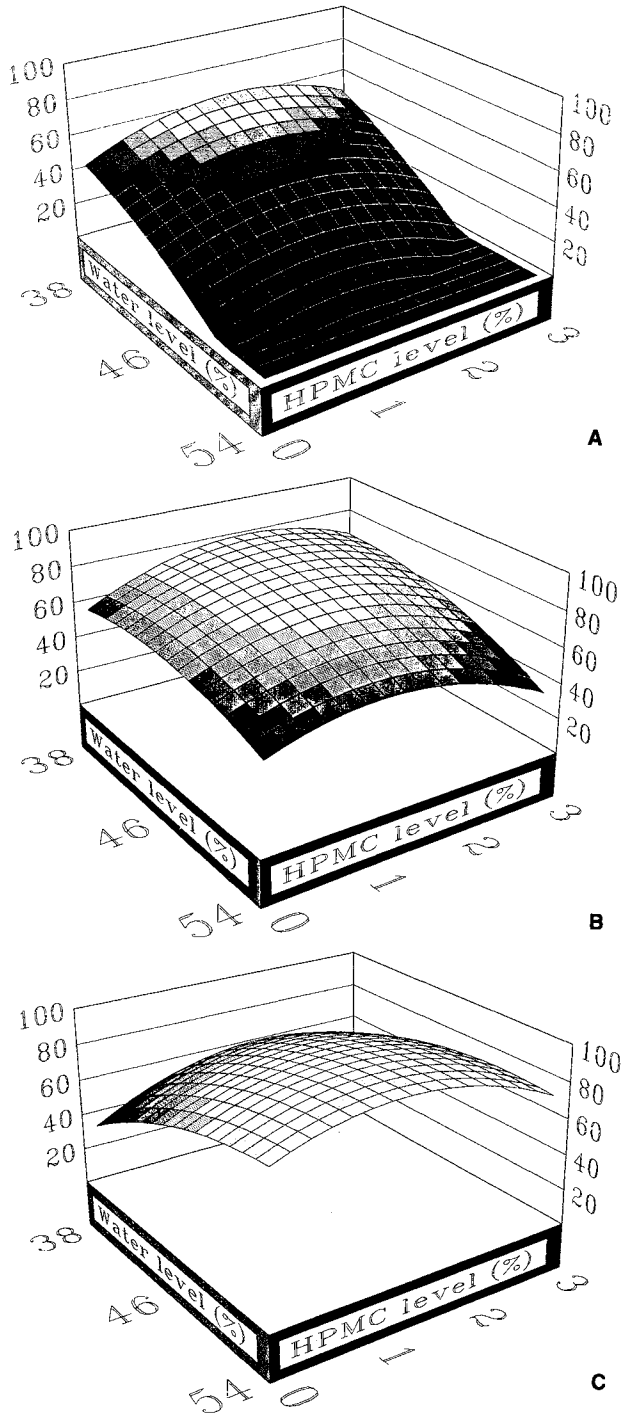

Fig. 10. Response surfaces of yield of 18/25 mesh cut (%) of dried pellets. 10A at 30% MCC, 10B at 50% MCC, and 10C at 70% MCC.

fering trends in tensile strength values obtained from split-die method and from extrudate weight.

The increase in the weight of extrudate for the three levels of MCC was not identical for a given increase in water level. At 30% MCC (Fig. 9a), there was a very rapid increase in weight of extrudate with water level compared to that at higher levels of MCC. Thus, at 30% MCC and high water levels the extrudates were in the form of long strands which did not break into small rods of uniform length during sphe-

ronization and were not processable. Also, at 70% MCC (Fig. 9b), and with decreasing water levels, the weight of extrudates decreased to a level where they were extremely friable and thus produced a comparatively high percentage of fines during spheronization.

Pellet Properties

Narrow particle size distribution and spherical shape are necessary for uniform application of coatings (28). High crushing strength and low friability are essential for withstanding the rigors of handling and coating of pellets. High bulk density may be required to fill pellets equivalent to the dose of the active in smallest possible capsule.

The response surfaces for yield of the 18/25 mesh cut showed that the local maxima for the three levels of MCC were different and reflect dependence on water level (Fig. 10). The local maxima for the yield of 18/25 mesh cut at 30% MCC (Fig. 10a) was observed at 38% water. Upon increasing the MCC level to 70% (Fig. 10c), the local maxima for the yield of 18/25 mesh cut had shifted to 54% water. At 50% MCC (Fig. 10b), the local maxima was noticed at 44% water. At 30% MCC, the regression equation predicted a negative yield of 18/25 mesh cut at water levels >50%, indicating that the masses in that region were overwet and could not be spheronized. Since no physical meaning can be attached to negative yield of 18/25 mesh cut, those values have been forced to zero (Fig. 10a).

Broad similarities were found in the shape of the response surfaces when either the rheological yield value (Fig. 6) or the yield of 18/25 mesh cut (Fig. 10) were compared with the formulation variables. One major exception was at 70% MCC, 3% HPMC and low water levels, where the regression equation predicted negative yield values but much higher values for yield of 18/25 mesh cut. The regions of high values of both these variables coincide, indicating that high rheological yield value is an important criteria for making spheres with narrow size distribution.

Formulations with higher water levels produced denser pellets (Table 3). The increase in bulk density with water level was most rapid at 70% MCC compared to lower levels of MCC.

From the trend exhibited by the crushing strength data (Table 3), an interesting observation was made in that at any particular water level and MCC level, the plot of crushing strength vs. HPMC level was concave with a minimum around 1.5% HPMC in all cases. As previously discussed, with increasing binder level, the system may be more influenced by HPMC than MCC. At low binder levels (close to 0%), water may be available to interact (hydrate) with MCC, resulting in higher crushing strength. With increasing binder, there may be competition between MCC and HPMC for water. At 1.5% HPMC, not enough binder may be available to influence the system, whereas at higher binder levels (close to 3%), it may form the bonds or linkages resulting in higher crushing strength.

The crushing strength is also related to the bulk density of the pellets. A comparison of the response surfaces reveals that higher bulk density is related to higher crushing strengths in most cases.

In most cases the spheres exhibited low friability (Table 3) and seemed likely to satisfactorily withstand packaging or coating operations. Run# H was an exception, with a very high friability of 2.79%. This formulation also showed a very low weight of extrudate and produced a large amount of fines in the sieve analysis of the dried pellets. All of these factors seem to be related to low water level in the formulation.

The response surfaces for pellet shape factor showed that, in general, more nearly spherical pellets (i.e., higher shape factors) were obtained at the lower levels of MCC (Fig. 11). At 30% MCC (Fig. 11a), and a given water level the shape factor increased with increasing binder levels. The regions of high values for shape factor and for yield of 18/25 mesh cut are not identical, indicating that the rheological requirements for the two may be different.

In general, formulations with lower yield values for the wet mass resulted in more spherical pellets. During spheronization, the forces exerted on the extrudates must exceed this yield value for it to be deformed into a sphere. Thus, for

Table 3. Pellet Properties of 18/20 Mesh Cut

Run #	Bulk Density (g/ml)	Crushing Strength mean (SD) (g)	Shape Factor mean (SD)	Friability (%)
A	0.774	935 (91)	0.88 (0.03)	0.138
B	0.816	770 (93)	0.88 (0.03)	0.314
C	0.793	1328 (59)	0.85 (0.05)	0.058
D	0.863	1800 (140)	0.90 (0.02)	0.082
E	0.782	845 (74)	0.87 (0.07)	0.125
F	0.777	961 (60)	0.88 (0.03)	0.156
G	0.710	1131 (165)	0.84 (0.05)	0.534
H	0.631	451 (68)	0.82 (0.06)	2.796
I	0.780	809 (90)	0.89 (0.02)	0.129
J	0.760	1055 (96)	0.84 (0.05)	0.399
K	0.763	725 (96)	0.86 (0.05)	0.242
L	0.859	1250 (98)	0.86 (0.06)	0.576
M	0.834	1556 (135)	0.90 (0.01)	0.053
N	0.784	1429 (159)	0.83 (0.05)	0.515
O	0.759	1023 (97)	0.84 (0.05)	0.227

SD = standard deviation.

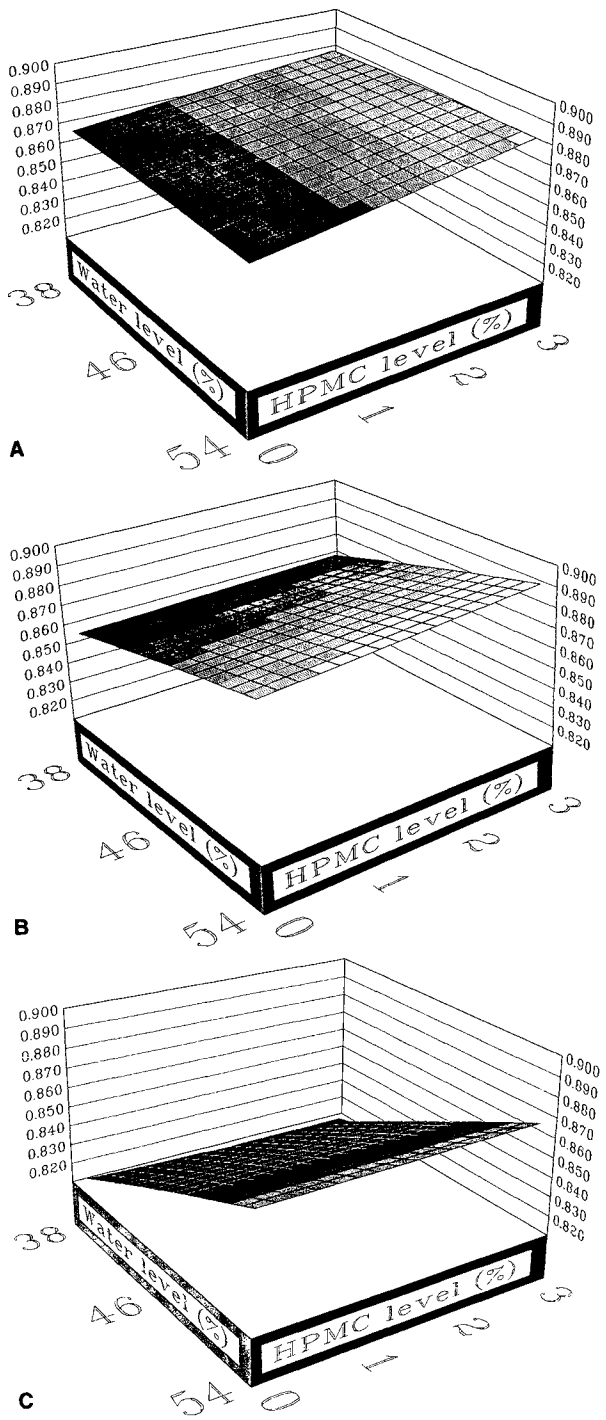

Fig. 11. Response surfaces of shape factor of 18/20 mesh cut dried pellets. A shape factor value of "1" indicates a perfect circle. 11A at 30% MCC, 11B at 50% MCC, and 11C at 70% MCC.

systems with lower yield value, this deformation is more likely and may explain the higher shape factor values for such systems. The only major exception was in the region of 70% MCC (Fig. 11c), low water level and high binder level, where lower yield values seems to correspond to low shape factor values. This indicates that other rheological criteria may be necessary to predict the shape of the pellets.

A multiple regression was performed using a statistical

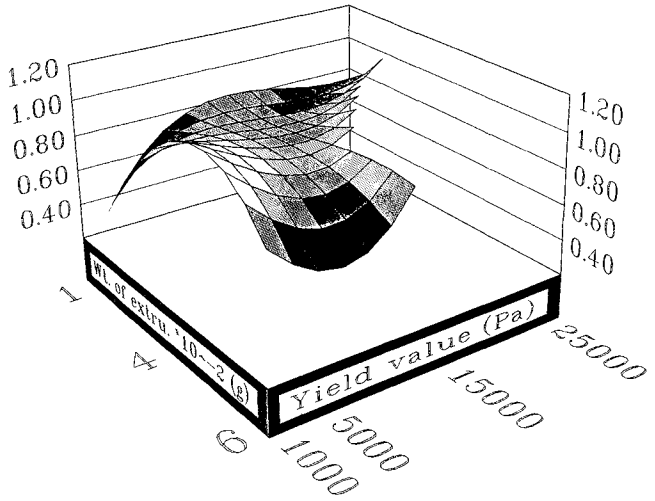

Fig. 12. Relationship between yield value (Pa), weight of extrudate (g), and shape factor. A shape factor value of "1" indicates a perfect circle.

software program (PC-SAS, ver. 6.03, SAS Institute Inc., Cary, NC 27512) in an attempt to relate weight of extrudate (representing tensile strength of the extrudate) and yield value to shape factor. Although yield value and weight of extrudate are properties dependent on the wet mass formulation, the above analysis was performed to establish the effect of these properties on the shape factor. The model generated from the regression (r^2 = 0.891) was used to produce a 3D plot of these variables (Fig. 12). This plot clearly describes the combination of rheological properties necessary to manufacture pellets with high values of shape factor. For example, the combination of rheological properties (in Fig. 12), extending from yield value of 6,000 to 11,000 Pa and weight of extrudate from 0.028 to 0.052 g, is expected to produce pellets with shape >0.85.

Statistical Analysis

Having identified the rheological criteria (i.e., yield value, tensile strength, etc.) influencing shape and yield of 18/25 mesh pellets, PC-SAS software was again used to further analyze the data. A multiple stepwise regression with second order interaction terms was performed with independent variables (X1 = screen pressure, X2 = screen temperature, X3 = weight of extrudate, X4 = yield value, and X5 = tensile strength from split-die method) vs. each of the two dependent variables (Y1 = yield of 18/25 mesh cut, and Y2 = shape factor). The independent variables in a stricter sense are derived from the formulation variables. Hence, it is possible that covariance between the former variables contributes to the outcome, i.e., yield of 18/25 mesh cut and shape factor. However, for the sake of simplicity, this contribution was discounted in the present analyses.

A correlation coefficient (r^2) >0.97 was observed in both the analyses. The general procedure for stepwise regression always included all the first order terms, and then the second order terms were entered at a significance level of at least 0.100. The terms were entered or removed in a stepwise manner to optimize the correlation coefficient. After building the model, the residual values were examined to

ensure their random distribution. The stepwise regression models for Y1 and Y2 are shown in Tables 4 and 5, respectively.

The regression model for yield of 18/25 mesh cut indicates that X1 (F = 55.15) and $X1^2$ (F = 42.85) have the maximum influence on Y1. This observation further confirms the results seen earlier (18) that screen pressure can be used to optimize the yield of the given size fraction of the pellets.

The shape factor regression model reveals the greater influence of X3, X4 and X5, and also of interaction between X3–X4 and X3–X5. The coefficient values indicate that increases in the weight of extrudate, yield value, and tensile strength have a negative influence on the shape factor. The results increase the significance of Figure 12, which provides the combination of yield value and weight of extrudate required to produce more spherical pellets.

Though not possible to mathematically define precisely from the present experimental design, it is apparent that there is a critical range of rheological variables within which pellets are produced which meet the criteria of yield of 18/25 mesh cut >60%, shape factor > 0.85, and friability < 0.75%. Though subjective, these criteria do represent pellets of a highly desirable quality. This critical range (Table 6) may be defined as the rheological "window" within which both extrusion and spheronization can be carried out satisfactorily, based on the aforementioned criteria. However, this "window" may be specific to the levels of the process variables used in this study. Within this window, the process variables can be optimized to further improve the quality of the pellets.

Many more experiments need to be performed to confirm the universal applicability of this rheological "window". However, a partial validation was achieved in an experiment with 100% MCC and 110% water (as percentage of solids). This system was treated in a manner similar to the fifteen experimental runs mentioned earlier. The results are presented in Table 7.

As can be seen, the data certainly supports the claim for the rheological "window." The existence of such a "window" makes possible the ability to make objective decisions about formulations in the extrusion/spheronization process.

Table 4. Stepwise Regression Model for Yield of 18/25 Mesh Cut (%), r^2 = 0.973

	DF	SS	MS	F	Prob > F
Reg.	6	12570.0	2095.0	48.21	0.0001
Error	8	347.6	43.4		
Total	14	12917.6			
Variable	Parameter estimate	Std. error	SS	F	Prob > F
Intercept	−127.96	34.3	605.5	13.93	0.0058
X1	0.04621	0.0	2396.2	55.15	0.0001
X2	−3.1500	2.7	57.7	1.33	0.2822
X3	143.427	372.5	6.4	0.15	0.7103
X4	−0.0013	0.0	155.3	3.58	0.0953
X5	0.00240	0.0	261.5	6.02	0.0397
$X1^2$	−0.0000	0.0	1861.9	42.85	0.0002

DF, degrees of freedom; SS, sum of squares; MS, mean sum of squares; F, F-value for testing the hypothesis that all parameters are zero except for the intercept; Prob > F, probability of getting a greater F statistic than that observed if the hypothesis is true; Reg., Regression; X1, screen pressure; X2, screen temperature; X3, weight of extrudate; X4, yield value; X5, tensile strength from split-die method; Y1, yield of 18/25 mesh cut.

Table 5. Stepwise Regression Model for Shape Factor, r^2 = 0.973

	DF	SS	MS	F	Prob > F
Reg.	8	0.00759	0.0009	26.86	0.0004
Error	6	0.00021	0.0000		
Total	14	0.00780			
Variable	Parameter estimate	Std error	SS	F	Prob > F
Intercept	1.12899	0.109	0.0038	107.72	0.0001
X1	0.00000	0.000	0.0000	1.66	0.2445
X2	−0.0066	0.003	0.0002	5.95	0.0505
X3	−6.4203	1.908	0.0004	11.33	0.0151
X4	−0.0000	0.000	0.0002	4.46	0.0791
X5	−0.0000	0.000	0.0004	11.62	0.0143
$X4^2$	0.00000	0.000	0.0001	4.24	0.0851
X3 * X4	0.00034	0.000	0.0002	6.62	0.0422
X3 * X5	0.00040	0.000	0.0010	27.10	0.0020

Y2, shape factor.

CONCLUSIONS

There has been a tendency in the literature to concentrate on the influence of process variables on pellet formation. As a result, guidelines were already available on how to manipulate the process variables to obtain the optimum quality of the pellets. The goal of this study has been the identification and development of techniques to measure rheological properties responsible for successful extrusion and spheronization.

Previously described instrumentation (18) was used to measure screen pressure. Techniques were developed to measure three properties of the wet mass, viz., yield value, tensile strength, and yield loci. While none of the existing rheological models could be fitted, the rheogram did show a characteristic yield point. During spheronization, the stresses applied must exceed this yield value for the extrudate to be deformed into a sphere. The tensile strength measurements using the split-die method exhibited a trend of increasing values with decreasing water levels, which is contrary to the theoretical models. However, the weight of the extrudate could be used as an indicator of relative tensile

Table 6. Rheological "Window" for Successful Extrusion and Spheronization

Variable	Values
Screen Pressure	6,000 to 11,000 kPa
Screen Temperature Increase	7 to 15°C
Weight of Extrudate	0.016 to 0.022 g
Yield Value	20 to 24 kPa
Tensile Strength	6,000 to 12,000 N/m^2
Cohesion	<20 g/cm^2
Angle of Internal Friction	>25°

Table 7. Validation of the Rheological "Window"

Rheological Variables		Pellet Variables	
Screen Pressure	7936 kPa	Yield of 18/25 Mesh Cut	87.1%
Screen Temperature Increase	14°C	Shape Factor	0.87
Weight of Extrudate	0.024 g	Friability	0.125%
Yield Value	20990 Pa	Bulk Density	0.833 g/ml
Tensile Strength	7908 N/m^2	Crushing Strength	2585 g

strength and exhibited a trend in agreement with the theoretical models. The yield loci indicated that the system of wet masses is cohesive.

A statistical experimental design was adopted to study the relationship of the above mentioned rheological/mechanical variables and finished pellets characteristics with the formulation variables of the overall extrusion/spheronization process. The results supported an upper threshold of screen pressure (15,000 kPa), beyond which successful extrusion is not possible. Such a threshold could be used to prevent damage to the screens or the dies during extrusion. In addition, screen pressure provided an objective measure of the extrudability of a given formulation. In many instances, formulations having lower yield values produced pellets having greater sphericity. However, a combination of yield value and weight of extrudate is required (as shown in Fig. 12) to predict the shape of the pellets.

Also, the rheological/mechanical properties were related to the finished pellet characteristics with an empirical model. It was observed that the yield of 18/25 mesh cut was most influenced by the screen pressure, and that the shape factor was most influenced by yield value and tensile strength and interactions between these properties.

It was apparent that there was a critical range of rheological/mechanical variables within which pellets having desirable criteria such as a yield of 18/25 mesh cut >60%, a shape factor >0.85, etc., can be prepared. For the formulations studied, this critical range was defined as a rheological "window" (Table 6) within which both extrusion and spheronization can be carried out satisfactorily. With the definition of a rheological "window" of such variables, an approach is now available to guide formulators and facilitate the systematic design and development of pellet dosage forms.

ACKNOWLEDGMENT

Dr. Ir. I. Peschl, Institute for Powder Technology, Rugenparkstrasse 13, CH-3800 Interlaken, Switzerland, for performing the shear cell analysis of the wet masses.

REFERENCES

1. J. M. Newton. The preparation of spherical granules by extrusion/spheronization. *S.T.P. Pharma.* 6, 396–398 (1990).
2. C. W. Woodruff and N. O. Nuessle. Effect of processing variables on particles obtained by extrusion-spheronization processing. *J. Pharm. Sci.* 61, 787–790 (1972).
3. H. J. Malinowski and W. E. Smith. Use of factorial design to evaluate granulations prepared by spheronization. *J. Pharm. Sci.* 64, 1688–1692 (1975).
4. H. J. Malinowski and W. E. Smith. Effects of spheronization process variables on selected table properties, *J. Pharm. Sci.* 63, 285–288 (1974).
5. I. M. Jalal, H. J. Malinowski, and W. E. Smith. Tablet granulations composed of spherical-shaped particles. *J. Pharm. Sci.* 61, 1466–1468 (1972).
6. M. Chariot, J. Frances, G. A. Lewis, D. Mathieu, R. Phan Tan Luu, and H. N. E. Stevens. A factorial approach to process variables of extrusion-spheronization of wet powder masses. *Drug Dev. Ind. Pharm.*, 13, 1639–1649 (1987).
7. P. J. Harrison, J. M. Newton, and R. C. Rowe. The characterization of wet powder masses suitable for extrusion/spheronization. *J. Pharm. Pharmacol.* 37, 686–691 (1985).
8. P. J. Harrison. Extrusion of wet powder masses. Ph.D. Dissertation, University of London, Chelsea College (1982).
9. K. E. Fielden, J. M. Newton, and R. C. Rowe. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. *J. Pharm. Pharmacol.* 41, 217–221 (1989).
10. I. Ghebre-Sellassie. *Pharmaceutical Pelletization Technology.* Marcel Dekker, New York, NY, 1989.
11. R. E. O'Connor, J. Holinej, and J. B. Schwartz. Spheronization I: processing and evaluation of spheres prepared from commercially available excipients. *Am. J. Pharm.* 156, 80–87 (1984).
12. R. C. Rowe and G. R. Sadeghnejad. The rheology of microcrystalline cellulose powder/water mixes–measurement using a mixer torque rheometer. *Int. J. Pharm.* 38, 227–229 (1987).
13. K. E. Fielden, J. M. Newton, P. O'Brien and R. C. Rowe. Thermal studies on the interaction of water and microcrystalline cellulose. *J. Pharm. Pharmacol.* 40, 674–678 (1988).
14. G. Zhang, J. B. Schwartz, and R. L. Schnaare. Effect of spheronization technique on drug release from uncoated beads. *Drug Dev. Ind. Pharm.* 16, 1171–1184 (1990).
15. G. P. Millili and J. B. Schwartz. The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures. *Drug Dev. Ind. Pharm.* 16, 1411–1426 (1990).
16. G. P. Millili, R. J. Wignet, and J. B. Schwartz. Autohesion in pharmaceutical solids. *Drug Dev. Ind. Pharm.* 16, 2383–2407 (1990).
17. I. A. S. Z. Peschl. Measurement and evaluation of mechanical properties of powders. *Powder Handling & Processing.* 1, 135–141 (1989).
18. R. D. Shah, M. Kabadi, D. G. Pope, and L. L. Augsburger. Physico-mechanical characterization of the extrusion-spheronization process; Part-I: Instrumentation of the extruder. *Pharm. Res.* 11, 355–360 (1994).
19. H. Schubert. Tensile strength of agglomerates. *Powder Tech.*, 11, 107–119 (1975).
20. K. B. Shah, L. L. Augsburger, and K. Marshall. An investigation of some factors influencing plug formation and fill weight in a dosing disk-type automatic capsule-filling machine. *J. Pharm. Sci.*, 75, 291–296 (1986).
21. J. S. Murray, Jr. *X-STAT software manual.* John Wiley & Sons, Inc., New York, NY.
22. C. G. Barlow. The granulation of powders. *Chem. Engr.* No. 220, CE196–CE201 (1968).
23. H. G. Kristensen, P. Holm, and T. Schaefer. Mechanical properties of moist agglomerates in relation to granulation mecha-

nisms; Part I. Deformability of moist, densified agglomerates. *Powder Tech.* 44, 227–237 (1985).
24. M. J. Gamlen and C. Eardley. Continuous extrusion using a Baker Perkins MP50 (Multipurpose) extruder. *Drug Dev. Ind. Pharm.* 12, 1701–1713 (1986).
25. N.-O. Lindberg, C. Tufvesson and L. Olbjer. Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50 D. *Drug. Dev. Ind. Pharm.* 13, 1891–1913 (1987).
26. K. Lovgren. Disintegrants and fillers in the manufacture of spheres, their influence on dissolution rates and binding properties. *Labo-Pharma-Probl. Tech.* 32, 110–114 (1984).
27. U. Shah, unpublished results.
28. K. Lovgren and P. J. Lundberg. Determination of sphericity of pellets prepared by extrusion/spheronization and the impact of some process parameters. *Drug Dev. Ind. Pharm.* 15, 2375–2392 (1989).