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EFFECTS OF CHANGES IN ROLLER COMPACTOR PARAMETERS ON GRANULATIONS PRODUCED BY COMPACTION

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ABSTRACT

A Chilsonator (Model L-83, The Fitzpatrick Company, Elmhurst, IL) was studied to gain a better understanding of how compactor parameters influence product characteristics. The materials chosen for this study were Avicel PH 101, hydrous lactose and an acetaminophen blend. The blend consisted of 20% Avicel PH 101, 20% hydrous lactose and 60% acetaminophen crystals. The compactor parameters studied were the roll speed, horizontal feed speed and vertical feed speed. Various combinations of high, medium and low levels of these compactor parameters were tested. The system was modeled using a quadratic regression model. Changes in particle size distribution and

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recompressibility of the roller compacted granulations were used to monitor the effects of the changes in compactor parameter levels. The models differed for each of the materials evaluated. The response surface plots produced using the models helped in predicting the compactor parameter levels which would produce granulations with the necessary physical characteristics for successful tablet production.

INTRODUCTION

Dry granulation using roller compaction is a continuous process which offers better control of the pressure and dwell time than the batch slugging process. Roller compaction has been used to densify and granulate many pharmaceutical materials such as aspirin and vitamin formulations.(1) Roller compaction has also been used to densify material for capsule fill. The pharmaceutical literature has few references on roller compaction.(2,3) The pharmaceutical formulator who chooses roller compaction must rely on previous experience or the recommendations of the compaction system manufacturer to determine compactor parameter settings.

The use of roller compaction for the densification and granulation of materials in other fields is widely published. Johanson (4,5,6,7,8) did extensive research on the design of roller compaction systems. He determined several equations to predict compactor parameter settings and compactor design. These equations utilized the roller compactor dimensions and material characteristics to determine the best compactor parameter settings. By using simple bench scale tests described by Johanson, it was anticipated that compactor parameter settings for producing optimal granulations could be obtained. These calculations did not define the levels for all independent parameters of the roller compaction system. The goal of this study was to develop a statistical model that would enable the prediction of the undefined compactor parameter levels.

MATERIALS AND METHODS

Materials

The materials used in this study were Avicel PH 101, hydrous lactose (impalpable grade) and acetaminophen crystals. All materials were used as obtained from the manufacturer. The acetaminophen crystals were blended with 20% Avicel PH 101 and 20% hydrous lactose for 10 minutes in a twin shell blender with an intensifier bar.

Methods

The independent variables used in the model were the roll speed, horizontal feed speed and vertical feed speed. A high, medium and low level of each variable was chosen to study the entire range of levels available. These levels would differ for each material evaluated and with the settings of the other compactor parameters. For the Fitzpatrick Model L-83 Chilsonator, the roll speeds ranged from 4 to 15 RPM. The levels chosen for this study were 4, 8, and 12 RPM.

The horizontal and vertical feed screw settings had a potentiometer range of 0 to 3 in units of tenths. It was not possible to use all settings for all materials. In most cases the lower settings did not produce compact strong enough to remain intact in the collection system. At some of the very lowest potentiometer settings material is not moved through the feed system. A minimum setting of 0.65 for the horizontal feed screw and 0.30 for the vertical feed screw were necessary to produce initial material movement. At some of the highest settings the automatic override system of the Model L-83 Chilsonator would cause feed system shutdown. A method was designed to experimentally determine the limits of the feed system.

In the first phase of the experiment the horizontal and vertical feed screws were set at the same potentiometer settings. The roll speed setting was held constant throughout the experiment. The rolls were started and the potentiometer settings increased by increments of two tenths until compact which survived collection in a receiver was formed. This setting was used as the lower level of the feed settings. Feed settings were increased further until shutdown of the system or visibly overcompacted material was produced. The last setting tested before shutdown or overcompaction was the upper limit for the feed settings.

In the second phase of the experiment one of the feed screws was set at a constant setting. This constant setting was either the upper or lower setting determined in the first phase of the experiment. The other feed screw was varied to determine an upper and lower setting. A plot of the results of this experiment can be seen in Figure 1. The plot shows the factor space in which experiments can be conducted for a particular material at a particular roll speed.

For the statistical study three horizontal and vertical feed levels were chosen from the factor space plot for a material at each roll speed. Nine combinations of feed variables were tested at each roll speed. For each material 27 combinations of the three independent variables were tested. These 27 combinations were randomly assigned to three different experimental days. The compact was milled the day after production. The milling conditions were the same for all materials in this study. A Fitzmill with knives forward was used to mill compact which was

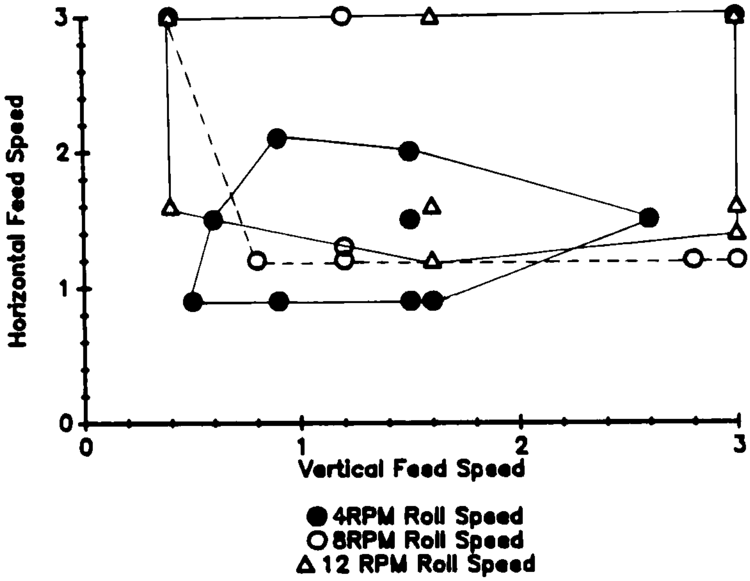

Figure 1.
Example plot of data obtained from feed speed experiment for hydrous lactose at all roll speeds tested.

broken by hand before milling. The screen size used was 4 openings per inch of screen surface.

For this study the two granulation characteristics chosen as dependent variables were the particle size distribution and the recompressibility. The particle size distribution was determined using sieve analysis. Five 100gm samples were tested for each batch of roller compacted granulation. The sieve sizes used are listed in Table I. The sieve time used was six minutes for each sample. The data obtained were evaluated using a particle size analysis program based on a log-probability plot of the data (WTREG,

Table I

Sieve sizes used in particle size distribution analyses.

U.S. Standard Sieves	Opening Size(microns)
16	1190
20	840
30	590
40	420
50	297
100	149
140	105
170	88
230	62
270	53

Purdue Research Foundation, West Lafayette, IN). The geometric mean particle size for the roller compacted granulation was determined and used to monitor the effects of the compaction conditions on the granulation size distribution.

The second granulation characteristic evaluated was the compressibility or K value. Compacts of the material to be tested were produced at various pressures on a motorized hydraulic press. Table II lists the compression pressures used for this experiment. Three compacts were produced at each pressure tested. The compacts were weighed and measured to obtain a calculated density. This density was plotted versus the compression pressure on a log-log scale. Figure 2 illustrates the plots obtained for

Table II.

Compression pressures used to determine compressibility of granulations produced by compaction.

Gauge Pressure(psi)	Punch Face Pressure(psi) 1 Inch Punch	1/2 Inch Punch
1000	1274	5096
1500	1911	7644
2000	2548	10192
2500	3185	12740
3000	3822	15288
3500	4459	17836
4000	5096	20834
4500	5733	22932
5000	6370	25480
6000	7644	30576
7000	8918	35672
8000	10192	40768
10000	12740	50960

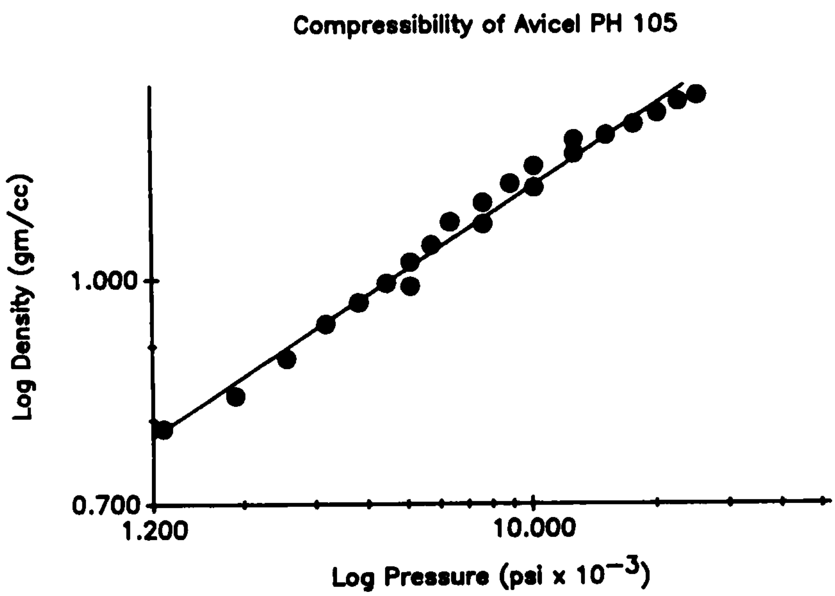

Figure 2.
Example plot of compressibility data.

these data. The compressibility was the inverse of the slope of the straight line that can be fit to the data using the least squares method. (8) This characteristic was used to evaluate changes in the recompressibility of the roller compacted granulations.

RESULTS AND DISCUSSION

The effects of changes in granulation characteristics due to changes in compactor parameter settings were described using the quadratic regression model in equation 1.

$$Y = BH+BV+BR+BH^2+BV^2+BR^2+BHV+BHR+BVR+E \qquad \text{Eqn. 1}$$

Student t-tests were conducted for each variable in the model and a reduced model containing only the significant variables was determined for each material. The testing of the data was done using the SAS package (SAS, Version 6, SAS Institute, Cary, N.C.). The models were also plotted to enable prediction of compactor parameter settings which produced granulations with good tableting characteristics.

Equations 2 and 3 show the significant factors in the reduced models for Avicel PH 101.

$$K = 2.31 + 8.11H - 0.89R + 0.08R^2 - 0.65HR \qquad \text{Eqn. 2}$$

$$Geo = -248.38+1609.56H-187.55R+16.15R^2-120.54HR \qquad \text{Eqn. 3}$$

For Avicel PH 101 the reduced models for both compressibility (K) and geometric mean particle size

(Geo) contained the same significant factors. The horizontal feed speed and roll speed had the greatest effects on the changes in the granulation characteristics. The horizontal feed screw metered the flow of materials to the rolls. By controlling the amount of material between the rolls, the horizontal feed screw controlled the roll gap and the pressure or compacting force produced by the hydraulic system to overcome the roll separation. Roll speed controlled the dwell time of the material in the compaction area. For Avicel and other plastically deforming materials the dwell time has been shown to have a significant influence on the type and extent of binding. In previous studies of slugging when Avicel was compressed with too short a dwell time more brittle fragmentation behavior was seen. (9,10) Other factors of importance in this reduced model included the interaction of the horizontal feed speed and the roll speed.

Figure 3 is the graphical representation of the reduced models for Avicel PH 101. Although the reduced models for geometric mean particle size and compressibility were similar, the response surfaces had a different appearance. There was a minimum horizontal feed speed setting which produced a change in the geometric mean particle size. This was due to both the minimum value of the horizontal feed speed which produced material movement and the fact that a certain

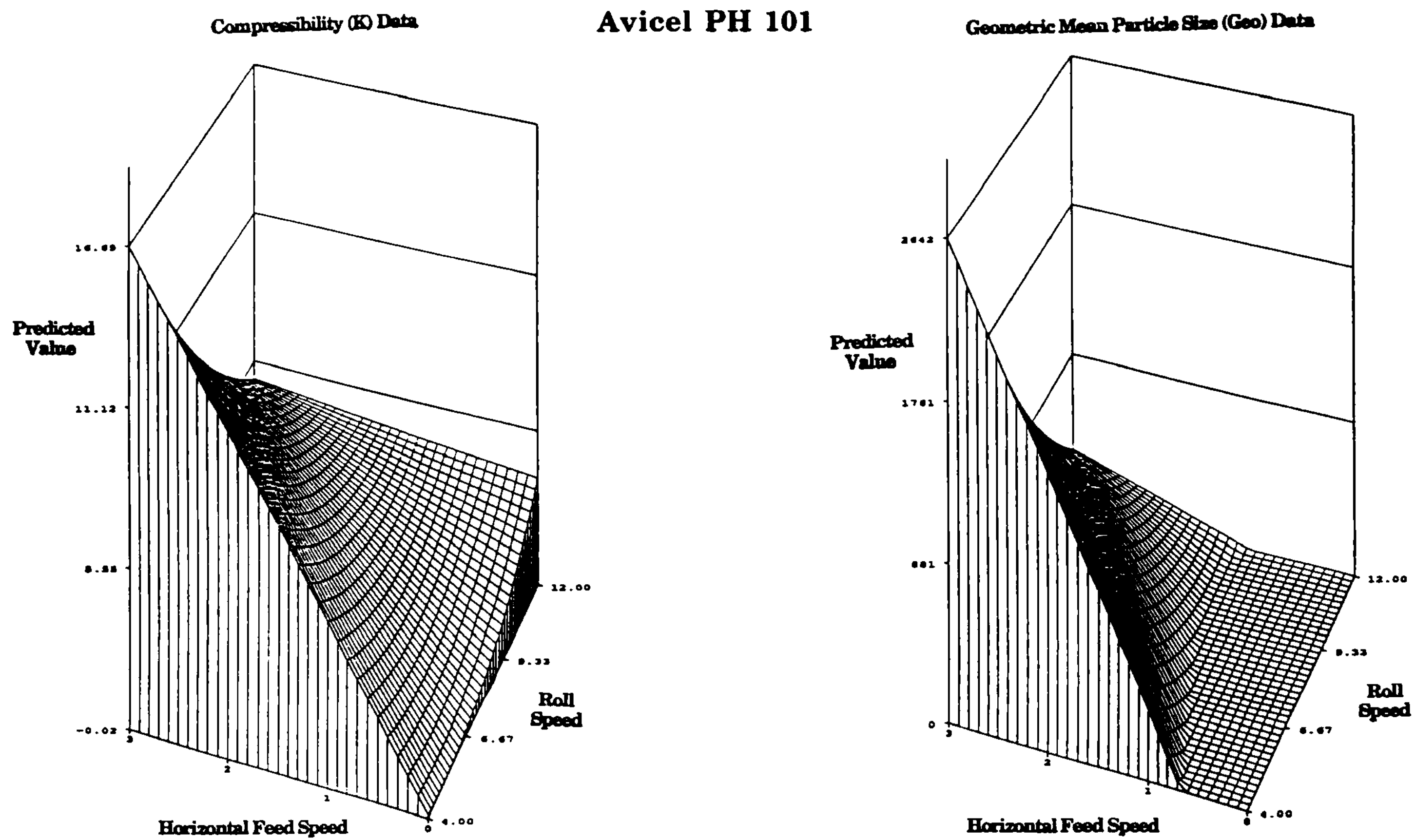

Figure 3. Plots of the models for compressibility and geometric mean particle size data for Avicel PH 101

amount of material had to be in the compaction area to cause roll movement and produce a response from the hydraulic system. The plots for the compressibility changes showed no minimum values. Overall the vertical feed speed had no statistically significant effects and was not included in the models for Avicel PH 101.

The reduced models for compressibility and geometric mean particle size for hydrous lactose did not contain the same significant factors. Equations 4 and 5 show the reduced models obtained for hydrous lactose.

$$K = 20.51+7.16H-1.68V-2.04R-1.25\ H^2+1.01V^2 + 0.11R^2 - 0.73\ HV \qquad \text{Eqn. 4}$$

$$Geo=378.92-49.33H-53.02V+19.26R-21.57H^2 + 16.46V^2 - 3.58R^2 + 17.37\ HR \qquad \text{Eqn. 5}$$

In the lactose models all three compactor parameters had some effect on the changes in granulation characteristics. The compressibility was influenced by the interaction of the horizontal feed speed with the vertical feed speed. The vertical feed speed determined the densification of the material before compaction. The density of the materials between the rolls as well as the roll separation influenced the compaction conditions for this material. The geometric mean particle size changes showed a greater influence of the roll speed settings than the compressibility changes. The significant interaction term in this reduced model was that of the horizontal feed speed with the roll speed. Lactose has been reported to deform by both brittle fracture and plastic deformation. (10) The dwell time influence indicates that the plastic deformation characteristics had an effect on the particle size changes in the granulations produced.

The plots of the reduced models for hydrous lactose are shown in Figures 4 and 5. The shape of the response surfaces for compressibility and geometric mean particle size were similar. The geometric mean particle size plots, however, showed a shift of the maximum of the response surface along the horizontal feed speed axis with increasing roll speed. This shift was due to the significant interaction of the horizontal feed speed with the roll speed as described by the model.

The reduced model for the acetaminophen blend is described by equation 6.

$$K = 15.69+1.57H -1.18V-0.53R-2.41H^2-0.12R^2 + 1.01\,HR + 0.75HV \qquad \text{Eqn.6}$$

For the acetaminophen blend only one response variable could be modeled. All three compactor parameters had a significant effect on the changes in the compressibility factor. The horizontal feed speed-roll speed and horizontal feed speed-vertical feed speed interactions were again significant. Acetaminophen

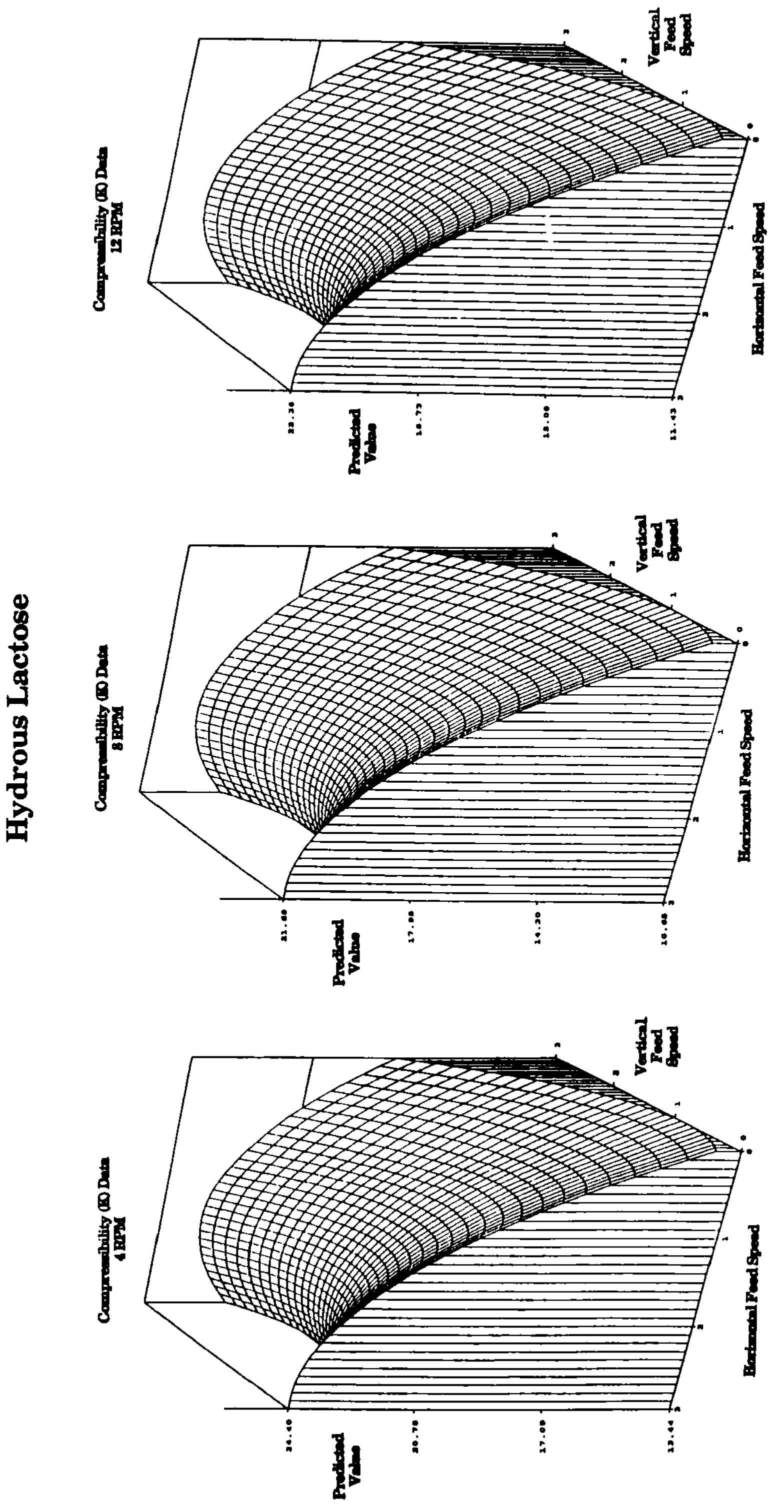

Figure 4. Plots of the model of compressibility data for hydrous lactose.

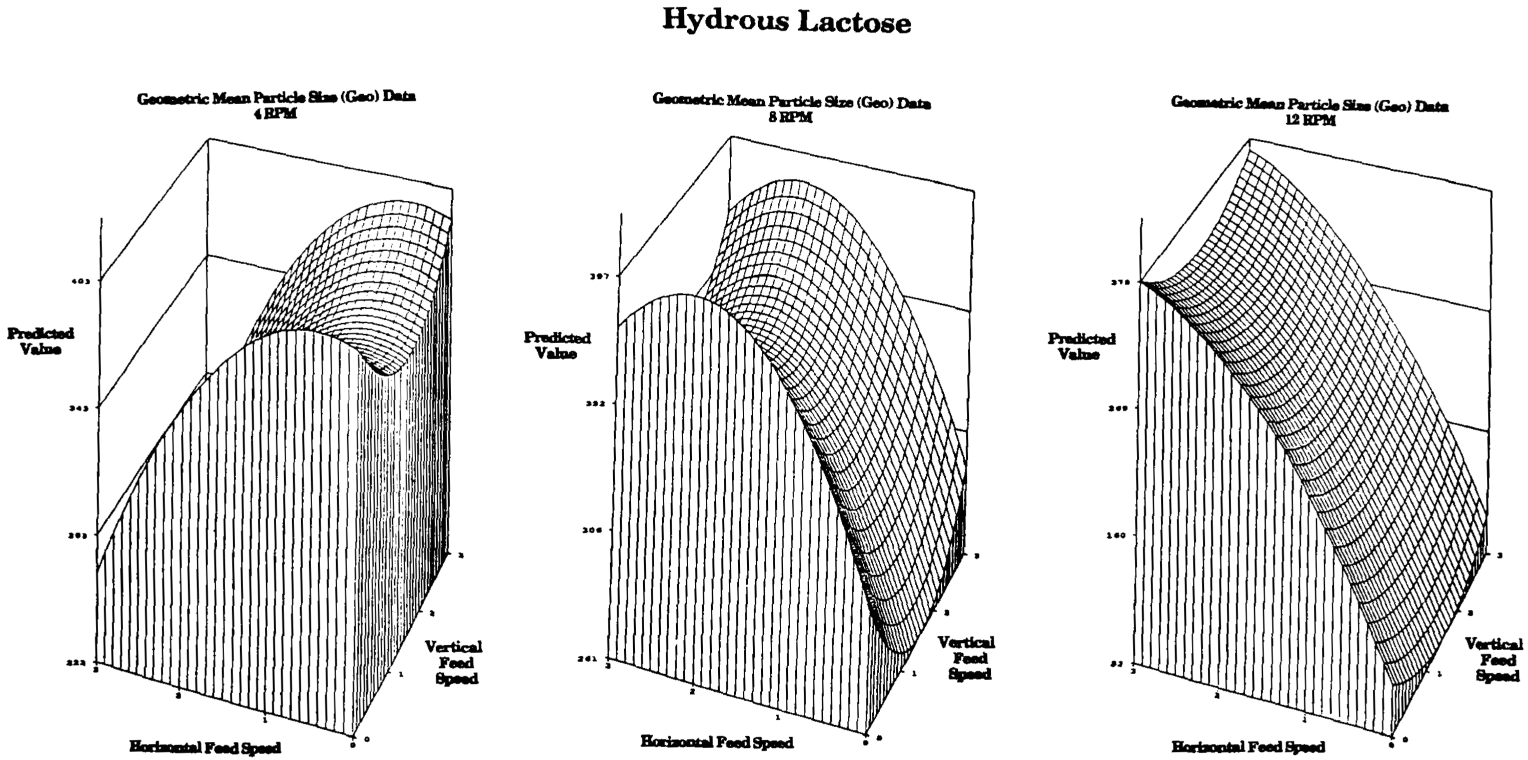

Figure 5. Plots for the model of the geometric mean particles size data for hydrous lactose.

crystals and hydrous lactose were both reported to deform by a brittle fracture mechanism. (10,11) Because of these brittle fracture tendencies, predensification effects represented by the horizontal feed speed-vertical feed speed interaction were significant in the deformation of this blend. Acetaminophen crystals had previously shown capping and laminating problems because of their considerable elastic expansion upon release of compaction pressures.(12) This expansion was sensitive to material dwell time which made the horizontal feed speed-roll speed interaction especially significant for this blend.

The response surface plots for this compressibility model are illustrated in Figure 6. The response surfaces had a smooth surface with an upward grade which indicated a difference from the horizontal feed speed-vertical feed speed relationships seen with either the Avicel or lactose alone. There was a significant shift of the maximum of the response surface along the horizontal feed speed axis with increasing roll speed that indicated the effect of horizontal feed speed-roll speed interaction.

The geometric mean particle size changes for the acetaminophen granulations could not be modeled using the quadratic regression model. The geometric mean particle sizes obtained for the acetaminophen

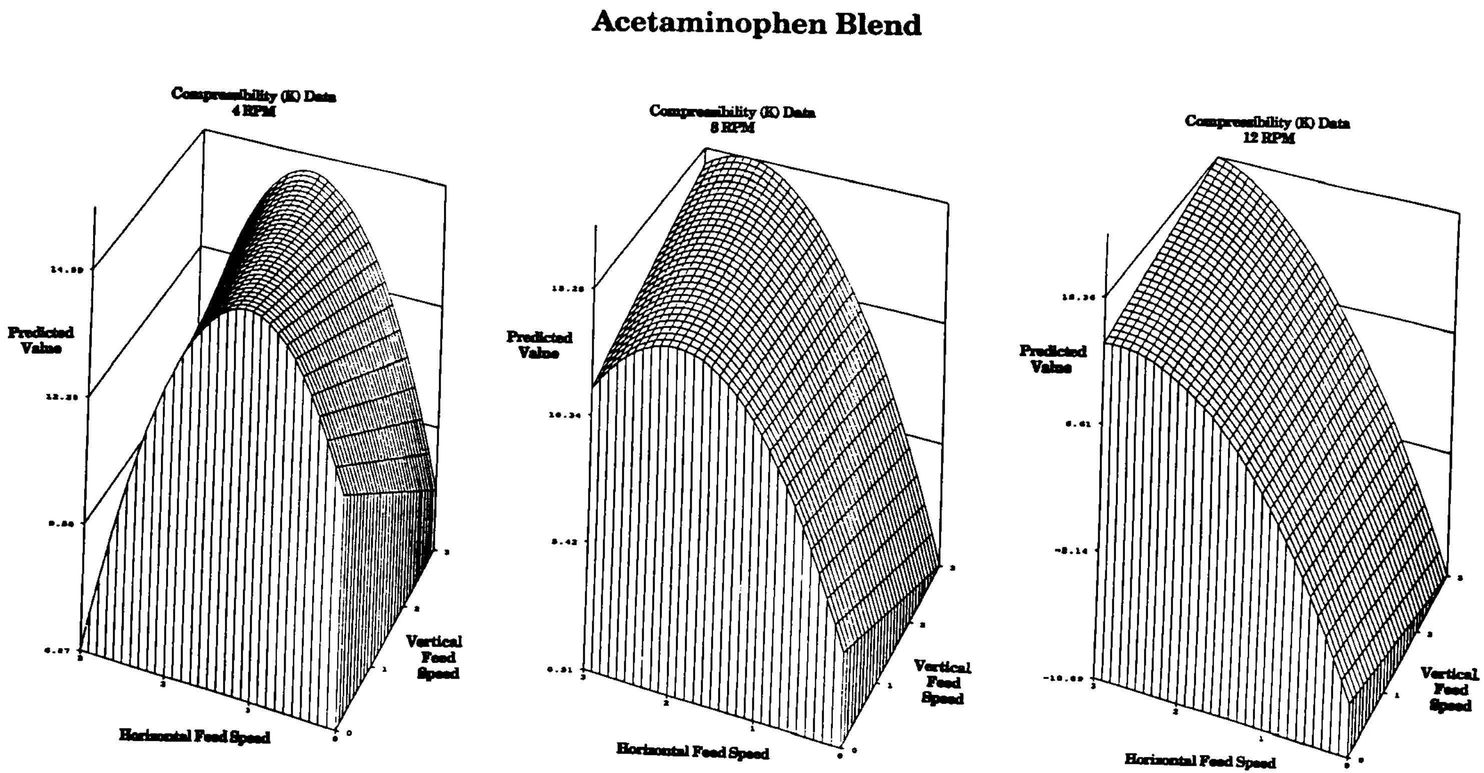

Figure 6. Plots for the model of compressibility data for the acetaminophen blend.

granulations were the same as or less than the geometric mean particle size of the starting material. To determine the reason for these geometric mean particle size decreases, samples were observed under a light microscope. Figures 7, 8, and 9 illustrate the materials as observed under the light microscope. Figure 7 shows the powder blend before roller compaction. Figure 8 shows the granulation after roller compaction and milling. The acetaminophen crystals in Figure 8 appeared fractured and fragmented. The fragmenting may have occurred during roller compaction or during the milling of the compact to form the granulation. To determine if any of the observed fragmenting occurred during roller compaction the surface of the compact was sampled. The powder obtained was placed in oil and observed. The appearance of this material is shown in Figure 9. Fragmenting of the acetaminophen crystals was again observed. This fragmenting would account for the decrease in the geometric mean particle size of the roller compacted granulations despite the visible agglomeration of the processed blend.

The statistical modeling showed that the horizontal feed speed, because of its influence on the compaction pressure, was a significant determinant of the granulation characteristics for all three materials. Roll speed also had a significant effect on granulation characteristics by controlling the dwell

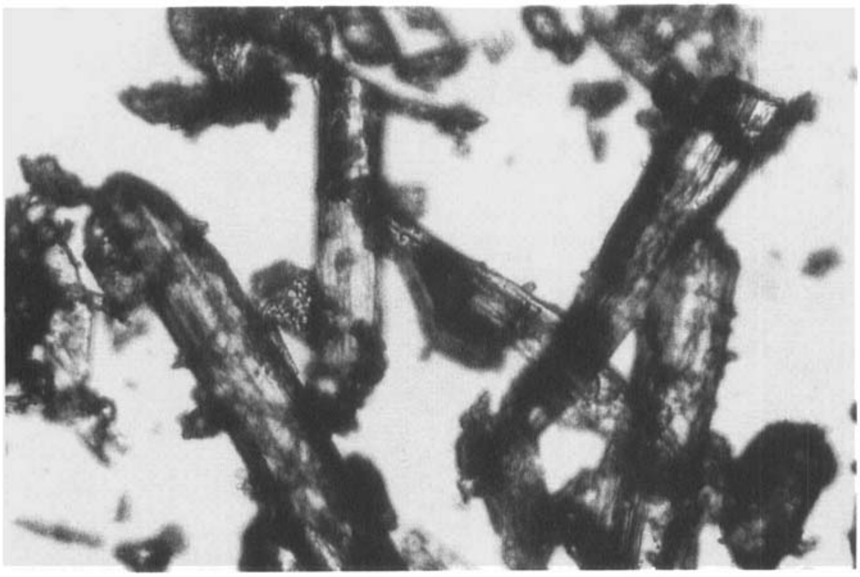

Figure 7.
Photograph of acetaminophen blend before roller compaction as observed under a light microscope at 400x magnification.

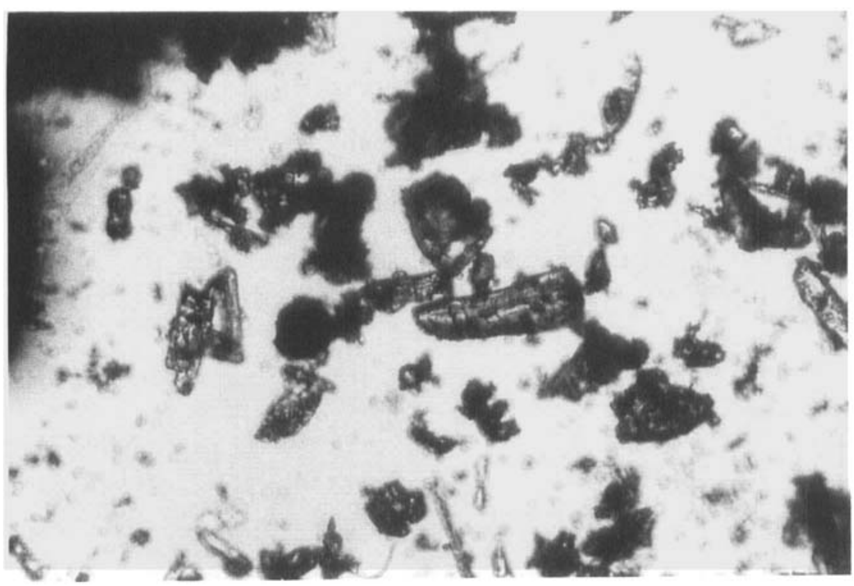

Figure 8.
Photograph of roller compacted acetaminophen granulation as observed under a light microscope at 200x magnification.

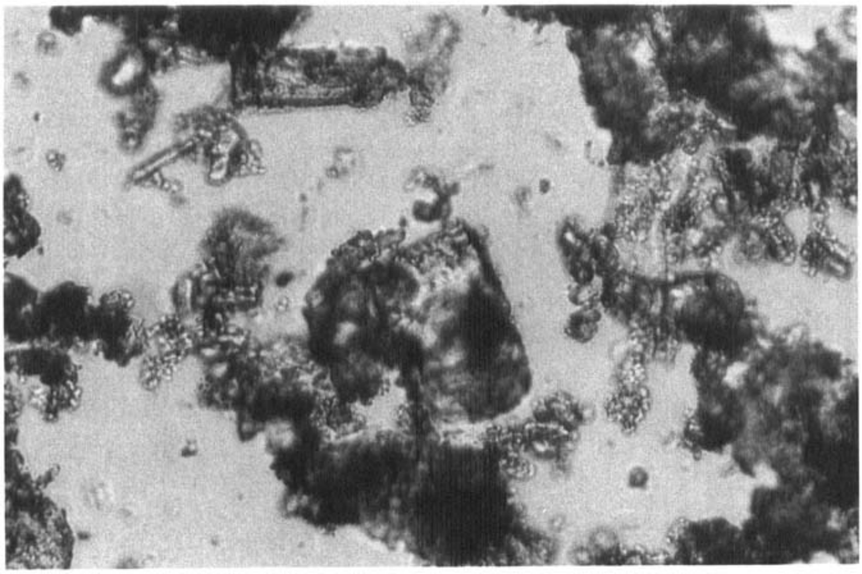

Figure 9.
Photograph of powder sample obtained from acetaminophen blend compacted ribbon surface as observed in oil under a light microscope at 200x magnification.

time of the material at a particular compaction pressure. Despite these observations a general model for the excipients and the drug blend could not be determined. The response surface plots showed that this was because the actual effects of the compactor parameters depended on the bonding and deformation characteristics of the material being roller compacted.

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