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RESEARCH PAPER

Endpoint Determination and Its Relevance to Physicochemical Characteristics of Solid Dosage Forms*

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ABSTRACT

The focus of this research paper is on various aspects of endpoint determination of a typical wet granulation process. The determination of endpoint is highly variable for a conventional wet granulation process. However, high-shear granulators provide for precision in granulation, via the control of a majority of variables that are critical in wet granulation. Therefore, the use of precision in determination of endpoint to beneficially affect the performance of compressed tablets is very desirable. The main objective of this study is to examine the relevance of endpoint determination in controlling performance characteristics of compressed tablets such as hardness, friability, disintegration time, and dissolution time.The effect of three variables—namely endpoint of wet granulation process, press speed (or dwell time), and compression force—on the performance of compressed tablets has been evaluated using a full-factorial experimental design and response surface methodology. Also, the hypothesis of counteracting inherent variability of a wet granulation process by rational selection of press speed and compression force has been investigated.

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INTRODUCTION

Granulation is the pharmaceutical unit operation of particle agglomeration, which is a process of increasing the effective particle size of powder, or a blend of powders. The two principal methods of granulation are *dry granulation* and *wet granulation*. The determination of endpoint of a wet granulation process and its relevance in controlling the physicochemical performance characteristics of compressed tablets form the focal point of investigation in this paper.

Wet granulation is a common pharmaceutical operation. Until the beginning of the last decade, wet granulation remained an operation based completely on empiricism rather than on sound scientific rationale. During the last decade, many diligent efforts have been devoted to gaining a fundamental conceptual understanding of this unit operation. The contribution of Leuenberger et al. in propounding a theoretical explanation of wet granulation is noteworthy (1).

Leuenberger and coworkers have extensively studied the monitoring of wet granulation and its endpoint determination. They postulated a theory to describe the granulating-liquid requirement in a granulation process. They used the power consumption of a conventional mixer to quantitatively characterize the wet granulation process. Since that report, many workers in this area have characterized the wet granulation process through various physical measurements like torque, rotation rate, beam deflection, conductance, and capacitive-sensor methods (2–9). Terashita et al. reported the determination of endpoint by frequency analysis using fast Fourier–transform to power consumption changes during granulation (10). Consequently, the development of instrumentation to facilitate such measurements has evolved to be an area of interesting research. Also, instrumentation of high-shear mixers to facilitate reproducible granulations has become popular (11). In this study, a high-shear granulator instrumented to facilitate torque measurement has been used.

The endpoint of a wet granulation process as described in Leuenberger et al.'s theory is not a discrete point but a wide zone in the torque curve. As a result, the decision to end the granulation process within the recommended wide zone is subjective in nature. The primary aim of this study is to investigate the variability in the physicochemical performance characteristics of tablets resulting from the subjective choice of endpoint within the recommended acceptable zone. Also, we wanted to explore the possibility of counteracting such variability by the rational selection and control of tablet press parameters. An optimization protocol for a model acetaminophen tablet formulation with varying endpoint of granulation, tablet press speed, and compression force has been developed using a full-factorial experimental design and response surface methodology.

FORMULATION METHODOLOGY

The model formulation chosen for this study was acetaminophen USP, 500 mg tablet. The composition of each tablet as a percentage of weight is:

Acetaminophen USP	79%
Explotab®	3% (50/50 intra- and intergranular)
Avicel® PH-101	16% (50/50 intra- and intergranular)
Cabosil®	1%
Magnesium stearate	1%

A 5% w/v solution of Methocel® K3 in water was used as the granulating liquid. The batch size was kept constant at 3 kg for all batches.

Acetaminophen USP, Explotab and Avicel were granulated in a high-shear granulator (Key International, Inc., NJ). The torque measurements were performed by Universal Instrumentation Monitor (Metropolitan Computing Corp., NJ). The impeller speed was 200 rpm and chopper speed was 1585 rpm. The vertical chopper was kept at full low position and granulating liquid was added at a rate of 128.75 ml/min. The powders were dry blended for 1 min before switching on the chopper and granulating fluid.

The granules were then dried at 60°C overnight. The dried granules were milled using a Fitzmill to pass through a 0.0093-in. mesh. The milled granules were then blended with other excipients in a V-blender for 3 min. Compression of processed blends was performed on an instrumented tablet press (Pharmapress 230, Korsch America, Inc., NJ) at predetermined levels of compression force and press speed defined in each run of the experimental design.

Hardness of tablets was measured using a Key Hardness Tester (Key International, Inc., NJ). The mean hardness of five tablets is reported in this study and the associated standard deviations are not reported as they were found to be not significant. Friability was recorded on a Vanderkamp® Friabilator (Vankel Industries, Inc., NJ) after 100 rotations using 20 tablets. Disintegration time was determined using the USP method without disks.

EXPERIMENTAL DESIGN AND DATA ANALYSIS

A full-factorial experimental design has been employed in this study. The endpoint of the wet granulation process (as *Endpoint* in minutes), compression force (as *Comforce* in kilonewtons), and press speed (as *Prespeed* in rpm) were chosen as independent variables. Hardness (in Strong–Cobb units, SCU), friability (in percent), and disintegration time (as *Disintime* in seconds) were chosen as response variables. As tablets from all runs disintegrated in less than 4 min, the measurement of dissolution time was not thought to be appropriate. Endpoint was set at three levels, 5, 7, and 9 min (low, medium, and high); whereas Comforce and Prespeed were set at two levels, 20 and 40 kN, 30 and 90 rpm (low and high), respectively. The levels for each independent variable were decided based on results from preliminary studies and to reflect the complete range of tablet press operation. In addition to the 12 experimental runs defined by the full-factorial design, 3 arbitrarily defined experimental runs were also included to reflect the dependency of responses on intermediate levels for Comforce and Prespeed. Hence, the experimental design contained a total of 15 experimental runs.

All statistical analyses and model fitting were performed using X-STAT, Ver. 1.1 (Softpower, Inc.). Graphic plots and response surfaces were generated using Sigmaplot® Scientific Graphing Software, Ver. 2.0 (Jandel Corp.).

RESULTS AND DISCUSSION

The torque measurement curve for the granulation of acetaminophen is shown in Fig. 1. As described in Leuenberger's theory, the torque curve has been divided into five zones. The zone to end granulation process as recommended by Leuenberger and coworkers to obtain good granulates is between 5 and 9 min on the torque curve for our formulation. Hence, the three levels for Endpoint were fixed at 5, 7, and 9 min to reflect the entire acceptable zone to end the granulation process. Also, we observed good reproducibility in the acceptable zone for Endpoint upon scaling the batch size from 0.5 kilo to 3 kilos. However, the scale-up data are not reported in this paper.

The complete experimental design and responses are listed in Table 1. An examination of the responses shows clear variability in the physicochemical performance characteristics of tablets when the Endpoint is

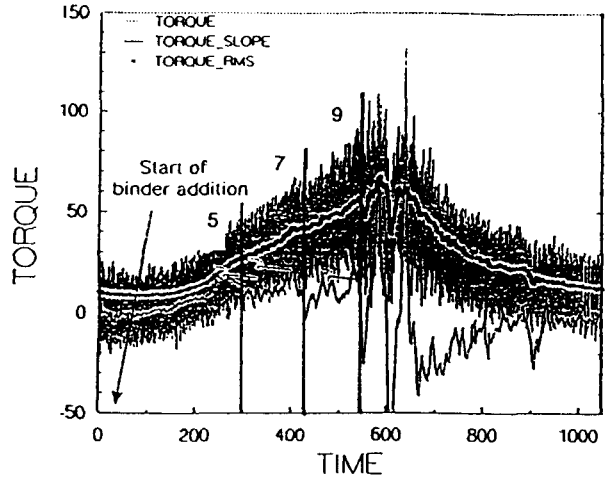

Figure 1. Torque measurement curve for acetaminophen granulation endpoint determination.

varying. With increasing Endpoint levels, tablets were found to be harder. This observation is a direct result of increasing binder level in the formulation. Figures 2 and 3 portray the trends in disintegration time and friability as a function of hardness, respectively. As expected, increasing hardness of tablets leads to higher disintegration time and lower friability. Figures 4 and 5 show the plots of hardness against compression force at press speeds of 90 and 30 rpm, respectively. It is

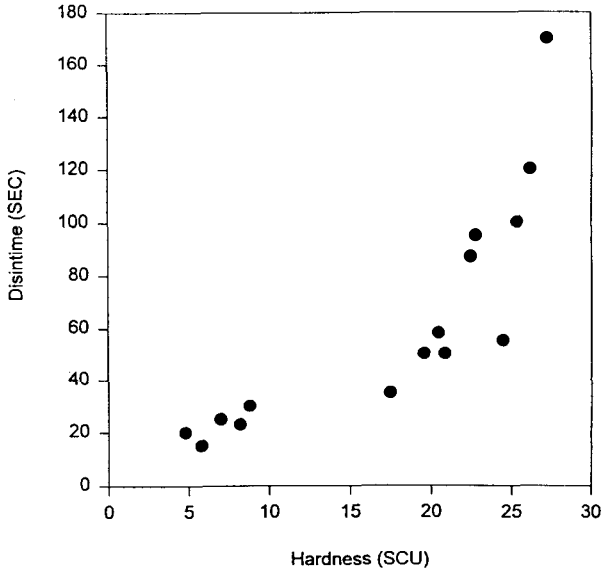

Figure 2. Hardness–Disintime trend.

Table 1

Experimental Design and Responses

Run	Endpoint (min)	Prespeed (rpm)	Comforce (kN)	Hardness (SCU)	Friability (%)	Disintime (sec)
1	-1	-1	-1	8.8	32.46	30
2	0	-1	-1	19.6	5.34	50
3	1	-1	-1	25.4	0.76	100
4	-1	1	-1	8.2	33	23
5	0	1	-1	17.5	1	35
6	1	1	-1	24.5	0	55
7	-1	-1	1	5.8	34.97	15
8	0	-1	1	22.8	5.06	95
9	1	-1	1	27.3	5.28	170
10	-1	1	1	4.8	32.62	20
11	0	1	1	20.9	3.15	50
12	1	1	1	26.2	0.1	120
13	-1	-0.5	0	7	34.4	25
14	0	0.233	0.5	20.5	4	58
15	1	-0.1	-0.5	22.5	0.9	87

Level	Endpoint (min)	Prespeed (rpm)	Comforce (kN)
-1	5	30	20
0	7	—	—
1	9	90	40

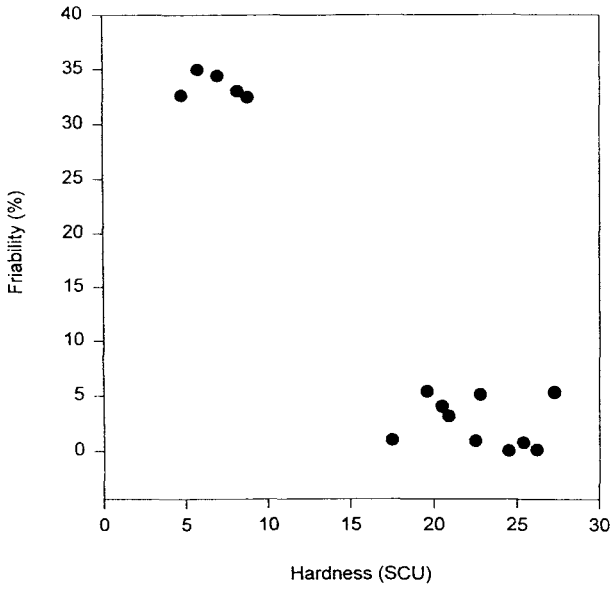

Figure 3. Hardness–Friability trend.

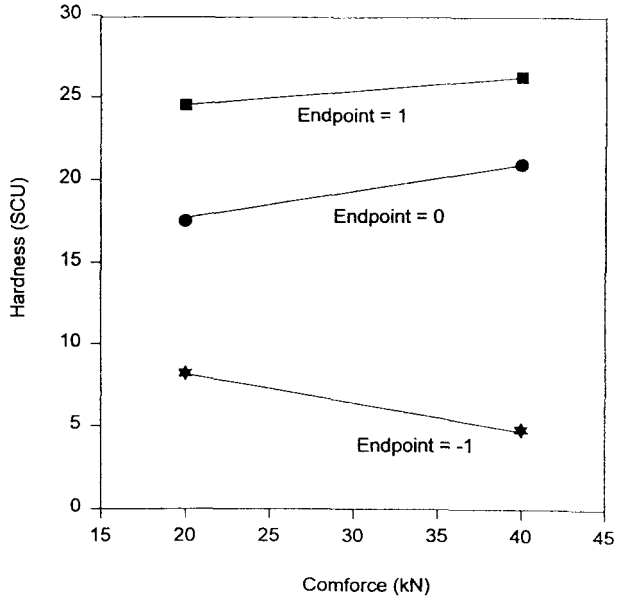

Figure 4. Plots of Hardness against Comforce at Prespeed = 90 rpm.

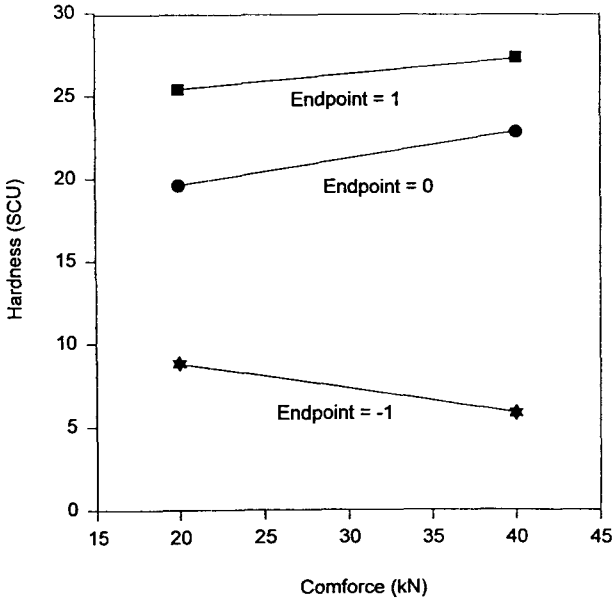

Figure 5. Plots of Hardness against Comforce at Prespeed = 30 rpm.

observed from these plots that increasing levels of Endpoint result in higher hardness at specified compression force and press speed. However, at the lowest Endpoint level, hardness decreases with increasing compression force. This anomalous behavior can be attributed to the insufficient amount of binder, due to which the tablets were capping before fracture during hardness testing. Hence, the resulting measurement of hardness is inaccurate.

Figures 6 and 7 show the plots of hardness against press speed at compression force of 20 and 40 kN, respectively. These plots show that hardness decreases with increasing press peed. As press speed increases, the dwell time decreases and hardness falls at a specified compression force. To test the significance of the effect of press speed on hardness at specified compression force, a two-tailed paired t test at 95% confidence was performed. Results showed that the effect of press speed was not significant at 20 kN compression, whereas the same was significant at 40 kN compression. But this significance is in contrast to cursory inspection of the data, which does not suggest any marked difference. This inconsistency may be due to the very small sample size ($N = 3$) and restricted degrees of freedom ($df = 2$), due to which the test may not be very robust.

The responses obtained from 15 experimental runs were used to develop statistical models to describe the response variables. The reason for including 3 arbitrarily defined runs with the 12 runs derived from the full-factorial design is to "feed" the model information about the dependency of responses on the intermediate

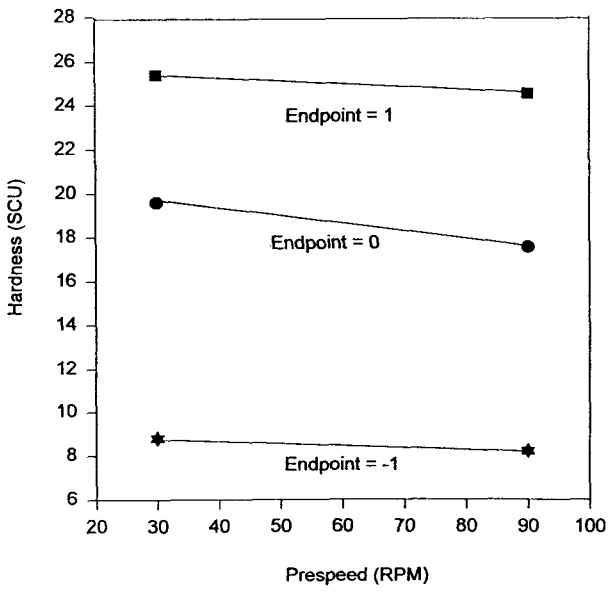

Figure 6. Plots of Hardness against Prespeed at Comforce = 20 kN.

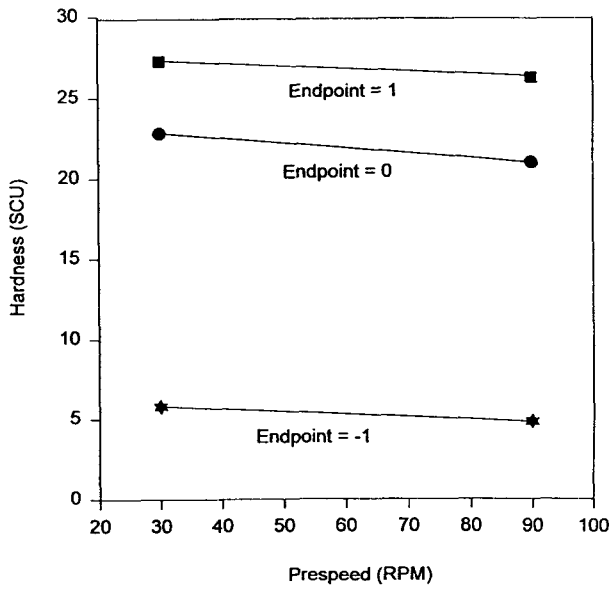

Figure 7. Plots of Hardness against Prespeed at Comforce = 40 kN.

levels of Prespeed and Comforce. Quadratic models with interaction terms were found to best describe the responses. The models developed for responses are:

$$\text{Hardness} = 19.69 + 9.36(\text{Endpoint}) - 0.60(\text{Prespeed}) + 0.41(\text{Comforce}) - 0.04(\text{Endpoint}) \times (\text{Prespeed}) + 1.31(\text{Endpoint}) \times (\text{Comforce}) - 0.02(\text{Prespeed}) \times (\text{Comforce}) - 4.24(\text{Endpoint}^2) + 2.90(\text{Prespeed}^2) - 2.11(\text{Comforce}^2) \quad [R^2 = 98.44\%]$$

$$\text{Friability} = 4.15 - 15.89(\text{Endpoint}) - 1.16(\text{Prespeed}) + 0.73(\text{Comforce}) - 0.51(\text{Endpoint}) \times (\text{Prespeed}) + 0.32(\text{Endpoint}) \times \text{Comforce}) - 0.40(\text{Prespeed}) \times (\text{Comforce}) - 13.68(\text{Endpoint}^2) + 1.50(\text{Prespeed}^2) - 1.96(\text{Comforce}^2) \quad [R^2 = 99.76\%]$$

$$\text{Disintime} = 55.19 + 44.41(\text{Endpoint}) - 13.02(\text{Prespeed}) + 14.91(\text{Comforce}) - 11.61(\text{Endpoint}) \times (\text{Prespeed}) + 19.24(\text{Endpoint}) \times (\text{Comforce}) - 1.90(\text{Prespeed}) \times (\text{Comforce}) - 8.36(\text{Endpoint}^2) + 21.28(\text{Prespeed}^2) - 18.46(\text{Comforce})^2 \quad [R^2 = 99.06\%]$$

Figures 8, 9, and 10 show the response surfaces for hardness, friability, and disintegration time at a specified press speed of 90 rpm. Figures 11, 12, and 13 show the contour plots for hardness, friability, and disintegration time at a specified press speed of 90 rpm.

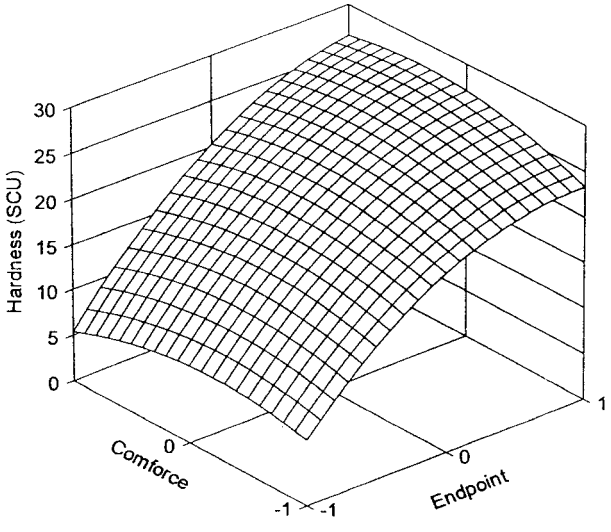

Figure 8. Response surface for Hardness at Prespeed = 90 rpm.

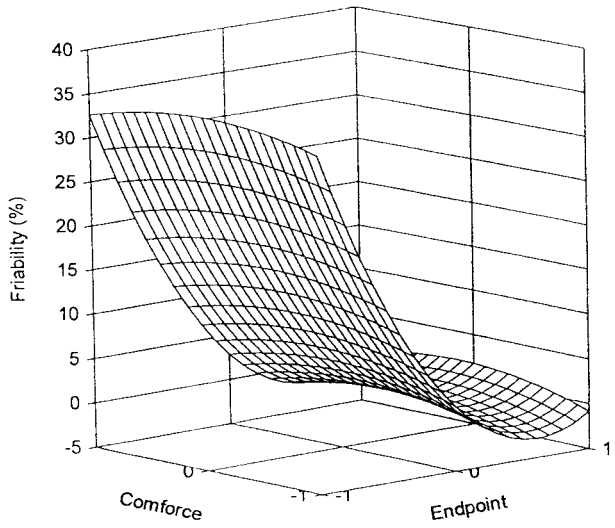

Figure 9. Response surface for Friability at Prespeed = 90 rpm.

To evaluate the predictive ability of the statistical models, three arbitrarily defined test runs were performed and the responses recorded. The data describing the test conditions and the responses are shown in Table 2. This table also shows the residuals, which are indicators of the accuracy of prediction. The predicted values for hardness and disintegration time exceed the observed values in test 1. The predictions for friability

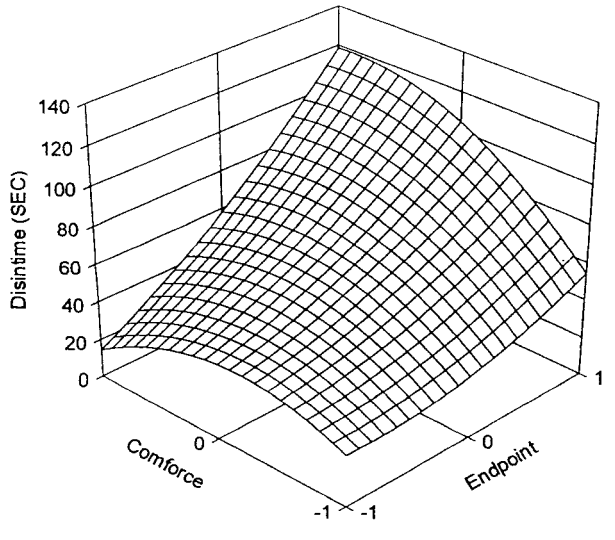

Figure 10. Response surface for Disintime at Prespeed = 90 rpm.

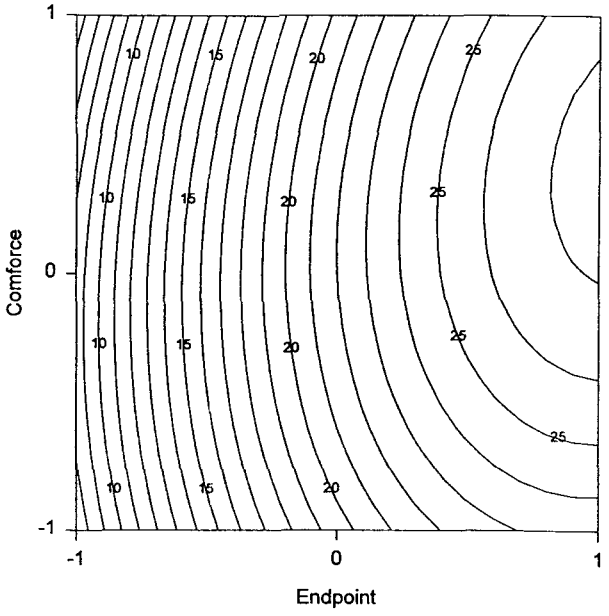

Figure 11. Contour plot for Hardness at Prespeed = 90 rpm.

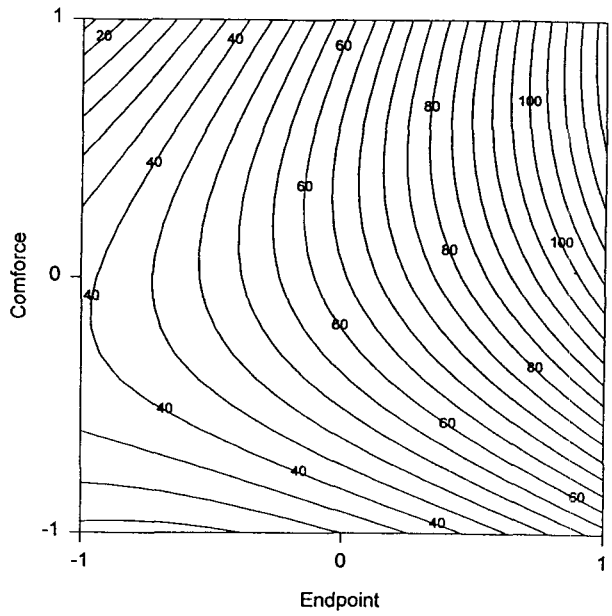

Figure 13. Contour plot for Disintime at Prespeed = 90 rpm.

were less than the observed values in test 2 and test 3. The other predictions are in good agreement with the observed values. A possible explanation for the deviation between predicted and observed values may be the model's inability to "pick" curvature or nonlinearity in the dependence of responses. This limitation of the model may be attributed to the nature of the experimental design. As Prespeed and Comforce were specified only at two levels (high and low), it may be difficult for the model to "read" information regarding the dependence of responses on the intermediate levels of these variables.

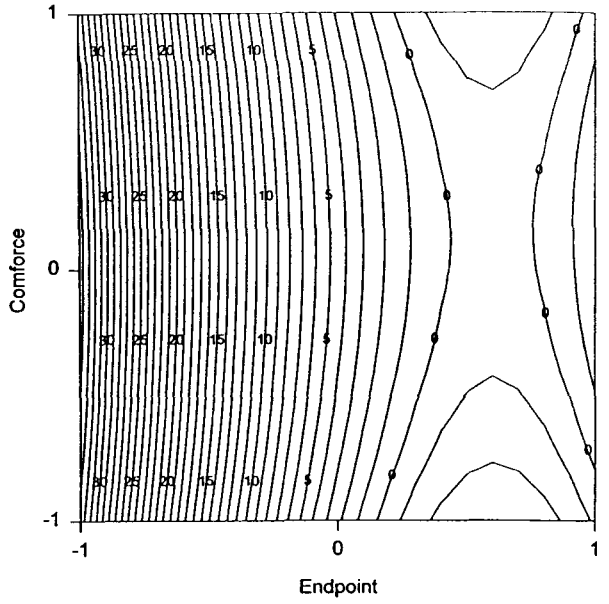

Figure 12. Contour plot for Friability at Prespeed = 90 rpm.

A comprehensive evaluation of data suggests that contour plots and response surfaces are valuable tools, along with torque or power measurements, in the determination of endpoint. For example, the contour plot for friability offers formulators freedom to choose the exact combination of endpoint, compression force, and press speed to achieve their desired friability. Also, they can determine the hardness and disintegration time corresponding to their selected combination from the contour plots for other response variables. Hence, this method of endpoint determination allows the formulator to exercise precise control over the physicochemical performance characteristics of solid dosage forms.

CONCLUSION

Precision in the determination of endpoint is important in controlling reproducibility in the physicochemical performance characteristics of solid dosage forms. The variability in the performance of physicochemical characteristics due to subjective endpoint choice can be

Table 2

Evaluation of Predictability of the Model

Run	Observed Hardness (SCU)	Predicted Hardness (SCU)	Residual (Pred - Obs)
Test 1	4.86	8.9	4.04
Test 2	21.2	19.9	-1.3
Test 3	27.3	24.7	-2.6
Run	**Observed Friability (%)**	**Predicted Friability (%)**	**Residual (Pred - Obs)**
Test 1	31.3	34.96	3.66
Test 2	4.8	0.1	-4.7
Test 3	4.31	1.1	-3.21
Run	Observed Disintime (SEC)	Predicted Disintime (SEC)	Residual (Pred - Obs)
Test 1	5.45	35	29.55
Test 2	64.3	60	-4.3
Test 3	153	138	-15
Run	Endpoint (min)	Prespeed (rpm)	Comforce (kN)
Test 1	5	64	20
Test 2	7	35	25
Test 3	9	37	35

counteracted by rational control of tablet press parameters. An optimization protocol for the model acetaminophen tablet formulation has been developed. The response surfaces and contour plots, along with torque or power measurements, are of immense value in endpoint determination.

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