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RESEARCH PAPER

Modeling the Effects of Hydroxypropylcellulose in Acetaminophen Tablet Formulation

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ABSTRACT

The objective of the research described here was to develop a set of predictive models that would be used to show the performance of hydroxypropylcellulose as a pharmaceutical tablet binder. A statistically designed set of experiments was used to relate tablet formulation to functionality. It was found that the binder level affected both hardness and dissolution time. Useful predictive models were generated for tablet hardness and dissolution time as a function of the binder or binder-drug ratio. The optimal formulation can be predicted from this study, and will depend upon the combination of desired hardness and the dissolution time for a particular drug.

INTRODUCTION

The formulation of tablet forms has undergone rapid change and development over the past several years with the emergence of precompression, induced die feeding, high-speed presses, the availability of many new direct compression materials, and upper-punch tightness on tablet presses. However, the major concerns in tablet formulation and design are still whether the correct amount of the drug is delivered in the right form at, or over, the proper time at the proper rate and in the desired location. Therefore, the contribution and influence of active drugs and nonactive ingredients, especially the binder, must be considered for measuring their impact on the pharmacologic response of any tablet system.

Binders are materials that provide the necessary bonding to hold powders together to form granules which, under compaction, form a tablet. Since a binder, even a water-soluble one, will retard the disintegration of a tablet, the use of binders in tablet formulation should be limited;

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not because binders are unnecessary, but because of the two-way action of the binders themselves (1,2). The granulation process is used regularly in the pharmaceutical industry to improve the properties of powders that have poor flow and compression behavior. There are many acceptable excipients used in the process of granulation as binders; these include hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, and sodium carboxymethylcellulose (3–7).

Currently, there exists no single complete set of data for any single binder that can be statistically analyzed to quantify the relationships between formulation and the various tablet properties of interest, such as hardness and dissolution. We ran a statistically designed set of experiments to better understand these relationships. The data from the experiments were used to develop models that can be used to predict formulations providing desired hardnesses and dissolution times.

MATERIALS AND METHODS

The materials used in the study were hydroxypropylcellulose (Klucel® EXF, Pharm, Hercules Incoporated, Aqualon Division, Wilmington, DE), acetaminophen powder, USP (Rhone-Poulenc Inc. Specialty Chemicals, Cranbury, NJ), magnesium stearate, NF (Witco Corp. Organics Division, Chicago, IL), croscarmellose sodium (Ac-Di-Sol, NF, FMC Corp. Food and Pharmaceutical Division, Newark, DE), lactose, regular grind, NF (Wisconsin Dairies, Formost Ingredient Group, Baraboo, WI), and calcium sulfate, hydrous, NF (US Gypsum Co., Industrial Gypsum Division, Chicago IL).

The tablet formulation consisted of drug, binder, lubricant, disintegrant, and filler. In this case, the drug was acetaminophen (APAP), and hydroxypropylcellulose was used as the binder. The lubricant, magnesium stearate, was fixed at 0.5%, and the disintegrant, croscarmellose sodium, was fixed at 2% in all formulations. The filler was a combination of lactose and calcium sulfate in equal parts. The levels of binder, drug, and filler were varied in the study as follows:

Binder: 2–8%.
Drug: 50, 66 or 83.33%.
Filler: No constraint.

Although no constraints were placed on the filler level, the level was automatically limited to 6.17–42.5%, since the binder, drug, and filler always added up to a constant 97.5%.

To study the effects of these variables, we used a mixture design (8). For three variables, the design regions were simplexes, with each vertex representing 100% of one of the components. However, upper and lower bounds further constrained two of the components (variables) in this case. Therefore, the resulting experimental region was not the full triangle region of a simplex, but a section of the simplex. The formulation components were expected to have nonlinear effects on the tablet properties; therefore, a quadratic mixture design was generated. Experiments were run at the vertices of the region, at the center of each edge, and at the center of the region. The nine-run mixture design is given in Table 1.

Tablets were formed at five compression forces (5, 10, 15, 20, or 25 kN) to generate profiles for hardness vs. compression force. All experiments generated in the mixture design were run at each of the five compression forces. This resulted in a combination of a mixture and a factorial design.

Data Analysis

The hardness and dissolution data were analyzed using regression analysis. The variable (or component) proportions were normalized before the analysis as follows:

$$\text{Normalized value (\%)} = \frac{(\text{Raw value} - \text{lower bound})}{(97.5 - \text{sum (all lower bounds)})} \quad (1)$$

$$\text{Sum (all lower bounds)} = 2 + 50 + 6.17 = 58.17 \quad (2)$$

Therefore, normalized binder = (binder − 2)/39.33; normalized filler = (filler − 6.17)/39.33; and normalized drug = (drug − 50)/39.33

The process variable (compression force) was also normalized to −1 for the low value and 1 for the high value.

The hardness data were transformed to their natural logarithms to obtain more homogeneous variance across the range of hardness values and, therefore, a more reliable model. No transformation was necessary for dissolution. Useful predictive models, in normalized variables, were generated for ln(hardness) and dissolution time, with a high adjusted correlation coefficient, R^2 (adjusted) of around 96%, and a low error of regression. The R^2 (adjusted) is the percent variation in the data explained by the model, and is an indicator of the adequacy of the model. The error of regression is an estimate of the experimental error, and is also an indicator of the adequacy of

Table 1

Experimental Design and Data

Binder (%)	Filler (%)	Drug (%)	Croscarmellos Sod (%)	Mg Stea-rate (%)	Compression Force (kN)	Hardness (Kp)	Friability (%)	Dissolution Time (min)
2	12.17	83.33	2	0.5	5	3.7	2.93	
2	12.17	83.33	2	0.5	10	8	1.53	
2	12.17	83.33	2	0.5	15	7.5	19.61	9.6
2	12.17	83.33	2	0.5	20	8.7	28.24	
2	12.17	83.33	2	0.5	25	9.5	29.59	
2	29.5	66	2	0.5	5	3.1	3.84	
2	29.5	66	2	0.5	10	6.9	1.36	
2	29.5	66	2	0.5	15	10.3	0.99	11.3
2	29.5	66	2	0.5	20	7.9	29.36	
2	29.5	66	2	0.5	25	8	31.95	
5	9.16	83.33	2	0.5	5	4.3	2.914	
5	9.16	83.33	2	0.5	10	8.3	1.097	
5	9.16	83.33	2	0.5	15	12.8	0.684	14.6
5	9.16	83.33	2	0.5	20	15.5	2.444	
5	9.16	83.33	2	0.5	25	*	7.231	
5	26.5	66	2	0.5	5	3.6	5.11	
5	26.5	66	2	0.5	10	8.3	0.78	
5	26.5	66	2	0.5	15	11.7	0.72	26
5	26.5	66	2	0.5	20	15.9	0.48	
5	26.5	66	2	0.5	25	18.2	0.61	
5	42.5	50	2	0.5	5	3.9	2.294	
5	42.5	50	2	0.5	10	8	0.796	
5	42.5	50	2	0.5	15	12.6	0.63	36
5	42.5	50	2	0.5	20	14.9	0.4	
5	42.5	50	2	0.5	25	17.9	0.399	
8	6.17	83.33	2	0.5	5	3.2	4.4	
8	6.17	83.33	2	0.5	10	7.4	0.96	
8	6.17	83.33	2	0.5	15	12.4	0.55	22.8
8	6.17	83.33	2	0.5	20	14.7	0.5	
8	6.17	83.33	2	0.5	25	17.6	0.38	
8	23.5	66	2	0.5	5	3.4	7.91	
8	23.5	66	2	0.5	10	7.4	0.71	
8	23.5	66	2	0.5	15	12	0.53	37.1
8	23.5	66	2	0.5	20	15	0.45	
8	23.5	66	2	0.5	25	16.2	0.5	
8	39.5	50	2	0.5	5	3.3	23.97	
8	39.5	50	2	0.5	10	7.1	0.6	
8	39.5	50	2	0.5	15	10.7	0.45	56.7
8	39.5	50	2	0.5	20	14.9	0.33	
8	39.5	50	2	0.5	15	15.9	0.38	
2	12.2	83.3	2	0.5	5	4.2	2.961	
2	12.2	83.3	2	0.5	10	9.7	1.404	
2	12.2	83.3	2	0.5	15	10.4	15.278	12.3
2	12.2	83.3	2	0.5	20	10.5	16.733	
2	12.2	83.3	2	0.5	25	11.2	24.182	
2	29.5	66	2	0.5	5	3.8	3.92	
2	29.5	66	2	0.5	10	8.1	1.24	
2	29.5	66	2	0.5	15	11.8	2.72	12.6
2	29.5	66	2	0.5	20	8.8	30.01	
2	29.5	66	2	0.5	25	9.7	34.7	

(continued)

Table 1 (*Continued*)

Binder (%)	Filler (%)	Drug (%)	Croscarmellos Sod (%)	Mg Stea-rate (%)	Compression Force (kN)	Hardness (Kp)	Friability (%)	Dissolution Time (min)
2	45.5	50	2	0.5	5	5.6	0.52	
2	45.5	50	2	0.5	10	7.3	0.41	
2	45.5	50	2	0.5	25	9.4	0.25	
5	9.16	83.33	2	0.5	5	4.4	3.293	
5	9.16	83.33	2	0.5	10	9.7	0.833	
5	9.16	83.33	2	0.5	15	14.8	0.771	19.6
5	9.16	83.33	2	0.5	20	20.1	0.539	
5	9.16	83.33	2	0.5	25	19.8	2.31	
5	26.5	66	2	0.5	5	4	2.64	
5	26.5	66	2	0.5	10	9.2	1	
5	26.5	66	2	0.5	15	12.8	0.59	23.3
5	26.5	66	2	0.5	20	17.2	0.54	
5	26.5	66	2	0.5	25	19.9	0.51	
5	42.5	50	2	0.5	5	3.9	2.294	
5	42.5	50	2	0.5	10	8	0.796	
5	42.5	50	2	0.5	15	12.6	0.63	37.3
5	42.5	50	2	0.5	20	14.9	0.4	
5	42.5	50	2	0.5	25	17.9	0.399	
8	6.2	83.3	2	0.5	5	3.6	4.448	
8	6.2	83.3	2	0.5	10	8.5	0.938	
8	6.2	83.3	2	0.5	15	13.6	0.538	23.8
8	6.2	83.3	2	0.5	20	18	0.448	
8	6.2	83.3	2	0.5	25	20	0.384	
8	23.5	66	2	0.5	5	3.5	27.95	
8	23.5	66	2	0.5	10	8.6	0.94	
8	23.5	66	2	0.5	15	14.3	0.55	45.1
8	23.5	66	2	0.5	20	17.2	0.46	
8	23.5	66	2	0.5	25	19	0.42	
8	39.5	50	2	0.5	5	3.3	0.68	
8	39.5	50	2	0.5	10	7.8	0.69	
8	39.5	50	2	0.5	15	12.1	0.4	56.3
8	39.5	50	2	0.5	20	16.3	0.29	
8	39.5	50	2	0.5	25	17.4	0.29	

the model. The models obtained (in normalized variables) are given below.

1. Ln(hardness) =

$$
\begin{aligned}
&-16.21*B + 2.25*F + 2.37*D \\
&+ 23.95*B*F + 24.01*B*D \\
&+ 0.214*F*D - 19.6*B*CF \\
&+ 0.317*F*CF + 0.393*D*CF \\
&+ 27.2*B*F*CF \\
&+ 26.7*B*D*CF \\
&+ 0.130*F*D*CF - 10.6*B*CF^2 \\
&- 0.361*F*CF^2 \\
&- 0.388*D*CF^2 \\
&+ 11.1*B*F*CF^2 \\
&+ 11.5*B*D*CF^2 \\
&- 0.503*F*D*CF^2
\end{aligned} \tag{3}
$$

With R^2-(adj) = 96.4% and s = 0.105.

2. Dissolution time =

$$
\begin{aligned}
&379*B + 14.08*F \\
&+ 12.54*D \\
&- 92*B*F - 334*B*D \\
&- 3.51*F*D
\end{aligned} \tag{4}
$$

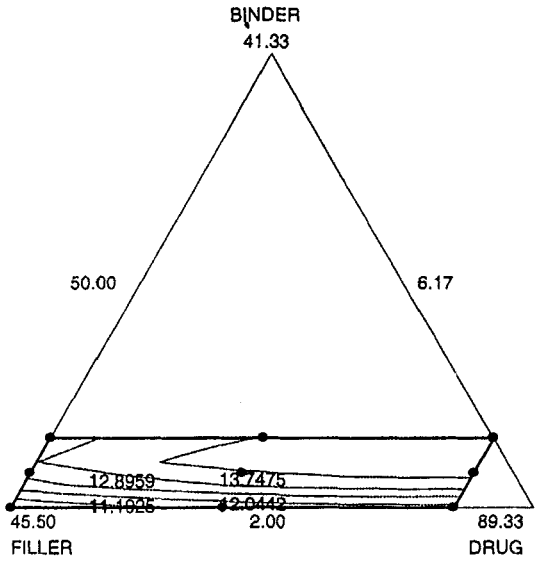

Figure 1. Trilinear contour plot of tablet hardness at a compression of 15 kN.

With R^2(adj) = 96.0% and s = 3.1

In both equations (3) and (4), B = binder, F = filler, D = drug, CF = compression force, and s = standard deviation

Because of the nature of mixture models, especially when there are constraints on components, it is not always appropriate to interpret variable effects from model coefficients. Conclusions about variables may be drawn from the trilinear contour plots generated from the models. A trilinear contour plot of hardness at a compression force of 15 kN is included as an example in Fig. 1. Each axis in the plot represents a component of the formulation. The plots show contours of average predicted hardness or dissolution as a function of the formulation. For a desired hardness or dissolution time, the formulation can be determined by the coordinates of the point relative to the three axes. Separate plots were generated for each compression force.

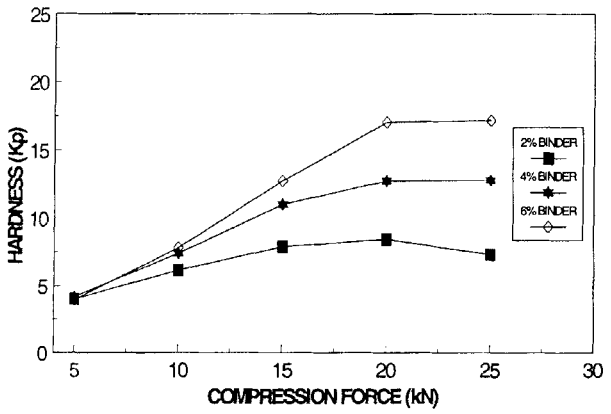

Figure 2. Predicted hardness vs. compression force. [Tablet weight = 600 mg, drug level = 50%, (◆) 6% binder, (✱) 4% binder, and (■) 2% binder].

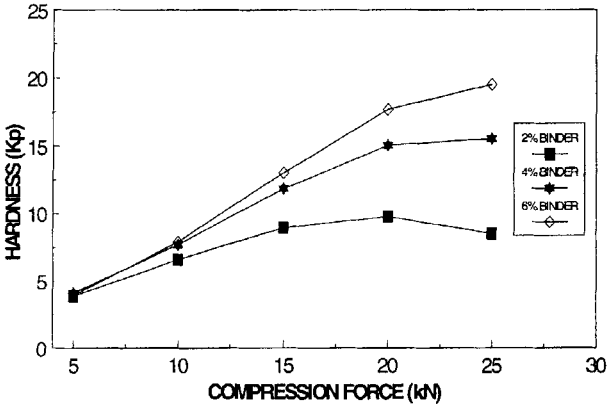

Figure 3. Predicted hardness vs. compression force. [Tablet weight = 600 mg, drug level = 83.33%, (◆) 6% binder, (✱) 4% binder, and (■) 2% binder].

RESULTS AND DISCUSSION

Predicted hardness vs. compression force for the 50% and 83.33% drug levels are shown in Figs. 2 and 3, re-

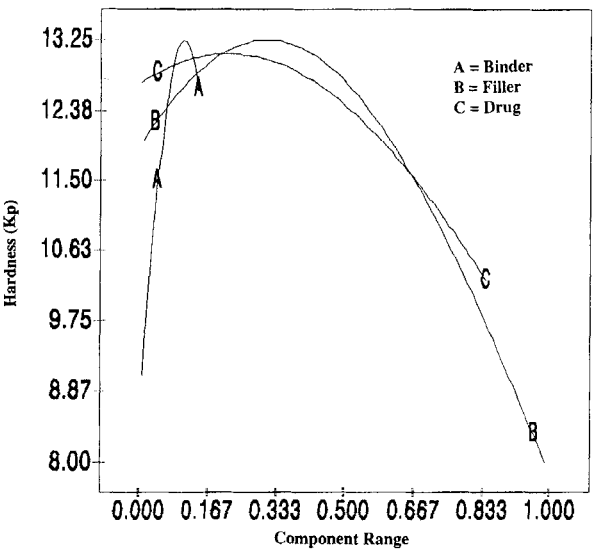

Figure 4. Effects of componet range on the hardness of tablets. (A = binder, B = filler, and C = drug).

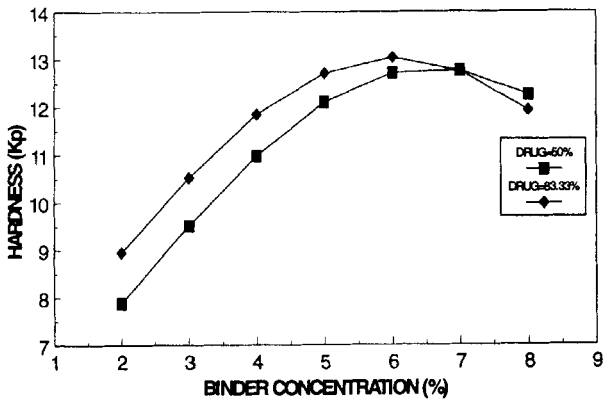

Figure 5. Predicted hardness vs. binder concentration. (Tablet weight = 600 mg, compression force = 15kN, (◆) drug level = 83.33%, and (■) drug level = 50%).

spectively. Binder concentration in the formulation appeared to have the most dominant effect on hardness. The amount of drug and filler also appeared to have significant effects on hardness, and the two effects were approximately equal (Fig. 4.) Figure 5 shows predicted hardness as a function of binder level at a compression force of 15 kN for the 50% and 83.33% drug levels. The maximum predictive hardness could be obtained at roughly a 5–7% binder concentration regardless of the drug level. A surface plot of hardness as a function of both binder and drug simultaneously is shown in Fig. 6.

Figure 7 shows dissolution time as a function of binder level for the 50% and 83.33% drug levels. The dissolution time was measured only for tablets formed at the compression force of 15 kN. Both binder and drug level had significant effects on the dissolution time. For any

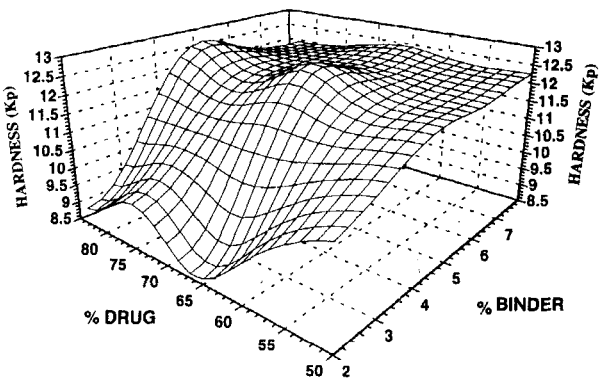

Figure 6. Hardness vs. binder and drug concentrations.

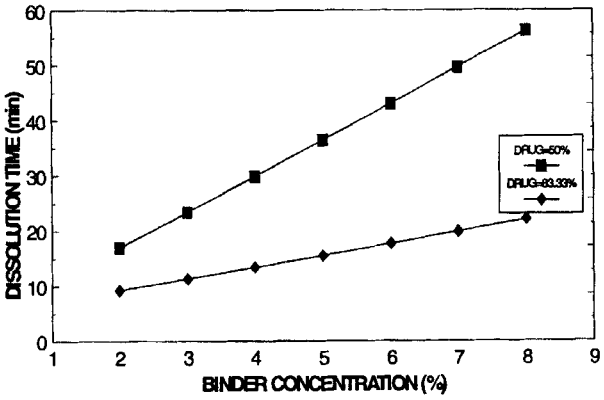

Figure 7. Predicted dissolution time vs. binder concentration. (Tablet weight = 600 mg, compression force = 15kN, (◆) drug level = 83.33%, and (■) drug level = 50%).

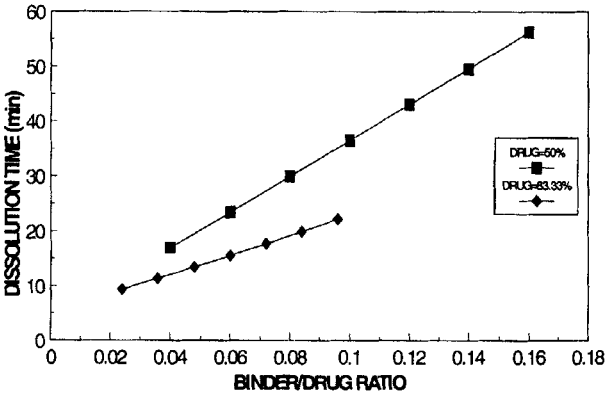

Figure 8. Predicted dissolution time vs. binder/drug ratio. (Tablet weight = 600 mg, compression force = 15kN, (●) drug level 83.33%, and (■) drug level 50%).

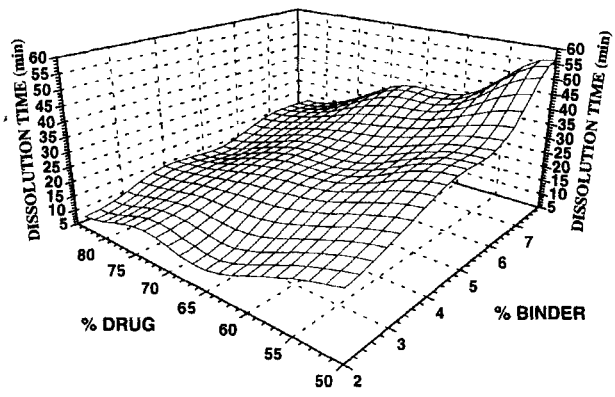

Figure 9. Dissolution time vs. binder and drug concentrations.

Table 2

Actual vs. Predicted Hardness and Dissolution Time: Compression Force = 15kN

	Binder (%)	Filler (%)	Drug (%)	Hardness (Kp)	Dissolution Time (min)
Run 1	4	12.17	83.33	14.8*	14.2*
				11.9†	13.4†
Run 2	6	12.17	83.33	13.6*	16.1*
				13.0†	17.5†
Run 3	8	39.5	50	10.7*	56.7*
				12.3†	56.3†
Run 4	5	42.5	50	12.6*	36*
				12.1†	36.4†
Run 5	2	45.5	50	14.9*	18.1*
				7.9†	17.0†
Run 6	3	44.5	50	13.2*	36.8*
				9.5†	23.4†

* Actual value.
† Predicted value.

given drug level, increasing binder level increased dissolution time, with the most dramatic impact at the lower drug level. The higher drug level in the formulation gave the lower dissolution times in our study.

As shown in Fig. 8, when the dissolution times for 50% and 83.33% drug levels, were presented as a function of binder-drug ratio, the data for the dissolution times of those two formulations were much closer to each other, but still significantly different. The existing high level of fillers in the formulation containing 50% drug can explain the difference in dissolution times between the two formulations in Fig. 8. A varying filler level can cause a varying intensity of interaction between drug and binder, and can create different degrees of crystallinity in the tablets. These interactions and crystal formation may create a diffusion barrier for the active drug, delaying drug diffusion. Future work will address this preliminary hypothesis. Fig. 9 shows a surface plot of dissolution time as a function of both binder and drug simultaneously.

Data from additional experiments not included in this analysis were used to check the validity of the models generated. These are summarized in Table 2. In most cases, the observed value is very close to the predicted value.

Reliable predictive models were generated for hardness and dissolution time, with R^2 (adj) ranging around 96%. The models were used to generate contour and trace plots for all table properties measured. These provide an easier interpretation of the effects of formulation and process variables on the tablet properties. Binder concentration in the formulation appeared to have had the most dominant effect on hardness. Under ideal conditions, at the same binder-drug ratio, the dissolution times of tablets should be the same, despite the drug level in the formulations. However, the different levels of fillers can cause other interactions between drug and binder, and can further affect the dissolution time.

CONCLUSIONS

Binder level has a significant effect on both tablet hardness and dissolution time. Useful predictive models were generated for tablet hardness and dissolution time as a function of formulation and compression force. The optimal formulation can be predicted from this study, and will depend upon the combination of desired hardness and dissolution time for a particular drug.

REFERENCES

1. J. Carstensen, J. Pharm. Sci., 65:992–998 (1976).
2. A. A. Chalmers and P. H. Elsworthy, J. Pharm. Pharmacol., 28:228–230 (1976).
3. J. L. Johnson, J. Holinej, and M. D. Williams, Int. J. Pharm., 90:151–159 (1993).

4. A. K. Hilton and P. B. Desay, Int. J. Pharm., 86:79–88 (1992).
5. A. S. Hussain, R. D. Johnson, P. Shivand, and M. A. Zoglio, Drug. Dev. Ind. Pharm., 20:2645–2657 (1994).
6. D. Harris, J. T. Fell, D. C. Taylor, J. Lynch, and H. L. Sharma, Int. J. Pharm., 56:97–102.
7. M. Efentakis, M. Vlachou, and N. H. Choulis, Drug Devl. Indus. Pharm., 23:107–112 (1997).
8. J. A. Cornell, *Experiments with Mixtures—Designs, Models and Analysis of Mixture Data*. John Wiley & Sons, New York, 1990.