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RESEARCH PAPER

Lubricant Susceptibility of Cellactose and Avicel PH-200: A Quantitative Relationship

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ABSTRACT

The lubricant susceptibility of two direct compression excipients, Avicel PH-200 and Cellactose, was determined using a model mix with metamizol sodium (dipyrone) and designed experiments to obtain a quantitative relationship by multiple regression. As a result, a new constant called specific lubricant sensibility L_s *is proposed for the comparison of lubricant susceptibility in other drug-excipient systems.*
Key Words: *Cellactose; Lubricant susceptibility; Metamizol sodium; Microcrystalline cellulose.*

INTRODUCTION

Lubricants are best identified as excipient ingredients that, when present in small amounts between two contacting, rubbing surfaces, reduce interfacial friction (1,2). It has been observed that some excipients in binary drug-excipient mixtures have better compactability when used without lubricants, as shown by the higher values of compact hardness obtained when a drug is compacted alone with an excipient in a single-punched machine with no lubricant added. If the same system is augmented with magnesium stearate, for example, a significant reduction of hardness achieved with the same compacting pressure is observed. Such change is due to the diminution in adhesion and cohesivity caused by the lubricant action.

The absolute reduction in cohesivity is a function of lubricant efficiency, but the same lubricant can affect diverse excipients in a different manner. Some of them are more susceptible than others, but that difference has only been evaluated qualitatively, and comparisons between excipients are difficult due to a lack of a quantitative relationship.

The objective of this paper is to provide a method to determine quantitatively, using factorial design, the lubri-

cant sensibility of excipients. The excipients utilized, Avicel™ PH-200 (a novel grade of microcrystalline cellulose) and Cellactose™ (a coprocessed material composed of pulverized lactose and hydrated lactose), are two direct-compression materials that recently appeared in the market and, because of the experience we obtained with the quantitative determination of load capacity (3), were chosen for the experiments in association with the drug metamizol sodium (dipyrone), known for its low deformation properties and lack of flow properties.

MATERIALS AND METHODS

Materials

Dipyrone (metamizol sodium DAB VIII) was obtained from Sashun Chemicals (Madras, India). Avicel PH-200 (FMC Corporation, Cork, Ireland) was obtained from Electroquímica Mexicana S.A., the same as croscarmellose sodium (Ac-Di-Sol™). Colloidal silicon dioxide (Aerosil™ 200) was obtained from Degussa GmbH, and stearic acid and magnesium stearate NF ultrafine powders were purchased from Helm de México, S.A. All materials were tested for accomplishment of specifications from USP 23, internal, or supplier specifications.

Methods

Preparation of Mixtures Drug/Excipients

A blend of 50% stearic acid, 25% magnesium stearate, and 25% colloidal silicon dioxide was obtained by blending of components in a bag and screening through a no. 30 mesh screen. This blend is called the lubricant mixture.

For the determination of lubricant susceptibility, the proportion 33.33:66.67 drug:excipient was selected as a base from previous studies (3). Each mixture (dipyrone: Cellactose and dipyrone:Avicel) was blended with 2% croscarmellose sodium NF and variable proportions of lubricant mixture ranging from 1% to 4 %. The complete composition of the 8 tests is described in Table 1.

Each sample was tested for bulk and tapped density using an Erweka SVM 2/DW tamped volumeter (Erweka Apparatebau GmbH, Germany) and repose angle as measured by a metallic cylinder with a circular base of known diameter (4,5). The repose angle presented here is the average of three determinations.

Each blend was also tested for compactability (6) at four different pressures in a Carver Press model C (Fred S. Carver Inc., USA) using a set of die and punches with a compacting area of 1 cm^2. A sample of 500 mg of each blend was weighed and put in the die with the lower punch in place; the upper punch was put over the set, and pressure was exerted by the press for 10 sec. The resulting compact was released from the die, and its weight, thickness, and hardness (as measured by an Erweka TBH-28 hardness tester) was registered. For each pressure, 10 tablets were obtained, with the aim of obtaining a profile of hardness versus compacting pressure.

In addition, 1 kg of each formulation was compressed in a Stokes tablet press with 16 stations, using 13-mm diameter, concave standard punches at a weight equivalent to 500 mg of dipyrone. The tablets obtained were tested for appearance, mass uniformity, hardness, thickness, and disintegration time.

Statistical Evaluation

Results of the test of compactability in the Carver Press were fitted into an empirical statistical model using the type of excipient (2 levels), pressure (4 levels), and percentage of lubricant mix (4 levels) as factors to obtain quantitative relationships between the variables. The response was the hardness of the compact. The statistical model was proposed and analyzed using the software SAS, release 6.0 (SAS Institute, Cary, IN). From the model proposed, some parameters and constants were de-

Table 1

Tentative Formulations of DipCel and DipAvi with Lubricants

	Amount per Formula (%)							
Ingredient	I	II	III	IV	V	VI	VII	VIII
DipCel blend	97	96	95	94				
DipAvi blend					97	96	95	94
Croscarmellose sodium	2	2	2	2	2	2	2	2
Lubricant mix	1	2	3	4	1	2	3	4
Total amount	100	100	100	100	100	100	100	100

Table 2

Rheological Results of Powder Blends I–VIII

Formulation	Repose Angle (°)	Bulk Density (g/ml)	Tapped Density (g/ml)
Blend dipyrone-Cellactose	59.0	0.535	0.633
DipCel-Ac-Di-Sol	57.0	0.527	0.643
I	55.9	0.527	0.643
II	55.7	0.514	0.643
III	53.1	0.527	0.644
IV	57.8	0.508	0.627
Blend dipyrone-Avicel	56.7	0.490	0.612
DipAvi-Ac-Di-Sol	56.2	0.483	0.611
V	55.1	0.520	0.642
VI	56.2	0.517	0.638
VII	58.3	0.501	0.638
VIII	58.0	0.495	0.626

fined to evaluate the differences between the behavior of both excipients.

In addition, disintegration times of the tablets compressed in the Stokes tablet press were taken as a variable of response in a design in which independent variables were type of excipient A and lubricant mixture concentration L. Such a design was also analyzed by SAS.

RESULTS AND DISCUSSION

Evaluation of the Blends

Table 2 shows the rheological results of the powder mixtures I to VIII and of the intermediate mixtures dipyrone/main excipient and dipyrone/excipient/croscarmellose sodium. The compactability profiles of the powder mixtures as obtained by Carver Press are seen in Figs. 1 and 2.

The compression in the Stokes tablet machines gave tablets with good appearance; the determinations for each formulation are shown in Table 3. In a general manner, it can be said that all the formulations are suitable for compression since there was no need of overpressure to obtain tablets with hardnesses higher than 7 kp and fragilities less than 1%; all disintegration times were lesser than 15 minutes.

Mathematical Modeling of Lubricant Susceptibility

From the results of the compactability tests, an empirical model was obtained with an R^2 value higher than 0.8 (0.9249), indicating that almost all of the variability is explained by the model. It can be represented by the following equation:

$$H = -2.9244 + 0.0193P + 1.2581L - 0.00084PA - 0.3383LA - 0.0012PL + 0.0006287PLA - 0.000004878P^2$$

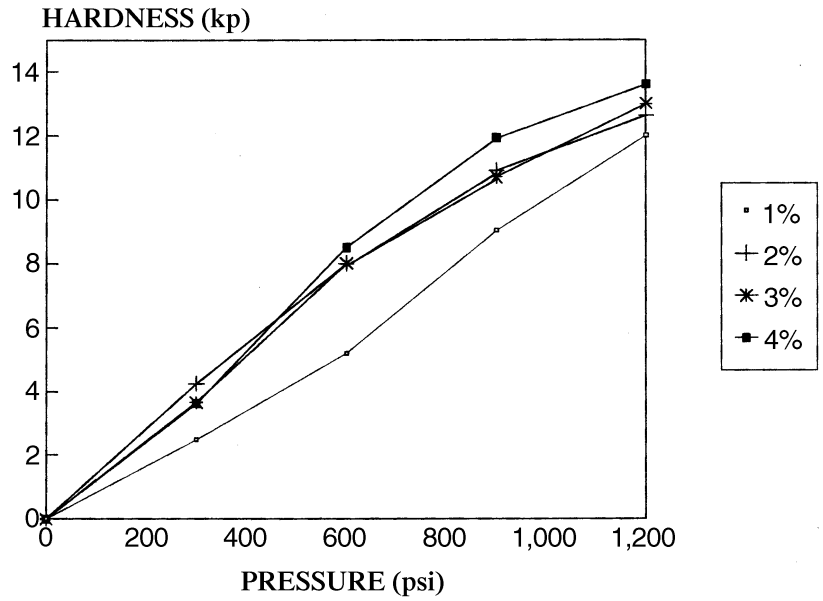

Figure 1. Compacting profile of the four formulations with Avicel PH-200 for which the amount of lubricant mix was varied.

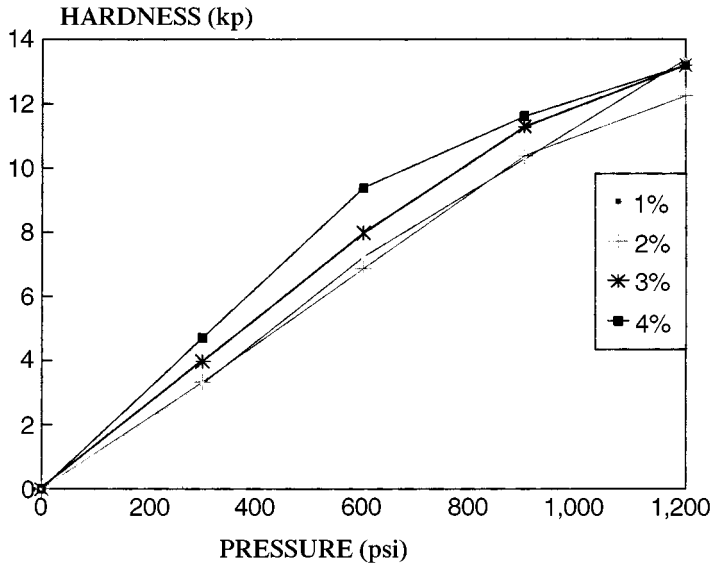

Figure 2. Compacting profile for the formulations with Cellactose.

where H is the hardness obtained at a given pressure P, L is the lubricant mix concentration, and A is an arbitrary term that denotes the type of excipient (1 for Cellactose, 2 for Avicel). The response surfaces predicted by the model can be seen in Figs. 3 and 4. Prediction of compactibility profiles for both systems related to the lubricant concentration are shown in Figs. 5 and 6.

When $A = 1$ (Cellactose), the model simplifies to

$$H = -2.9244 + 0.0193P + 1.2581L - 0.00084P - 0.3383L - 0.0012PL + 0.0006287PL - 4.878 \times 10^{-5} P^2$$

$$= -2.9244 + 0.0185P + 0.9198L - 0.0005713PL - 4.878 \times 10^{-5}P^2$$

It is possible to find four cases:

Case 1. When $L = 1$.

$$H = -2.0046 + 0.0179P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,\,A} = 0.0179 - 0.00009756P$$

Case 2. When $L = 2$.

$$H = -1.0848 + 0.0174P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,\,A} = 0.0174 - 0.00009756P$$

Table 3

Results in Compression in Stokes Tablet Machine

Formulation	Average Weight (mg)	Weight Variation (%)	Hardness (kP)	Thickness (mm)	Friability (%)
I	778.64	0.423	9.76	6.334	0.259
II	785.7	0.538	9.91	6.160	0.221
III	793.43	0.643	9.25	6.236	0.247
IV	803.12	0.484	10.09	6.271	0.209
V	777.71	0.501	8.5	6.197	0.484
VI	785.23	0.536	9.58	6.150	0.320
VII	798.57	0.781	8.57	6.279	0.261
VIII	800.27	0.608	9.00	6.269	0.300

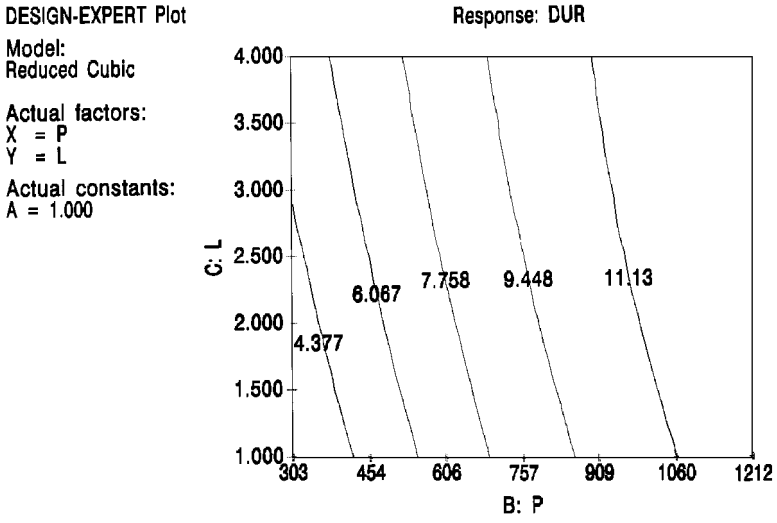

Figure 3. Response surface for blends containing Cellactose, according to the model.

Case 3. When $L = 3$.

$$H = -0.1650 + 0.0168P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,\,A} = 0.0168 - 0.00009756P$$

Case 4. When $L = 4$.

$$H = 0.7548 + 0.0162P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,\,A} = 0.0168 - 0.00009756P$$

Now, if $A = 2$ (Avicel), the model becomes

$$\begin{aligned} H &= -2.9244 + 0.0193P + 1.2581L \\ &\quad - 0.00168P - 0.6766L - 0.0012PL \\ &\quad + 0.0012574PL - 4.878 \times 10^{-5}P^2 \\ &= -2.9244 + 0.0176P + 0.5815L \\ &\quad + 0.0000574PL - 4.878 \times 10^{-5}P^2 \end{aligned}$$

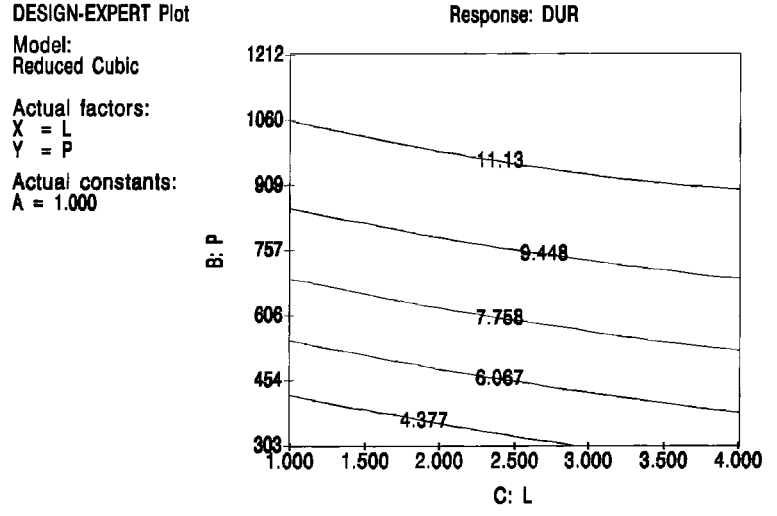

Figure 4. Response surface for blends containing Avicel, according to the model.

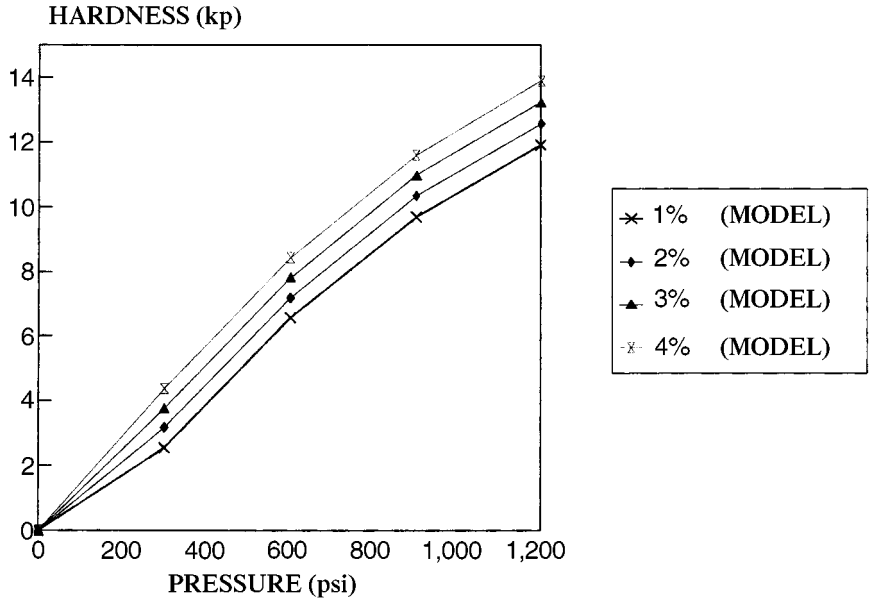

Figure 5. Compactability profiles of formulations with Avicel, as predicted by the model.

and the following cases apply:

Case 1. When $L = 1$.

$H = -2.3429 + 0.01766P - 4.878 \times 10^{-5}P^2$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,A} = 0.01766 - 0.00009756P$$

Case 2. When $L = 2$.

$H = -1.7614 + 0.01771P - 4.878 \times 10^{-5}P^2$

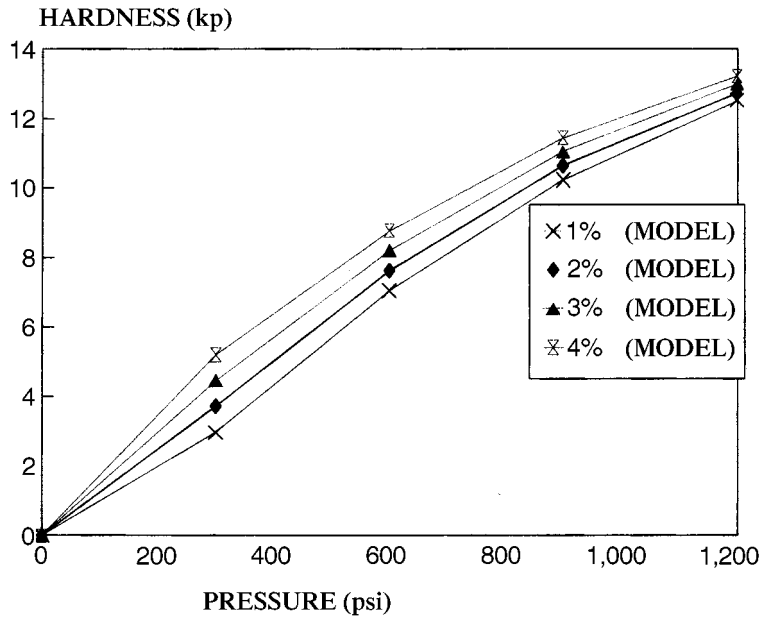

Figure 6. Compactability profiles of formulations with Cellactose, as predicted by the model.

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,A} = 0.01771 - 0.00009756P$$

Case 3. When $L = 3$.

$$H = -1.1799 + 0.01777P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,A} = 0.01777 - 0.00009756P$$

Case 4. When $L = 4$.

$$H = -0.5984 + 0.01783P - 4.878 \times 10^{-5}P^2$$

where

$$\left(\frac{\delta(H)}{\delta P}\right)_{L,A} = 0.01783 - 0.00009756P$$

It can be seen that, in each case, the coefficient of P is a linear function of lubricant mix content L. When plotting such coefficients against L (Fig. 7), we can obtain the following relationships:

Cellactose $m = I_{lub}^{cel} + K_{lub}^{cel}L$
$= 0.0185 - 0.0006L$

Avicel $m = I_{lub}^{av} + K_{lub}^{av}L$
$= 0.0176 + 0.0001L$

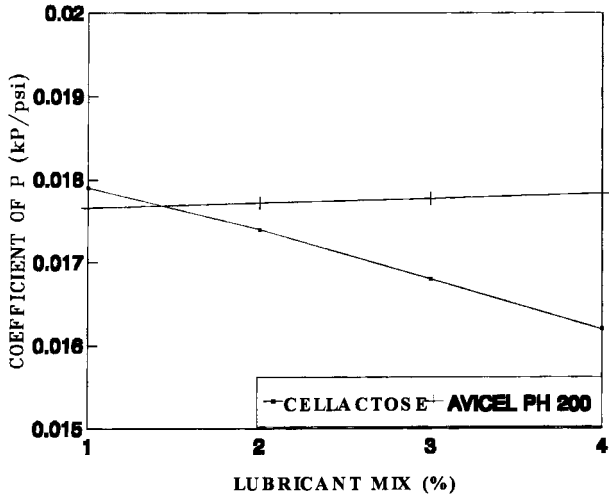

Figure 7. Determination of lubricant susceptibility: comparison of Cellactose with Avicel.

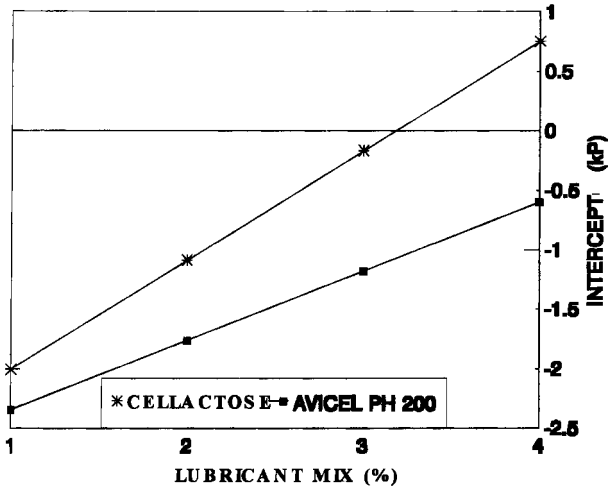

Figure 8. Comparison of intercepts between Cellactose and Avicel.

The examination of these results shows that, in the case of Cellactose, the hardness at a given pressure decreases slightly as the lubricant increases, while in the case of Avicel, hardness is almost constant at a constant pressure; this an indication of the low sensibility of Avicel to the action of lubricants, less than that of Cellactose (Figs. 7 and 8). It must be remarked that, in both cases, lubricant susceptibility is low, as shown by the hardness increase with the increase of lubricant mix due to the influence of the lubricant over the intercept, which becomes more positive, as can be seen in Fig. 8. Again, this effect is more intense in formulations containing Cellactose.

Modeling of Disintegration Data

Disintegration times obtained from the eight formulations apparently were strongly influenced by the lubricant proportion. To support the hypotheses, the disintegration times obtained from the batches compressed in the Stokes tablet machine were introduced into a statistic factorial model with interactions in which controlled variables are the excipient type A and lubricant mix concentration L, while the variable of response is disintegration time DES. The statistical analysis of the model by SAS allowed discrimination from two possible models, and the best fit was obtained for the following model:

$$DES = 4.1631 + 4.1970\,L - 0.38172\,LA - 0.3193\,L^2$$

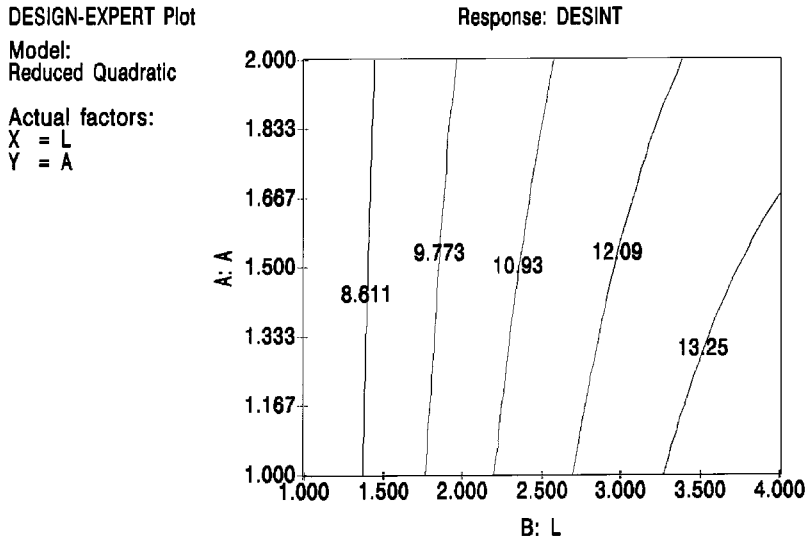

Figure 9. Response surface for disintegration model. $A = 1$ is Cellactose; $A = 2$ is Avicel.

with $R^2 = .8683$. The response curve can be observed in Fig. 9.

Again, there is a difference between both excipients, as when $A = 1$ (Cellactose), the model becomes

$$DES = 4.1631 + 3.8153L - 0.3193L^2$$

and when $A = 2$ (Avicel), the model is reduced to

$$DES = 4.1631 + 3.4335L - 0.3193L^2$$

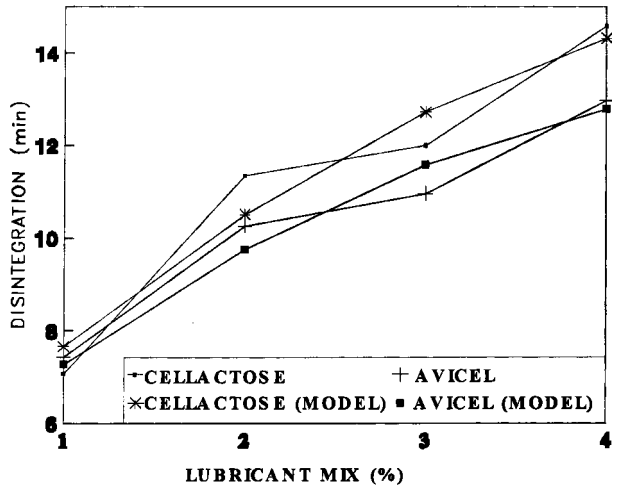

Figure 10. Modeling of disintegration data for both excipients.

From this, it is deduced that Avicel gives disintegration times shorter that those of Cellactose. Figure 10 shows both real data and data predicted by the model.

Choice of an Ideal Formulation

All the formulations gave good results in tableting performance. However, study of actual disintegration profiles shows little difference between profiles with 2% or 3% lubricant mix percentage, both in Cellactose and Avicel. If the criteria for an ideal formulation includes such formulations with minimum disintegration times and also good compressibility, then the formulation with Avicel PH-200 and 2% lubricant mix might be chosen because of adequacy of both criteria. In addition, the response curve of disintegration times shows that such a choice enables the maintenance of disintegration times less than 10 minutes.

We believe that methods outlined here may be used in studies for lubricant/excipient selection in the formulation of pharmaceutical solids and in preformulation studies.

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