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COMMUNICATION

Study of Load Capacity of Avicel PH-200 and Cellactose, Two Direct Compression Excipients, Using Experimental Design

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ABSTRACT

The load capacity of two excipients, a large particle size grade of microcrystalline cellulose (Avicel™ PH-200) and a coprocessed material composed of lactose and pulverized cellulose (Cellactose™) was determined using a model mix with Dipyrone (metamizol sodium) and experiments planned by design of experiments. A multiple-regression model was proposed, and as a result, a new parameter, called specific load capacity S_{LC} *was obtained. This constant can be determined for other excipients and drugs; it depends only on the excipient and the drug used.*
Key Words: *Cellactose; Load capacity; Metamizol sodium; Microcrystalline cellulose.*

INTRODUCTION

The term *load capacity* (LC) for an excipient has appeared frequently in the pharmaceutical literature, but most of the time, such a parameter is not clearly defined; the data offered by the supplier of the excipient are not objective, quantitatively defined, or specific. Load capacity of an excipient can be defined as the minimum concentration at which the excipient can be mixed with a drug and the mix keeps the desirable properties of the excipient, such as compressibility, flow rate, the ability to form hard compacts at low pressures, and so on.

Recently, two new excipients for direct compression have appeared in the market: Avicel™ PH-200, a grade

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of microcrystalline cellulose with larger particle size than Avicel PH-102 (FMC Corp., Cork, Ireland), and Cellactose, a coprocessed material composed of pulverized cellulose and hydrated lactose (Meggle GmbH, Wasserburg, Germany). Suppliers of these materials provide information about each that suggests a high load capacity caused by high binding capacity and the ability to form strong and hard tablets (1–4). Both excipients have great possibilities in direct compression.

The aim of this paper was to determine the load capacity of Avicel PH-200 and Cellactose using binary mixtures with a model drug. Dipyrone (metamizol sodium) was selected because of its difficulty in forming a compact, its low plastic properties, and its lack of flow properties. The objective was to determine quantitatively the load capacity using design of experiments (DOE) and response surface methodology (RSM).

EXPERIMENTAL

Materials

Dipyrone (metamizol sodium DAB VIII) was obtained from Sashun Chemicals (Madras, India). Avicel PH-200 was obtained from Electroquímica Mexicana, S. A., as was croscarmellose sodium (Ac-Di-Sol™). Colloidal silicon dioxide (Aerosil™ 200) was obtained from Degussa GmbH (Frankfurt, Germany), 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

Compressibility Evaluation of Binary Mixtures of Dipyrone-Excipient

Four binary combinations of dipyrone and each of the main excipients (Cellactose or Avicel) were manufactured according to a factorial design $2^1 \times 4^2$ (three factors, one with two levels and two with four levels) using the following drug concentrations: 33.33% (blend 1:3), 50% (blend 1:1), 66.67% (blend 2:1), and 75% (blend 3:1). Each sample was tested for bulk and tapped densities using an Erweka SVM 2/DW tamped volumeter (Erweka Apparatebau GmbH, Heusenstamm, Germany) and for repose angle as measured by a metallic cylinder with a circular base of known diameter (5,6).

Each blend was also tested for compactability at four different pressures in a Carver Press model C (Fred S. Carver, Inc., Menomonee, WI) using a set of die and punches with a compacting area of 1 cm^2. A sample of 500 mg of each blend was compressed, and the 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 the Erweka TBH-28 hardness tester) was registered. For each pressure, 10 tablets were obtained, and a profile of hardness versus compacting pressure was plotted with the data obtained.

Statistical Evaluation

Results of the test of compactability were fitted to an empirical statistical model using the type of excipient (2 levels), pressure (4 levels), and fractional drug content (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, Carey, IN). From the model proposed, some parameters and constants were defined to evaluate the differences between the behavior of both excipients.

Experimental Comparison of Load Capacity

Using the hardness data obtained at a constant compacting pressure of 62.673 Pa for each blend of Dipyrone-excipient, a graphical comparison was made between load capacity of Cellactose and Avicel PH-200, plotting hardness versus Dipyrone percentage (Fig. 1).

DISCUSSION

Evaluation of the Blends

The rheological behavior of the blends of Dipyrone-Cellactose (DipCel) and Dipyrone/Avicel (DipAvi) can

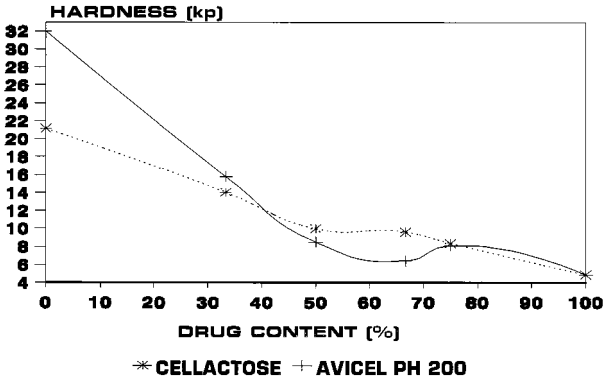

Figure 1. Comparison of load capacity between Cellactose and Avicel PH-200.

Table 1

Rheological Evaluation of Dipyrone/Cellactose Blends

Dipyrone Content (%)	Repose Angle (°)	Bulk Density	Tapped Density
33.00	57.7	0.426	0.540
50.00	62.4	0.451	0.585
66.67	63.6	0.457	0.603
75.00	66.1	0.453	0.613
100.00	64.6	0.492	0.669

be seen in Tables 1 and 2. Figures 2 and 3 show the compacting profile of blends Dipyrone-Cellactose and Dipyrone-Avicel in compact hardness. It can be observed that, in both cases, an increase in Dipyrone concentration led to a decrease in the compactability of the blend, as measured by the hardness obtained at a given pressure.

Load Capacity

According to the data from Figs. 1–3, there are significant differences among blends containing Cellactose or Avicel. It can be seen from the analysis of Fig. 1 that the blends with Cellactose gave lower values of hardness than blends with Avicel when the Dipyrone percentage was below 40%; then, the inverse phenomenon occurs, and Cellactose blends yielded higher values of hardness than Avicel up to 75%, when the values are almost equalized. For each excipient, a plateau can be observed at which the hardness is almost constant between 50% and 70% of Dipyrone fraction.

The question that must be posed is which is the best excipient. In our case, the best excipient was defined as the one that, when mixed with Dipyrone, was less affected in its flow and compactability properties. These conditions are best accomplished by Cellactose, even though lesser flow angles can be obtained using Avicel PH-200 (see Fig. 4).

Table 2

Rheological Evaluation of Dipyrone/Avicel PH-200 Blends

Dipyrone Content (%)	Repose Angle (°)	Bulk Density	Tapped Density
33.00	57.4	0.422	0.535
50.00	61.8	0.444	0.570
66.67	64.1	0.452	0.602
75.00	63.1	0.460	0.618
100.00	64.6	0.492	0.669

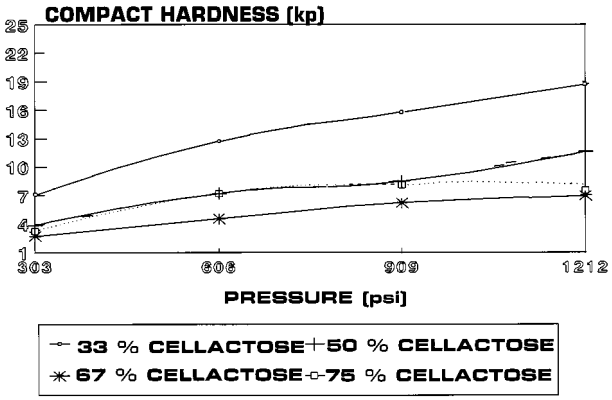

Figure 2. Pressure-hardness profile for blends of Dipyrone-Cellactose.

Analysis of the Statistical Model

To obtain an adequate relationship between the hardness data and the type of excipient, it was supposed that hardness H depends on the following factors: (*a*) type of excipient (Cellactose or Avicel, A in the model); (*b*) compaction pressure P; Dipyrone content in terms of fraction of weight D; and its interactions. During the statistical modeling process, the following general model was tested:

$$H = 87.09 + 2.91 \times 10^{-5}P - 242.27D - 1.68 \times 10^{-5}PD - 1.22 \times 10^{-6}PDA$$

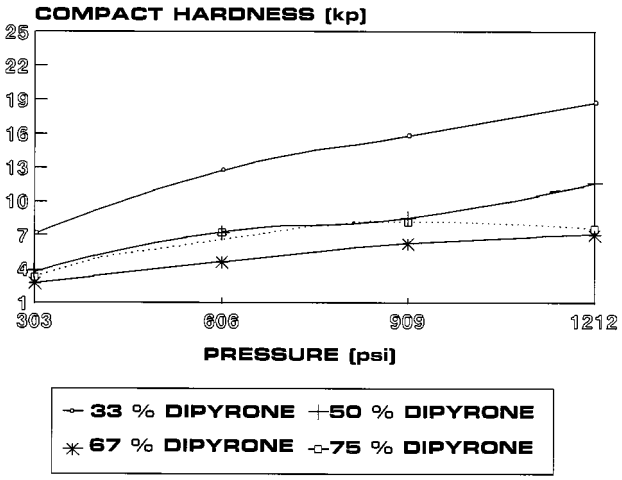

Figure 3. Pressure-hardness profile for blends of Dipyrone-Avicel.

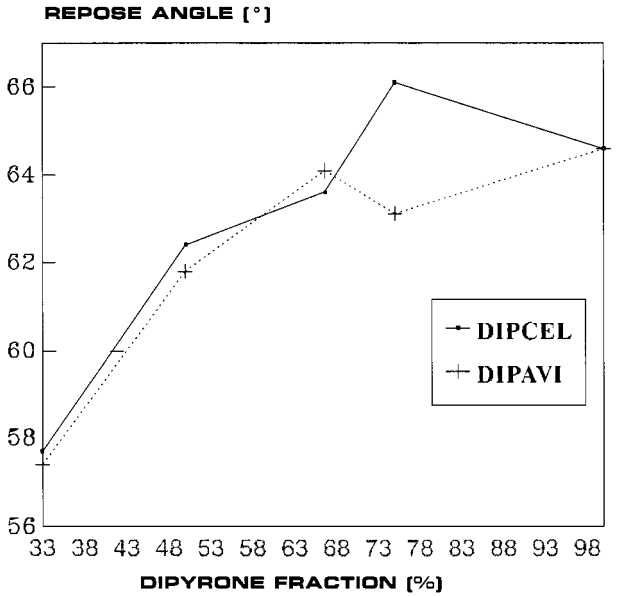

Figure 4. Repose angle comparison obtained with binary mixtures of Cellactose and Avicel PH-200.

$$- 7.49 \times 10^{-13} P^2 + 172.82D^2$$

with H expressed in newtons and P in N/m^2. When Cellactose was used, $A = 1$, and the model simplifies to

$$DUR = 87.09 + 2.91 \times 10^{-5}P - 242.2678D - 1.81 \times 10^{-5}PD - 7.49 \times 10^{-13}P^2 + 172.82D^2$$

Making constant the Dipyrone content D, we obtained a second-order equation in which H depends only on pressure. For example, when $D = 0.33$,

$$H = 26.30 + 2.32 \times 10^{-5}P - 7.49 \times 10^{-13}P^2$$

$$\left(\frac{\delta(H)}{\delta P}\right)_{D,A} = 2.32 \times 10^{-5} - 1.50 \times 10^{-12}P$$

The coefficient on P is a lineal function of Dipyrone content D. In the case of $A = 2$ (Avicel), the model simplifies to

$$H = 87.09 + 2.91 \times 10^{-5}P - 242.27D - 1.94 \times 10^{-5}PD - 7.49 \times 10^{-13}P^2 + 172.82D^2$$

and when $D = 0.33$,

$$H = 26.31 + 2.28 \times 10^{-5}P - 7.49 \times 10^{-13}P^2$$

$$\left(\frac{\delta(H)}{\delta P}\right)_{D,A} = 2.28 \times 10^{-5} - 1.50 \times 10^{-12}P$$

In the same way as with Cellactose, the coefficient on P is a lineal function of Dipyrone content D. When plotting such coefficients against D (Fig. 5), we can obtain the following relationships:

Cellactose $K' = 2.91 \times 10^{-5} - 1.7928 \times 10^{-5}D$

Avicel $K'' = 2.91 \times 10^{-5} - 1.9350 \times 10^{-5}D$

We can define a constant called specific load capacity S_{LC} for each excipient, expressed in square meters when the hardness is expressed in newtons: for Cellactose, it is -1.793×10^{-5}, and for Avicel PH-200, it is -1.935×10^{-5}. This constant may be considered as the real surface over which the pressure is applied, excluding voids, and the difference between both values is a function of parameters such as crystallinity, plasticity, yield stress, and other physical constants. We believe this parameter can be used to distinguish between load capacities of two or more excipients. According to our results, Cellactose has a 12% higher load capacity than Avicel PH-200. In a blend with 67% Dipyrone, it is possible to obtain a hardness of 10.23 kp at a pressure of 1653 psi if the excipient

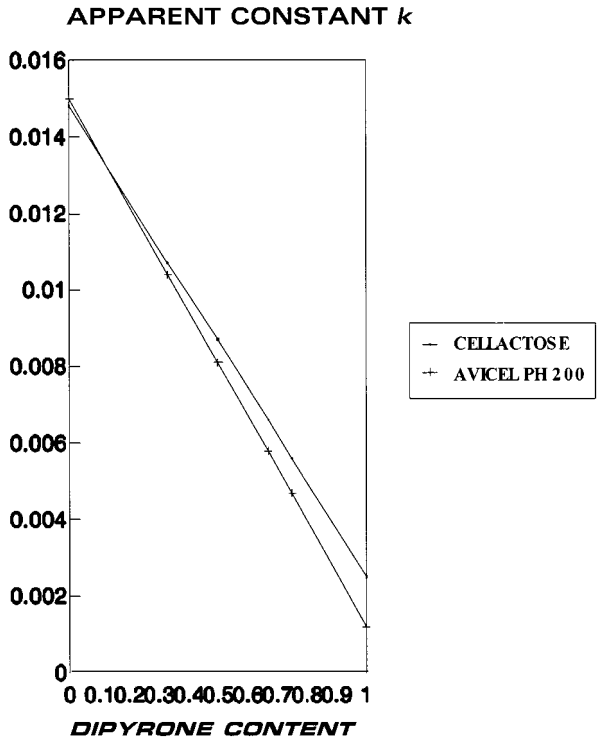

Figure 5. Comparing apparent constants to determine specific load capacity in both excipients.

is Cellactose and of 9.23 kp at the same pressure if Avicel PH-200 is used.

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