DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(14-16), 2419-2440 (1989)



# STATISTICAL OPTIMIZATION OF A CONTROLLED RELEASE FORMULATION OBTAINED BY A DOUBLE COMPRESSION PROCESS: APPLICATION OF AN HADAMARD MATRIX AND A FACTORIAL DESIGN

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## ABSTRACT

A formulation containing an antiinflammatory agent (diclofenac sodium), two inert matrices (ethylcellulose and polyvinyl chloride) and two lubricants (magnesium stearate and talc) was optimized by a double compression process.

In a first stage, preliminary trials were performed in order to study the effect of lubricants added before and after precompression.

An Hadamard matrix H(8) was applied to estimate the main effects of four parameters: applied force at the upper punch (**UPF**) during precompression, particle size range after grinding, **UPF** during the final

compression and concentration of ethylcellulose added before the final compression.

Following the Hadamard matrix, a factorial design $2^2$ was built. The complete linear models were fitted by regression for each response reflecting the compression behaviour and dissolution kinetics.

In an optimal point, the validation was carried out with the area under the dissolution curve, being the major response to be optimized.

The dissolution curves were well fitted by the Weibull distribution.

## INTRODUCTION

Dry granulation is a process which consists of granulating a powder by compression, avoiding the wetting and drying steps.

The advantages and inconveniences of this process were described by Sheth (1).

The two methods used for dry granulation are compaction and double compression. Compaction being the subject of other papers (2, 3), the main goal of this study was to optimize a sustained release formulation obtained by double compression.

Two polymers were incorporated in the inert matrix system: ethylcellulose and polyvinyle chloride. The process used to prepare tablets containing such polymers often includes direct compression (4, 5, 6), wet granulation (7, 8), coating (9-11) and rarely, dry granulation (12).

In a previous work, the formula used in this study, was optimized by direct compression (13). Three parameters were implied: tablet weight, ethylcellulose/Pevikon ratio and talc concentration.

The area under the dissolution curve was optimized and validated thanks to the application of a composite design. However, the formulation presented a poor powder flow as well as an important variability between tablets regarding the dissolution parameters.

The double compression process was investigated in order to change the powder into solid aggregates and therefore to enhance homogeneity, density, and powder flow; in addition it was expected that this process reduce the variability between tablets.

Statistical optimization was conducted in three steps:

- An Hadamard matrix H(8) was first applied to study the main effects of four parameters.
- A factorial design $2^2$ was built to obtain a complete linear model including only 2 parameters.
- Validations of the mathematical model and the optimum formulation were then performed.

## MATERIALS

The formula contained the drug, two inert matrices and two lubricants :

| | | |
|---|---|---|
| Diclofenac sodium | (Secifarma)..... | 25.0 % |
| Ethylcellulose N-7 | (Hercules)..... | 26.1 % |
| Pevikon PE 737 P | (SEPPIC)..... | 45.9 % |
| Magnesium stearate | (Prophac)..... | 1.0 % |
| Talc USP | (Prophac)..... | 2.0 % |

## METHODS

### The Manufacturing Process

When using a dry granulation process, it is highly recommended to add a dried binder to the mixture in

order to ensure an acceptable cohesion between particules.

Therefore, in this present study, ethylcellulose was incorporated in 2 parts :

- before precompression as a binder,
- before the final compression as an independent variable in the experimental design.

The manufacturing process was followed as described below :

- POWDERS MIXING during 5 min in a Turbula WAB (T2C, Willy A. Bachofen AG),
- PRECOMPRESSION using a Frogerais 0A single punch instrumented press (Ets. Ed. Frogerais), equipped with flat punches 11.28 mm in diameter (surface 1 $cm^2$). The speed of the machine was adjusted to one tablet/second.
- MILLING carried out in an Erweka oscillating granulator equipped with two screens with 3.15 mm perforation for premilling and 0.8 mm perforation for the final milling.
- GRINDING and separation of the particle size range desired in a Russell vibratory motion machine (Russell Finex, London & New York),
- MIXING and lubrication during 3 min.
- FINAL COMPRESSION in the same instrumented tablet machine. The depth of the die was adjusted for each formulation in order to obtain a 400 mg tablet.

## TESTS PERFORMED

### Powder test

The powder flow rate test was performed using a standardized glass funnel. The volume before and after tapping ($\Delta V = V_{10} - V_{500}$) was measured in the Eberhard

Bauer (J. Engelsmann AG) tapping volume meter (14, 15, 16).

Physics of compression

The method of the physics of compression used in this study was described in a previous paper (14).

In a sampling of 10 tablets, the following parameters were studied : the lubrication index (R), the ejection force (Fe), the residual force (Fr) and the cohesion index (CI=ratio of the pressure applied to the upper punch and the tensile strength) proposed by Guyot (17).

In one of the 10 tablets, the mechanical work was calculated using the parameter of the total energy liberated during the compression (Et).

In a sampling of 120 tablets, the friability, the variability of the tablet weight and the variability of the upper punch force were determined.

Tablet tests

Friability was determined on 20 tablet samples in a friabilaty tester Erweka TA3R (15 min, 25 rpm).

The weight variation was evaluated on 20 tablets in an electronic balance Mettler AK 260 (Sofranie).

Tablet hardness was measured on 10 tablets using a Schleuniger hardness tester (Soteco).

Dissolution studies

Six tablets were subjected to dissolution using USP dissolution apparatus (Vanderkamp 600, Van-Kel Ind., New Jersey, USA) in 500 ml buffer pH 1.2 (the first hour) and 650 ml buffer pH 6.8 (1-14 h), maintained at 37°C and rotated with paddles at 50 rpm (first hour) and 130 rpm (1-14 h). The dissolution apparatus was connected to a UV-Vis spectrophotometer

(Uvikon 810, Roche bioéléctronique Kontron, Marseille) and a computer VAX 780 (Digital). Absorbance of the dissolution medium at 275 nm was recorded automatically at the intervals: 1, 2, 4, 5, 8, 10, 12 and 14 hours. Percentage of the drug released was calculated and the corresponding release profiles were obtained.

## PRELIMINARY TRIALS

The objective of the preliminary trials was to define the best way to incorporate the lubricants, before or after the precompression operation. Three experiments were carried out :

Exp. A : Talc was added before precompression and magnesium stearate before the final compression.

Exp. B : 50% of each lubricant was incorporated before and after precompression.

Exp. C : Magnesium stearate was mixed before precompression and Talc before the final compression.

In these three experiments, 50% of EC was added before precompression and the other 50% before the final compression.

Precompression was conducted at 10 kN (UPF) and 10 mm depth of the die. After milling and grinding, the 100-800 $\mu$m particle size range was collected and lubricated. For final compression, the powder was compressed at 10 kN .

### Results and discussion

Results obtained from the preliminary trials described above are indicated in Table 1. The mean values of three trials performed for validation of the optimized formulation by direct compression (13) are given for comparison. The release profiles are illustrated in Figure 1.

**TABLE 1**

| EXPERIMENT / PARAMETER | | A | B | C | DIRECT COMPRESSION |
|---|---|---|---|---|---|
| Powder Flow Rate (g/sec) | | 16.7 | 16.7 | 9.0 | 0.0 |
| ΔV (mL) | | 21.0 | 18.0 | 17.0 | 52.0 |
| R | (pc) | 0.73 | 0.76 | 0.84 | 0.82 |
| | (fc) | 0.88 | 0.87 | 0.79 | |
| Fe (kN) | (pc) | 0.50 | 0.32 | 0.16 | 0.21 |
| | (fc) | 0.17 | 0.18 | 0.33 | |
| Fr (kN) | (pc) | 0.56 | 0.34 | 0.13 | 0.17 |
| | (fc) | 0.05 | 0.06 | 0.23 | |
| Cohesion Index | (pc) | 84 | 84 | 78 | 71 |
| | (fc) | 91 | 130 | 385 | |
| Et N·m | (pc) | 37.1 | 34.8 | 34.6 | 33.5 |
| | (fc) | 21.6 | 19.7 | 19.2 | |
| UPF Variation (C.V. %) | | 2.5 | 1.9 | 2.2 | 4.0 |
| Weight Variation (C.V. %) | | 1.1 | 0.4 | 0.8 | 1.8 |
| Friability (%) | | 0.83 | 1.14 | 1.65 | 0.09 |
| % Dissolved at 8 h<br>C.V. (%) | | 63.7<br>5.3 | 88.4<br>1.1 | 109.8<br>1.1 | 56.5<br>12.4 |
| AUC (% h)<br>C.V. (%) | | 657<br>7.6 | 975<br>1.7 | 1226<br>1.6 | 667<br>9.0 |

pc = precompression ; fc = final compression

As expected, the flow rate, ΔV, R, Fe, Fr, Et, UPF variation and Weight variation were better than direct compression results. CI and friability were affected due to the poor crushing strength (hardness) of the tablets obtained after the final compression.

Double compression largely decreases the coefficients of variation of the percentage dissolved at 8 hours and AUC.

Adding lubricants before or after precompression shows an effect on the different studied properties. Experiments A and B give better values than experiment

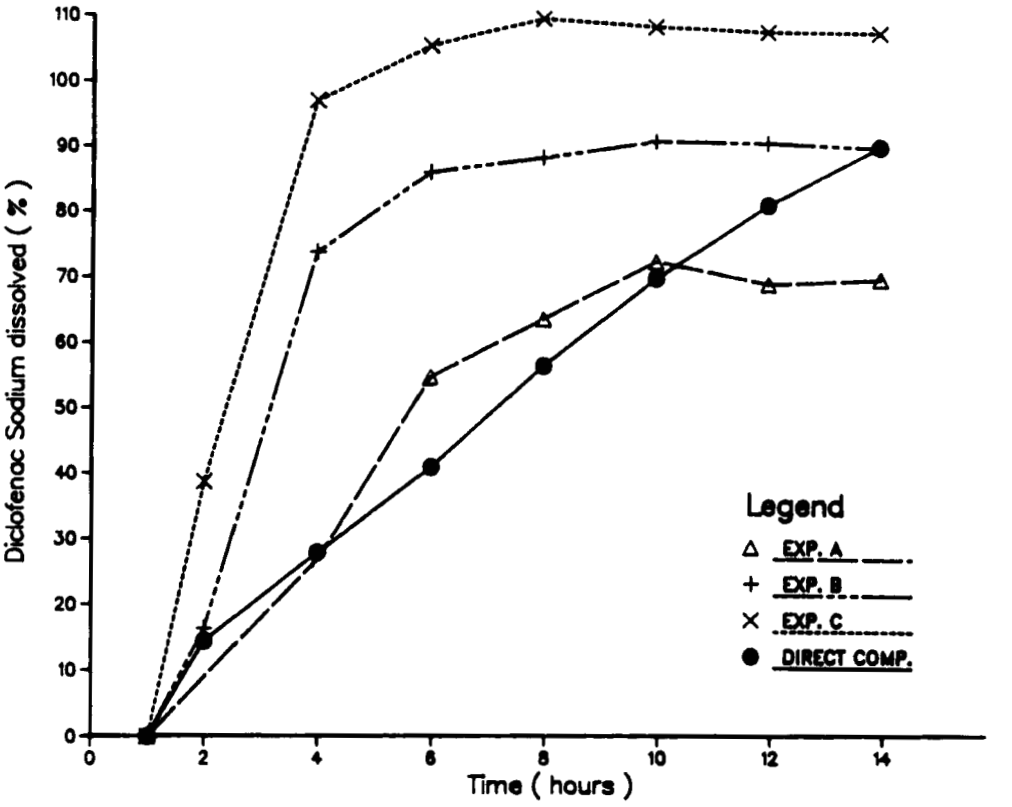


**FIGURE 1**
Release profiles of Preliminary Trials

C. In addition, R, Fe, Fr and CI parameters are affected when talc is added alone before the final compression.

In conclusion, the incorporation of 50% of magnesium stearate and talc before precompression and the other 50% before the final compression, improves the compression behaviour. At the same time, it decreases the coefficients of variation of UPF, weight tablet and dissolution parameters.

Regarding these results, the process from experiment B was chosen for the experimental designs.

**TABLE 2**

Independent Variable Levels

| $P_i$ | $X_i$ level: | −1 | +1 |
|---|---|---|---|
| $P_1$ : | UPF during precompression (kN) | 8 | 12 |
| $P_2$ : | Particle size range ($\mu$m) | 100-400 | 400-800 |
| $P_3$ : | UPF at the final compression (kN) | 8 | 12 |
| $P_4$ : | EC before the final compression (%) | 20 | 30 |



## APPLICATION OF AN HADAMARD MATRIX H(8)

### Experimental Design

The theory and application of an Hadamard matrix were shown by Ozil and Rochat (18). This design is an optimum strategy leading to a good accuracy of the main effects from a minimal experiments number (N parameters + 1 = number which is a power of 2). With the coefficients ($b_i$) a linear model can be found for a given response Y :

$$Y = b_o + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_nX_n + \text{Residue}$$

$X_i$ is a reduced variable associated with each parameter $P_i$ :

$$X_i = [\, 2(P_i - P_{mean}) \,/\, (P_{maxima} - P_{minima}) \,]$$

**TABLE 3**

| $Y_i$ | Responses | Optima values |
|---|---|---|
| $Y_1$ | $\Delta V = V_{10} - V_{500}$ (ml) | < 20 |
| $Y_2$ | Cohesion Index | < 100 |
| $Y_3$ | Weight variation (C.V., %) | < 1 |
| $Y_4$ | Friability of tablets (%) | < 1 |
| $Y_5$ | Drug dissolved at 8 h (%) | ~ 60 |
| $Y_6$ | AUC (% dissolved·hour) | ~ 713 |
| $Y_7$ | Coefficient of variation of $Y_5$ (%) | < 5 |
| $Y_8$ | Coefficient of variation of $Y_6$ (%) | < 5 |

Four independent variables were chosen for optimizing the rheology, the compression behaviour and the dissolution kinetics. Table 2 lists these four variables and their experimental ranges (levels). In order to decrease friability and CI, the percentage of EC before the final compression was decreased.

Table 3 shows the responses to be optimized among which AUC was considered as the major one. A constant release between one and twelve hours (passing by 60% dissolved at 8 h) and a complete dissolution after 14 h was chosen as an optimum profile (AUC=713 %·h).

As 4 parameters were studied, 3 dummy variables $X_5$, $X_6$, $X_7$ were included to build an Hadamard matrix H (8) composed of 7 parameters :

$$X_i \rightarrow \quad \begin{matrix} & 1 & 2 & 3 & 4 & 5 & 6 & 7 \end{matrix}$$

$$H(8) = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 & 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 & 1 & -1 & -1 & 1 \\ 1 & 1 & 1 & 1 & -1 & -1 & -1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & 1 & -1 & -1 & -1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 \end{bmatrix}$$

**TABLE 4**

Experimental Design

| Experiment | $P_1$ (kN) | $P_2$ ($\mu$m) | $P_3$ (kN) | $P_4$ (%) |
|---|---|---|---|---|
| 1 | 12 | 400-800 | 12 | 30 |
| 2 | 8 | 400-800 | 8 | 30 |
| 3 | 12 | 100-400 | 8 | 30 |
| 4 | 8 | 100-400 | 12 | 30 |
| 5 | 12 | 400-800 | 12 | 20 |
| 6 | 8 | 400-800 | 8 | 20 |
| 7 | 12 | 100-400 | 8 | 20 |
| 8 | 8 | 100-400 | 12 | 20 |

The columns 1 to 4 lead to the matrix of experiments. According to the original units (Table 2), 8 trials were carried out (Table 4). To avoid systemic errors, the trials were performed in randomised order.

The analysis of variance (ANOVA) gives information on significant main effects. Data were analyzed using the GLM procedure (General Linear Model) from SAS (Statistical Analysis System, SAS Institute, Cary NC). A discussion and explanation of the statistics involved are described in Davies (19).

Responses $Y_2$, $Y_5$ and $Y_6$ were transformed in the natural logarithm to homogenize the distribution of the residues. Then, the F-test was used to determine the statistical significance of the effects. As an indication, an effect was considered as significant when $F>4$ [$4=F_{0.95}(1,60)$].

**TABLE 5**

Hadamard Matrix H(8) results

| EXP / $Y_i$ | $Y_1$ | $Y_2$ | $Y_3$ | $Y_4$ | $Y_5$ | $Y_6$ | $Y_7$ | $Y_8$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 12 | 126 | 0.55 | 0.78 | 85.7 | 869 | 3.2 | 4.6 |
| 2 | 17 | 332 | 1.68 | 2.73 | 84.1 | 892 | 4.9 | 6.9 |
| 3 | 18 | 123 | 0.44 | 1.80 | 98.5 | 1159 | 0.7 | 2.6 |
| 4 | 20 | 132 | 1.71 | 0.91 | 94.2 | 1041 | 0.9 | 0.9 |
| 5 | 16 | 169 | 0.83 | 0.93 | 87.0 | 910 | 3.8 | 5.4 |
| 6 | 14 | 126 | 0.30 | 1.30 | 91.4 | 997 | 0.9 | 1.2 |
| 7 | 33 | 169 | 0.52 | 2.63 | 99.3 | 1197 | 1.2 | 0.7 |
| 8 | 26 | 84 | 0.50 | 0.75 | 100.0 | 1135 | 0.7 | 2.2 |

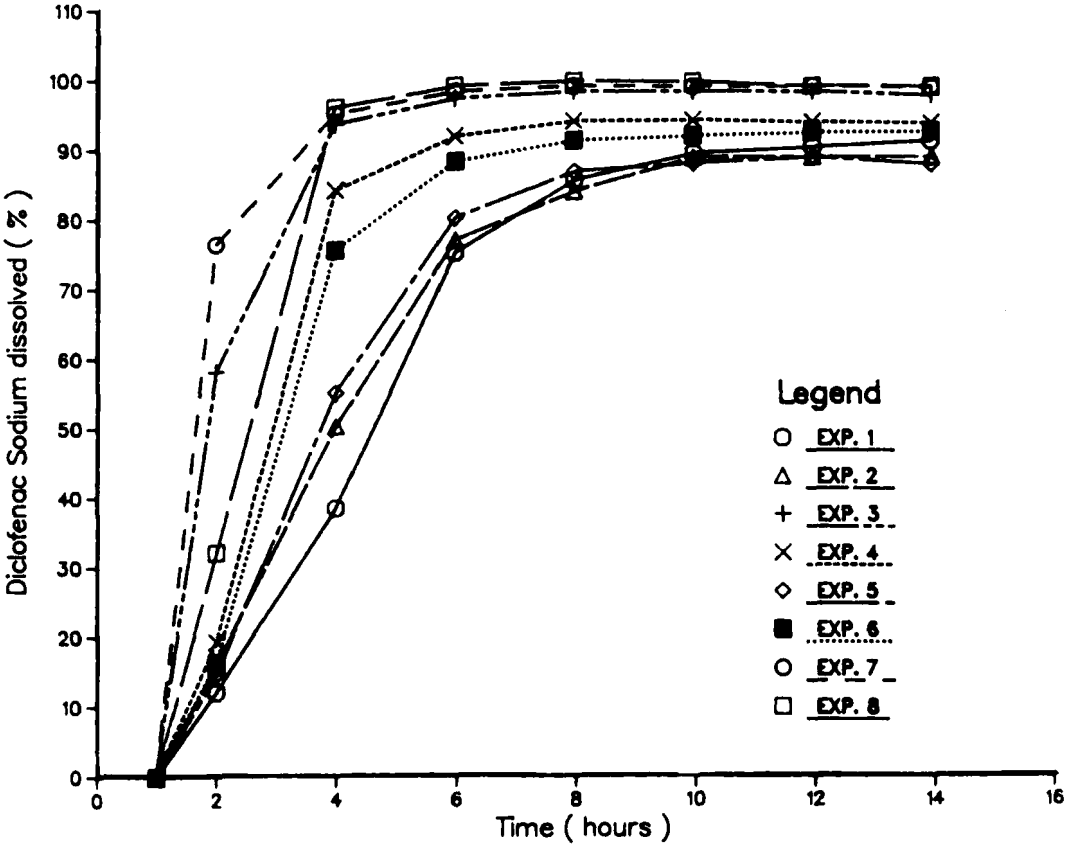


**FIGURE 2**

Release profiles from the study of main effects

**TABLE 6**

Results from the analysis of variance (F-values)

| SOURCE OF VARIATION | $Y_1$ | ln $Y_2$ | $Y_3$ | $Y_4$ | ln $Y_5$ | ln $Y_6$ | $Y_7$ | $Y_8$ |
|---|---|---|---|---|---|---|---|---|
| $X_1$ | 0.0 | 0 | 1.2 | 0.1 | 0 | 1 | 0.1 | 0.1 |
| $X_2$ | 6.6 | 25 | 0.0 | 0.0 | 194 | 347 | 4.6 | 3.3 |
| $X_3$ | 0.3 | 23 | 0.1 | 7.2 | 4 | 37 | 0.0 | 0.1 |
| $X_4$ | 2.2 | 9 | 1.7 | 0.1 | 24 | 37 | 0.5 | 0.7 |
| s | 5.24 | 0.31 | 0.61 | 0.67 | 0.03 | 0.04 | 1.54 | 2.27 |
| df | 3 | 75 | 3 | 3 | 43 | 43 | 3 | 3 |

## Results and discussion

Table 5 contains results for each dependent variable. The release profiles are illustrated in Figure 2.

ANOVA shows that $X_2$ is the most significant variable. It explains a great part of the variability of the main responses (Table 6).

In addition for $Y_6$, the principal response to be optimized, $X_2$, $X_3$ and $X_4$ are all significant.

The ln $Y_6$ model estimated by regression, is:

$$\ln Y_6 = 6.93 - 0.11X_2 - 0.03X_3 - 0.03X_4$$

(Error: s=0.04, df=44;
$R^2$=0.91, lack of fit test: p =0.05)

From the models, when $X_2$, $X_3$ and $X_4$ decrease, the dissolution parameters increase. This can be explained by the hydrophobic effect of the EC ($X_4$); furthermore, an increased effective drug surface area occurs when the particle size range and the UPF at the final compression are in the minima levels. A consequent increase in dissolution rate is shown.

**TABLE 7**
Factorial Design $2^2$

| EXPERIMENT | EXPERIMENTAL UNITS | | PHYSICAL UNITS | |
|---|---|---|---|---|
| | $X_3$ | $X_4$ | $P_3$ (kN) | $P_4$ (% EC) |
| 9 | 1 | 1 | 18 | 40 |
| 10 | -1 | 1 | 12 | 40 |
| 11 | 1 | -1 | 18 | 35 |
| 12 | -1 | -1 | 12 | 35 |

Regarding results given in Table 5, the area under the dissolution curve is far over the optimum value (713 %·h); this suggests that another experimental design must be explored.

## FACTORIAL DESIGN : SEARCHING FOR AN OPTIMUM

### Design

In order to improve $Y_6$ and according to the linear model previously found for this response, it was first decided to fix $X_1$ and $X_2$ at -1 (8 kN) and +1 (400-800 $\mu$m) levels respectively ; then, a $2^2$ factorial design was built with the two other significant parameters $X_3$ and $X_4$ at upper levels.

Table 7 gives the experimental and physical units of this factorial design.

### Results and discussion

As shown in Table 8, the AUC ($Y_6$) from experiment 12 is near the optimum value. $Y_2$, $Y_3$ and $Y_4$ were also improved while $Y_7$ and $Y_8$ were affected. The release profiles are presented in Figure 3.

**TABLE 8**

Results from the Factorial Design $2^2$

| EXP \ $Y_i$ | $Y_1$ | $Y_2$ | $Y_3$ | $Y_4$ | $Y_5$ | $Y_6$ | $Y_7$ | $Y_8$ |
|---|---|---|---|---|---|---|---|---|
| 9 | 13 | 101 | 0.47 | 0.40 | 49.5 | 603 | 13.2 | 5.8 |
| 10 | 13 | 101 | 0.81 | 0.39 | 65.0 | 667 | 9.7 | 4.5 |
| 11 | 13 | 91 | 0.99 | 0.31 | 55.6 | 622 | 12.1 | 6.6 |
| 12 | 13 | 96 | 0.36 | 0.45 | 72.3 | 721 | 8.3 | 4.3 |

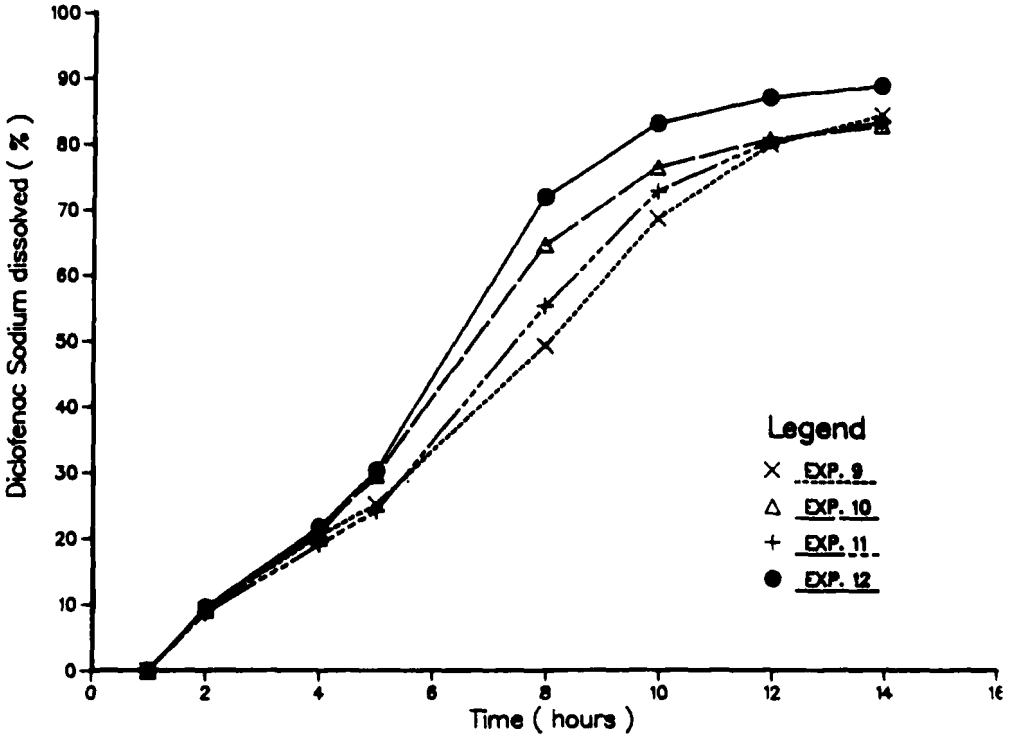


**FIGURE 3**

Release profiles from the Factorial Design

**TABLE 9**

Complete linear models

| COEFFICIENT | ln $Y_2$ | $Y_3$ | $Y_4$ | ln $Y_5$ | ln $Y_6$ | $Y_7$ | $Y_8$ |
|---|---|---|---|---|---|---|---|
| $b_0$ | 4.57 | 0.66 | 0.39 | 4.09 | 6.48 | 10.83 | 5.30 |
| $b_3$ | -0.01 | 0.07 | -0.03 | -0.13 | -0.06 | 1.83 | 0.90 |
| $b_4$ | 0.04 | -0.02 | 0.01 | -0.06 | -0.03 | 0.63 | -0.15 |
| $b_3b_4$ | 0.01 | - | - | -0.0 | 0.01 | - | - |
| RESIDUAL ERROR | | | | | | | |
| s | 0.054 | 0.485 | 0.075 | 0.108 | 0.053 | 0.150 | 0.500 |
| df | 36 | 1 | 1 | 20 | 20 | 1 | 1 |
| $R^2$ | 0.42 | 0.09 | 0.44 | 0.69 | 0.67 | 0.99 | 0.93 |

The complete linear models were directly carried out by regression (Table 9).

The $R^2$-values for ln $Y_2$, $Y_4$, ln $Y_5$, ln $Y_6$ and mainly for $Y_3$, are quite low, indicating that the linear model is inadequate to describe the situation for these variables and that a quadratic model could better fit the data. Nevertheless, $Y_6$ from experience 12 is a good value, as well as the other responses in this trial. Then, experiment 12 may accomplish the optimum.

Validity of the optimum formulation

Two trials were carried out in the same levels as experiment 12, that means: $P_1$ = 8 kN, $P_2$ = 400-800 $\mu$m, $P_3$ = 12 kN and $P_4$ = 35 % EC. Table 10 gives the results of the three trials implied in this validation. As an indication, the predicted responses from the linear models and the relative errors are presented. If $Y_3$, $Y_4$ and $Y_8$ present the worst variabilities, the results on the main responses are suitable.

**TABLE 10**

Validity of the optimum formulation

| EXPERIMENT | $Y_2$ | $Y_3$ | $Y_4$ | $Y_5$ | $Y_6$ | $Y_7$ | $Y_8$ |
|---|---|---|---|---|---|---|---|
| 12 | 96 | 0.36 | 0.45 | 72.3 | 721 | 8.3 | 4.3 |
| 12b | 91 | 0.82 | 0.52 | 69.0 | 690 | 10.3 | 6.9 |
| 12c | 88 | 0.56 | 0.57 | 68.5 | 691 | 6.2 | 3.5 |
| RELATIVE ERROR | | | | | | | |
| PREDICTED RESPONSE | 95 | 0.61 | 0.41 | 72.2 | 721 | 8.4 | 4.6 |
| MEAN RESPONSE | 92 | 0.58 | 0.51 | 69.9 | 701 | 8.3 | 4.9 |
| C.V. (%) | 4.4 | 39.8 | 11.7 | 3.0 | 2.5 | 24.8 | 36.3 |
| RESIDUE | -3 | -0.03 | 0.10 | -2.3 | -20 | -0.1 | 0.3 |
| RELATIVE ERROR (%) | 3.3 | 5.2 | 19.6 | 3.3 | 2.9 | 1.2 | 6.1 |

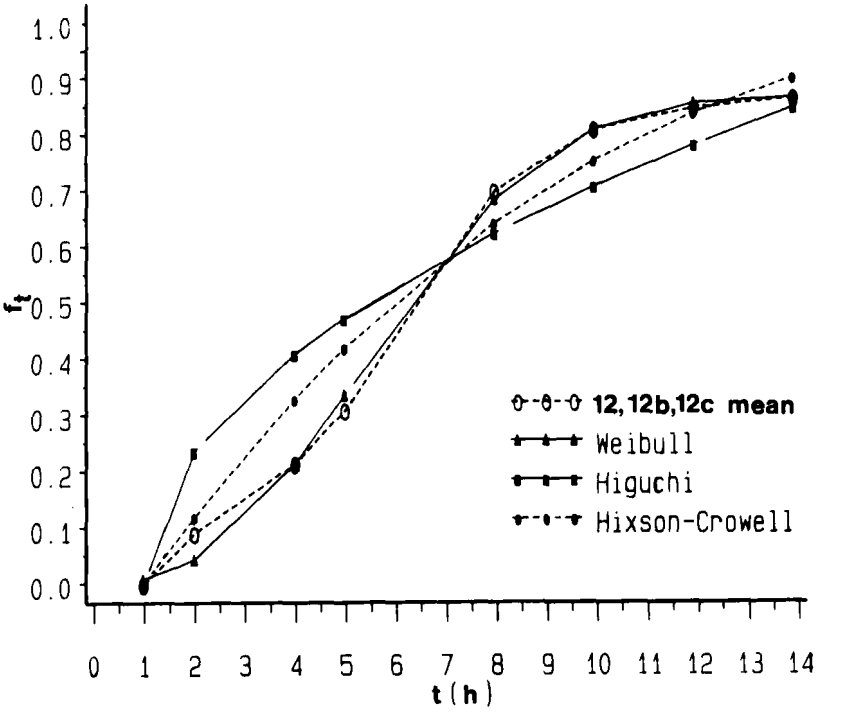


**FIGURE 4**

Mean data dissolution and theoretical release profiles

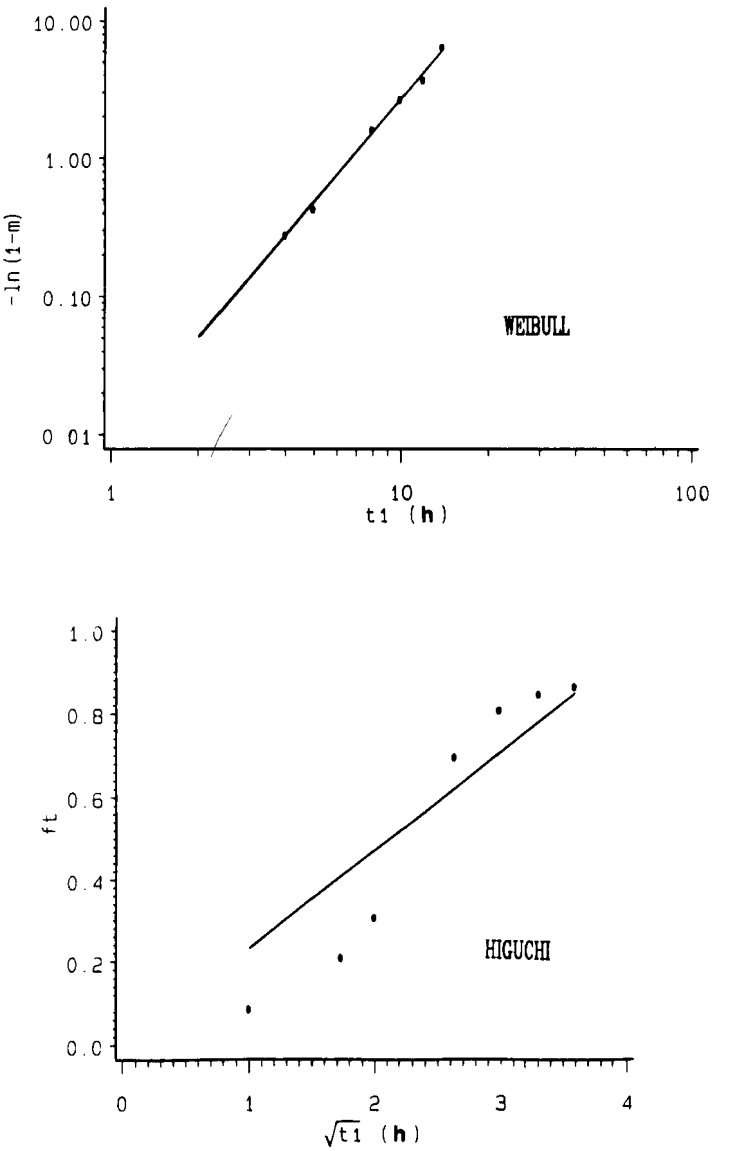


**FIGURE 5**
Linearization of the release profiles
Weibull and Higuchi models

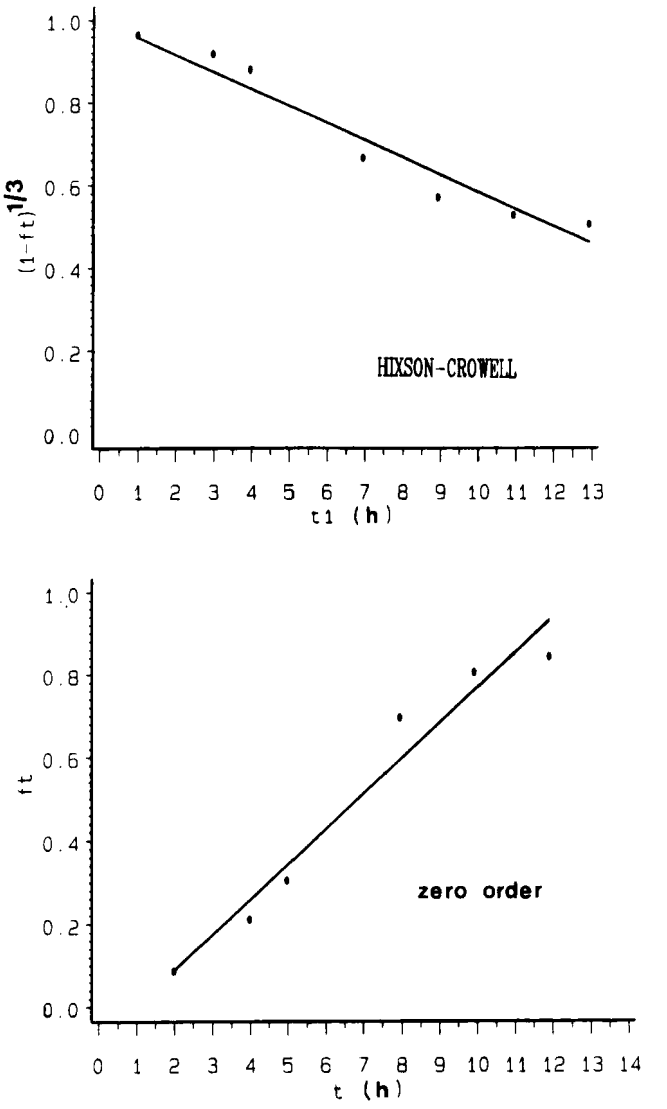


**FIGURE 6**

Linearization of the release profiles Hixson-Crowell and zero-order models

**TABLE 11**

Results from the fits by theoretical dissolution models

| MODEL | WEIBULL | HIGUCHI | HIXSON AND CROWELL | ZERO-ORDER $f_t = a + K_0 t$ |
|---|---|---|---|---|
| PARAMETER ESTIMATES | $F_\infty = 0.87$<br>$t_0 = 0$<br>$t_d = 6.70$<br>$\beta = 2.46$ | $K_H = 0.235$ | $K_{HC} = 0.041$ | $a = -0.081$<br>$K_0 = 0.084$ |
| $\sigma^2$ ESTIMATE | 0.0016 | 0.0163 | 0.0025 | 0.0051 |

$\sigma^2$ is estimated by the MS Residual (Sum of Squares/df)



Linearization of the dissolution data

Drug release from controlled release matrix tablets was described by many kinetic theories (20,21). Figure 4 illustrates the release profiles of the validated mean data dissolution (Exp 12, 12b, 12c), and the release profiles obtained from the fits by Weibull, Higuchi and Hixson-Crowell models. Figures 5 and 6 show the curves after linear transformation.

Table 11 contains the pertinent information about the parameter estimates and the residual error for each release model. From these results and from Figures 4, 5, and 6, it can be concluded that the release of diclofenac sodium is well fitted by the Weibull distribution. $\beta>1$ ($\beta$ being the shape parameter) is characteristic for a slower initial rate (diclofenac sodium is insoluble in pH 1.2) followed by an accelerated approach to the final plateau (a sigmoid appearance). As seen in the direct compression optimization, after "infinite" time, the fraction released ($F_\infty$), is estimated to only 90% (13).

## CONCLUSION

From a minimum number of experiments, Hadamard matrix gave the possibility to estimate the mean effects of four parameters. Among them, the particle size range showed the most important effect in the release of diclofenac sodium. By interpreting data, a factorial design including only two parameters was applied from which an optimum formulation was found.

As expected, when compared with the direct compression results (13), the double compression considerably enhanced the rheology of the powder and it largely decreased the variability between tablets of the studied dissolution parameters.

The release of the drug from precompressed tablets followed Weibull distribution.

The inert matrix formulation provided by ethylcellulose and Pevikon (polyvinyle chloride), was an effective vehicle for controlled release drug delivery systems.



## ACKNOWLEDGEMENT

The authors express their gratitude to A.T. Luong, general manager of SEARLE-Sophia Antipolis, for his helpful comments.

Angelina Peña Romero wishes to thank "El Consejo Nacional de Ciencia y Tecnología", "La Facultad de Estudios Superiores de la Universidad Nacional Autónoma de México", "Le Comité d'Etudes sur la Formation d'Ingénieurs-Paris" and SEARLE-Sophia Antipolis, for their moral and financial support.

## REFERENCES

1. B.B. Sheth, F.J. Bandelin and R.F. Shangraw, in "Pharmaceutical Dosage Forms: Tablets. Volume 1", Marcel Dekker, New York, 1980, p. 127-128,173,177.

2. A. Peña Romero, J.B. Costa, D. Chulia, J. Pharm. Belg., in preparation.
3. A. Peña Romero, J.B. Costa, D. Chulia, A.T. Luong, 5th International Conference on Pharmaceutical Technology, APGI, Paris, 1989.
4. M.H. Rutz-Coudray, J. Giust and P. Buri, Pharm. Acta Helv., 54, 363 (1979).
5. A.R. Fassihi, Int. J. Pharm., 37, 119 (1987).
6. C. Thomas, Thesis of the University of Bourgogne, France (1987).
7. S. Chandrashekhar, S.B. Jayaswal and K.D. Gode, Indian J. Hosp. Pharm., 14, 72 (1977).
8. M.L. Costa, H. Fessi and J.P. Marty, Pharm. Acta Helv., 61, 298 (1986).
9. F.W. Goodhart, M.R. Harris, K.S. Murthy and R.U. Nesbitt, Pharm. Tech., 8, 64 (1984).
10. T. Lindholm and M. Juslin, Pharm. Ind., 44, 937 (1982).
11. M. Donbrow and S. Benita, J. Pharm. Pharmacol 547 (1982).
12. J.-L. Salomon and E. Doelker, Pharm. Acta Helv., 55, 174 (1980).
13. A. Peña Romero, M. Poncet, J.C. Jinot and D. Chulia, Pharm. Acta Helv., 63, 333 (1988).
14. J.C. Jinot, F. Nevoux, A. Peña Romero and M. Poncet, S.T.P. PHARMA, 5, 12 (1989).
15. C. Cohard, D. Chulia, Y. Gonthier and A. Verain, Int. J. Pharm. Tech. & Prod. Mfr., 6, 10 (1985).
16. A. Delacourte-Thibaut, J.C. Guyot and M. Traisnel, Sci. Techn. Pharm., 11, 131 (1982).
17. J.C. Guyot, 4th International Conference on Pharmaceutical Technology, APGI, Paris, 4, 32 (1986).
18. P. Ozil and M.H. Rochat, Int. J. Pharm., 42, 11 (1988).
19. O.L. Davies, "Design and Analysis of Industrial Experiments", Oliver & Boyd, London, 1967.
20. J. Cobby, M. Mayersohn and G.C. Walker, J. Pharm. Sci., 63, 725 (1974).
21. F. Langenbucher, Pharm. Ind., 38, 472 (1976).