DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(17), 2685-2694 (1994)

APPLICATION OF THE STATISTICAL MULTIVARIATE ANALYSIS TO THE RELEASE CHARACTERIZATION OF MATRIX TABLETS.

G. Frutos (*), P. Frutos and M.A. Alonso.
(*) Dpto. Química Física II.
Dpto. Farmacia y Tecnología Farmacéutica
Facultad de Farmacia. Universidad Complutense Madrid.
Spain.

ABSTRACT

The introduction of new sustances that can be used as excipient in controlled release formulations constitutes a relevant step in obtaining simple, reliable and accurate methods which makes it possible to reproduce the controlled release of drugs.

Therefore, the aim of this work is to study the influence of different technological variables on the modulation of the release of the active principle compressed with a new excipient to formulate matrix tablets. A Poliamyde 12 was used as the rate-controlling polymer in controlled-release tablet formulation. Different techniques of multivariate analysis have been applied to the release characterization of matrix tablets studied.

INTRODUCTION

One of the more common methods of manufacturing controlled-release dosage forms is the incorporation of the drug substance in a matrix containing a rate controlling polymer. So, when talking about polymeric formulations we must refer to matricial systems, which could be defined as a mechanism formed by an active principle, scattered or dissolved in a tough and biocompatible polymerical mesh (1,2). In these systems, the active agent is physically blended with the polymeric powder and then fused together by compression moulding. The ability of polymeric matrices to meter drugs at

controlled and reproducible rates for extended time periods provides significant benefits over conventional dosage forms (3).

There have been several studies reported which have evaluated how a variety of factors effect sustained drug release from polymeric tablet matrix. Among these factors have been the effect of drug loading, drug particle size (4), compression force (6,7, 8) and particle size on drug release. The effects of air entrapment (8) and formulation additives (6, 7) have also been studied. Some authors (9, 10) demonstrated the usefulness of combining experimental design and other methodology to optimize a sustained matrix tablet.

In this work, we have used a new polymeric excipient (ORGASOL), that has been extensively used in our Department and can be used as a plastic matrix to allow constant release of the active principle for 8 hours (11,12,13). We also study several mathematical methods which can be applied in the release characterization of different series of tablets performed. Seven parameters were used for the differentiation.

MATERIALS AND METHODS.

Excipient and trazer element.

To develop the experimental work we produced tablets with polyamide 12, Orgasol^{R} 2002 ES 5NAT (APSA commercial, Spain)(14) as excipient of direct compression. As trazer element a dye, Punzo Brillante 3RF (Robama, Spain) was used (15). It is an artificial dye. The Punzo Brilliant release was measured in UV Spectrophotometry (Beckman DU-6). A peak was obtained at 506 nm.

Experimental design.

The experimental design used is a factorial 3^2 with two factor, Compression Relation (Rc) and percentage of dye (%); each factor has three levels of variation as can be seen in table 1.

Tablet fabrication.

Tablets were obtained with Orgasol as excipient and Punzo Brilliant dye as release indicator. A five rotatory machine with 14.2 mm diameter punches was used in the manufacture of the tables by direct compressing.

TABLE 1. *Experimental design used in this work.*

Rc %	0.37	0.45	0.54
1 %	F1,1	F1,2	F1,3
5.5 %	F2,1	F2,2	F2,3
10 %	F3,1	F3,2	F3,3

Rc is a parameter that allows the evaluation of the compression degree of a substance. It influences tablet porosity and can be defined as (16):

$$Rc = \frac{ht}{Ho}$$

where Rc: Compression Relation.
ht: real tablet height.
Ho: matrix height of compression machine.

Dissolution test.

Dissolution profiles were obtained for three replicates of each formulation using a continuous fluid cell without amount reservoir (17) : see Figure 1. The eluate was collected by means of a fraction collector at intervals of 20 minutes for up to 12 hours. The amount of dye in solution was determined as a function of time by direct spectrophotometry (max = 506nm).

Statistical analysis.

Several statistical treatment have been applied to the experimental results. BMDP (18) computer program was used.

We have used Factor Analysis by means of Principal Components methods to find whether the tablets studied are distributed in natural groups. Also, Factorial Analysis is useful in exploratory data analysis to study the relationships between the different variables involved in the tablet release process. Seven parameters for the differentiation were used: Dissolution

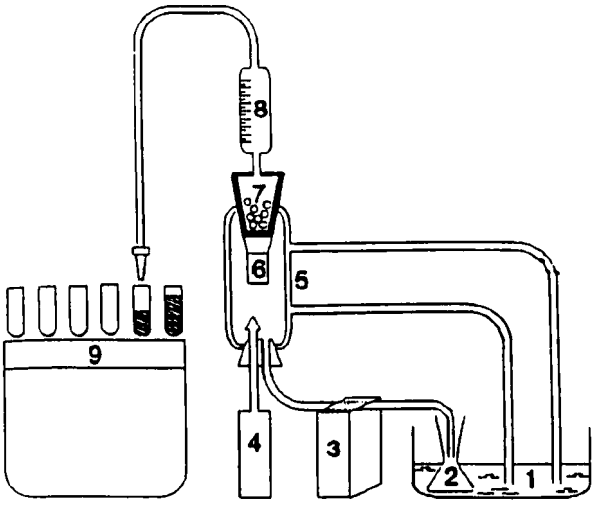

FIGURE 1.
Dissolution cell.

Efficiency at 12 hours (E), Tablet height (h), Tablet weight (W), Apparent density (d), Porosity (@), Compression Relation (Rc), Percentage of dye (%).

RESULTS.

Table 2 showns the mean values corresponding to variables: dissolution efficiency (calculated as defined in material and methods), tablet height, tablet weight, apparent density and porosity, all of them related to Fi,j formulations.

Figure 2 shows the evolution of dye concentration with respect to time in the release test done on the batches corresponding to tablets prepared with Rc=0,45. Similar curves have been obtained with the other two compression relations.

In addition to this technological evaluation, a Factor analysis by the principal components method was performed. From a general standpoint the differences between nine batches of tablets could be explained by this analysis.

Table 3 shows the correlation matrix performed by means of BMDP4M program. In this matrix we can observe the squared multiple correlations, SMC,

TABLE 2. *Mean value of variables. E, h (mm)*, W (g), d (g/cc) and @ (%), corresponding to each Fi,j formulation.

	F1,1	F2,1	F3,1	F1,2	F2,2	F3,2	F1,3	F2,3	F3,3
E	0.24	0.49	0.55	0.20	0.43	0.51	0.19	0.40	0.46
h	2.91	2.96	2.98	3.58	3.60	3.60	4.26	4.25	4.23
W	0.37	0.38	0.41	0.36	0.37	0.38	0.39	0.41	0.41
d	0.85	0.87	0.90	0.65	0.68	0.70	0.60	0.62	0.63
@	0.17	0.15	0.12	0.36	0.33	0.31	0.41	0.39	0.39

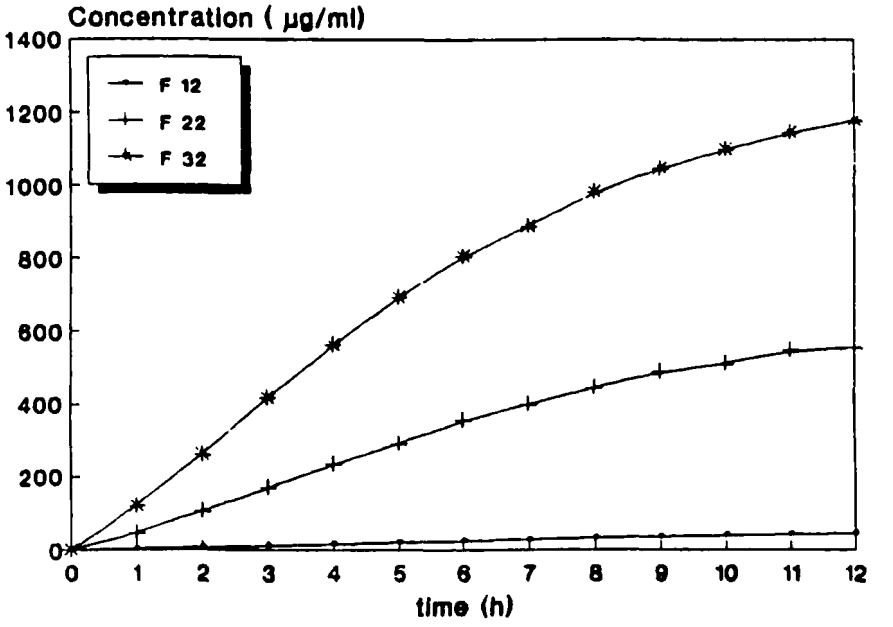

FIGURE 2.
Cumulative concentration of drug release versus time for the three batches shown in the inset, corresponding to Rc: 0,37.

TABLE 3. *Correlation matrix.*

	WEIGHT	HEIGHT	POROS	EFFIC	Rc	PERCEN
WEIGHT	1.000					
HEIGHT	0.324	1.000				
POROS	0.014	0.937	1.000			
EFFIC	0.480	-0.232	-0.397	1.000		
Rc	0.269	0.997	0.955	-0.246	1.000	
PERCEN	0.555	0.013	-0.165	0.912	0.000	1.000

TABLE 4. *Rotated Factor loadings of the first two principal components, variance explained and cumulative proportion of variance total.*

	Factor 1	Factor 2
Rc	0.996	0.000
HEIGHT	0.996	0.000
POROSITY	0.959	0.000
PERCENTAGE	0.000	0.946
EFFICIENCY	0.299	0.908
WEIGHT	0.271	0.770
EXPLAINED VARIANCE %	51.8	38.53
CUMULATIVE PROPORTION %	51.8	90.33

of each variable with all other variables. When we used the seven variables described in this analysis, the correlation matrix is singular. In that case some SMC´s are understimated.

Since the correlation matrix is singular, it may be desirable (19) to repeat the analysis eliminating the variable density, because it is hightly correlated with porosity.

Table 3 showns the correlation matrix of such analysis, pointing out, from an exploratory point of view, the good correlation presented by the height, porosity and compression relation variables as well as between efficiency and the percentage of dye.

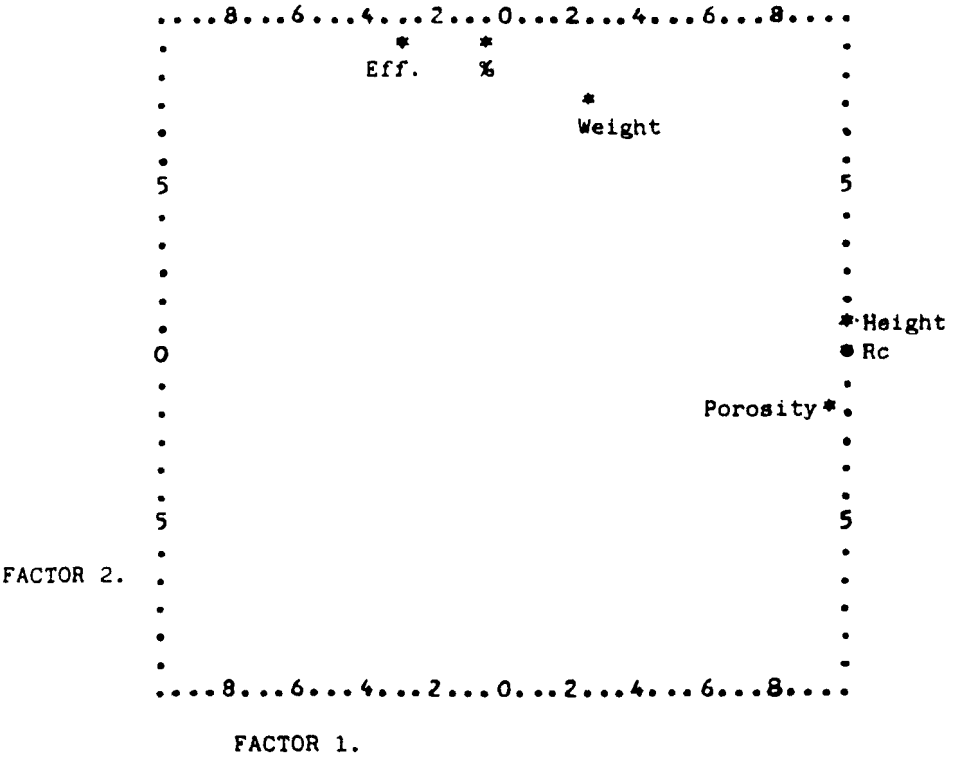

FIGURE 3.
Representation of the studied variables on the Factor 1 and 2 axis space.

In table 4 the first two components (Factor 1 and Factor 2) are given. The variables have been reordered. The first principal component accounts for 51.8 % of the total variation in the six variables and the second component for 38.5 % of the total variation . Consequently the total proportion of variance of the variables that can be predicted by the two factors is 90.3 %.

The first component is more correlated with the following variables: compression relation, height and porosity; these may be interpreted as a "Pharmacotecnic Factor". The second component is more correlated with the following variables: percentage, efficiency and weight; these may be interpreted as an "Availability Factor".Figure 3 shows the representation of the variables studied on the Factor 1 and 2 axis space.

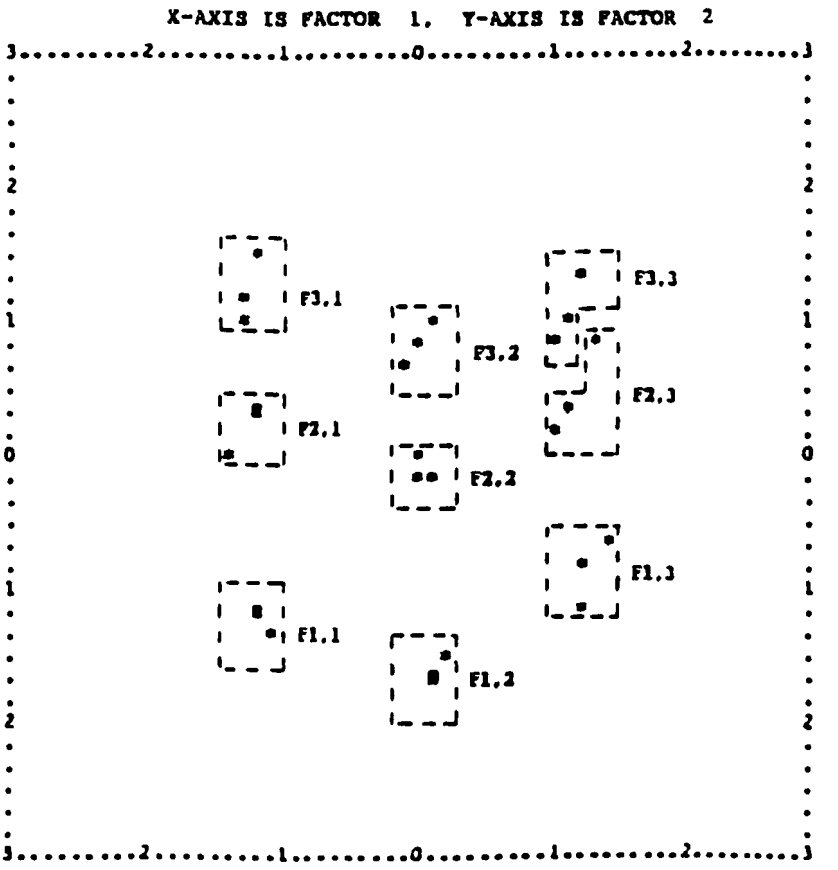

FIGURE 4.
Representation of 27 tested tablets on the Factors space.

It can be observed that some variables (Rc, height and porosity) that are grouped in the middle area, have a constant value related to Factor 1 axis. The group (dissolution efficiency, percentage and weight) are concentrated on the upper part, having a constant value related to Factor 2 axis.

These Factors can be defined by following equations:

$$F1 = 0.963\ Rc + 0.956\ h + 0.975\ @ \qquad \text{(eq. 1)}$$
$$F2 = 0.912\ \% + 0.821\ E + 0.811\ W \qquad \text{(eq. 2)}$$

Figure 4 shows the 27 tested tablets represented on the Factors space. The tablets are grouped according to the formulations, which are separated, and maintain their analogy to the design used.

CONCLUSIONS

A parallelism appears with respect to Factor 1 axis defined by the technological variables, and this is proved showing that there is a parallelism between formulations with the same Rc. This parallelism shows that technological variables have influence in a linear way as can be seen in equation 1.

Thus the overall results justify the conclusion that the Factor Analysis approach can give more information about the behaviour of the release process and allows a critical study of similarities involved in the tablet release process.

REFERENCES

(1) J.R. Robinson, "Sustained and Controlled Release drug Delivery systems". Marcel Dekker. New York (1978).
(2) L. Illum and S.S. Davis, "Polymers in controlled drug delivery". Wright 1987.
(3) T.C. Dahl, T. Calderwood, A. Bormeth and E.J. Piepmeier, J. Controlled Release, 14, 1 (1990).
(4) J.L. Ford, M.H. Rubinstein and J.E. Hogan. Int. J. Pharm., 23, 327 (1985).
(5) H. Lapidus and N. Lordi, J. Pharm. Sci., 55, 840 (1966).
(6) H. Lapidus and N. Lordi, J. Pharm. Sci., 55, 1292 (1966).
(7) H.E. Huber and G.L. Christenson, J. Pharm. Sci., 57, 164 (1868).
(8) R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri and N.A. Peppas, J Pharm. Sci., 72, 1189 (1983).
(9) R.M. Franz, J.A. Sytsma, B.P. Smith and L.J. Lucisano, J. Controlled Release, 5, 159, (1987).
(10) P. Wehrlé, P. Nobelis and A. Stamm, S.T.P. Pharma 5, 481 (1989).
(11) C.V. Pabón, P. Frutos, J.L. Lastres and G. Frutos, Drug Dev. Ind. Pharm.,18 (20), 2163 (1992).
(12) P. Frutos, A. Rodriguez, G. Frutos and P.J. Martin, Pharm. Acta Helv., 66, Nr 12, 339 (1991).
(13) A. Rodriguez, P. Frutos, G. Frutos and F. Vazquez, S.T.P. Pharma, 6 (8), 574 (1990).

(14) Orgasol Es 5Nat. Ato Chimie ATO. "La Défense". Cedex 24.92091 Paris. Le Défense (France).
(15) Punzo Brillante 3RF. Robama SA RBM. Gran Vía de les Corts 774, 08013 Barcelona.
(16) K.A. Khan, J. Pharm. Pharmacol., 27 48 (1975).
(17) S. Romano and F. Vazquez, Ind. Farma., 1, 81 (1988).
(18) W.J. Dixon, "BMDP" . University of California Press. California (1981).