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Investigations of tablets prepared from pellets produced by extrusion and spheronisation. II. Modelling the properties of the tablets produced using regression analysis

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Abstract

Tablets prepared from three different types of pellets were produced either in a mechanical press or in a tabletting machine. The experiments were carried out according to a centre of gravity design. The properties of the tablets produced were predicted from the models based on linear equations with the variables selected by canonical analysis and principal component analysis. The results showed that the variables to be used in the equations of the models for the two machines had to be different, proving the differences in the compaction mechanisms involved. For the Manesty machine, five variables reflected the properties of the tablets produced, whereas for the Instron machine seven variables had to be considered. From the regression it was possible to select the dependent variables (properties of the tablets) that provide a better reflection of the independent variables (formulation and processing factors). Properties such as the value of '*R*' (ratio between the lower to the upper compression pressures), the density of the tablets, the tensile strength of the tablets, the disintegration time of the tablets, and the mean dissolution time of the model drug (indomethacin) seemed to be well defined by the model. On the other hand, the porosity of the tablets, the force required to crush the tablets, and the friability were not well reflected by the model. Predictions of the changes in the dependent variables when the independent variables were increased by 20% are also presented in the form of star diagrams. © 1997 Elsevier Science B.V.

Abbreviations: A, hard pellets with model drug; *b*, vector of the regression coefficient; B, disintegrable pellets with barium sulphate; *c*, intercept constant; C, soft pellets with glyceryl monostearate; *Co*, concavity of the tip of the punch; *Crusf*, diametral crushing force; *D*, load of model drug in pellets of type 'A'; $d^2_{X|V}$ and $d^2_{Y|U}$, interranging communality of a variable; *Densi*, density of tablets; *Di*, diameter of the punch; *Disit*, disintegration time; *Disso*, mean dissolution time; *Ejefor*, ejection force required to eject a tablet from the die; *F*, variance ratio; *Friab*, friability of tablets; *G*, percentage of pellets of type 'C' in the tablets; $g^2_{X|U}$ and $g^2_{Y|V}$, extracting measures; $g^2_{X|V}$ and $g^2_{Y|U}$, measures of redundance; *P*, compression pressure applied to the pellets; *Poros*, porosity of tablets; p_0, predicted value for the centre of gravity; *R*, ratio of the lower to the upper punch force; RMS, root mean square; r_0, experimental value for the centre of gravity; R^2_{adj}, adjusted coefficient of correlation; *S*, size of the pellets; S.E., standard error; *Tensi*, tensile strength of tablets; $\underline{X}_i$, factor matrix of the independent variables; y_i, dependent variable.

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1. Introduction

The production of tablets is a complex process depending on many factors, related to both formulation and processing factors. Tablets are still the most favoured dosage form, prepared by tabletting machines with large output, which justifies the full study of the factors affecting the properties of such dosage form and the development of mathematical models. Traditionally, factors such as the compression pressure required to make tablets or the size of the individual particles of the materials used in the production of the tablets have been studied individually (Ganderton and Selkirk, 1970; Sixsmith, 1980), but the complexity of the events occurring throughout the process of tabletting justifies the use of experimental designs and analytical techniques of the results which take into account interactions between the variables and tend to extract all the available information (Hagman and Jacobsson, 1990; Merkku et al., 1993; Frutos et al., 1994; Gottfries et al., 1994; Wehrle et al., 1995). Once the factors and the interactions are found it should be possible to develop a model which takes into consideration such factors and can be used to make predictions about the properties of tablets produced from different formulations manufactured under different conditions.

Part I of the present study showed the complexity of producing tablets from pellets made by extrusion and spheronisation (Pinto et al., 1997). The different formulation and processing factors were analyzed by canonical analysis and principal component analysis (Hotelling, 1936; Bartlett, 1938). The combination of these methods allowed the selection of the variables that principally affect the properties of the tablets. The variables selected can be related by multiple regression analysis allowing for the establishment of correlations between one dependent variable y_i (i.e. a property of a tablet) and a group of independent variables $\underline{X}_i$ selected (i.e., the formulation and processing factors studied). Once the best regression equations are found, predictions can be made and the results represented in the form of star diagrams when the independent variables are increased by 20% (Hartung and Elpert, 1984).

The aim of this study was to illustrate the effect of changes in the formulation and processing conditions of different mixtures of pellets on the properties of tablets.

2. Materials and methods

The materials and methods used to prepare the tablets and the combination of variables have been described by Pinto et al. (1997).

2.1. Analysis of data

The calculations for the multiple regression analysis were performed using the SPSS program (Statistical Package for Social Sciences, SPSS Int. BV, USA version 4.0). The independent variables considered were the load of indomethacin in the pellets of type 'A' (D), the percentage of pellets of type 'B' (B), the percentage of pellets of type 'C' (G), the compression pressure applied to the pellets (P), the size of the pellets (S) and for the tablets produced by the Universal Testing Machine the diameter of the punches (Di) and the concavity of the tip of the punch (C_0). The properties of the tablets studied were the value of 'R' (defined as the ratio of the lower to the upper punches' forces), the ejection force (*Ejefor*), for the tablets produced by the tabletting machine, the density (*Densi*), the porosity (*Poros*), the diametral crushing force (*Crusf*), the tensile strength (*Tensi*), the friability (*Friab*), the disintegration time (*Disit*) and the mean dissolution time (*Disso*). The variables were combined in an experimental design as described previously (Pinto et al., 1997). The experimental results (r_0) and the predictions (p_0) for the centre of gravity are presented in Tables 1 and 2.

Table 1
Vectors of regression coefficients (b) to predict the dosage form properties (y_i) for the tablets produced by the Manesty

y_i	'R'	*Ejefor*	*Densi*	*Poros*	*Crusf*	*Tensi*	*Friab*	*Disit*	*Disso*
D	2.59	-2.66×10^{1}	−5.22	1.74	−2.20	−2.44	-6.41×10^{0}	−1.76	4.59
	$\times10^{-3}$		$\times10^{-2}$	$\times10^{-2}$	$\times10^{-1}$	$\times10^{-3}$		$\times10^{-1}$	$\times10^{-1}$
B	−4.15	-4.07×10^{0}	1.75	−1.05	−8.62	−6.23	−7.23	−5.04	7.22
	$\times10^{-3}$		$\times10^{-2}$	$\times10^{-4}$	$\times10^{-2}$	$\times10^{-4}$	$\times10^{-2}$	$\times10^{-2}$	$\times10^{-3}$
G	−7.60	-1.00×10^{1}	3.27	4.76	−2.92	−5.21	-1.29×10^{0}	7.97	3.18
	$\times10^{-3}$		$\times10^{-3}$	$\times10^{-4}$	$\times10^{-2}$	$\times10^{-4}$		$\times10^{-1}$	$\times10^{-2}$
P	−5.79	5.66×10^{0}	−1.19	4.33	6.45	7.69	−8.10	3.43	7.76
	$\times10^{-4}$		$\times10^{-3}$	$\times10^{-4}$	$\times10^{-2}$	$\times10^{-4}$	$\times10^{-1}$	$\times10^{-2}$	$\times10^{-4}$
BG	−1.43	−1.88	−1.17	4.04	2.33	2.98	−3.42	−1.28	−1.96
	$\times10^{-4}$	$\times10^{-1}$	$\times10^{-4}$	$\times10^{-5}$	$\times10^{-3}$	$\times10^{-5}$	$\times10^{-2}$	$\times10^{-2}$	$\times10^{-4}$
c	1.79×10^{0}	3.31×10^{2}	1.41×10^{0}	1.34	3.30×10^{0}	1.63	1.96×10^{2}	-1.53×10^{0}	8.78
				$\times10^{-2}$		$\times10^{-2}$			$\times10^{-3}$
r_0	0.88	136	1.97	28.3	7.75	0.090	4.11	3.5	1.6
p_0	0.88	227	2.04	26.0	7.92	0.090	23.2	3.4	1.5

r_0 and p_0, experimental and predicted values for the centre of gravity attempt.

Multiple regression analysis results were analyzed statistically and special attention was paid to the analysis of residuals, i.e. the difference between the observed and predicted values of the dependent variables, expressed as the root mean square (RMS), which further allowed the examination of the quality of the regression model proposed, making possible the acceptance or rejection of the model. The adjusted coefficient of correlation (R^2_{adj}), the standard error (S.E.) and an F-test complemented the statistical analysis of the multiple regression. Predictions are represented in the form of star diagrams when the independent variables were increased by 20% (axes represent an increase of 100% of the dependent variables).

3. Results and discussion

In Part I of this study the properties of the tablets produced in two different machines showed that the tablets produced by the Manesty tabletting machine depended on the content of the drug in the pellets of type 'A' (D), on the amount of pellets of type 'B' (B), on the amount of pellets of type 'C' (G), on the interaction of these two factors (BG), and on the pressure used for the compression of the tablets (P). It was also found that for the tablets produced by the Instron machine, seven variables had to be considered because when only five variables were included a poor explanation of the properties of the tablets produced was obtained. Therefore, the variables chosen for this study were the drug content in the pellets of type 'A' (D), the content of pellets of types 'B' and 'C' and their interaction (B, G, BG, respectively), and for the Instron, the additional results for the diameter of the punch (Di), the concavity of the tip of the punch (C_0) and their interaction (DiC).

Once the independent variables were selected a general equation, such as Eq. (1), can be suggested to provide the relationship between the variables, assuming a linear relationship between the variables:

$$y_i = \underline{X}_i^{T} \cdot \underline{b}_i + c \quad (1)$$

Table 2
Vectors of regression coefficients (b) to predict the dosage form properties (y_i) for the tablets produced by the Instron (7 variables)

y_i	*Densi*	*Poros*	*Crusf*	*Tensi*	*Friab*	*Disit*	*Disso*
D	7.58×10^{-3}	-3.42×10^{-3}	2.11×10^{-1}	6.75×10^{-4}	-7.04×10^{-1}	4.75×10^{-2}	5.69×10^{-1}
B	2.02×10^{-2}	-4.01×10^{-4}	-3.28×10^{-2}	-3.85×10^{-4}	-2.80×10^{-1}	2.29×10^{-3}	9.87×10^{-3}
G	5.75×10^{-3}	-3.10×10^{-4}	-1.22×10^{-1}	-9.13×10^{-4}	-2.91×10^{-1}	3.89×10^{-1}	3.58×10^{-2}
S	3.51×10^{-1}	-1.27×10^{-1}	-1.54×10^{1}	-3.78×10^{-2}	-2.18×10^{0}	7.11×10^{-2}	1.40×10^{0}
Di	9.83×10^{-2}	-3.62×10^{-2}	2.85×10^{-1}	7.94×10^{-3}	-7.43×10^{-1}	-1.25×10^{0}	4.45×10^{-2}
C	-9.72×10^{-1}	3.69×10^{-1}	-2.20×10^{1}	-7.26×10^{-1}	2.77×10^{2}	4.51×10^{-1}	-1.27×10^{0}
BG	-1.15×10^{-4}	3.97×10^{-5}	-4.50×10^{-4}	-1.66×10^{-5}	4.76×10^{-4}	-6.67×10^{-3}	-3.80×10^{-4}
DiC	9.42×10^{-1}	-3.58×10^{-1}	2.10×10^{1}	8.44×10^{-1}	-2.66×10^{2}	-4.32×10^{-1}	1.28×10^{0}
c	-2.76×10^{-1}	7.15×10^{-1}	2.67×10^{1}	6.27×10^{-2}	3.54×10^{1}	1.52×10^{1}	-1.78×10^{0}
r_0	2.38	17.5	9.40	0.104	1.0	2.0	1.9
p_0	2.32	17.0	9.65	0.097	2.9	1.8	1.8

r_0 and p_0, experimental and predicted values for the centre of gravity attempt.

where, y_i is any dependent variable, $\underline{X}_i^T$ is the transposed factor matrix of the independent variables selected, $\underline{b}_i$ is a vector of the regression coefficients and c the interception constant.

Tables 1 and 2 present the coefficients for equations proposed in the models which tend to describe the properties of the tablets produced by the two machines or the dependent variable studied (9 variables for the Manesty and 7 variables for the Instron, respectively) as a function of the independent variables chosen (4 variables for the tablets produced by the Manesty machine and 6 variables for the tablets produced by the Instron machine). The values of the experimental results (r_0, for the centre of gravity attempt) can be compared to the predicted values (p_0, for the centre of gravity, Tables 1 and 2, lower part). Once the equations are accepted, based on statistical analysis (Table 3), the influence of an increase of the independent variables by 20% on the dependent variables was simulated.

The first two properties of the tablets, the value of '*R*' (defined as the ratio between the lower to the upper punch pressures) and the value of the ejection force (*Ejefor*, defined as the force required to eject a tablet) are usually analyzed together. In fact, the ejection force reflects the lubrication between the die wall and the tablet as a consequence of the radial force exerted by the tablet on the die. For unlubricated tablets the force to eject a tablet is much higher than for tablets with a lubricant, the stearates (such as the glyceryl monostearate) being the most commonly used. On the other hand, the values of '*R*' tend to reflect more than the efficiency of the lubricant. In fact, throughout the transmission of the applied pressure, changes in the materials occur (for instance, plastic deformation or granules broken). From Table 1 it can be observed that the equation for the value of '*R*' tends to reflect the results in a better way than the value of the ejection force, reflected by the lower value for the RMS (root mean square) and a higher value of R^2_{adj} (for '*R*', RMS = 4.40 and $R^2_{adj} = 0.8107$, whereas for *Ejefor*, RMS = 170.30 and $R^2_{adj} = 0.6219$, Table 3). This occurs when the result (r_0) and the prediction (p_0) for the centre of gravity attempt are compared (for '*R*', r_0 and $p_0 = 0.88$ and for the *Ejefor*, $r_0 = 136$ N and $p_0 = 227$ N, Table 1). This observation suggests that the determination of '*R*' can be used as an indicator of the performance of the formulation and the processing conditions. This

finding can be accepted once it is realised that the factors affecting the variable '*R*' are larger in number when compared to the lubrication of the system, a factor which greatly affects the value of the ejection force. Fig. 1a–d presents the effect of an increase of 20% of the independent variables on the dependent variables. As a consequence of the poor ability to predict the experimental results, the ejection force was not taken into consideration. A small increase in the value of '*R*' was observed when the drug load in pellets of type 'A' increased (Fig. 1a), or when the percentage of pellets of types 'B' and 'C' increased (Fig. 1, b and c) but not when the pressure increased (Fig. 1d). Explanations for these observations may be suggested by the changes at the surface of the individual pellets or by the materials released from pellets of types 'B' and 'C' when broken (this point is discussed below). A better transmission of the applied pressures may be suggested as a consequence of modifications of the surface properties of the pellets. Therefore, reduced attraction between pellets is reflected by smaller forces between them and consequently better transmission of the force within the whole tablet. The same effect was observed when the amount of barium sulphate and glyceryl monostearate was increased. However, the system was sufficiently well lubricated to be unaffected by an increase in the pressure applied.

Table 3
Summary of the results from the multiple linear regression analysis

Dependent variables		Manesty	Instron
'*R*'	RMS	4.40	
	R^2_{adj}	0.8107	
	S.E.	0.056	
	F	46.38	
Ejefor	RMS	170.3	
	R^2_{adj}	0.6219	
	S.E.	83.23	
	F	18.43	
Densi	RMS	4.63	4.02
	R^2_{adj}	0.7968	0.8339
	S.E.	0.102	0.096
	F	42.57	41.80
Poros	RMS	14.1	17.2
	R^2_{adj}	0.3067	0.7199
	S.E.	0.037	0032
	F	5.69	21.88
Crusf	RMS	14.0	40.2
	R^2_{adj}	0.7918	0.3417
	S.E.	1.010	3.910
	F	41.32	5.22
Tensi	RMS	14.2	13.2
	R^2_{adj}	0.7728	0.9608
	S.E.	0.012	0.013
	F	37.05	199
Friab	RMS	90.6	223.9
	R^2_{adj}	0.6857	0.9595
	S.E.	22.77	5.750
	F	24.13	194
Disit	RMS	55.0	32.8
	R^2_{adj}	0.9845	0.9943
	S.E.	1.800	0.462
	F	674	1426
Disso	RMS	10.9	12.9
	R^2_{adj}	0.8801	0.8700
	S.E.	0.177	0.205
	F	78.79	55.35
		$F_{(5,48,0.01)} = 929$	$F_{(8,57,0.01)} = 5.12$

RMS, root mean square; S.E., standard error; *F*, variance ratio; R^2_{adj}, adjusted coefficient of correlation.

For the second set of properties, the density (*Densi*) and porosity (*Poros*) of the tablets show different patterns according to the property studied and the type of machine. Regarding the density of the tablets, the regression equations for the two machines tend to reflect the changes with good agreement (RMS = 4.63, $R^2_{adj} = 0.7968$, Manesty and RMS = 4.02, $R^2_{adj} = 0.8339$, Instron, Table 3). This observation is supported by comparison of the experimental and predicted values ($r_0 = 1.97$ g cm^{-3}, $p_0 = 2.04$ g cm^{-3}, Manesty, Table 1 and $r_0 = 2.38$ g cm^{-3}, $p_0 = 2.32$ g cm^{-3}, Instron, Table 2). One explanation may be the high dependence of the density of the tablets on the densities of the individual materials, and consequently variations in the proportions of the ingredients affected the density of the tablets. Ganderton and Selkirk (1970) on tabletting lactose and sucrose observed that tablets tend to keep the integrity of the starting materials, but Sixsmith (1980) found that the porosity tends to be affected by the process as well as by the concavity of the tip of the punch. In fact, the

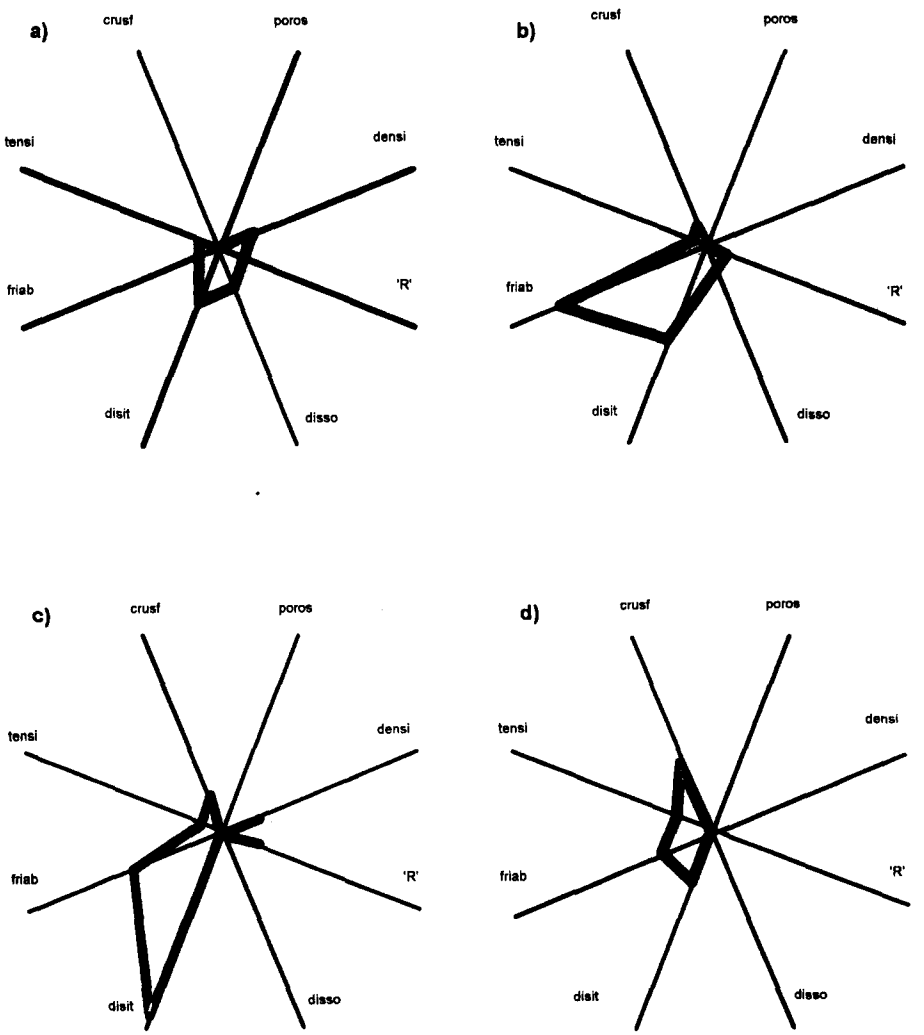

Fig. 1. Effect on the dependent variables when the independent variables are increased. (a) Increase in load of model drug in pellets of type 'A', (b) increase in percentage of pellets of type 'B' in the tablets, (c) increase in disintegrable pellets with barium sulphate, (d) increase in size of the pellets, and (d) increase in compression pressure applied to the tablets.

equations proposed to reflect variations in the porosity of the tablets are not as robust as the previous equations (RMS = 14.1, $R^2_{adj} = 0.3067$, Manesty and RMS = 17.2, $R^2_{adj} = 0.7199$, Instron, Table 3). The predictions are similar to the experimental results ($r_0 = 28.3\%$, $p_0 = 26.0\%$, Manesty, Table 1 and $r_0 = 17.5\%$, $p_0 = 17.0\%$, Instron, Table 2). An explanation for this observation may be that changes in the independent variables affected the properties of the tablets in different ways such that the porosity provides a poor way to characterisation of the tablets. This fact is stressed when the results of the two machines are compared. For the Manesty, with short compression cycles a poor fit and correlation was obtained (Table 3), whereas for the Instron (longer compression cycles) the correlation between the variables increased although the fit of the curve remained poor. This suggests that the factors affecting the porosity of the tablets are dependent

on the time of compression, or in other words, that plastic deformations of some materials might justify the different significance of the equations. Looking now at Figs. 1 and 2, an increase in the independent variables had a different effect on the tablet density and porosity of the tablets produced by the two machines. Fig. 1a–d present the variations for the tablets produced by the Manesty. Neither an increase in the percentage of pellets with glyceryl monostearate (type 'C') nor an increase in the compression pressure produced tablets with higher density. On the other hand, the amount of drug in pellets of type 'A' and an increase in the percentage of pellets of type 'B' showed a slight increase in the density of the tablets. With respect to porosity, the model equation was unable to reflect any alterations. Fig. 2a–e reveals the effect of the increase of the independent variables on density and porosity. The effect of the drug load (pellets of type 'A', Fig. 2a) and the percentage of pellets of type 'C' (Fig. 2b) did not change as opposed to the density of tablets produced by the Manesty (Fig. 1a, b). However, the increase in the percentage of the pellets of type 'B' (Fig. 2c), the size of the pellets (Fig. 2d), the concavity of the tip of the punch (Fig. 2f) and especially the increase in the diameter of the punch (Fig. 2e) had a significant effect on density. Porosity was mainly affected by changes in the percentage of pellets of types 'B', 'C' and diameter of the punch (Fig. 2b, c, e), a medium effect due to an increase on the concavity of the tip of the punch (Fig. 2f) and minimal effect due to the size of the pellets.

Analysis of the results of the crushing force (*Crusf*) defined as the force required to break the tablets diametrically and the tensile strength (*Tensi*), calculated from the crushing force, presented a different level of significance from the ones discussed before (Table 3). Table 3 presents the results of the statistical analysis for the regression equations of the crushing force as a function of the variables selected (RMS = 14.0, R^2_{adj} = 0.7918, Manesty and RMS = 40.2, $R^2_{adj} = 0.3417$, Instron, Table 3). Experimental results and predictions ($r_0 = 7.75$ N, $p_0 = 7.92$ N, Manesty, Table 1 and $r_0 = 9.40$ N, $p_0 = 9.65$ N, Instron, Table 2), suggest a higher quality of the model than the one that the statistical analysis has shown. The different correlations found for the regressions, for the two machines and for the crushing force (R^2_{adj} = 0.7918, Manesty and $R^2_{adj} = 0.3417$, Instron, Table 3), suggest that, for the Instron, the longer compression cycle might imply that there are some more important variables than others, whereas for the Manesty all the independent variables seem to play a role in the regression. Comparison of the results based on the crushing force of a tablet may not be the most adequate, as variations on the dimensions of the tablet may not be reflected in linear relationships with the crushing force. On the other hand, the tensile strength, being a fundamental property of a tablet (Newton et al., 1971), should provide a better representation. The results reflect this view as the tensile strength seems to be a better predictor according to the statistical analysis (RMS = 14.2, $R^2_{adj} = 0.7728$, Manesty and RMS = 13.2, $R^2_{adj} = 0.9608$, Instron, Table 3) confirmed by the experimental and predicted values ($r_0 = 0.090$ N m^{-2}, $p_0 = 0.090$ N m^{-2}, Manesty, Table 1 and $r_0 = 0.104$ N m^{-2}, $p_0 = 0.097$ N m^{-2}, Instron, Table 2). From this analysis it can be concluded that the tensile strength can be predicted in a better way than the crushing forces, as the tensile strength considers the dimensions of the tablet, whereas the crushing force does not. For the tablets produced by the Manesty machine, increases in the selected independent variables were reflected in the dependent variables, except for pressure, which predicts a significant increase in the crushing force and a minor increase in the tensile strength (Fig. 1d). Regarding the Instron, predictions of changes are very significant for the concavity of the tip of the punch (Fig. 2f) and less significant for the diameter of the punch (Fig. 2e) or for the increase in the percentage of the pellets of type 'C' (Fig. 2b). All the other independent variables did not produce significant variations. The sections of the tablets exposed after the tests showed intact pellets of type 'A' (yellowish) surrounded by white powder. The failure occurred on surfaces bonded during compression (Butcher et al., 1974).

Friability reflects the ability of tablets to withstand both shock and abrasion without losing material. However, from all the properties of the

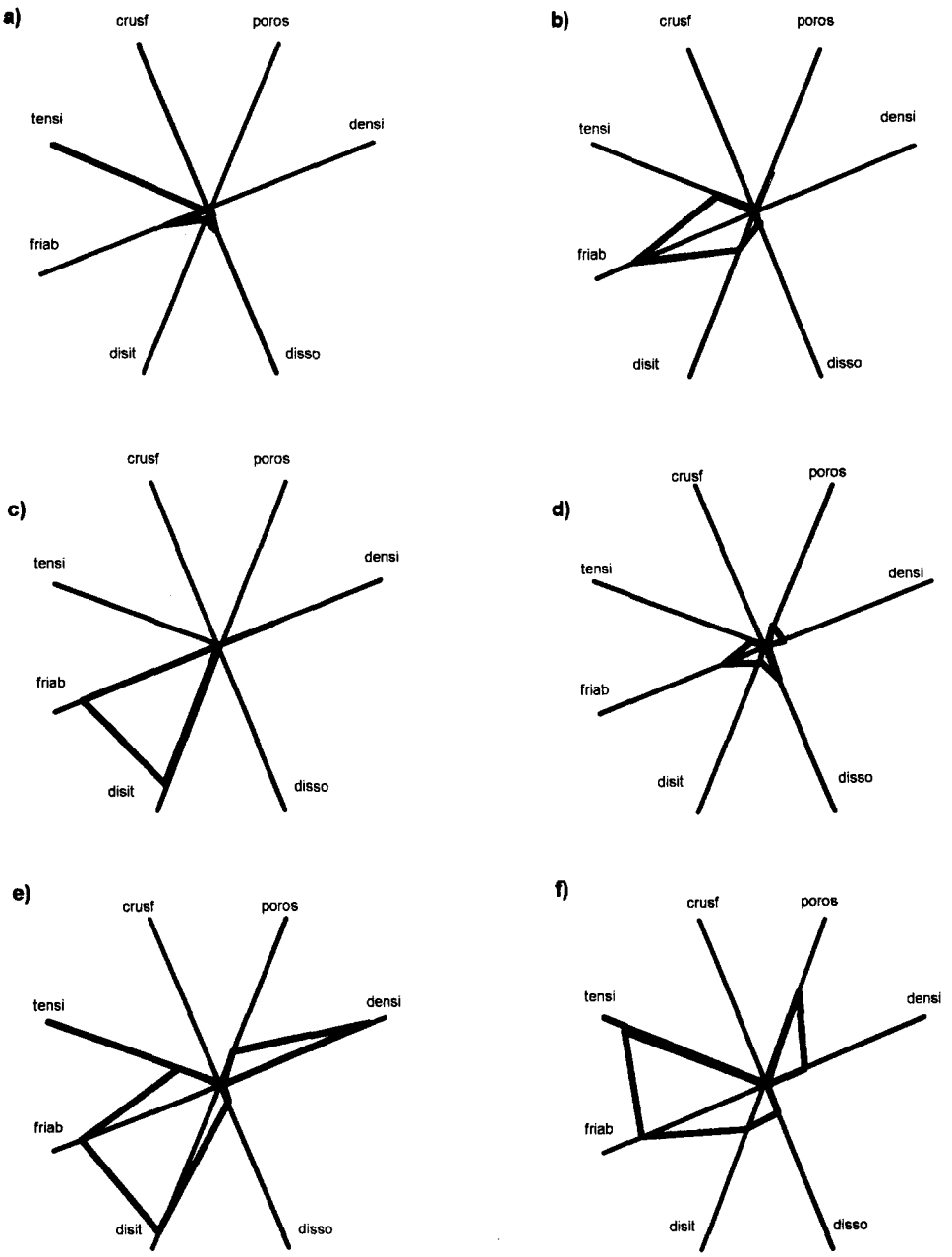

Fig. 2. Effect on the dependent variables when the independent variables are increased. (a) Increase in load of model drug in pellets of type 'A', (b) increase in percentage of pellets of type 'B' in the tablets, (c) increase in disintegrable pellets with barium sulphate, (d) increase in size of the pellets, (e) increase in diameter of the punch, and (f) increase in concavity of the punch.

tablets studied, the equations for friability (*Friab*) show the poorest fit of all. For the tablets produced by the Manesty machine the ($r_0 = 4.11\%$ and $p_0 = 23.2\%$, Table 1) and the tablets produced by the Instron ($r_0 = 1.0\%$ and $p_0 = 2.91\%$, Table 2) poor predictions are supported by the statistical

analysis presented in Table 3 (RMS = 90.6, $R^2_{adj} = 0.6857$, Manesty and RMS = 223.9, $R^2_{adj} = 0.9595$, Instron). The failure of the model may indicate that the friability of the tablets depends on factors other than the ones studied, although sometimes relationships can be made with other properties such as the crushing force to break a tablet and the applied pressures (Knoeckel et al., 1967). However, there is generally no physical principle to support or explain the variation in friability. Due to the poor ability of the model to make predictions graphical representations were not considered.

Analysing the results of the disintegration time (*Disit*) and of the mean dissolution time (*Disso*), which depends partially on the first variable (*Disit*), good predictions could be made, especially for the disintegration time of the tablets (RMS = 55.0, $R^2_{adj} = 0.9845$, Manesty and RMS = 32.8, $R^2_{adj} = 0.9943$, Table 3). The comparisons between the experimental and predicted values are in good agreement, suggesting the acceptance of the models ($r_0 = 3.5$ min, $p_0 =$ 3.4 min, Table 1 and $r_0 = 2.0$ min, $p_0 = 1.0$ min, Instron, Table 2). The good correlation and relatively small values for the residuals suggest that disintegration can be used as a predictor of these properties of the tablets. As expected, the disintegration of tablets depends on all independent variables such as the applied pressure (Lowenthal, 1972).

The experimental results of the mean dissolution time of indomethacin support the regression equations which tend to predict the results accurately. For the Manesty (RMS = 11.0 and $R^2_{adj} = 0.8801$, Table 3, $r_0 = 1.6$ h versus $p_0 = 1.5$ h, Table 1) and for the Instron (RMS = 12.85 and $R^2_{adj} = 0.8700$, Table 3, $r_0 = 1.9$ h and $p_0 =$ 1.6 h, Table 2). Again, the good ability of measurements of the dissolution of the drug to reflect the independent variables (such as the drug load in the pellets of type 'A', the size of the pellets and the pressure applied to the system) can be concluded from the results. The factors which affected the time for disintegration to occur also affected the mean dissolution time. Figs. 1 and 2 show that the dissolution time of the drug was only slightly affected by changes in the independent variables whereas the time required for the disintegration of the tablets was greatly affected.

4. Conclusions

The study has shown the possibility of identifying equations that can model the complex phenomena that occur throughout the process of compression of pellets. The model proposed has made possible the identification of the different properties of the tablets such as the '*R*' value, the density of the tablets, the tensile strength and the disintegration and mean dissolution time of the drug as the most relevant parameters worth monitoring in the preparation of tablets, and at the same time permitted the selection of a particular formulation required. On the other hand, parameters such as the force required to eject a tablet from the die, the porosity of the tablet, the force necessary to crush a tablet and, especially the friability of the tablet provided only poor information for both formulation and processing conditions. The study has also shown differences between the machines used to prepare the tablets. The differences were reflected by the changes in significance of the variables mentioned previously. Finally, the star diagrams allowed the visualisation of the relative variations of all the dependent variables when a single independent variable was increased.

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