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Investigations of tablets prepared from pellets produced by extrusion and spheronisation
Part I: The application of canonical analysis to correlate the properties of the tablets to the factors studied in combination with principal component analysis to select the most relevant factors

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Abstract

Three different types of pellets prepared by extrusion and spheronisation were mixed and tabletted by a mechanical press and by a tabletting machine. The objective was to prepare tablets of drug containing pellets which would disintegrate into the pellets from which they were made on adding to fluid. Several factors involved in the production of the tablets were analysed by canonical analysis, which identified relationships between the drug loading in the pellets, the proportion of pellets without the drug, the compression pressure used to prepare the tablets, the size of the pellets, the diameter of the die, the concavity of the punch and the density, the porosity, the crushing force to break the tablets, the tensile strength, the friability, the disintegration time of the tablets and the mean dissolution time of the drug. On one hand, the results have shown that the glyceryl monostearate within the pellets interacted with the barium sulphate pellets regarding the disintegration times of the tablets. The glyceryl monostearate was important as a lubricant, whereas the barium sulphate was important for the disintegration of the tablets. The

Abbreviations: A, hard pellets with model drug; B, disintegrable pellets with barium sulphate; 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 $d^2_{x|u}$, interranging communality of a variable; Densi, density of tablets; Di, diameter of the punch; Disit, disintegration time of tablets; Disso, mean dissolution time; Ejefor, ejection force required to eject a tablet from the die; Friab, friability of tablets; G, percentage of pellets of type 'B' 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; H, percentage of pellets of type 'C' in the tablets; P, compression pressure applied to the pellets; Poros, porosity of tablets; R, ratio of the lower to the upper punch force; S, Size of the pellets; Tensi, Tensile strength of tablets.

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pressure applied and the size of the pellets were not major factors to be considered. However, the shape of the tip of the punch and the diameter of the punches were very important for the properties of the tablets. By combining the Principal Component Analysis with the Canonical Analysis, it was possible to select the variables which had a greater effect on the properties of the tablets. © 1997 Elsevier Science B.V.

Keywords: Canonical analysis; Extrusion; Pellets; Principal-component analysis; Spheronisation; Tablets

1. Introduction

Tablets are the most accepted dosage form accounting for the largest share of the market of medicines. They have been used to provide drugs for controlled release formulation, but as single unit dosage forms the tablets present several disadvantages such as a possible irritation of the mucosae in the gastrointestinal tract (Bechgaard and Nielsen, 1978; Lordi, 1986). One way to overcome the problem is to prepare capsules filled with pellets produced by extrusion and spheronisation of wet masses (Conine and Hadley, 1970), or to tablet mixtures of powders with pellets or mixtures of pellets (Aulton et al., 1994). These dosage forms can be considered as multiunit dosage forms, as the capsules or tablets disintegrate in the stomach or small intestine, releasing the pellets, which act as dosage forms and are dispersed throughout the gastrointestinal tract, avoiding the risk of local high concentrations of drug.

Tabletting of materials depends on several factors such as the size of the particles and the compression pressure employed (Higuchi et al., 1954), which contribute to the final properties of the tablets produced. Therefore, the experimental design and the analysis of the results should help to relate the contribution of each factor studied to the property of the tablet considered. By changing the levels of the variables in the formulation (e.g. increasing the drug content in a formulation) or by changing the processing conditions (e.g. increasing the pressure applied to the pellets) further experiments can be designed. If the original experiment is considered as the starting point, i.e. a centre point, further experiments allow the building of an experimental design. This concept constitutes the basis for the 'Centre of Gravity Design' which has the major advantage over the traditional experimental designs (e.g. factorial designs) of providing the largest amount of information for a reduced number of experiments (Podczeck and Wenzel, 1990). The data collected from the experiments can be analysed by multivariate statistical techniques such as Canonical Analysis or Principal Component Analysis.

Canonical Analysis, according to Hotelling (1936) and Bartlett (1941) is a technique able to correlate simultaneously several matrix dependent variables with several matrix independent variables (Tabachnick and Fidell, 1989), maximising the correlation between the two groups of variables. This is achieved by the transformation of the variables (X and Y) into canonical variables (U and V) following the analysis of the relationship between these two variables (Manly, 1986). The significance of the canonical analysis can be tested by the Hotelling's T^2 test, based on a normal multivariate distribution function, which can be approximated to the F distribution, allowing the test values to be compared with a common table of critical values to test the significance (Gaensslen and Schubö, 1976).

Once the factors studied have been correlated to the properties of the tablets, a Principal Component Analysis according to Hotelling (1936) can be used to select the most relevant factors studied, as the primary purpose of this technique is to reduce the number of variables (Hair et al., 1992). Principal Component Analysis is mathematically related to the Canonical Analysis. Combining the two techniques it is possible to select the variables accounting for the largest share of variance, i.e. the most relevant variables studied.

The aim of the work was to study the contribution of several factors (drug load, percentage of three different types of pellets, compression pressure, size of the pellets, punch diameter and concavity of the tip of the punch) on the properties of the tablets produced and to select the factors which have the greatest influence on the proper-

ties of the tablets. This will allow the identification of the formulations which can provide tablets from pellets containing drug pellets which can be released intact on disintegration.

2. Materials and methods

2.1. Materials

Indomethacin EP (Bechpharm, UK) medium volume particle diameter 57.0 ± 1.86 μm, melting range 155–156°C (the drug was in a polymorphic form I (O'Brien et al., 1984)). Lactose monohydrate EP (Meggle-Wasseburg, Germany) medium volume particle diameter 16.8 ± 0.35 μm. Microcrystalline cellulose (Avicel PH 101, FMC, USA) medium volume particle diameter 53.8 ± 0.54 μm. Glyceryl monostearate, technical grade (Pfaltz and Bauer, USA), melting range 76–77°C, molar weight 359.0 g was sieved and the fraction smaller than 125 μm was used. Barium sulphate (BDH, GPR grade, UK), medium volume particle diameter 16.3 ± 0.84 μm. The water used was freshly distilled.

2.2. Methods

The particle size determination of the materials (except for the glyceryl monostearate) was carried out in a Malvern Master Sizer (Series 26OOC Malvern Instruments, UK). The melting range of indomethacin was found using a Mettler hot stage (Mettler FP52) mounted on an Olympus microscope (model B201).

Three different types of pellets of three size fractions (0.71–1.0, 1.0–1.4 and 1.4–1.7 mm) were produced by extrusion and spheronisation. Pellets of type A included the model drug indomethacin (0.25 up to 3 parts in the formulation), lactose (2 up to 4.25 parts in the formulation), microcrystalline cellulose (3 parts in formulation) and water (3.36 parts in formulation). The amount of indomethacin and lactose was kept constant at 5 parts in each formulation. Pellets of type B included barium sulphate (8 parts in the formulation), microcrystalline cellulose (2 parts in the formulation) and water (3 parts in the formulation). Pellets of type C included glyceryl monostearate (3 parts in the formulation), barium sulphate (5 parts in the formulation), microcrystalline cellulose (2 parts in the formulation) and water (3 parts in the formulation). The powders were mixed for 20 min (Turbula, T2C, Switzerland) and then transferred to a planetary mixer (Kenwood Chef, UK) where the water was added.

The masses were extruded in a ram extruder fitted to a mechanical press MX50 fitted with a 50 kN load cell, (Lloyds Instruments, UK). The extruder was fitted with a die of 1 mm diameter and 4 mm length. The speed of displacement of the cross head was 400 mm/min. The extrudate was spheronised in a spheroniser fitted with a radial plate, 225 mm diameter at 1000 rpm (Caleva, UK) for 10 min. The wet pellets were dried in a fluidized bed dryer (model FBD/L70, PRL Eng, UK) for 20 min at 60°C for pellets of type A and B and 30°C for pellets of type C. Except where stated, the pellets of the size fraction 1.0–1.4 mm were used.

Tablets were produced from different mixtures of pellets using an Universal Testing Instrument (Instron, model MPA 6888, UK) or an instrumented tablet machine (Manesty F3, UK) fitted with piezoelectric load cells (type 9031, Kistler, Switzerland). The densities of the powders, pellets and tablets were measured by a comparison air pycnometer (Beckam, model 930, USA) and the porosities of the tablets were calculated from the densities of the tablets and the densities of the powders. The force to crush the tablets diametrically was measured using a tablet strength tester (CT-40 Engineering Systems, UK) and the tensile strength calculated after taking into consideration the dimensions and shapes of the tablets (Fell and Newton, 1970; Pitt et al., 1988). The friability of the tablets was measured in a Roche type friabilator (Erweka, Germany), rotating at 25 rpm for 4 min. The disintegration times of the tablets were determined using a tablet disintegration tester (Manesty, model TD 41T 166, UK) in water at 37°C. The mean dissolution time of the drug from the different tablets produced was calculated based on the statistical moments of the cumulative amount of drug released (Voegele et al.,

1988). The dissolution tests were carried out according to the USP XXIII (Pharmatest dissolution tester, Germany), paddle method (100 rpm) in 1000 ml phosphate buffer, pH 7.4 (BP, 1993) at 37°C.

The calculations for the Canonical 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). 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 diametrical crushing force (Crusf), the tensile strength (Tensi), the friability (Friab), the disintegration time (Disit) and the mean dissolution time (Disso), for tablets produced on both machines as shown in Table 1. Table 2 presents the experimental design ('Centre of Gravity Design', Podczeck and Wenzel, 1990) where bold characters represent the centre of gravity of the experimental design.

Table 1
3Variables and levels of the variables studied in the experiments

Variable	Level in the experiment[a]
Drug loading (D[b]) (parts in the formulation)	0.25, 0.5, **1**, 2, 3
Proportion of pellets of type A (%)	15, **25**, 35, 50
Proportion of pellets of type B (B[b]) (%)	0, 25, **50**, 75
Proportion of pellets of type C (G[b]) (%)	0, 15, **25**, 35, 50, 75
Pressure (P[b]) (MPa)	43, 65, 87, **108**, 130, 173
Size of the pellets (S[b]) (mm, by weight)	0.71–1.00
	1.00–1.40
	1.40–1.70
Die diameter (Di[b]) (mm)	8, 10, **12**
Punch concavity (C[b]) (mm)	**0**, 1.5, 2.8

[a]Bold characters represent the level in the experiment for the centre of gravity.
[b]Variables entered in the statistical analysis.

From the Canonical Analysis three measures were used to analyse the results. The extracting measures ($g^2_{X|U}$ and $g^2_{Y|V}$) describe the part of the whole variance of the variables X or Y which can be explained by the corresponding canonical variables U or V. The measures of redundance ($g^2_{X|V}$ and $g^2_{Y|U}$) of the shared variance of the canonical functions describe the part of the whole variance of one group of variables, X or Y, that can be explained by the canonical variables of the other group, V or U. The amount of variance of one original variable, X or Y, that is described by the canonical variables of the opposite variable group ($d^2_{X|V}$ and $d^2_{Y|U}$ and is called the interranging communality of the variable (Podczeck et al., 1993).

3. Results and discussion

The results showing the properties of the tablets produced by the Manesty and the Instron machines are presented in Tables 3 and 4, respectively. Tables 5–8 present the results of the statistical analysis, Table 5 of the Canonical Analysis and Tables 6–8 of the Principal Component Analysis.

Table 5 summarises the results of the Canonical Analysis. The results shown were highly significant ($p < 0.01$) for the three sets of experiments as the values for Hotelling's T^2 test and the approximation to the F distribution indicate. From the same table and for the tablets produced with the Instron machine it can be observed that for the two sets of results more significant information was obtained about the system studied when the number of independent variables considered was increased from 5 to 7. Although the results of the second set (Instron, 7 variables) include the results of the first set (Instron, 5 variables) and the number of variables increased, the measures of redundance increased ($g^2_{Y|U}$) from 37 to 71% when two extra variables were included in the design (Table 5). Also the interranging communalities

Table 2
Design of the experiments according to the centre of gravity design[a]

Number of experiment	Drug load (parts in the formulation)	Combination of types of pellets (%)			Compression pressure (MPa)	Pellet size (mm)	Die diameter (mm)	Punch concavity
		Type A	Type B	Type C				
1	3	25	50	25	108	1.00	12	0.0
2	2	25	50	25	108	1.00	12	0.0
3[a]	1	25	50	25	108	1.00	12	0.0
4	0.5	25	50	25	108	1.00	12	0.0
5	0.25	25	50	25	108	1.00	12	0.0
6	1	15	50	35	108	1.00	12	0.0
7	1	35	50	15	108	1.00	12	0.0
8	1	50	50	0	108	1.00	12	0.0
9	1	25	0	75	108	1.00	12	0.0
10	1	25	25	50	108	1.00	12	0.0
11	1	25	75	0	108	1.00	12	0.0
12	1	25	50	25	43	1.00	12	0.0
13	1	25	50	25	65	1.00	12	0.0
14	1	25	50	25	87	1.00	12	0.0
15	1	25	50	25	130	1.00	12	0.0
16	1	25	50	25	170	1.00	12	0.0
17	1	25	50	25	108	0.71	12	0.0
18	1	25	50	25	108	1.40	12	0.0
19	1	25	50	25	108	1.00	10	0.0
20	1	25	50	25	108	1.00	8	0.0
21	1	25	50	25	108	1.00	12	1.5
22	1	25	50	25	108	1.00	12	2.8

[a]Characters in row 3 represent the levels of the variables for the centre of gravity experiment.

Table 3
Properties of the tablets produced by the Manesty F3 machine (mean results shown)

Number of experiment	R ($n = 20$)	Ejection force (N) ($n = 20$)	Density (g cm^{-3}) ($n = 5$)	Porosity (%) ($n = 5$)	Crushing force (N) ($n = 5$)	Tensile strength (Nm^{-2}) ($n = 5$)	Friability (%) ($n = 3$)	Disintegration (min) ($n = 3$)	Mean dissolution (h) ($n = 3$)
1	0.86	121	1.89	38.26	70.6	0.082	3.37	3.5	2.28
2	0.89	146	1.91	30.56	84.1	0.100	2.80	3.5	1.92
3	0.88	136	1.97	28.29	76.0	0.090	4.11	3.5	1.64
4	0.88	138	2.12	22.88	85.9	0.102	6.22	3.5	1.10
5	0.88	104	1.80	24.85	78.7	0.093	4.33	5.0	0.94
6	0.89	122	2.03	27.79	73.4	0.088	5.69	4.5	1.87
7	0.86	132	2.11	22.06	89.9	0.108	61.2	0.01	1.26
8	0.62	863	2.10	19.90	42.8	0.050	100	0.01	0.98
9	0.88	133	1.48	23.38	77.9	0.060	1.21	60	2.82
10	0.90	168	1.69	27.94	89.1	0.086	3.51	30	2.43
11	0.70	640	2.55	19.61	34.3	0.048	100	0.01	1.21
12	0.87	97	2.21	19.82	25.3	0.026	100	0.01	1.35
13	0.86	87	2.08	24.33	51.9	0.056	36.4	0.01	1.46
14	0.88	141	2.26	17.71	60.1	0.071	100	3.0	1.40
15	0.89	158	2.12	23.09	100.9	0.120	1.18	3.5	1.44
16	0.89	977	2.07	24.84	103.9	0.120	1.14	3.5	1.47
17	0.88	170	2.03	26.18	91.2	0.100	2.26	3.35	1.10
18	0.88	112	2.04	25.85	81.02	0.089	4.95	3.5	1.79

n = Number of observations.
[a]Bold characters represent the levels of the variables for the centre of gravity experiment.

Table 4
The properties of tablets produced by the INSTRON machine (mean results shown)

Number of experiment	Density (g cm^{-3}) ($n = 5$)	Porosity (%) ($n = 5$)	Crushing force (N) ($n = 5$)	Tensile strength (Nm^{-2}) ($n = 5$)	Friability (%) ($n = 3$)	Disintegration time (min) ($n = 3$)	Mean dissolution time (h) ($n = 3$)
1	2.29	16.4	101.9	0.102	0.7	2	2.56
2	2.30	16.2	88.2	0.100	1.0	2	2.29
3	2.38	17.5	92.1	0.104	1.0	2	1.91
4	2.28	17.2	94.1	0.105	1.0	2	1.13
5	2.30	16.5	94.1	0.105	1.2	2	0.90
6	2.47	11.9	85.3	0.096	1.9	2	1.85
7	2.30	14.7	100.0	0.111	1.6	2	1.65
8	2.34	10.5	135.2	0.148	0.5	0.01	1.16
9	1.68	12.9	58.8	0.052	3.5	30	3.42
10	1.95	16.6	65.7	0.065	1.4	10	2.25
11	2.79	11.7	119.6	0.150	1.7	0.01	1.45
12	2.26	17.8	59.8	0.062	20.6	2	1.91
13	2.31	16.0	60.8	0.065	3.8	2	1.92
14	2.26	17.8	82.3	0.090	1.9	2	1.80
15	2.28	17.1	81.3	0.091	1.3	2	1.75
16	2.28	17.1	95.1	0.107	1.6	2	1.79
17	1.96	28.7	102.9	0.118	1.4	2	0.82
18	2.26	17.8	79.4	0.089	0.5	2	1.90
19	1.94	29.5	75.5	0.068	3.4	4	1.44
20	1.95	29.1	90.2	0.071	6.4	7	1.51
21	1.94	29.5	18.6	0.078	100	3	1.26
22	1.97	28.4	24.5	0.038	100	3	1.40

n = Number of observations.
[a]Bold characters represent the levels of the variables for the centre of gravity experiment.

Table 5
Results of the canonical analysis of the relationship between formation variables and tablet properties.

	Manesty F3	Instron (5 variables)	Instron (7 variables)
Significance of the canonical variables			
Hotelling T2	198.3	28.0	128.5
Approximation F	220.1[a]	41.9[a]	131.8[a]
Measures of redundance			
$g^2_{X\|V}$	0.727	0.547	0.606
$g^2_{Y\|U}$	0.640	0.372	0.710
Interranging communalities			
$d^2_{D\|V}$	0.845	0.836	0.836
$d^2_{B\|V}$	0.936	0.976	0.976
$d^2_{G\|V}$	0.985	0.902	0.902
$d^2_{P\|V}$	0.978	0.255	0.255
$d^2_{S\|V}$	0.373	0.486	0.485
$d^2_{Di\|V}$			0.721
$d^2_{C\|V}$			0.991
$d^2_{R\|U}$	0.805		
$d^2_{Ejefor\|U}$	0.768		
$d^2_{Densi\|U}$	0.881	0.732	0.890
$d^2_{Poros\|U}$	0.502	0.341	0.796
$d^2_{Crust\|U}$	0.807	0.470	0.640
$d^2_{Tensi\|U}$	0.773	0.327	0.815
$d^2_{Friab\|U}$	0.782	0.115	0.898
$d^2_{Disit\|U}$	0.934	0.911	0.924
$d^2_{Dissi\|U}$	0.958	0.894	0.909

[a] $p < 0.01$.

($d^2_{Y|U}$) for the results obtained for the Instron (7 variables) are higher (mostly above 0.8) compared to the results obtained when 5 variables were studied (4 of them below 0.5) (Table 5). This suggests that more variables are involved in the process of formation for the tablets produced by the Instron machine.

From the measures of redundance extracted, $g^2_{Y|U}$, the ability to predict the dependent variables from the formulation and production variables (the independent variables) can be achieved with the experiments carried out. A prediction of 64 and 71% (Table 5) for the tablets produced with the Manesty or in the Instron (7 variables) allows the discussion of the results with confidence, whereas for the tablets produced with the Instron (5 variables) a prediction of 37% means that it is unlikely that predictions of the tablet performance can be made from the factors studied. Therefore, this set of results will not be discussed further.

The results for the interranging communalities ($d^2_{X|V}$, Table 5) first set, present changes according to the machine used. The results of the tablets produced by the Manesty machine indicate that the glyceryl monostearate present in the pellets of type 'C' was the factor that affected the properties of the tablets to the greatest extent ($d^2_{G|V} = 0.985$, Table 5). The presence of glyceryl monostearate in the formulation was also relevant for the tablets produced by the Instron machine ($d^2_{G|V} = 0.902$, Table 5). In fact, the structure and the production of the tablets, and consequently the properties of the tablets (experiments 6–11, Tables 3 and 4) were affected by this factor. The glyceryl monostearate affected the times for the disintegration of the tablets, an increase in the time with an increase in the amount of glyceryl monostearate in the formulation. The effect of the glyceryl monostearate was extended to other properties of the tablets such as the value of R (ratio between the

Table 6
Component matrix for the results of the tablets produced in the Manesty F3 from principal component analysis[a]

Variables	Principal component 1	Principal component 2	Principal component 3
D	0.0522	0.7334	−0.1499
B	0.9769	−0.0052	0.0021
G	−0.9761	0.0118	−0.0047
P	−0.0275	0.6601	0.4483
S	0.0153	−0.2105	0.8836

[a]Three components extracted from five.

lower to the upper punches pressures) and the 'ejection force' (experiments 8 and 11, Table 3). These two variables have been shown to be reliable in predicting the alterations in the properties of the tablets as the values for the $d^2_{R|U} = 0.805$ and $d^2_{Ejefor|U} = 0.768$ (Table 5) suggest. The glyceryl monostearate contributed 12.5% w/w to the final weight of the tablet, which is higher than the percentages referred to in the literature for stearates as lubricants (2–5%) (Nelson et al., 1954). Moreover, the experiments have shown that unless 25% of pellets of type B were present in the formulation, dramatic changes were observed (experiments 6–11, Tables 3 and 4). With less than 25% of type B pellets present in the formulations the values for R and for the ejection forces changed to unacceptable values (experiments 8 and 11, Table 3); on the other hand, the tablets did not disintegrate when large amounts of glyceryl monostearate were present (experiments 9 and 10, Tables 3 and 4). The relevance of the presence of glyceryl monostearate and barium sulphate in the formulations is also emphasised by the highly significant values of the interranging communalities for the tablets produced in the Instron machine ($d^2_{G|V} = 0.902$, and $d^2_{B|V} = 0.976$, Table 5). Comparing the two values for $d^2_{G|V}$ and $d^2_{B|V}$ for both machines an inversion in their importance can be seen. For the tablets produced by the Instron the presence of barium sulphate becomes more important than the glyceryl monostearate. As the main difference between the two machines is the velocity of punch movement the results suggest that the transformations which occurred on the pellets of type B required more time to occur than those of the pellets of type C.

Higher amounts of glyceryl monostearate in the formulation affected the crushing force and the tensile strength of the tablets. Comparing the results for the two machines and for the different amounts of glyceryl monostearate and barium sulphate in the formulations (experiments 7–11, Tables 3 and 4) it can be observed that the mechanical properties of the tablets improved when the lower amounts of glyceryl monostearate were present, whereas for higher amounts of glyceryl monostearate where present, the forces required to crush the tablets and the tensile strengths decreased. The same pattern of results has been reported by York and Pilpel (1973) when the authors studied the effect of the fatty acids on the tensile strength of the tablets. This suggests that these materials do not bond easily with the other materials, therefore the structure of the tablets is affected. Also the presence of glyceryl monostearate seems to decrease the friability of the tablets (experiments 6–11, Tables 3 and 4) suggesting that the glyceryl monostearate can compensate for the presence of barium sulphate, which makes the formation of bonds between the particles forming a network within the tablet even more difficult. The results have also shown the high dependence of the disintegration times on the presence of glyceryl monostearate and barium sulphate. The absence of glyceryl monostearate resulted in tablets with the lowest disintegration times (experiments 6–11, Tables 3 and 4). As the glyceryl monostearate is a hydrophobic material the penetration of water into the tablets was delayed and consequently so was the disintegration of the tablet. On the other hand, when the amount of barium sulphate in the formulation was decreased, the disintegration times increased

Table 7
Component matrix for the results of the tablets produced in the Instron from principal component analysis[a]

Variables	Principal component 1	Principal component 2	Principal component 3
D	0.0426	0.7322	−0.1553
B	0.9767	−0.0043	0.0018
G	−0.9762	0.0094	−0.0040
P	−0.0231	0.6616	0.4399
S	0.0126	−0.2002	0.8864

[a]Three components extracted from five

above 5 min, which was considered unacceptable for the purpose of the tablets produced. The same explanations as before can be given regarding the changes of the mean dissolution times. For instance, in the formulations with the highest amount of glyceryl monostearate the mean dissolution time increased.

The effect of the compression pressure applied was different for the two machines. For the tablets produced by the Manesty tabletting machine, the pressure applied was relevant ($d^2_{P|V}$ = 0.978, Table 5) whereas for the tablets produced by the Instron, the pressure was irrelevant ($d^2_{P|V}$ = 0.255, Table 5). Experiments 12 to 16 (Table 3) showed a slight increase of the R values for the pressures applied. Such findings were also reported by Miller and York (1988). This suggests that the lubrication due to the presence of glyceryl monostearate increases with the pressure applied. The glyceryl monostearate was either softened under pressure or squeezed through the spaces between the pellets and the space between the die and the punches. It was observed that when the pressures applied were higher than 173 MPa, as the upper punch moved down some glyceryl monostearate was released from the tablet and appeared between the die wall and the punches. This suggests either that the surface of the tablet in contact with the die wall becomes free of glyceryl monostearate due to the release of the latter, or that the radial force increases with the axial force in such a way that the glyceryl monostearate present is insufficient to provide a proper lubrication to the system.

Several authors came to the conclusion that the porosity as a function of pressure is non-linear (Armstrong, 1982; Higuchi et al., 1953). From the results in Tables 3 and 4 it can be observed that the conclusions cannot be applied to the system under study as the porosity increased slightly from 21.2 to 25.8%, probably due to relaxation of the tablets. The powder which results from the crushing of pellets of types B and C, did not result in tablet densification in the manner anticipated. When formulations without glyceryl monostearate were compressed, the density of the tablets increased, which suggests that the presence of glyceryl monostearate in the formulation is the important factor which changes the behaviour of the system. That the values for $d^2_{Densi|U}$ are generally high ($d^2_{Densi|U}$ = 0.881 for the Manesty and $d^2_{Densi|U}$ = 0.796 for the Instron, Table 5), suggests that these properties might reflect the structure of the tablets. However, care must be taken in the interpretation of the results as the densities of the starting materials are very different (e.g. barium sulphate and glyceryl monostearate) and therefore, these properties may not be good indicators in reflecting changes in the production of the tablets.

Several authors have tried to explain the effect of pressure on mixtures with waxes or fatty acids but the results are ambiguous. It is accepted that the temperature in the die increases a few degrees during the compression cycle (Knoeckel et al., 1967). Considering that the total temperature increase in the system is a consequence of the increased temperature at the contact points between the pellets, suggests that the increase in temperature in these points is much higher than that observed overall. In the present work the results failed to provide evidence that the glyceryl monostearate melted. It can be assumed that the glyceryl monostearate was softened or simply ex-

Table 8
Component matrix for the results of the tablets produced in the Instron from principal component analysis[a]

Variables	Principal component 1	Principal component 2	Principal component 3	Principal component 4	Principal component 5
D	0.035	0.020	0.851	0.321	−0.087
B	0.977	0.001	0.006	−0.003	0.001
G	−0.974	−0.002	−0.012	0.006	−0.002
P	−0.019	−0.009	−0.189	0.923	0.223
S	0.010	0.005	0.088	−0.174	−0.971
Di	−0.072	0.743	0.350	−0.111	0.042
C	0.069	0.730	−0.381	0.116	−0.043

[a]Five components extracted from seven.

truded within the tablet for lower pressures, and out of the die and punches for higher pressures, as was observed by visual inspection. What can be suggested is that the glyceryl monostearate formed a film which acted as a lubricant agent and closed the pores at the surface. Higher pressures made the glyceryl monostearate move towards the surface and then out of the die. Assuming that the glyceryl monostearate closed the pores at the surface of the tablets, which were produced with the same volume, the air in the pycnometer during the measurement of the volume of the tablet was not allowed to penetrate into the tablet.

The effect of pressure on the formulations has been reported by several authors (Higuchi et al., 1953, 1954; Knoeckel et al., 1967) who found a linear relationship between crushing force and the logarithm of the maximal compression force up to a limit. However, non linear relationships were found here between the crushing force and the compression forces, which suggests that the systems in this study reacted in a different way to changes in pressure than the ones described in the literature. A possible explanation may be that a preferable deformation for the different pellets occurred. Since the pellets of type A are more resistant to deformation than the pellets of types B and C, as was observed when the pellets were submitted to diametral pressure, they were broken and these materials surrounded the pellets of type A within the limits of pressure used in this study. After the tablets were submitted to the crushing test, the new surfaces exposed showed pellets of type A (yellowish) at the surface. This observation was confirmed by a disintegration test, after which it was possible to recover the pellets containing indomethacin. The linear relationship suggests that the deformation of the pellets of types B and C is more sensitive to pressure than the materials used in previous studies (Higuchi et al., 1953, 1954; Knoeckel et al., 1967). Also for the lowest pressure the tablets were not completely formed. As the crushing force can be related to the porosity of the tablets (Shotton and Ganderton, 1960) the values found for the porosity and crushing force are in good agreement. With an increase in the pressure applied, a dramatic decrease in the friability of the tablets produced by the two machines was observed. The differences were higher for the tablets produced by the Manesty where the tablets collapsed for the lower compression pressures (up to 108 MPa). Higuchi et al. (1953) and Lowenthal (1972) suggested that the disintegration times increase with the applied pressure, often in an exponential fashion as the packing fraction of the tablets tended to increase (Zubair et al., 1988). The disintegration times were independent of the applied pressure (Table 3) once the tablet was formed, i.e. for pressures higher than 87 MPa. It was suggested previously that applied pressures below the range used to produce the tablets resulted in high porosities, which tended to decrease with the applied pressure. However, the presence of glyceryl monostearate at the surface of the tablets may be the origin of the delay in the disintegration time (around 3 min). When the water overcomes this barrier, it penetrates easily

into the tablets, causing major disruptions in their structures with disintegration. The dissolution time of the indomethacin seems to be unaffected by the applied pressure, provided the disintegration time does not change.

The amount of drug in the pellets of type A was relevant ($d^2_{D|V} = 0.845$, for the tablets produced in the Manesty machine and $d^2_{D|V} = 0.836$, and for the tablets produced by the Instron machine, Table 5). The importance of this factor was more relevant to the mean dissolution time of the indomethacin. In fact, the results for the other properties did not show significant differences, whereas the mean dissolution times of the indomethacin decreased systematically when the percentage of drug decreased in the formulation. Such a change could be as a consequence of the higher amounts of lactose, a more soluble material than indomethacin, present in the formulation of the pellets of type A. Therefore, the porosity of the tablets in the dissolution medium for lower amounts of drug increases more rapidly, allowing a faster dissolution of the drug. From Table 5, the mean dissolution time of drug $d^2_{Disso|U} = 0.958$ (Manesty) and $d^2_{Disso|U} = 0.909$ (Instron) and the disintegration times $d^2_{Desit|U} = 0.934$ (Manesty) and $d^2_{Desit|U} = 0.924$ (Instron) are the properties which reflect by themselves the qualities of the tablets prepared. The release profile of the indomethacin from the tabletted pellets and from the untabletted pellets was the same.

The effect of the size of the pellets was not important ($d^2_{S|V} = 0.373$, for the tablets produced by the Manesty machine and $d^2_{S|V} = 0.485$ for the tablets produced by the Instron machine, Table 5). The observation suggests that the constituents of the pellets of types B and C, as particles, did not play an important role in the process of tabletting, i.e. the pellets with drug were not damaged during the process, as was observed when disintegration tests were performed and the number of pellets of type A counted and found equal to the expected value, whereas the other pellets were broken at early stages of the process, releasing the materials which were responsible for the formation of bonds between the materials. The diameter of the pellets did not affect the transmission of the force, suggesting that the pellets of types B and 'C' fragment rather than deform when submitted to pressure. If fragmentation is the main transformation of the pellets, then the forces induce low fragmentation of the material. On increasing the force, the fragmentation of the materials increases, releasing materials that have plastic properties (e.g. microcrystalline cellulose). Highly fragmented pellets produce a more homogeneous and less porous tablet than the pellets for which fragmentation is not complete, and consequently the transmission of the pressure to the lower punch (axial pressure) and to the die wall (radial pressure) becomes easier. The results presented herein contradict the observations by Hunter and Ganderton (1972), who stated that the properties of the granules or tablets produced from a certain formulation depend on the size of the primary particles. Fell and Newton (1970) using different sizes of particles of lactose (150–210 μm) concluded that higher densifications were obtained when the particle size increased and the time of the compression cycle increased, as a consequence of a better particle rearrangements. Fell and Newton (1970) also concluded that the rate of increase in tensile strength with compaction force also increased when the particle size decreased, as the strength of a tablet depends on the initial particle size of the material, but the value of $d^2_{S|V} = 0.373$ (Table 5) contradicts the explanations presented. The influence of the size of the pellets on the friability for the tablets produced by the two machines seems to be contradictory. For short compression cycles (Manesty) the friability increased with the size of the pellets, whereas for longer cycles (Instron) the opposite effect was observed. The observation suggests that for long compression cycles, which implies a higher degree of fragmentation and plastic deformation, the size of the pellets did not produce a major change in the friability. The mean dissolution time of indomethacin increased when the size of the pellets increased, probably due to the lower surface available for dissolution.

The effect of the diameter of the punch was important ($d^2_{Di|V} = 0.721$, Table 5). The results showed that when the punch diameter is decreased the density of the tablets tends to decrease and the porosity tends to increase. This observa-

tion suggests that for a smaller diameter of the punch, the bonds between the particles within the tablets were not as strong as for the tablets produced with larger diameter. The distribution of the pressure applied by the upper punch in the Instron machine changes when the ratio length to diameter of the punch is increased. Also the movement of the pellets during the compaction changed, because for smaller diameters, the radial movement of the particles in the die decreases, preventing the fragments and powder produced in the process of compaction to fill the voids. The changes in the crushing forces seemed not to be relevant. However, tensile strengths showed a decrease from 0.1 Nm^{-2} for a 12 mm punch diameter, to approximately 0.06 Nm^{-2} for tablets produced in a 10 and 8 mm punch diameter (experiments 19 and 20, Table 4). The results suggest that the best ratio for the dimensions of the tablet regarding the tensile strength is achieved with a 12 mm punch diameter. Using single-ended compaction the pressure is applied only by the upper punch, which means that the force was not uniformly distributed throughout the tablet. Therefore, when the thickness of the tablet is increased when compacting a constant weight of pellets, the loss of pressure within the die wall will also increase, resulting in a less dense tablet, especially in the lower portion, which is reflected in a decrease of the tensile strength.

When the die diameter is reduced for a constant mass of pellets, the thickness of the tablet is increased and, as a consequence the edges of the longer cylinder will be subjected to higher shocks since it moves away from a spherical shape. Therefore, the movement of the tablets inside the friabilator is less regular, providing some explanation for the higher friability found (experiments 19 and 20, Table 4). Moreover, the tablets with smaller diameter may not have been as completely compacted as the others because of the single-ended compaction. The results indicate that the disintegration times decrease with the increasing punch diameter. The density decreases for the smaller punch diameter, suggesting the presence of larger pores in the structure of the tablet. It was therefore expected that the disintegration time decreased when the tablets were produced with a punch with smaller diameter. However, the results presented in Table 4 (experiments 19 and 20) followed the opposite trend. The explanation must be found elsewhere. The external surface area of the tablets produced with a punch with larger diameter is larger than the surface of the tablets produced with a punch smaller diameter. This external surface of the tablet may be the important factor which explains the observation. These effects are due to the fact that the external area of the tablets was stressed when the concavity of the tip of the punch was changed (experiments 21 and 22, Table 5), a factor which was revealed to be important ($d^2_{C|V} = 0.991$, Table 5). However, the changes in the concavity might have been responsible for changes of the compression mechanism within the die (Sixsmith, 1980).

Principal component analysis was used to check interactions and to identify the main effects of the factors studied. Tables 6–8 show the principal components extracted (significant at $p < 0.01$). By combination of the results analysed by the Canonical Analysis and Principal Component Analysis, the selection for each set of results can be made. It can be suggested that the properties of the tablets produced by the Manesty F3 depend on the drug load (D), on the amount of pellets of types B and C (B and C) and their interaction (BC) and on the pressure used (P). Finally, the properties of the tablets produced by the Instron (7 variables) depend on the amount of drug in the pellets of type A (D), on the amount of the pellets of types B and C (B and G) and their interaction (BG), on the size of the pellets (S), on the diameter of the punch (Di), on the concavity of the punch (C) and on their interaction (DiC).

4. Conclusion

The study has indicated the possibility of producing tablets with drug loaded pellets plus deforming pellets and disintegrating pellets. These tablets have shown the ability to release the intact pellets in a disintegration or dissolution medium while maintaining an identical dissolution profile to the non tabletted pellets, suggesting their phys-

ical integrity. The results revealed the high dependence of the properties of the tablets on the amounts of barium sulphate and glyceryl monostearate pellets present. A minimum amount of barium sulphate (50% of pellets of type B) was required for quick disintegration of the tablets, whereas the glyceryl monostearate supplied by the pellets of type C (minimum 25%) was essential to provide a cushioning effect to the pellets with drug, and in addition to act as a lubricant.

The other factors proved to be less significant. The formation pressure and the size of the pellets were not the most important factors, suggesting a different compaction mechanism for the system studied. The diameter of the punches or the concavity of the tip of the punch have shown some significance.

As parameters to be controlled, the analysis suggests that the values of R and the ejection force are good parameters to control the processing of the tablets, whereas the disintegration times of the tablets and the dissolution times of the drug are good parameters to control the formulation.

The statistical techniques used provided information to explain the results and select the most relevant variables which are believed to affect the properties of tablets. For the Manesty machine the drug content in the pellets of A (D), the percentage of pellets of types B and C (B, G and BG) and the compression pressure (P) were the most relevant factors. On the other hand, for the Instron machine seven variables had to be included in further studies, such as the amount of drug in the pellets of A (D), the percentages of pellets of types B and C, (B, G and BG), the size of the pellets (S), the diameter and the concavity of the tip of the punch (Di, C, DiC). The large amount of information obtained for a small number of experiments also stressed the quality of the experimental design used.

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