International Journal of Pharmaceutics, 97 (1993) 15–28

IJP 03082

Research Papers

The application of canonical analysis to the evaluation of the influence of changes in components of standard direct compression tablet formulations

Fridrun Podczeck [a,1], Gabriele Merkel [a] and Piroska Révész [b]

[a] *Martin-Luther-University Halle-Wittenberg, Institute of Pharmaceutical Technology, Halle (Germany) and*
[b] *Albert Szent-Györgyi Medical University, Institute of Pharmaceutical Technology, Szeged (Hungary)*

(Received 14 August 1992)
(Accepted 13 October 1992)

Key words: Multivariate statistical analysis; Canonical analysis; Cellulose powder; Direct compression; Basic mixture; Pharmaceutical technology

Summary

Different types of microcrystalline and microfine celluloses are often used in direct tabletting mixtures. An evaluation has been undertaken of the connection between the pharmaceutical behaviour of a range of the cellulose products and the powder and tablet properties of the tabletting mixtures, using the multivariate statistical technique of canonical analysis. The cellulose properties were reflected in the behaviour of the tabletting mixtures, in particular the bulk volume, the particle size range, the formation energy (force-displacement-curves, E_2) and the elastic recovery energy (E_3). The approach demonstrated that an exchange of the cellulose product in direct tabletting mixtures is only possible in special cases.

Introduction

Tablets can be made by granulation or direct tabletting. The approach of direct tabletting is an economical method. Its simplicity is obvious, but it requires a new and critical approach to the selection of raw materials, flow properties of powder blends, and effects of formulation variables on compressibility (Shangraw, 1989). Most drug manufacturing firms prefer standard basic mixtures for direct tabletting, which have proved a success in attempts and in practice (Fiedler, 1989). In this way the expense of development can be reduced and the manufacturing process is easier to handle. Most of the basic mixtures include microcrystalline or micro fine celluloses as the main excipient, e.g., as described in the patent literature (Salpekar and Haag, 1985; Bauer et al., 1986). There are several pharmaceutical properties of the cellulose powders, which should influence the tablet formulation behaviour both as single factors and as related variables. To qualify and quantify each effect, a statistical test procedure is required, which is able to detect single and cross effects in a multivariate data material. In that way, the properties of the cellulose powders investigated could be related to those of the

Correspondence to ([1] present address): F. Podczeck, The School of Pharmacy, Dept of Pharmaceutics, University of London, 29–39 Brunswick Square, London WC1N 1AX, U.K.

basic mixtures. Such results would give a clue, which properties of the single materials must be controlled to guarantee a uniform quality of the tablet formulations. Furthermore, a judgement would be possible about the exchangability of excipients in formulations. Hence, canonical analysis was chosen to study the influence of the properties of different microcrystalline and microfine cellulose products on the behaviour of two basic mixtures. The pharmaceutical properties of the cellulose powders used were described in a previous paper (Podczeck and Révész, 1993).

Canonical Analysis

Canonical analysis can be used in the explanation of relations between two groups of variables. It was introduced in statistics by Hotelling (Lebart et al., 1984).

Two groups of variables are required – the group of the influencing factors X (independent variables) and the other group of the dependent variables Y. It is of interest whether and to which degree the two groups of variables depend on each other (Hartung and Elpelt, 1984). The two groups of variables are described as 'dependent on each other', if it is possible to form linear combinations for both groups, which correlate interchangable significantly (Gaensslen and Schubö, 1976). The dimension q of Y must be greater or equal to the value p of X. The mathematical treatment of this problem involves matrix algebra (Röhr, 1987):

The variance-covariance-matrix $\boldsymbol{S}$ is divided into four parts:

$$\boldsymbol{S} = \begin{pmatrix} \boldsymbol{S}_{XX} & \boldsymbol{S}_{XY} \\ \boldsymbol{S}_{YX} & \boldsymbol{S}_{YY} \end{pmatrix} \tag{1}$$

where $\boldsymbol{S}_{XX}$ denotes the variances and covariances of the independent variables, $\boldsymbol{S}_{YY}$ are the variances and covariances of the dependent variables and $\boldsymbol{S}_{XY}$ and $\boldsymbol{S}_{YX}$ represent the covariances of both groups.

The generalized problem of eigenvalues is to solve:

$$\left(\boldsymbol{S}_{XY}\boldsymbol{S}_{YY}^{-1}\boldsymbol{S}_{YX} - r_m^2\boldsymbol{S}_{XX}\right)\boldsymbol{a}_m^o = \boldsymbol{O}_p \quad m = 1(1),\ p \tag{2}$$

where r_m denotes estimation of the coefficients of canonical correlation, $\boldsymbol{a}_m^o$ is the estimation of the canonical moments of $\boldsymbol{X}$ and $\boldsymbol{O}_p$ represents the zero matrix.

The generalized eigenvalue problem, Eqn 2, can be transformed into a simple eigenvalue one (Eqn 4), when the matrix $\boldsymbol{S}_{XX}$ is factorized ($\boldsymbol{S}_{XX} = \boldsymbol{F}_X\boldsymbol{F}_X^T$) and used to calculate $\boldsymbol{A}$:

$$\boldsymbol{A} = \boldsymbol{F}_X^{-1}\boldsymbol{S}_{XY}\boldsymbol{S}_{YY}^{-1}\boldsymbol{S}_{YX}\left(\boldsymbol{F}_X^{-1}\right)^T \tag{3}$$

$$(\boldsymbol{A} - \boldsymbol{\lambda}\boldsymbol{I}_n)\boldsymbol{p} = \boldsymbol{O}_n \tag{4}$$

where $\boldsymbol{\lambda}$ are the eigenvalues of $\boldsymbol{A}$, $\boldsymbol{I}_n$ denotes the unit matrix, $\boldsymbol{p}$ are the eigenvectors of $\boldsymbol{A}$ and $\boldsymbol{O}_n$ represents the zero matrix.

When the simple eigenvalue problem is solved $\boldsymbol{\lambda}$ and $\boldsymbol{p}$ must be transformed back into r_m and $\boldsymbol{a}_m^o$. Then the canonical moments $\boldsymbol{b}_m^o$ of $\boldsymbol{Y}$ can be calculated:

$$\boldsymbol{b}_m^o = 1/r_m \cdot \boldsymbol{S}_{YY}^{-1}\boldsymbol{S}_{YX}\boldsymbol{a}_m^o \tag{5}$$

Because $\boldsymbol{A}$ has the dimension of $\boldsymbol{S}_{XX}$, only p canonical variables (linear combinations) are determinable. For the canonical correlations the following rule is valid:

$$r_1 \geqq r_2 \geqq \ldots \geqq r_p \tag{6}$$

Under empirical conditions the uniformity of two values of r is not possible and no value can be zero (Gaensslen and Schubö, 1976).

The significance of the canonical correlation coefficients is proved with the Wilks Λ-test (Hartung and Elpelt, 1984):

$$\Lambda = \left(1 - r_1^2\right)\left(1 - r_2^2\right)\ldots\left(1 - r_p^2\right) \tag{7}$$

Commonly, Λ will be approximated by F using the following equations (Gaensslen and Schubö, 1976):

$$s = \sqrt{\frac{p^2q^2 - 4}{p^2 + q^2 - 5}} \tag{8}$$

$$f_1 = pq \tag{9}$$

$$f_2 = s\left(N - 1 - \frac{p + q + 1}{2}\right) - \frac{pq - 2}{2} \tag{10}$$

$$F = \frac{f_2\left(1 - \sqrt[s]{\Lambda}\right)}{f_1\sqrt[s]{\Lambda}} \tag{11}$$

where N is the total observation number, p the dimension of X, q the dimension of Y, Λ the test value according to Wilks, f_1, f_2 the degrees of freedom and F the test value (approximation of Λ).

For the interpretation of the results, the following matrices and values are useful (Röhr, 1987):

The loads $\boldsymbol{R}$

Loads are correlation coefficients between the variables X and Y and the canonical variables U and V:

$$\boldsymbol{R}_{XU} = \boldsymbol{S}_X^{-1/2}\boldsymbol{S}_{XX}\boldsymbol{a}_m^o \quad m = 1(1),\ p \tag{12}$$

$$\boldsymbol{R}_{YV} = \boldsymbol{S}^{-1/2}\boldsymbol{S}_{YY}\boldsymbol{b}_m^o \quad m = 1(1),\ p \tag{13}$$

$$\boldsymbol{R}_{XV} = \boldsymbol{S}_X^{-1/2}\boldsymbol{S}_{XY}\boldsymbol{b}_m^o \quad m = 1(1),\ p \tag{14}$$

$$\boldsymbol{R}_{YU} = \boldsymbol{S}_Y^{-1/2}\boldsymbol{S}_{YX}\boldsymbol{a}_m^o \quad m = 1(1),\ p \tag{15}$$

where $\boldsymbol{R}_{XY}$ and $\boldsymbol{R}_{YV}$ are structural matrices (intraranging loads) and $\boldsymbol{R}_{XV}$ and $\boldsymbol{R}_{YU}$ are matrices of redundance (interranging loads).

The extracting measures $\boldsymbol{g}^2_{X|U}$ *and* $\boldsymbol{g}^2_{Y|V}$

The extracting measures describe which part of the whole variance of one range (X or Y) can be explained by the canonical variables of the same range. They can be calculated from the diagonal elements of the matrix product $\boldsymbol{R}^T_{XU}\boldsymbol{R}_{XU}$:

$$\boldsymbol{g}^2_{X|U} = 1/p\ dg\left(\boldsymbol{R}^T_{XU}\boldsymbol{R}_{XU}\right) \tag{16}$$

$$\boldsymbol{g}^2_{Y|V} = 1/q\ dg\left(\boldsymbol{R}^T_{YV}\boldsymbol{R}_{YV}\right) \tag{17}$$

The measures of redundance $\boldsymbol{g}^2_{X|V}$ *and* $\boldsymbol{g}^2_{Y|U}$

These measures describe which part of the whole variance of one range can be explained by the canonical variables of the other range and can be calculated from:

$$\boldsymbol{g}^2_{X|V} = 1/p\ dg\left(\boldsymbol{R}^T_{XV}\boldsymbol{R}_{XV}\right) \tag{18}$$

$$\boldsymbol{g}^2_{Y|U} = 1/q\ dg\left(\boldsymbol{R}^T_{YU}\boldsymbol{R}_{YU}\right) \tag{19}$$

Intraranging communalities $\boldsymbol{d}^2_{X|U}$ *and* $\boldsymbol{d}^2_{Y|V}$

These values describe the part of variance of one variable, which can be explained by the canonical variables of the same range and can be calculated from:

$$\boldsymbol{d}^2_{X|U} = dg\left(\boldsymbol{R}_{XU}\boldsymbol{R}^T_{XU}\right) \tag{20}$$

$$\boldsymbol{d}^2_{Y|V} = dg\left(\boldsymbol{R}_{YV}\boldsymbol{R}^T_{YV}\right) \tag{21}$$

Interranging communalities $\boldsymbol{d}^2_{X|V}$ *and* $\boldsymbol{d}^2_{Y|U}$

The interranging communalities describe the part of variance of one variable, which can be explained by the canonical variables of the other range. They can be calculated from:

$$\boldsymbol{d}^2_{X|V} = dg\left(\boldsymbol{R}_{XV}\boldsymbol{R}^T_{XV}\right) \tag{22}$$

$$\boldsymbol{d}^2_{Y|U} = dg\left(\boldsymbol{R}_{YU}\boldsymbol{R}^T_{YU}\right) \tag{23}$$

The interpretation of the results of canonical analysis could be difficult. Steward and Love (1968) showed that, although two canonical variables correlated very well, the explained variances were not important. The practical relevance of the canonical correlation coefficients depends strongly on the observation number N.

Therefore, Thorndike (1978) recommended the following expression:

$$[p+q] < N < \left[(p+q)^2 + 50\right] \tag{24}$$

The relevance of the canonical communalities is given for values greater than 0.1 (Röhr, 1987). A complete canonical solution is given, if at first:

$$\sum_{i=1}^{p} g^2_{X|U_i} = 1 \wedge \sum_{i=1}^{p} g^2_{Y|V_i} \leq 1 \tag{25}$$

and secondly

$$\sum_{i=1}^{p} g^2_{X|V_i} < 1 \wedge \sum_{i=1}^{p} g^2_{Y|U_i} < 1 \tag{26}$$

This compression of the results is useful to show the success of the analysis.

The approach of canonical analysis described briefly will be used to examine the relationship between the cellulose powder properties and the formulation behaviour of two basic mixtures. To be successful, a number of tests (cf. Eqn 24) performed with replications is required. The values included in the group of independent variables should be significantly different and must be unrelated to each other. Intercorrelations between the dependent variables should also be avoided. The range of the numerical values of the independent variables predicts the range of validity of the model deduced. So, if for example the bulk volume of the cellulose powders is between 2 and 5 $cm^3\ g^{-1}$, the influence of this property on the basic mixture behaviour, if another cellulose product was included, can only be predicted in the case where this product has a bulk volume between these limits. Therefore, the investigations, which will be undertaken, must be designed carefully before starting the experiments. Among other things, in a previous paper (Podczeck and Révész, 1993), the application of multivariate analysis of variance (MANOVA) has shown that the cellulose properties, which shall be used as independent variables, fulfill the requirements listed.

Computer programs such as the SPSS package provide the approach of canonical analysis, but require a full mathematical understanding of algorithms and results. Hence, a specific program was written for canonical analysis, which makes the output of the results readable for 'only users' such as pharmacists.

Materials and Methods

Materials

The following materials were obtained from the indicated sources: magnesium stearate (research grade; Laborchemie Apolda, Germany); potato starch (Stärkefabrik Loitz, Germany); Aerosil® (Degussa AG, Frankfurt-Main, Germany); Avicel® PH101 (FMC Corp., American Viscose Division, Markus Hood, U.S.A.); microcrystalline cellulose, types 0.038 and 0.019 (Serva Feinbiochemica, Heidelberg, Germany); Sanaq® 101L (Pharma Trans Sanaq AG, Switzerland); Elcema®, types P050, P100, F150 and G250 (Degussa AG, Frankfurt-Main, Germany); Vitacel®, types M80 and F120 A300, Heweten®, types 10 and 12 (Rettenmaier & Söhne, Ellwangen-Holzmühle, Germany).

Tabletting

Single weighed samples (300.0 mg) were pressed on a rotary tablet press instrumented with strain gauges using 11 mm flat punches (Pharmapress 103, Fa. KORSCH Maschinenfabrik, Berlin, Germany). The tabletting force was registrated using a x-y-recorder (endim 620.02, Meßapparatewerk Schlotheim, Germany).

Diametral crushing strength

The tablet crushing strength was determined using a crushing strength tester. The breaking load is measured according to the Erweka TBT tablet strength tester. The principle is that a sliding weight is moved electrically along a lever and the tablet is loaded incrementally. The maximal crushing strength value which can be determined is 90 N. Above this value, the tablets can be considered to be too strong. In practice, it is not important to know the exact breaking load of

such tablets, because the disintegration time will be the limiting factor in that case.

Friability

10 tablets were divided into groups of two tablets and each group was marked, cleaned from dust and weighed. The tablets were then placed together in a friabilator (Ingenieurbüro für Rationalisierung der pharmazeutischen Industrie Dresden, Germany) for 4 min ($= 25\ min^{-1}$). The tablets were cleaned from dust and each group were weighed again and the change of weight determined.

Disintegration time

The disintegration time was determined for five single tablets using the Erweka disintegration tester (Erweka Apparatebau GmbH, Heu-senstamm, Germany) in distilled water of 37 ± 1°C.

Bulk and tapped density

For the determination of the bulk and tapped densities a 25 ml measuring cylinder (0.5 ml scale) was used. 20 ml of powder was added into the measuring cylinder, the volume was read and the mass determined by weighing. The cylinder was closed and then tapped manually until there was no change in volume. The volume was read again. The densities were calculated from the bulk and tapped volume and the powder mass.

Flow properties

A 20 g powder mixture was used. The powder flow meter consists of four strain gauges made from gold, which are placed on a metal sheet according to the Wheatstone principle. The metal sheet is incremented like a scale. The electrical signals are transported to a computer (KC 81/1, Robotron Dresden, Germany) and the mass flow is recorded by an on-line-technique.

Funnel: copper coated with nickel; lower orifice diameter 1 cm^2; orifice angle 60°; low vibration (vibration machine, type Thyr 2, MLW Labortechnik Ilmenau, Germany). Mean powder flow rate: mean of the measuring values (frequency of the microprocessor 110 s^{-1}; eight of the values according to the microprocessor frequency give one measuring value). Flow regularity: standard deviation of the measuring values.

Mixing of powders

The sieved substances without the lubricant were mixed using a mortar and pestle for 5 min. The mortar wall was cleaned with a flexible spatula frequently. Then the lubricant was added and mixed for a further 2 min.

Calculation

Canonical analysis: program written in Turbo-Pascal 6.0 for MS-DOS 4.01/Intel 386.

Results and Discussion

According to industrial manufacturing practice, two basic mixtures for direct tabletting have been developed using mathematical methods (Podczeck and Wenzel, 1990):

■ BM1 (Podczeck, 1986)	potato starch	9.00%
	magnesium stearate	0.40%
	microcrystalline cellulose (Heweten® 12)	90.60%
■ BM2 (Podczeck and Wenzel, 1990)	potato starch	9.10%
	colloidal silica (Aerosil® 200)	1.60%
	magnesium stearate	0.25%
	microcrystalline cellulose (Heweten® 12)	89.05%

Table 1 provides the powder and tablet properties, which will be regarded as characteristics of a good formulation behaviour.

The properties of either basic mixture obtained in the present study are listed in Tables 2–5. Using the original microcrystalline cellulose product Heweten®12, the tablet properties of basic mixture 2 may be regarded as satisfactory according to Table 1, and also the tablet properties of basic mixture 1, if a tabletting pressure greater than 200 MPa was used. The powder properties, however, do not always correspond to the values, which are required in Table 1. Only the flowability can be regarded as excellent.

The investigation of the basic mixtures described above was repeated using other types of

TABLE 1

Characteristic values of a direct tabletting mixture with good powder and tablet properties

Property		Directive value
Bulk volume	V_b	2–4 ml g^{-1}
Hausner's ratio	H	$\leqq 1.25$
Mean powder flow rate	v_m	$\geqq 4$ g s^{-1}
Flow regularity	s_{vm}	< 50% of v_m
Diametral crushing strength	rBf	> 65 N
Friability	RFV	< 0.8%
Disintegration time	Z	< 300 s

microcrystalline and microfine cellulose powders. The complete results are also listed in Tables 2–5.

The substitution of Heweten®12 led in all cases to a greater bulk volume, and the powdered Elcema® and Vitacel® products gave values greater than the prefered value of 4 cm^3 g^{-1}. In general, the Hausner's ratio was unsatisfactory. The flowability was also decreased. In most cases, basic mixture 1 showed no powder flow, only the granulated products (Elcema®G250, Vitacel® A300) and the Serva product 0.038 gave a lower, but acceptable mean powder flow rate. The flowability of basic mixture 2 was well below that of the Heweten®12 mixture, if another cellulose product was used. Also here, not all cellulose products led to a flow rate in accordance to the requirements given in Table 1, but the Aerosil® content improved the flowability significantly. The granulated products are not suitable, if included in basic mixture 1, because the tablets had no mechanical strength. Using basic mixture 2, an acceptable tablet strength was found for the granulated products. The Aerosil® content appears to be the limiting factor. Sekulovic et al. (1988) also reported the good tablet properties of Elcema®G250, if 3% colloidal silica was used. Aerosil® is able to compensate for the mixing effects of magnesium stearate (Lerk et al., 1977), which could lead to a lubricant film surrounding the cellulose particles (Jarosz and Parrott, 1984), without a loss of magnesium stearate lubricant activity (Ofner and Schott, 1987), but improving the mechanical strength of the tablet. However, the literature also reports the incident, where Aerosil® showed an adverse influence on powder mixture properties (Cartillier and Moës, 1986), or did not effect an improvement or deterioration, e.g., of the compressibility, friability or disintegration time (Tasic et al., 1991). Schrank-Junghani et al (1983) observed, that colloidal silica partly counteracted the lubricant effect of magnesium stearate by adsorption of the lubricant onto the silica, but the crushing strength was not increased significantly, and the disintegration time was unaffected. Sugimori et al (1989) reported, that the addition of colloidal silica increased the bonding strength but had not prevent capping. The use of the microcrystalline products or Elcema®F150

TABLE 2

Powder properties of basic mixture 1 prepared using different types of cellulose products ($\bar{x} \pm s$; $n = 5$; [a] no powder flow obtained)

Cellulose product	V_b (cm^{-3} g^{-1})	H	v_m (g s^{-1})	s_{vm} (g s^{-1})
Avicel® PH 101	3.11 ± 0.06	1.55 ± 0.01	[a]	[a]
Serva® 0.038	3.22 ± 0.02	1.45 ± 0.00	4.3 ± 0.4	2.0 ± 0.2
Serva® 0.019	3.91 ± 0.12	1.94 ± 0.02	[a]	[a]
Sanaq® 101L	3.50 ± 0.01	1.73 ± 0.02	[a]	[a]
Heweten® 10	3.29 ± 0.02	1.75 ± 0.02	1.6 ± 0.4	1.1 ± 0.6
Heweten® 12	1.83 ± 0.03	1.39 ± 0.00	11.2 ± 0.6	4.7 ± 0.3
Elcema® P 050	4.56 ± 0.04	2.35 ± 0.01	[a]	[a]
Elcema® P 100	4.32 ± 0.11	2.44 ± 0.01	[a]	[a]
Elcema® F 150	4.66 ± 0.07	2.10 ± 0.01	1.2 ± 0.2	0.6 ± 0.2
Elcema® G 250	1.92 ± 0.02	1.24 ± 0.01	7.4 ± 0.5	2.9 ± 0.6
Vitacel® M 80	4.51 ± 0.06	2.08 ± 0.13	[a]	[a]
Vitacel® F 120	4.60 ± 0.16	2.07 ± 0.01	[a]	[a]
Vitacel® A 300	2.72 ± 0.05	1.51 ± 0.01	4.3 ± 0.3	1.7 ± 0.3

TABLE 3

Tablet properties of basic mixture 1 prepared using different types of cellulose products ($\bar{x} \pm s$; $n = 5$)

Cellulose product	P_{max} (MPa)	rBf (N)	RFV (%)	Z (s)
Avicel® PH 101	100	> 90	0.93 ± 0.33	31 ± 7
	150	> 90	1.47 ± 0.28	24 ± 5
	200	> 90	1.23 ± 0.34	30 ± 3
	250	> 90	1.74 ± 0.57	37 ± 6
	300	> 90	1.86 ± 0.13	56 ± 6
Serva® 0.038	100	> 90	0.03 ± 0.06	15 ± 1
	150	> 90	0.05 ± 0.06	14 ± 1
	200	> 90	0.05 ± 0.03	25 ± 2
	250	> 90	0.20 ± 0.14	35 ± 1
	300	> 90	0.24 ± 0.15	49 ± 6
Serva® 0.019	100	> 90	0.16 ± 0.20	295 ± 109
	150	> 90	0.42 ± 0.06	940 ± 166
	200	> 90	0.29 ± 0.18	1 112 ± 440
	250	> 90	0.60 ± 0.38	3 479 ± 417
	300	> 90	0.50 ± 0.12	4 521 ± 836
Sanaq® 101L	100	> 90	0.22 ± 0.09	66 ± 10
	150	> 90	0.41 ± 0.11	116 ± 26
	200	> 90	0.49 ± 0.18	186 ± 40
	250	> 90	0.26 ± 0.10	160 ± 42
	300	> 90	0.54 ± 0.10	169 ± 30
Heweten® 10	100	74 ± 15	0.45 ± 0.25	16 ± 2
	150	> 90	1.12 ± 0.29	26 ± 4
	200	> 90	0.72 ± 0.25	31 ± 3
	250	> 90	1.45 ± 0.51	37 ± 8
	300	> 90	0.94 ± 0.46	43 ± 5
Heweten® 12	100	31 ± 4	0.00 ± 0.00	7 ± 1
	150	61 ± 12	0.03 ± 0.08	6 ± 1
	200	54 ± 9	0.00 ± 0.00	8 ± 1
	250	67 ± 5	0.01 ± 0.02	12 ± 1
	300	77 ± 5	0.17 ± 0.24	20 ± 2
Elcema® P 050	100	20 ± 10	4.34 ± 0.33	29 ± 9
	150	36 ± 7	1.29 ± 0.52	253 ± 126
	200	40 ± 7	0.57 ± 0.27	486 ± 230
	250	49 ± 10	0.25 ± 0.31	825 ± 365
	300	46 ± 8	0.22 ± 0.19	990 ± 407
Elcema® P 100	100	24 ± 3	1.71 ± 0.56	70 ± 16
	150	36 ± 3	1.47 ± 0.34	133 ± 110
	200	40 ± 4	0.44 ± 0.12	214 ± 57
	250	44 ± 3	0.66 ± 0.50	372 ± 76
	300	50 ± 2	0.34 ± 0.33	606 ± 152
Elcema® F 150	100	49 ± 15	0.52 ± 0.45	137 ± 29
	150	58 ± 15	0.14 ± 0.13	324 ± 102
	200	> 90	0.27 ± 0.02	822 ± 252
	250	> 90	0.29 ± 0.26	885 ± 388
	300	> 90	0.50 ± 0.34	1 093 ± 478
Elcema® G 250	100	0	100	0
	150	0	100	0
	200	0	100	13 ± 1
	250	0	100	13 ± 3
	300	4 ± 1	100	16 ± 3

(continued overleaf)

TABLE 3 (continued)

Cellulose product	P_{max} (MPa)	rBF (N)	RFV (%)	Z (s)
Vitacel® M 80	100	49 ± 9	0.98 ± 0.57	132 ± 98
	150	62 ± 3	0.40 ± 0.27	166 ± 74
	200	67 ± 5	0.57 ± 0.20	353 ± 86
	250	63 ± 8	0.38 ± 0.33	384 ± 199
	300	60 ± 4	0.05 ± 0.07	1093 ± 611
Vitacel® F 120	100	37 ± 4	0.30 ± 0.22	241 ± 96
	150	47 ± 5	0.12 ± 0.16	318 ± 70
	200	50 ± 5	0.31 ± 0.27	981 ± 599
	250	52 ± 8	0.25 ± 0.13	876 ± 610
	300	58 ± 4	0.39 ± 0.12	816 ± 123
Vitacel® A 300	100	0	100	4 ± 1
	150	3 ± 1	100	4 ± 1
	200	7 ± 1	4.84 ± 1.90	4 ± 1
	250	9 ± 2	1.86 ± 0.57	6 ± 1
	300	12 ± 2	0.72 ± 0.19	7 ± 1

gave stronger tablets than using Heweten®12. The disintegration time, however, is longer. Tablets, which included the Serva product 0.019 or the powdered microfine celluloses, had disintegration times well over 300 s, which is regarded to be unsatisfactory (cf. Table 1). Stanley-Wood (1987) reported that there were differences in the specific surface areas of different grades of cellulose (BET method). Avicel® PH 101 and PH 102 had surface areas of approximately 1.1 $m^2\ g^{-1}$, whereas Avicel® PH 105 had a surface area of 2.5 $m^2\ g^{-1}$. The Elcema® products without G250 showed values between 1.4 and 1.9 $m^2\ g^{-1}$. The increase in the surface area could therefore be a reason for the longer disintegration times.

The relations between the cellulose properties investigated in a previous work (Podczeck and Révész, 1993) and the basic mixture behaviour investigated in this report provided interesting possibilities. These relationships were calculated using the Canonical Analysis. Significant relations between the group of the pure cellulose and the basic mixture properties were identified. Table 6 summarizes the important values.

The powder properties of basic mixture 2 are slightly better related to the cellulose properties

TABLE 4

Powder properties of basic mixture 2 prepared using different types of cellulose products ($\bar{x} \pm s$; $n = 5$)

Cellulose product	V_b ($cm^3\ g^{-1}$)	H	v_m ($g\ s^{-1}$)	s_{vm} ($g\ s^{-1}$)
Avicel® PH 101	3.15 ± 0.03	1.58 ± 0.00	1.6 ± 0.0	0.4 ± 0.0
Serva® 0.038	3.03 ± 0.08	1.50 ± 0.02	5.3 ± 0.8	6.5 ± 1.6
Serva® 0.019	3.87 ± 0.15	1.90 ± 0.02	6.0 ± 1.9	6.0 ± 3.0
Sanaq® 101 L	3.49 ± 0.15	1.65 ± 0.01	4.0 ± 0.8	3.7 ± 1.2
Heweten® 10	3.30 ± 0.12	1.73 ± 0.01	3.6 ± 0.4	3.2 ± 0.2
Heweten® 12	1.97 ± 0.03	1.44 ± 0.01	7.6 ± 0.6	7.8 ± 0.4
Elcema® P 050	4.75 ± 0.05	2.36 ± 0.01	0.7 ± 0.1	0.2 ± 0.0
Elcema® P 100	4.27 ± 0.03	2.12 ± 0.00	1.0 ± 0.1	0.3 ± 0.0
Elcema® F 150	4.71 ± 0.03	1.93 ± 0.01	1.2 ± 0.2	0.6 ± 0.2
Elcema® G 250	1.96 ± 0.02	1.45 ± 0.01	9.8 ± 0.8	6.6 ± 1.3
Vitacel® M 80	4.39 ± 0.03	1.96 ± 0.01	1.2 ± 0.0	0.3 ± 0.0
Vitacel® F 120	4.75 ± 0.16	2.03 ± 0.01	3.4 ± 0.6	2.8 ± 0.6
Vitacel® A 300	2.85 ± 0.04	1.66 ± 0.01	5.9 ± 0.9	5.7 ± 0.9

TABLE 5

Tablet properties of basic mixture 2 prepared using different types of cellulose products ($\bar{x} \pm s$; $n = 5$)

Cellulose product	P_{max} (MPa)	rBf (N)	RFV (%)	Z (s)
Avicel® PH 101	100	> 90	0.03 ± 0.06	14 ± 2
	150	> 90	0.38 ± 0.30	17 ± 3
	200	> 90	0.52 ± 0.50	45 ± 4
	250	> 90	0.91 ± 0.39	72 ± 19
	300	> 90	0.64 ± 0.24	98 ± 27
Serva® 0.038	100	> 90	0.53 ± 0.13	20 ± 4
	150	> 90	0.70 ± 0.28	27 ± 8
	200	> 90	0.59 ± 0.31	26 ± 6
Serva® 0.019	100	> 90	0.00 ± 0.00	312 ± 74
	150	> 90	0.39 ± 0.29	561 ± 228
	200	> 90	0.14 ± 0.20	1375 ± 722
	250	> 90	0.08 ± 0.08	1328 ± 462
	300	> 90	0.04 ± 0.07	4547 ± 1488
Sanaq® 101 L	100	> 90	0.00 ± 0.00	45 ± 8
	150	> 90	0.00 ± 0.00	104 ± 49
	200	> 90	0.00 ± 0.00	338 ± 225
	250	> 90	0.00 ± 0.00	524 ± 183
	300	> 90	0.08 ± 0.14	539 ± 120
Heweten® 10	100	> 90	0.26 ± 0.19	29 ± 8
	150	> 90	0.47 ± 0.06	27 ± 9
	200	> 90	0.50 ± 0.37	64 ± 23
	250	> 90	1.05 ± 0.17	122 ± 47
	300	> 90	0.96 ± 0.35	121 ± 36
Heweten® 12	100	53 ± 5	0.42 ± 0.18	4 ± 1
	150	75 ± 8	0.36 ± 0.17	8 ± 1
	200	> 90	0.65 ± 0.44	17 ± 2
	250	> 90	0.57 ± 0.17	24 ± 3
	300	> 90	0.39 ± 0.06	25 ± 1
Elcema® P 050	100	63 ± 11	0.45 ± 0.29	1052 ± 390
	150	> 90	0.33 ± 0.60	1034 ± 408
	200	> 90	0.06 ± 0.09	1416 ± 272
	250	> 90	0.56 ± 0.33	3579 ± 1051
	300	> 90	0.37 ± 0.23	5503 ± 1009
Elcema® P 100	100	77 ± 6	0.05 ± 0.08	174 ± 65
	150	> 90	0.16 ± 0.25	861 ± 442
	200	> 90	0.29 ± 0.32	1062 ± 533
	250	> 90	0.14 ± 0.23	2005 ± 834
	300	> 90	0.03 ± 0.03	4646 ± 862
Elcema® F 150	100	> 90	0.01 ± 0.02	586 ± 283
	150	> 90	0.20 ± 0.15	1006 ± 413
	200	> 90	0.24 ± 0.28	2735 ± 825
	250	> 90	0.18 ± 0.20	7089 ± 472
	300	> 90	0.22 ± 0.25	6838 ± 434
Elcema® G 250	100	15 ± 3	0.76 ± 0.14	7 ± 1
	150	24 ± 2	0.50 ± 0.26	10 ± 2
	200	36 ± 3	0.28 ± 0.09	16 ± 3
	250	44 ± 2	0.27 ± 0.15	21 ± 3
	300	57 ± 4	0.27 ± 0.17	41 ± 6
Vitacel® M 80	100	> 90	0.57 ± 0.33	633 ± 350
	150	> 90	0.42 ± 0.36	605 ± 218
	200	> 90	0.55 ± 0.14	1608 ± 858
	250	> 90	0.48 ± 0.13	2454 ± 650
	300	> 90	0.50 ± 0.28	4838 ± 1865

(continued overleaf)

TABLE 5 (continued)

Cellulose product	P_{max} (MPa)	rBf (N)	RFV (%)	Z (s)
Vitacel® F 120	100	81 ± 3	0.12 ± 0.18	708 ± 183
	150	> 90	0.09 ± 0.15	2105 ± 857
	200	> 90	0.12 ± 0.20	4969 ± 1951
	250	> 90	0.01 ± 0.02	9112 ± 1246
	300	> 90	0.00 ± 0.00	8508 ± 928
Vitacel® A 300	100	25 ± 3	0.47 ± 0.11	11 ± 3
	150	48 ± 3	0.26 ± 0.11	34 ± 10
	200	65 ± 9	0.51 ± 0.27	65 ± 16

than those of basic mixture 1 as judged by a comparison of the Λ test values ($\Lambda_{BM2} < \Lambda_{BM1}$). Because the critical values of the Λ distribution are often not available, the approximation of Λ by the F distribution is also listed in Table 6, together with the critical value for F with 16 and 110 degrees of freedom ($p < 0.05$). The relation between the cellulose properties and the tablet behaviour of basic mixture 1 is far more obvious than the relationship between the cellulose properties and the tablet properties of basic mixture 2, indicated by a Λ, which is only a tenth of that calculated for basic mixture 2. The tablet properties of basic mixture 2 are more equivalent, and therefore the influence of the celluloses incorporated is not as distinguishable as when using basic mixture 1. In all four calculations, the extracting measuring values $g^2_{X|U}$ are 1.0 and $g^2_{Y|V}$ are less than 1.0, which indicates according to Eqn 25 that the investigations were well balanced and led to a complete canonical solution. Comparing the measures of redundance $g^2_{X|V}$, which are mainly greater than 0.8, it can be concluded that the information that is given by including the cellulose properties listed in Table 6 in the canonical analyses is adequate to describe the influence of the material chosen on the formulation behaviour. Hence, canonical analysis can be used to ascertain which cellulose properties must be controlled to guarantee the reproducability of the powder mixture and tablet properties. The actual importance of these cellulose properties is reflected in the interranging communalities $d^2_{Y|U}$. The bulk volume of the pure cellulose products mainly determines the powder mixture behaviour. Other variables such as the particle size range also play a certain role and should be controlled, but their influence on the powder behaviour of the basic mixtures is not as distinctive as found for the bulk volume, because the interranging communalities are only about 0.6 instead of approx. 0.9 for the bulk volume. The interranging communalities of about 0.7 for the particle size range, if the tablet properties are investigated, underline the necessity to keep the particle size range of the cellulose products in fixed limits. The formation energy of the compacts (E_2) and the elastic recovery energy (E_3) of the cellulose products appear to influence the tablet properties of basic mixture 1 because of the interranging communalities of approx. 0.7. Hence, the recording of force-displacement curves can be used as a preformulation quality parameter. These values are, however, less important in terms of basic mixture 2 (interranging communalities approx. 0.3). Comparing the measures of redundance $g^2_{Y|U}$, it must be concluded that the characterization of the powder and tablet properties of the basic mixtures is insufficient to obtain enough information to make suggestions about the theoretical most suitable cellulose product, because all values are only approx. 0.4 or less. The interranging communalities $d^2_{X|V}$ show that, with the exception of the bulk volume of the mixtures ($d^2_{Vb|V} > 0.98$) and the diametral crushing strength of basic mixture 1 ($d^2_{rBf|V} = 0.974$), the formulation properties are unsuitable for predictions in terms of useful cellulose properties. Comparing the results of the canonical analyses of the two basic mixtures, the relationship be-

TABLE 6

Results of the canonical analyses (−, value irrelevant being smaller than 0.1)

Parameter		Basic mixture 1	Basic mixture 2
Powder behaviour			
Canonical correlation coefficient			
r_1		0.987	0.948
r_2		0.676	0.833
Test of significance			
Λ		0.0136	0.0098
F		52.02	62.47
$F_{16;110;0.05}$		1.73	1.73
Extracting measures			
$g^2_{X\|U}$		1.001	1.000
$g^2_{Y\|V}$		0.510	0.437
Measures of redundance			
$g^2_{X\|V}$		0.874	0.921
$g^2_{Y\|U}$		0.418	0.398
Interranging communalities			
$d^2_{X\|V}$	V_b	0.988	0.984
	v_m	0.760	0.858
$d^2_{Y\|U}$	V_b	0.949	0.899
	H	0.522	0.498
	ρ_w	0.432	–
	PSI	0.573	0.589
	Kawakita a	0.580	0.647
Tablet behaviour			
Canonical correlation coefficient			
r_1		0.982	0.900
r_2		0.908	0.841
r_3		0.810	0.822
r_4		0.798	0.705
Test of significance			
Λ		0.0008	0.0091
F		10.45	4.70
$F_{30;164;0.05}$		1.36	1.36
Extracting measures			
$g^2_{X\|U}$		1.000	1.001
$g^2_{Y\|V}$		0.492	0.314
Measures of redundance			
$g^2_{X\|V}$		0.907	0.743
$g^2_{Y\|U}$		0.424	0.244
Interranging communalities			
$d^2_{X\|V}$	rBf	0.974	0.810
	RFV	0.840	0.677
	h	0.892	0.518
	Z	0.706	0.715
$d^2_{Y\|U}$	V_b	0.314	0.412
	H	0.452	0.248
	ρ_w	0.396	0.149
	PSI	0.738	0.674
	Higuchi b	0.361	–
	Heckel K_p	0.552	0.263
	Kawakita a	0.343	0.467
	Kawakita b	0.482	–
	E_2 (J)	0.716	0.270
	E_3 (J)	0.588	0.120
	E_3 (%)	0.694	0.308
	Vb	0.652	0.372
	h	0.637	0.245
	QV	0.317	0.430
	Z	–	0.460
	P	–	0.455

tween the cellulose properties and the powder mixture behaviour of basic mixture 2 appears to be less strong than that of basic mixture 1. Basic mixture 2 contains Aerosil® in addition to the components of basic mixture 1. Aerosil® disguises some of the material properties of the cellulose powders. Therefore, the influence of the cellulose products on the basic mixture behaviour is reduced.

Examination of the results suggests that it appears possible to divide the cellulose products into groups with similar behaviour. If the bulk volumes given in Tables 2 and 4 are compared, for either basic mixture the first group includes the Elcema® products P050, P100, F150 and the Vitacel® products M80 and F120. The second group consists of all microcrystalline products without Heweten®12, and the third group comprises the granulated products Elcema®G250 and Vitacel®A300 together with Heweten®12, which also has a grain particle structure.

Considering the results for the diametral crushing strength of tablets made from basic mixture 1, the group tendency previous reported for pure cellulose products (Podczeck and Révész, 1992) is evident. The first group comprises all microcrystalline products with the exception of Heweten®12, the second one includes Heweten®12, Elcema®F150 and Vitacel®F120 and M80. The third group consists of the fine powders and the granulated products. Fig. 1 illustrates this tendency. For basic mixture 2, no tendency can be found.

Fig. 2 shows the group tendencies of the disintegration time based on the various cellulose products included in basic mixture 1. The

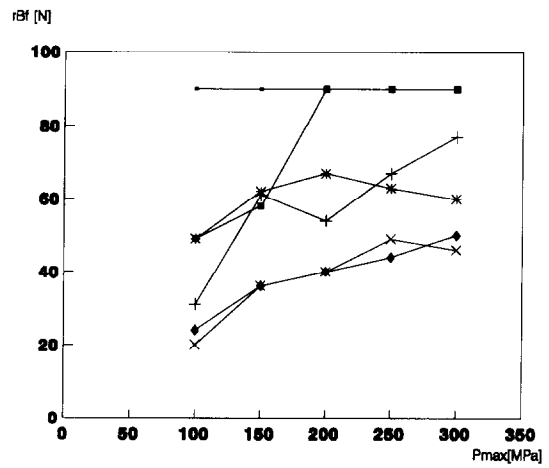

Fig. 1. Group tendency of cellulose products used for the tabletting of basic mixture 1 – diametral crushing strength ($\bar{x}$; $n = 5$). (●) Avicel PH101, (+) Heweten 12, (*) Vitacel M80, (■) Elcema F150, (×) Elcema P050, (♦) Elcema P100.

Serva®0.019 and Sanaq® 101L do not belong in the groups. They have different behaviour. Hence, the first group consists of Elcema®P050, P100, F150, M80 and Vitacel®F120, while the second group includes the remaining microcrystalline celluloses and the granulated microfine products. Using basic mixture 2 a different group tendency

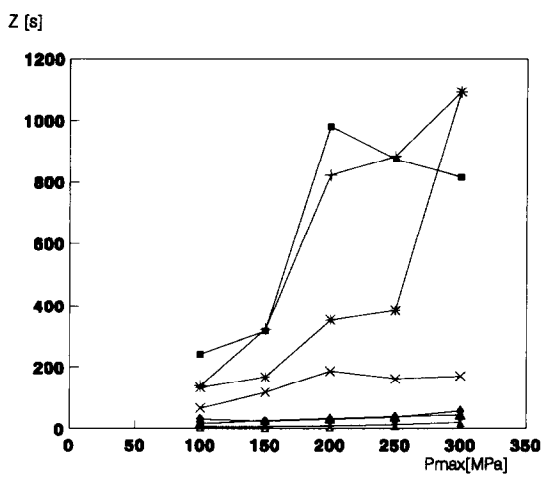

Fig. 2. Group tendency of cellulose products used for the tabletting of basic mixture 1 – disintegration time ($\bar{x}$; $n = 5$). (+) Elcema F150, (*) Vitacel M80, (■) Elcema F120, (×) Sanaq L101, (◇) Avicel PH101, (▲) Heweten 10, (⧖) Heweten 12.

can be considered. Here, the first group includes Serva®0.019, Elcema®P050, P100, F150, M80 and Vitacel®F120, the second one consists of Sanaq®101L, Avicel®PH101, Heweten®10 and Vitacel®A300, and the third group comprises Serva®0.038, Heweten®12 and Elcema®G250.

Summarizing the powder and tablet properties and the group tendencies it can be concluded, that the Heweten®12 content in basic mixture 1 can only be substituted with the Serva product 0.038. In basic mixture 2 the Heweten®12 could be changed with the microcrystalline products without Serva®0.019, and with Vitacel®A300, if the tablet pressure was higher than 200 MPa.

Conclusions

Canonical analysis can be advantageously used, if the relationship between two groups of variables is to be determined. In the present paper, canonical analysis was applied to test the influence of pharmaceutical properties of cellulose powders on the direct compression behaviour of basic mixtures, which include these products. The bulk volume of the pure microcrystalline and microfine cellulose powders as well as their particle size range influence the powder and tablet properties of the basic mixtures. Hence, both properties should be controlled in the form of a pre-process control to guarantee a reproducible quality of the tablet formulations. There are also indications that the recording of force-displacement curves to characterize the pure cellulose powders will be helpful as a preformulation quality parameter. The results were not only qualified, but also quantified by canonical analysis. The technique of canonical analysis is able to clarify interdependencies in a multivariate data material, which otherwise would not be evident from superficial examination. It requires, however, a carefully designed comprehensive data collection, including adequate replications. Commercial computer programs such as SPSS nowadays provide the multivariate technique of canonical analysis. The output produced by the programs, however, limits the application to someone well trained in mathematical techniques.

Nevertheless, the information that can be obtaincd from a multivariate data material by canonical analysis should encourage the use of this procedure more frequently.

Glossary

Symbol	Meaning
a_m^o	estimation of the canonical moments of X
BM	basic mixture
b_m^o	canonical moments
$d_{X\|V}^2$, $d_{Y\|U}^2$	interranging communalities
dg	diagonal elements of the matrix specified
E_2	formation energy of the compact
E_3	elastic recovery energy
F	value of the F distribution
f_1, f_2	degrees of freedom
$g_{X\|U}^2$, $g_{Y\|V}^2$	extracting measures
$g_{X\|V}^2$, $g_{Y\|U}^2$	measures of redundance
h	tablet thickness
H	Hausner's ratio
Heckel K_P	mean yield pressure (Heckel plot)
Higuchi b	constant of the Higuchi plot
I_n	unit matrix
Kawakita a	constant (Lüdde and Kawakita plot)
Kawakita b	constant (Lüdde and Kawakita plot)
Λ	test value according to Wilks
λ	eigenvalue
N	total observation number
n	number of replicates
p	dimension of X
p	eigenvector
P_{max}	tabletting pressure
PSI	particle size range
q	dimension of Y
QV	swelling volume
R	matrix of the loads
r	canonical correlation coefficient
rBf	diametral crushing strength
RFV	friability
r_m	estimation of the coefficients of canonical correlation
ρ_w	true density
s	standard deviation
S	variance-covariance matrix
s_{vm}	flow regularity
U	canonical variables of X
V	canonical variables of Y
Vb	compressibility
V_b	bulk volume
v_m	mean powder flow rate
X	group of independent variables
$\bar{x}$	arithmetic mean value
Y	group of dependent variables
Z	disintegration time

References

Bauer, K., Pritzwald-Stegmann, B. and Luft, W., Direkttablettiermittel. *EP 192080,* 24.01.1986.

Cartillier, L.H. and Moës, A.J., Effect of flowing adjuvants on the homogeneity and the kinetics of mixing of low dosage cohesive powder mixtures. *Drug Dev. Ind. Pharm.,* 12 (1986) 1203–1218.

Fiedler, H.P., Tabletten-Hilfsstoffe – eine Übersicht. *Seifen-Öle-Fette-Wachse,* 115 (1989) 253–255.

Gaensslen, H. and Schubö, W., *Einfache und komplexe statistische Analyse,* 2nd Edn, Ernst Reinhardt, München, 1976, pp. 166, 173, 176.

Hartung, J. and Elpelt, B., *Multivariate Statistik,* R. Oldenbourg, München, 1984, p. 172, p. 175.

Jarosz, P. and Parrott, E., Effect of lubricants on tensile strength of tablets. *Drug Dev. Ind. Pharm.,* 10 (1984) 259–273.

Lebart, L., Morineau, A. and Fenelon, J.-P., *Statistische Datenanalyse,* Akademie-Verlag, Berlin, 1984, p. 11.

Lerk, C.F., Bolhuis, G.K. and Smedema, S.S., Interaction of lubricants and colloidal silica during mixing with excipients: I. Its effect on tabletting. *Pharm. Acta Helv.,* 52 (1977) 33–39.

Ofner, C.M. and Schott, H., Swelling studies of gelatin: II. Effect of additives. *J. Pharm. Sci.,* 76 (1987) 715–723.

Podczeck, F., Beiträge zur rechnergestützten Arzneiformentwicklung. Dissertationsschrift, Martin-Luther-Univ., Halle (S.), 1986, p. 116.

Podczeck, F. and Révész, P., Evaluation of the properties of microcrystalline and microfine cellulose powders. *Int. J. Pharm.,* 91 (1993) 183–193.

Podczeck, F. and Wenzel, U., Entwicklung fester peroraler Arzneiformen mit Hilfe multivariater mathematischer Verfahren: I. Softwaresystem zur rechnergestützten Arzneiformentwicklung. *Pharm. Ind.,* 52 (1990) 230–233.

Podczeck, F. and Wenzel, U., Entwicklung fester peroraler Arzneiformen mit Hilfe multivariater mathematischer Verfahren: III. Die Modellierung des Rezepturproblems. *Pharm. Ind.,* 52 (1990) 496–500.

Röhr, M., *Kanonische Korrelationsanalyse,* Akademie-Verlag, Berlin, 1987, pp. 24–26, 85–91.

Salpekar, A. and Haag, T.E., Directly compressible pharmaceutical composition. *EP 159852,* 09.04.1985.

Schrank-Junghäni, H., Bier, H.-P. and Sucker, H., Studies in quantitative determination of lubricant properties for tabletting processes. *Pharm. Technol.,* 7 (1983) H9 71–84.

Seculović, D., Zajić, L., Nikitović, L., Radovanović, N. and Vaskovic, M., Investigation of the properties of Elcema®G250 tablets relative to the type of disintegrant used. *Pharmazie,* 43 (1988) 139.

Shangraw, R.F., Compressed tablets by direct compression. In Lieberman, H.A., Lachman, L. and Schwartz, J.B. (Eds), *Pharmaceutical Dosage Forms: Tablets,* Vol. 1, 2nd Edn, Dekker, New York, 1989, p. 196.

Stanley-Wood, N.G., Thermodynamic characterization of mi-

crocrystalline and microfine cellulose powders. *Part. Charact.*, 4 (1987) 106–111.

Stewart, D. and Love, W., A general canonical correlation index. *Psych. Bull. Washington,* 70 (1968) 160–163.

Sugimori, K., Mori, S. and Kawashima, Y., The role of binders in the prevention of capping within a tablet. *Chem. Pharm. Bull.,* 37 (1989) 1064–1067.

Tasic, L.J., Djurić, Z. and Jovanović, M., The influence of compression force on the physical characteristics of paracetamol tablets. *Pharmazie,* 46 (1991) 226–227.

Thorndike, R.M., *Correlational Procedures for Research,* Gardner Press, New York, 1978.