Investigations into the Relationship Between Drug Properties, Filling, and the Release of Drugs from Hard Gelatin Capsules Using Multivariate Statistical Analysis

James Hogan,[1] Pei-Inn Shue,[1] Fridrun Podczeck,[1] and J. Michael Newton[1,2]

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Purpose. The aim of the present work is to identify complex relationships between formulation variables and dosage form properties to aid the development of hard gelatin capsules.

Methods. Multivariate statistical analysis was employed based on a statistical design, which considered drug solubility, particle size and concentration, type and concentration of filler and disintegrant, and concentration of standard lubricant and glidant as the main influence factors. Both the filling properties of the formulations and the disintegration/dissolution properties of the capsule content were studied.

Results. From the two multivariate statistical methods used, nonparametric canonical analysis proved to be the superior method to deal with the complex information included in the data. While the filling performance of the formulation could clearly be attributed to the formulation variables such as drug particle size, type of filler, concentration of drug and glidant, the disintegration of the capsules and the dissolution of the drugs was not strongly related to the formulation variables chosen. In this respect as a trend, the drug solubility, and the type of disintegrant and filler appear to be more important factors.

Conclusions. Based on an appropriate number of experiments, organised in a statistical design, nonparametric canonical analysis can be used to identify relationships in a set of data that is grouped in influence and response variables to aid the development of a dosage form.

KEY WORDS: hard gelatin capsule formulation; multivariate statistical analysis; parametric and nonparametric canonical analysis; statistical design.

INTRODUCTION

The presentation of drugs in hard gelatin capsules as an oral dosage form has an historical background dating back to 1834 (1). Currently, their output continues to increase and the number of formulations listed in, for example, Physicians' Desk Reference (2), is 126. The basis of the formulation of powder-filled hard gelatin capsules is discussed by Cole (3). The objective of formulations is to ensure that each capsule provides the dose of drug required by Pharmacopoeial standards and that the drug should be released from the capsule to ensure drug bioavailability. The choice of type and quantity of ingredients to be incorporated to assist the formulation in terms of diluents, disintegrants, glidants, lubricants and wetting agents is part of the process of formulation and depends on the dose of drug and the physical and chemical properties of the drug. Just how the drug properties are related to the formulations is not known. Hence an investigation into this relationship could be a valuable aid to capsule formulation.

EXPERIMENTAL

Experimental Design

To relate drug properties to capsule performance is a complex task, hence there is a need for statistical design, which is appropriate for the use of multivariate statistical methods.

Five drugs were chosen according to their solubility, which covers a range between 0.2 gl^{-1} and 200 gl^{-1} giving a factor of 3 on a logarithmic scale. The drugs are phenytoin (0.2gl^{-1}), theophylline (8.0gl^{-1}), paracetamol (15.0gl^{1}), propranolol-HCl (50.0gl^{-1}) and aminophylline (200.0gl^{-1}). To describe the drug, if a relationship to the filling performance of the capsules is the target, the mean particle size has been determined, which was 26 μm for paracetamol and aminophylline, 57 μm for theophylline, 65 μm for phenytoin and 122 μm for propranolol-4HCl.

Five fillers have been chosen for their relative solubility, which apparently increases in the following order: calcium phosphate < microcrystalline cellulose < maize starch < starch 1500 < lactose monohydrate. Five disintegrants have been chosen randomly, and the swelling ability in water (22°C) has been measured as described by Podczeck and Révész (4). The disintegrants were ranked according to their relative swelling volume: Explotab (1680%) > AcDiSol (600%) > Amberlite (190%) > Polyplasdone XL (150%)> maize starch (110%). In all cases, magnesium stearate was used as a lubricant, and Aerosil was incorporated as a glidant. In both cases, levels of 0.0, 0.5, 1.0, 1.5 and 2.0% w/w have been used, and the midpoint of the experimental design was set to 1.0% in both cases. In the case of magnesium stearate, this is the widely accepted optimal lubricant concentration, whereas for Aerosil 0.5% appears the more usual concentration (5). However, from tabletting it is known that the optimum concentration of Aerosil can vary between 0.2 and 2.0% depending on the formulation property of main concern. For example, with respect to a rapid dissolution rate 1.0% Aerosol is optimal (6), whereas 0.5% only is insufficient (7). At the extreme, 2.0% Aerosil has been shown to be optimal for a satisfactory filling and necessary compact strength (8,9). Finally, the optimal Aerosil concentration has been reported to depend on the magensium stearate concentration and the way to incorporate both components into the powder mixture. Based on a statistical design, Staniforth et al. (10) found that at 1.0% magnesium stearate the coefficent of fill weight variation decreased with increased Aerosil concentration between 0.5 and 2.0%, again indicating that the Aerosil optimum might be above the commonly used 0.5%. Thus the use of the five levels of Aerosil in the experimental design for the current paper will be able to clarify this point, because both 0.5% and 1.0% Aerosil are included in the design. Recently, Jones (11) published a survey of excipients used in capsule formulation, based on the marketed formulations in France, Germany and Italy. Quantitative information about excipients used in Italy revealed that the most commonly used Aerosil concentration in powder filled hard gelatin capsules is 1.5%,

[1] Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, England.
[2] To whom correspondence should be addressed.

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and that more than 75% of the formulations contain more than 0.9% Aerosil. Thus, the value of 0.5% (5) appears even more doubtful.

Due to the nature of the data material, i.e., several influence factors and a variety of response variables, a multivariate analysis is required to identify relationships between these two groups of variables. The response variables (Y) are all of nominal (= numerical) nature, whereas the independent variables are nominal or ordinal depending on whether a rank number (ordinal) or an underlying variable (particle size, swelling volume) has been used to describe them. Hence, both parametric and nonparametric test procedures can be used. Such a parametric test procedure is the canonical analysis introduced by Hotelling (12). This method has been used for pharmaceutical problems, e.g., by Podczeck et al (13) and by Bohidar and Bohidar (14). The drug, disintegrant type and the concentrations of the excipients used are described by their physical properties, but for the filler type a dummy variable has to be used. Table I shows the variable group X used in this kind of analysis. All formulation properties (response variables, Y) are used as their original values (arithmetic mean, compare Materials and Methods) and presented in Table 2. Nonparametric canonical analysis (15) is the equivalent type of multivariate procedure if ordinal variables are to be used. The advantage compared to the classical canonical analysis is its acceptance of nonlinear relationships. However, all variables have to be transferred into ordinal data, which appears as a loss in information especially in the group of the response variables. Table 3 shows the data matrix of X using the rank of the physical properties of the excipients as ordinal data. Table 4 shows the classification of ordinal data for Y used in the nonparametric procedure.

Table 1. Variable Group X Used in the Classical (Parametric) Canonical Analysis

EN	D_1(ps)	d_2(sol)	ft	fl	dt	dl	ll	gl	dc
1	26.0	15.0	2	44.0	1680	5.0	1.0	0.0	50.0
2	26.0	15.0	2	43.5	1680	5.0	1.0	0.5	50.0
3	26.0	15.0	2	42.5	1680	5.0	1.0	1.5	50.0
4	26.0	15.0	2	42.0	1680	5.0	1.0	2.0	50.0
5	26.0	15.0	2	44.0	1680	5.0	0.0	1.0	50.0
6	26.0	15.0	2	43.5	1680	5.0	0.5	1.0	50.0
7	26.0	15.0	2	42.5	1680	5.0	1.5	1.0	50.0
8	26.0	15.0	2	42.0	1680	5.0	2.0	1.0	50.0
9	26.0	15.0	2	48.0	1680	0.0	1.0	1.0	50.0
10	26.0	15.0	2	45.5	1680	2.5	1.0	1.0	50.0
11	26.0	15.0	2	40.5	1680	7.5	1.0	1.0	50.0
12	26.0	15.0	2	38.0	1680	10.0	1.0	1.0	50.0
13	65.0	0.2	2	43.0	1680	5.0	1.0	1.0	50.0
14	57.0	8.0	2	43.0	1680	5.0	1.0	1.0	50.0
15	26.0	15.0	2	43.0	1680	5.0	1.0	1.0	50.0
16	122.0	50.0	2	43.0	1680	5.0	1.0	1.0	50.0
17	26.0	200.0	2	43.0	1680	5.0	1.0	1.0	50.0
18	26.0	15.0	2	73.0	1680	5.0	1.0	1.0	20.0
19	26.0	15.0	2	58.0	1680	5.0	1.0	1.0	35.0
20	26.0	15.0	2	28.0	1680	5.0	1.0	1.0	65.0
21	26.0	15.0	2	13.0	1680	5.0	1.0	1.0	80.0
22	26.0	15.0	1	43.0	1680	5.0	1.0	1.0	50.0
23	26.0	15.0	3	43.0	1680	5.0	1.0	1.0	50.0
24	26.0	15.0	4	43.0	1680	5.0	1.0	1.0	50.0
25	26.0	15.0	5	43.0	1680	5.0	1.0	1.0	50.0
26	26.0	15.0	2	43.0	600	5.0	1.0	1.0	50.0
27	26.0	15.0	2	43.0	190	5.0	1.0	1.0	50.0
28	26.0	15.0	2	43.0	150	5.0	1.0	1.0	50.0
29	26.0	15.0	2	43.0	110	5.0	1.0	1.0	50.0
30	26.0	15.0	1	48.0	1680	0.0	1.0	1.0	50.0
31	26.0	15.0	1	38.0	1680	10.0	1.0	1.0	50.0
32	26.0	15.0	5	48.0	1680	0.0	1.0	1.0	50.0
33	26.0	15.0	5	38.0	1680	10.0	1.0	1.0	50.0

Note: EN, experiment number; D_1(ps), drug characterised by particle size; d_2(sol), drug characterised by solubility; ft, filler type; fl, filler level; dt, disintegrant type; dl, disintegrant level; ll, lubricant level; gl, glidant level; dc, drug concentration.

MATERIALS

The five drugs used were of EP quality: aminophylline (Knoll AG, Germany), theophylline (BP-Knoll AG, Germany), propranolol hydrochloride (Becpharm U.K.), phenytoin (Recordati, Italy) and paracetamol (Becpharm, U.K.). The fillers employed included lactose monohydrate (Dairy Crest U.K.), maize starch (Beehive Industries, Holland), microcrystalline cellulose (Avicel PH102, FMC, USA), Starch 1500 (Colorcon Ltd., U.K.) and calcium phosphate (East Anglia Chemicals, U.K.), and were of EP quality. The disintegrating agents were maize starch (Beehive Industries, The Netherlands) (E.P.), polyplasdone XL (GAF Corporation, U.K.), Amberlite (Sigma Chemical, U.S.A.), Explotab (Forum Chemicals Ltd., U.K.) and Ac-Di-Sol (FMC, U.S.A.). Magnesium stearate (British Drug Houses, U.K.) and Aerosil 200 (Degussa, Belgium) were utilised as the lubricant and glidant respectively.

All materials were used as received from the suppliers except Aerosil 200 and Theophylline, which were sieved through a 60 and 100 mesh screen respectively to facilitate blending. Batches of 1 kg were prepared in a Y-cone blender (Erweka, AR400, Copley, U.K.) rotating for 20 minutes at approximately 56 rpm.

METHODS

The minimum bulk density of the various powders was determined in a 100 ml measuring cylinder, inverting the cylinder 10 times before measuring the volume occupied by the powder. The maximum bulk density was determined in accordance with BS 1440, 1967. The values reported represent the mean of 5 determinations.

Preparation of Capsules

The powder mixtures were filled into size no. 0 hard-gelatin capsules using an automatic capsule filling machine (Zanasi AZ-5, Italy). The dosator height, compression force and powder bed height were adjusted by trial and error to give the maximum bulk density of the formulation. At the desired settings, the machine was initially run until the powder bed came to an equilibrium by visual inspection, before approximately 100 capsules were collected from each run. These capsules were stored in tied polythene bags for further studies. The fill weight of 20 individual capsules was determined as required by BP.

Disintegration Test

Capsule disintegration times were measured in 800 ml of distilled water at 37 ± 1°C using "BP Disintegration Test for Hard-Gelatin Capsules."

Table 2. Variable Group Y Used in the Classical (Parametric) Canonical Analysis

	Packing and filling performance					Drug release			
EN	V_{min} [gcm^{-3}]	V_{max} [gcm^{-3}]	H	Carr [%]	CFV [%]	AUC [%min]	MDT [min]	VDT [min]	DT [min]
1	0.50	0.82	1.63	38.79	15.09	2480	28.6	107.6	10.5
2	0.50	0.79	1.58	36.71	1.19	1268	15.1	23.1	8.6
3	0.46	0.72	1.58	36.81	2.40	957	12.5	14.0	8.2
4	0.43	0.68	1.58	36.76	1.28	1907	19.0	42.4	7.5
5	0.50	0.76	1.52	34.21	2.51	1994	18.0	54.9	6.9
6	0.50	0.72	1.44	30.56	1.86	1733	17.4	33.0	7.2
7	0.48	0.71	1.48	32.39	1.36	1869	18.8	49.5	8.4
8	0.47	0.70	1.49	32.86	1.18	1775	17.3	45.5	10.4
9	0.49	0.72	1.47	31.94	0.95	1069	11.0	16.3	9.0
10	0.50	0.74	1.49	33.11	0.79	2087	20.8	72.4	8.2
11	0.50	0.71	1.43	30.28	1.44	2719	25.5	111.4	7.7
12	0.48	0.74	1.54	34.90	4.06	1834	19.7	55.9	7.9
13	0.54	0.78	1.44	30.57	1.40	200000	2000.0	200000.0	6.6
14	0.56	0.80	1.43	30.19	0.72	1980	19.1	70.6	8.2
15	0.49	0.74	1.51	33.78	0.75	706	9.0	7.8	9.9
16	0.62	0.83	1.33	24.70	1.90	2993	28.3	128.4	7.6
17	0.53	0.80	1.51	33.75	0.90	1571	22.2	41.3	11.5
18	0.55	0.78	1.42	29.49	0.80	1361	16.4	31.2	7.5
19	0.52	0.76	1.47	31.79	0.98	1593	16.9	45.6	7.7
20	0.44	0.67	1.51	33.58	2.38	2486	22.6	98.7	7.4
21	0.40	0.62	1.53	34.68	3.57	2032	18.8	74.8	11.4
22	0.54	0.80	1.48	32.50	0.85	2044	19.0	68.1	10.8
23	0.46	0.72	1.59	37.24	1.25	3081	28.1	147.8	7.4
24	0.40	0.58	1.46	31.30	1.64	1261	12.7	27.3	7.0
25	0.38	0.64	1.66	39.84	18.52	2012	19.9	56.6	7.6
26	0.44	0.73	1.64	39.04	0.84	1546	16.3	39.6	7.7
27	0.46	0.72	1.57	36.11	1.12	3356	29.1	172.8	9.3
28	0.44	0.68	1.57	36.50	1.10	3683	29.6	229.3	9.8
29	0.46	0.73	1.59	36.99	0.96	1336	14.5	29.4	7.6
30	0.54	0.83	1.52	34.34	2.42	7121	70.4	840.5	12.1
31	0.53	0.80	1.52	34.16	1.32	2798	25.0	117.1	8.9
32	0.40	0.61	1.54	35.25	20.67	82319	760.1	117068.5	10.0
33	0.42	0.65	1.57	36.15	5.94	2467	25.1	86.3	7.3

Note: EN, experiment number; V_{min}, minimum bulk density; V_{max}, maximum bulk density H, Hausner's ratio; Carr, Carr's compressibility index; CFV, coefficient of fill weight variation; AUC, area under the dissolution curve; MDT, mean dissolution time; VDT, variance of the dissolution time; DT, disintegration time.

Dissolution Test

The dissolution rates of the drugs from the various formulations were determined by means of the B.P. Apparatus II method. The paddles were rotated at 50rpm in 1000 ml of distilled water maintained at 37 ± 0.6°C. Six capsules from each batch were evaluated simultaneously using an automated dissolution apparatus (Pharma Test, PTWS, Germany) connected to a sample collector (Pharma Test, Type PTFC I, Germany). Ten or more samples were extracted from the dissolution medium of each capsule throughout its period of dissolution. Each sample was diluted 25 times and analysed by a *uv-vis* spectrophotometer (Perkin-Elmer 554, USA). The absorbance of the solution of paracetamol, theophylline, aminophylline and propranolol was determined at 242 nm, 271 nm, and 288 nm respectively. The absorbance values were transformed to concentrations by reference to standard calibration curves obtained experimentally. The solubility of phenytoin is too low to ensure sink condition, hence a low percentage release was achieved. To allow quantitative comparisons with the other drugs, arbitrarily assigned values indicating poor dissolution were given to this formulation. The dissolution profiles were characterised by the area under the curve (AUC), the mean dissolution time (MDT) and the variance of dissolution time (VDT) (16).

RESULTS AND DISCUSSION

First, parametric canonical analysis has been undertaken to describe the relationship between the excipients used in the formulations and the filling performance of the capsules characterised by the powder densities, powder flow and coefficient of fill weight variation. The mathematical outcome is summarised in Table 5. The relationship between filling performance and the formulation components is significant. However, with this method only 27.8% ($g^2_{Y|U}$) of the variability of the filling properties can be explained, and therefore a prediction of filling properties from a given formulation appears to be impossible. Looking in detail at the interranging communalities (d^2), it can be seen that the minimum bulk density of the powders is best described, whereas the Hausner's ratio is clearly less

Table 3. Variable Group X Used in the Nonparametric Canonical Analysis

EN	D_1(ps)	d_2(sol)	ft	fl	dt	dl	ll	gl	dc
1	4	3	2	6	1	3	3	1	3
2	4	3	2	6	1	3	3	2	3
3	4	3	2	4	1	3	3	4	3
4	4	3	2	4	1	3	3	5	3
5	4	3	2	6	1	3	1	3	3
6	4	3	2	6	1	3	2	3	3
7	4	3	2	4	1	3	4	3	3
8	4	3	2	4	1	3	5	3	3
9	4	3	2	7	1	1	3	3	3
10	4	3	2	7	1	2	3	3	3
11	4	3	2	4	1	4	3	3	3
12	4	3	2	3	1	5	3	3	3
13	2	1	2	5	1	3	3	3	3
14	3	2	2	5	1	3	3	3	3
15	4	3	2	5	1	3	3	3	3
16	1	4	2	5	1	3	3	3	3
17	4	5	2	5	1	3	3	3	3
18	4	3	2	9	1	3	3	3	1
19	4	3	2	8	1	3	3	3	2
20	4	3	2	2	1	3	3	3	4
21	4	3	2	1	1	3	3	3	5
22	4	3	1	5	1	3	3	3	3
23	4	3	3	5	1	3	3	3	3
24	4	3	4	5	1	3	3	3	3
25	4	3	5	5	1	3	3	3	3
26	4	3	2	5	2	3	3	3	3
27	4	3	2	5	3	3	3	3	3
28	4	3	2	5	4	3	3	3	3
29	4	3	2	5	5	3	3	3	3
30	4	3	1	7	1	3	3	3	3
31	4	3	1	3	1	3	3	3	3
32	4	3	5	7	1	3	3	3	3
33	4	3	5	3	1	3	3	3	3

Note: D_1(ps), drug characterised by particle size; d_2(sol), drug characterised by solubility; ft, filler type; fl, filler level; dt, disintegrant type; dl, disintegrant level; ll, lubricant level, gl, glidant level, dc, drug concentration.

dependent on the formulation components. The major influence factors are probably the particle size of the drug, the amount of glidant used and the type of filler and disintegrant incorporated into the formulation.

Secondly, the same set of data was used in the nonparametric canonical analysis (see Table 5). The test of significance already indicates that using this method the relationship between the two groups of variables can be identified in more detail, because nonlinear aspects are also evaluated. Furthermore, the ranking of the response variables to transfer them into ordinal data overcomes problems caused by the variability of the filling data, which can easily mask linear relationships caused by overlapping. In this way, 81.9% of the variability of the results can be contributed to the formulation. With the exception of Hausner's ratio all response variables depend on the composition of the formulations ($d^2 > 0.9$).

The particle size and the concentration of the drug are very important factors to be monitored, but the type of the filler and the glidant level incorporated into the formulations are also reflected in the filling data. Looking at the results presented in Table 2, it appears as though a coarse (here mean particle size $> 60\mu m$) particle size or a large concentration of drug in the powder results in poor filling performance. Calcium phosphate should be excluded from capsule filling, because in all 3 experiments used (exp. 25, 32, 33) the coefficient of fill weight variation is exceptionally high. There is obviously a minimum amount of glidant (0.5%) necessary, but the optimum concentration for Aerosil appears to be 1.0% both with respect to the coefficient of fill weight variation and to the flow properties (see Carr's compressibility).

Parametric canonical analysis was also used to highlight the relationships between the drug release and the formulations (see Table 5). The total assessment resulted in a statistically non-significant set of values, which hence can only be treated as trends. According to this trend it could be useful to study the influence of the drug solubility and concentration as well as the amount of disintegrant incorporated into the formulation in greater detail. To assure that this unsatisfactory outcome of the analysis is not partly due to Phenytoin, which gave an incomplete dissolution because of its very low solubility, the calculations were repeated without experiment 13. However,

Table 4. Classification of the Results Presented in Table 2 into Ordinal Data Used for Y in the Nonparametric Canonical Analysis

Ordinal value	V_{min} [gcm^{-2}]	V_{max} [gcm^{-3}]	H	Carr [%]	CFV [%]	AUC [%min]	MDT [min]	VDT [min]	DT [min]
1	<0.40	<0.60	<1.40	<25	<1.0	<1000	<10	<20	<7
2	<0.45	<0.65	<1.45	<30	<1.5	<1500	<15	<50	<8
3	<0.50	<0.70	<1.50	<33	<2.0	<2000	<20	<100	<9
4	<0.55	<0.75	<1.55	<36	<3.0	<2500	<25	<200	<10
5	<0.60	<0.80	<1.60	<39	<6.0	<3000	<30	<500	<11
6	<0.65	<0.85	<1.65	<42	>6.0	<4000	<100	<1000	<12
7	—	—	<1.70	—	—	<10000	>100	>1000	<13
8	—	—	—	—	—	>10000	—	—	—

Note: EN, experiment number, V_{min}, minimum bulk density; V_{max}, maximum bulk density; H, Hausner's ratio; Carr, Carr's compressibility index; CFV, coefficient of fill weight variation; AUC, area under the dissolution curve; MDT, mean dissolution time; VDT, variance of the dissolution time; DT, disintegration time.

Table 5. Results of the Parametric and Nonparametric Canonical Analysis

	Parametric		Nonparametric	
Criterion	filling	drug release	filling	drug release
significance	F = 4.44	F = 1.42 (ns)	F = 128.30	F = 2.72 (ns)
ncv	3	2	4	3
$g^2_{X\|V}$	0.510	0.120	0.487	0.357
$g^2_{Y\|U}$	0.278	0.078	0.819	0.572
d^2_{ps}	0.897	—	0.998	—
d^2_{sol}	—	0.541	—	0.709
d^2_{conc}	0.383	0.456	0.985	0.213
d^2_{ft}	0.660	0.333	0.663	0.484
d^2_{fl}	0.400	0.427	0.300	0.035
d^2_{dt}	0.563	0.402	0.075	0.635
d^2_{dl}	0.251	0.498	0.275	0.432
d^2_{ll}	0.137	0.325	0.017	0.015
d^2_{gl}	0.736	0.300	0.587	0.333
d^2_{min}	0.866	—	0.998	—
d^2_{max}	0.759	—	0.969	—
d^2_{H}	0.562	—	0.219	—
d^2_{Carr}	0.761	—	0.974	—
d^2_{CFV}	0.783	—	0.941	—
d^2_{AUC}	—	0.229	—	0.192
d^2_{MDT}	—	0.221	—	0.247
d^2_{VDT}	—	0.157	—	0.875
d^2_{DT}	—	0.741	—	0.975

Note: Ncv, number of canonical variates; g^2, measures of redundance; X|V, predictability of X by the canonical variables of Y(V); Y|U, predictability of Y by the canonical variables of X(U); d^2, interranging communalities; ps, particle size; sol, solubility; ft, filler type; fl, filler level; dt, disintegrant type; dl, disintegrant level; ll, lubricant level; gl, glidant level; min, minimum bulk density; max, maximum bulk density; H, Hausner's ratio; Carr, Carr's compressibility index; CFV, coefficient of fill weight variation; AUC, area under dissolution curve; MDT, mean dissolution time; VDT, variance of dissolution time; DT, disintegration time; (ns), not significant.

no improvement was achieved, confirming that experiment 13 did not bias the results discussed.

The overall outcome of the nonparametric canonical analysis is also not significant. However, for the disintegration time of the capsules and the dissolution speed of the drug after disintegration, reflected in the VDT, clear assumptions can be made because of the values of the interranging communalities ($d^2 > 0.85$). The solubility of the drug dominates the disintegration and dissolution process, and the type of the disintegrant, and partly the type of the filler incorporated are also important influence factors. Comparing these results with the actual measured values (Table 2), it can be seen that the disintegration time tends to increase with an increase in solubility of the drug. In the first instance, this appears to be odd. However, disintegration is caused by water penetrating into the capsules and causing the disintegrants to swell. With highly soluble drug it might come to a competition between the drug particles, which need to be dissolved, and the disintegrant particles, which need to swell. Obviously, water prefers to dissolve the drug first if possible, before the disintegrant becomes wet enough to swell. It also appears that the swelling degree is strongly related to the dissolution speed of the drug. However, starch, the least swelling disintegrant used, also causes a fast dissolution. The disintegration mechanism for starch is arguably not swelling, but a redeformation of the starch particles into their original shape after contact with water causing a weakening of the plug structure and hence disintegration rapidly.

None of the statistical methods could identify a relationship between the value of the MDT and the formulations. The value of the MDT of drug formulations increases in the following order: paracetamol (exp. 15), theophylline (exp. 14), aminophylline (exp. 17), propranolol-HCl (exp. 16) and phenytoin (exp. 13). If the solubility of the drugs is multiplied by their particle size, the following order would be obtained: phenytoin, paracetamol, theophylline, aminophylline and propranolol-HCl. With the exception of phenytoin, which is practically insoluble, the order obtained in this way matches that of the MDT. Solubility and particle size are therefore interacting factors.

It can be concluded that a combination of a statistical design and multivariate statistical analysis was useful to identify some relationships between the composition of capsule formulations and the filling performance of these formulations using a dosator-nozzle system. Nonparametric canonical analysis proved superior to parametric canonical analysis in this respect. The filling properties are related to the formulations in a complex manner. In particular, the mean particle size of the drug and the drug concentration dominate the filling performance, but the type of filler and the glidant concentration are also important influence factors. Calcium phosphate should be avoided as a filler due to its poor flow properties. The disintegration of the capsules and the dissolution of the drugs were related to the formulations used by trends rather than exact quantification. In this respect, drug solubility, type of disintegrant and type of filler are variables of considerable influence.

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