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RESEARCH PAPER

Investigation of Flow Properties of Powders by Means of a Uniaxial Tester, in Relation to Direct Tablet Compression

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ABSTRACT

Unexpected poor flowability during commercial production of a direct compression tablet formulation initiated an investigation of the flow properties of the powder mixture and its components by means of a uniaxial tester. The failure function—a curve describing the strength of the powder bed as a function of the maximum main stress that has consolidated the bed—of the powder mixture and its components was determined. The drug was more cohesive than the filler, which was somewhat more cohesive than the powder mixture. Three excipients—a binder, a glidant and a lubricant—constituting 3.5 w/w% of the formulation improved the flowability of the mixture of active ingredient and filler. The failure function discriminated powder mixtures with poor flow from mixtures with medium or good flow. However, it was not possible to discriminate medium from good flow by means of the failure function. Attempts to correlate univariately the flow property parameters of the powder mixtures with particle size data or flow property data of included active ingredient and filler batches failed. Therefore a multivariate approach was tested. Principal component

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analysis (PCA) and projection to latent structures by means of partial least squares (PLS) were employed. An excellent PCA model was obtained with the flow properties of the powder mixture. A good PCA model of tableting performance—based on tablet weight variation and tablet machine speed—was obtained.

INTRODUCTION

Pharmaceutical tablets are produced on a commercial scale by filling of a powder mixture (or granulation) by volume. Consequently, the flow properties of the powder mixture are important as to the uniformity of mass of the tablets.

Powder flows when the forces acting on the powder bed cause the resulting shear force to exceed the shear strength of the bed. The flow properties of powders are mainly influenced by particle size, size distribution and shape. But all factors acting on and between the particles in a powder mixture can influence the flowability as, for example, the humidity and state of compaction of the powder.

Powder flow characteristics are measured by such methods as angle of repose (1), Hausner ratio (2), electronic powder flow meters (3), or shear cells (4). Studying the avalanching behavior has also been proposed (5). Recently, a powder rheometer was suggested for testing of the flow properties (6). The Jenike shear cell was first used in connection with construction of silos. Theoretically, it is a suitable method for studying the flow properties of powders. However, some disadvantage such as slow and operator-dependent measurements have initiated development of alternatives to the Jenike shear cell, resulting in other types of shear cells and, for example, the uniaxial tester (7). The uniaxial tester gives reliable measurement of the flow properties of powders and is simple to use.

Unexpected poor flow properties of some powder mixture batches for direct compression of tablets initiated an investigation for a suitable method: the uniaxial tester was selected as the most suitable and available technique.

MATERIALS AND METHODS

Formulations

The formulation of the powder mixture for the commercial product is summarized in Table 1. To specifically study the influence of the active ingredient, some powder mixtures were made on a small scale and studied (Table 2).

In a third part, with a proportion of active ingredient to filler (DRU/FIL) in the ratio 0.642, including batches 40–42, the percentages of binder/disintegrant, glidant and lubricant were changed to 1.8, 0, and 0.6, respectively, i.e., somewhat different from Table 1.

Batches

Eleven tablet batches—802–805, 812–815, 821, 823, and 824—and 12 batches of active ingredient (Table 3) and 10 batches of filler (Table 4) forming part of the tablet batches were investigated. In addition, six powder mixture batches—2–4 and 7–9—from the small-scale study (Table 2) and three batches—40–42—with other percentages of

Table 1

Formulation of the Powder Mixture

Component	Percentage
Active ingredient	19.0
Filler	77.5
Binder/disintegrant	2.2
Glidant	0.5
Lubricant	0.8

Table 2

Formulation of Test Mixtures Where the Percentages of Binder/Disintegrant, Glidant, and Lubricant Are Identical to Table 1

	Percentage Batch No.					
Component	2	3	4	7	8	9
Active ingredient	0	11.3	19.0	26.8	38.1	96.5
Filler	96.5	85.2	77.5	69.7	58.4	0

Table 3

Batch Data of Active Ingredient

Batch	halt	aqua	bude	tade	haus	t2de	hau2	tret	sext	etth	tvah	femh	sema	semp	nkon	nslo	nint	lod	lodp	rhp	med	saut	mode2	mode1	span	fem	tio	tju
47	11.8	5	0.46	0.62	1.34	0.64	1.38	96	100	100	100	100	*	*	18.17	0.436	0.636	4.99	4.16	44	16.21	9.12	19.24	2.14	0.45	12.45	25.76	64.29
62	11.4	5.3	0.45	0.64	1.42	0.66	1.44	89.6	100	100	100	100	2	3	19.21	0.431	2.08	4.65	4.12	68	13.93	16.49	15.77	1.95	0.52	14.67	31.34	71.56
63	11.7	5.3	0.42	0.59	1.39	0.6	1.41	96.8	98.4	99.8	100	100	2	3	21.31	0.498	1.107	5.04	4.67	26	7.56	8.5	9.09	2.16	0.84	32.09	63.69	96.76
64	11.8	4.2	0.46	0.64	1.42	0.66	1.44	96	99	99	100	100	1	2	18.29	0.446	0.46	4.38	3.94	23	16.55	19.91	19.36	2.1	0.46	12.8	24.64	63.68
65	11.5	4.6	0.47	0.66	1.4	0.67	1.42	95.2	98.6	99.4	99.4	100	1	3	13.54	0.304	1.185	3.65	3.3	41	15.28	18.14	17.46	2	0.48	12.48	26.2	69.11
67	11.7	5.8	0.46	0.6	1.32	0.62	1.34	92	99.2	99.4	99.4	99.8	2	2	15.53	0.369	0.774	4.53	3.73	42	16.8	19.6	19.93	2.03	0.43	11.01	23.96	62.44
68	11.8	5.3	0.47	0.64	1.38	0.65	1.4	97.6	99	99.6	100	100	2	3	18.38	0.429	1.505	4.17	3.98	43	10.39	12.83	14.46	2.09	0.75	27.85	46.05	82.5
69	11.6	4.4	0.47	0.65	1.4	0.66	1.42	98	99.2	99.2	99	100	2	3	17.54	0.426	0.424	3.52	2.84	38	8.55	9.82	11.01	2.08	0.82	30.8	55.31	92.44
70	11.8	4.7	0.49	0.66	1.35	0.67	1.37	97.6	99	99.6	100	100	*	*	17.14	0.379	2.165	3.99	3.36	62	15.54	8.41	18.82	2.13	0.49	14.44	27.75	66.83
74	11.4	4.4	0.41	0.6	1.46	0.6	1.48	72.6	78.8	83.7	89.5	95.4	1	1	20.22	0.434	3.232	4.2	3.06	70	5.99	3.76	8.27	1.92	1.1	44.66	75.2	99.52
76	11.7	4.1	0.45	0.65	1.45	0.66	1.48	96	98.6	99.2	98.6	99.4	1	2	18.6	0.39	3.77	3.82	3.07	70	9.55	5.55	12.33	2.14	0.74	27.34	49.63	88.05
77	11.6	4	0.48	0.66	1.39	0.68	1.42	93.2	99.4	99.6	100	100	1	2	23.12	0.534	1.786	4	3.32	70	16.52	8.5	21.04	2.19	0.49	15.13	27.65	62.05

*Missing data.

halt assay (%)
aqua water assay (%)
bude aerated bulk density (g/cm^3)
tade tapped bulk density—1250 taps (g/cm^3)
haus Hausner ratio—1250 taps
t2de tapped bulk density (g/cm^3)—2500 taps
hau2 Hausner ratio—2500 taps
tret percentage <32 μm
sext percentage <63 μm
etth percentage <125 μm
tvah percentage <250 μm
femh percentage <500 μm
sema SEM aggregate
semp SEM particles
nint intercept—failure function
nslo slope—failure function
nkon strength at 40 kPa consolidation stress—failure function
lod loss on drying (%)—moisture balance
lodp loss on drying (%)—uniaxial tester measurement
rhp relative humidity (%)—uniaxial tester measurement
med median diameter (μm)—laser diffraction
saut Sauter diameter (μm)—laser diffraction
mode1 mode diameter, distribution 1 (μm)—laser diffraction
mode2 mode diameter, distribution 2 (μm)—laser diffraction
span specific surface per unit weight (m^2/g)—laser diffraction
fem percentage <5.2 μm—laser diffraction
tio percentage <9.5 μm—laser diffraction
tju percentage <20.9 μm—laser diffraction

Table 4

Batch Data of Filler

Batch	tret	sext	etth	trse	seet	etva	bude	tade	haus	fsvs	sfyt	lod	lodp	med	saut	model	mode2	spar	bet	bint	bslo	bkon	rhp
137	18	43.2	82.8	25.2	39.6	17.2	0.56	0.72	1.29	53	0.077	13.8	12.01	52.5	28.2	75.5	944.6	0.144	1.24	−0.323	0.214	8.267	44
148	20	50	90.8	30	40.8	9.2	0.58	0.75	1.29	51	0.081	13.76	13.49	42.9	25.2	85	*	0.162	1.11	0.183	0.144	5.943	35
150	25.2	55	92	29.8	37	8	0.58	0.74	1.28	54	0.076	13.58	13.41	46.1	26.7	83.1	*	0.153	1.04	−0.028	0.169	6.755	30
151	23.6	50	85.2	26.4	35.2	14.8	0.58	0.74	1.28	52	0.079	13.67	11.98	47.4	27.1	99.1	*	0.151	1.02	0.121	0.244	9.751	44
152	24	52.6	97.6	28.6	45	2.4	0.57	0.74	1.3	52	0.08	13.65	13.51	48	27.6	103.5	*	0.148	0.95	−0.089	0.211	8.358	39
153	40	77.4	92	37.4	14.6	8	0.55	0.72	1.31	51	0.081	13.32	13.61	41.6	25.3	108.7	*	0.162	1	0.193	0.228	9.443	36
161	34.6	50	95	15.4	45	3.8	0.58	0.74	1.28	50	0.082	12.91	12.44	51.4	27.6	71.8	1145	0.149	0.94	−0.246	0.194	7.329	39
165	33	52.6	86	19.6	33.4	13.6	0.56	0.73	1.32	50	0.082	12.84	12.82	53.4	28.3	75.4	964.4	0.145	0.94	0.412	0.173	7.217	77
166	27.4	50.6	96.2	23.2	45.6	3.8	0.54	0.68	1.27	50	0.082	12.46	12.63	51.3	27.6	72.7	960.3	0.149	0.91	−0.591	0.243	9.282	77
167	38.8	72	97.6	33.2	25.6	1.4	0.52	0.68	1.31	46	0.089	12.66	12.4	44.7	25.9	58	1167	0.158	0.83	−0.083	0.231	9.177	77

*Single modal distribution.

tret percentage <32 μm
sext percentage <63 μm
etth percentage <125 μm
trse percentage of fraction 32—63 μm
seet percentage of fraction 63—125 μm
etva percentage of fraction 125—250 μm
bude aerated bulk density (g/cm^3)
tade tapped bulk density (g/cm^3)—1250 taps
haus Hausner ratio—1250 taps
fsvs volume—surface mean diameter (μm)—Fisher subsieve sizer (FSSS)
sfyt specific surface (m^2/g)—FSSS
lod loss on drying (%)—moisture balance
lodp loss on drying (%)—uniaxial tester measurement
med median diameter (μm)—laser diffraction
saut Sauter diameter (μm)—laser diffraction
mode 1 mode diameter, distribution 1 (μm)—laser diffraction
mode 2 mode diameter, distribution 2 (μm)—laser diffraction
spar specific surface per unit weight (m^2/g)—laser diffraction
bet specific surface (m^2/g)—BET
bint intercept—failure function
bslo slope—failure function
bkon strength at 40 kPa consolidation stress—failure function
rhp relative humidity (%)—uniaxial tester measurement

binder/disintegrant, glidant, and lubricant from the third part were studied.

In addition, the binder/disintegrant, glidant and lubricant—only one batch of each—was investigated.

Uniaxial Tester

The uniaxial tester was developed in Porsgrunn with a die of a volume of 114 cm^3 (7). A smaller die with a volume of about 4 cm^3 was later introduced for expensive powders (8). This smaller die was used in all the tests. The tester is inter alia intended for relatively quick quality control of flow properties of different powders.

A powder body confined in a cylindrical die is uniaxially compressed (Fig. 1A). The die has a diameter of 10 mm and a height of 50 mm. Powder is filled into the die by a spoon. The powder is packed by the load of a brush (0.74 kPa) applied after every second spoon. The excess of powder is scraped off. This means that approximately 3–4 g powder is filled into the die. The powder is consolidated at 5, 10, 20, and 40 kPa with a stress rate of 1.5 mm/min. At some occasions when no cohesive plug is obtained at 40 kPa, a stress of 80 kPa is applied too. The die is removed from the plug, which is then uniaxially stressed at a rate of 0.6 mm/min (Fig. 1B). When the plug fails, the strength of the powder (f_c) is observed. Three measurements are made at each consolidation stress.

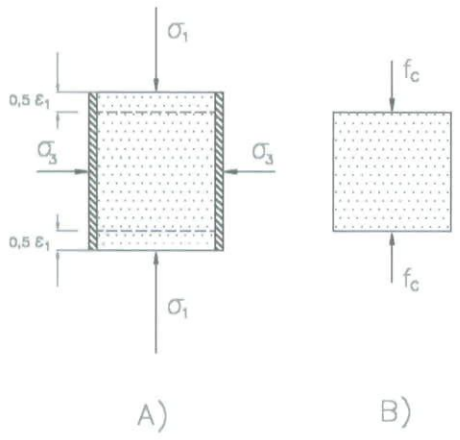

Figure 1. The main principles of uniaxial testing: A, Uniaxial consolidation; σ_1 is the consolidation stress (major principal stress), σ_3 = minor principal stress, and ε_1 = major principal deformation. B, Uniaxial compressive strength (f_c) measurement.

The failure function (FF) shows the strength of the powder (f_c) as a function of the main stress (σ_1) that has consolidated the powder (Fig. 2). FF describes the flow properties of the tested powder.

The loss on drying of the drug and powder mixture (lodp) is measured by drying approximately 10 g powder for about 6 hr at 105°C in connection with the measurements in the uniaxial tester. Also, the air temperature and relative humidity (rhp) is noted.

The flow function is calculated as the linear least-squares regression line, i.e.,

$$f_c = \text{slo} \cdot \sigma_1 + \text{int}$$

where slo is the slope of the line and int is the intercept on the f_c-axis. In the text and figures the slope with drug, filler, and powder mixture for tablets is designated nslo, bslo, and slope respectively. Similarly, the intercept is designated nint, bint, and inter, respectively. The strength of the powder plug compressed at 40 kPa is designated nkon, bkon, and konso40, respectively. These three variables—intercept, slope, and strength of the powder plug consolidated at 40 kPa—are defined by the failure function. The lowest applied consolidation stress giving a coherent powder plug is designated lkon for active ingredient, filler, and powder mixture.

Experimental Data

Assay of active ingredient (halt) was performed by an HPLC method.

Water content (aqua) was measured by Karl Fischer titration.

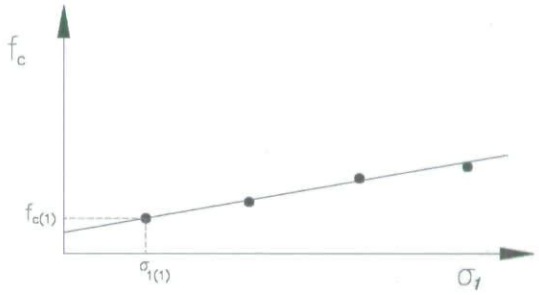

Figure 2. The failure function (FF), i.e., the compressive strength f_c as a function of the consolidation stress σ_1: x-axis, consolidation stress; y-axis, compressive strength.

Aerated bulk density (bude) and tapped bulk density after 1250 taps (tade) or 2500 taps (t2de) were measured principally according to Ph. Eur. (9). The Hausner ratio, i.e., tapped bulk density divided by aerated bulk density, was calculated: haus (1250 taps) and hau2 (2500 taps).

Sieve analysis—with the following sieves: 32, 63, 125, 250, 500 and 710 μm—was performed with an air jet sieve (Alpine, Germany); 5 g drug or filler was sieved for 5 min on each sieve. The percentage <32 μm (tret), <63 μm (sext), <125 μm (etth), <250 μm (tvaf), and <500 μm (femh) was measured. With the filler, the percentages of the following fractions were calculated: 32–63 μm (trse), 63–125 μm (seet), and 125–250 μm (etva).

The particle size, the volume–surface mean diameter (fsvs), of the filler was measured by means of the Fisher Sub-Sieve Sizer (Model95, Fisher Scientific, USA). A mass corresponding to the density was tested at " porosity" values of 0.40–0.80. The tabulated fsvs values were read at "porosity" values of 0.4–0.425. A calculation of the specific surface (sfyt) was performed.

Loss on drying of drug and filler (lod) was measured by a Shimadzu electronic moisture balance (EB-280 MOC, Japan) at 100°C pan temperature until equilibrium was reached.

Laser diffraction technique (Malvern MastersizerX, England) was also applied for measurement of particle size. A dry powder feeder (MSX64) was used with the filler. With the drug a suspension in acetonitrile was measured in the Small Volume Unit MSX1 after 2 min sonication. The median diameter (med), Sauter diameter (saut, i.e. volume–surface mean diameter), mode diameters (mode1 and mode2), specific surface per unit weight [spar (with the filler) and span (with the drug)] were calculated. In addition, the percentage lower than 5.2 μm (fem), 9.5 μm (tio), and 20.9 μm (tju) of the drug was calculated.

Powder surface areas of the filler (bet) were measured by means of a gas adsorption technique, the multipoint BET method (Gemini 2375, Micromeritics, USA). Data were obtained using five relative pressures, 0.05–0.30, of nitrogen adsorbent. Conditioning of the powder was performed by evacuation at 250 mmHg/min for 2 min.

Scanning electron microscopy (SEM) of the drug was performed at suitable magnifications, 35–1000×, after gold sputtering (Jeol, JSM-7200, Japan). The occurrence of aggregates (sema) was assessed: 1 = no aggregates, 2 = few aggregates, 3 = many aggregates. Also, the general shape of the particles (semp) was assessed: 1 = most equants (10), 2 = most plates (10), 3 = equants and plates.

Twenty-eight variables were included in the drug data matrix (Table 3); 23 variables were included in the matrix with filler data (Table 4). No specific shape factors were included in the drug and filler matrices.

The matrix with tablet data contained 14 variables (Table 5). Four of the variables described the principal properties (11) of the active ingredient and the filler, i.e., the active ingredient matrix with 28 variables was reduced to two principal components and the t-values of these (principal properties or scores) were used as variables (DRUt1 and DRUt2). Similarly, the filler matrix with 23 variables was reduced to two principal components (FILt1 and FILt2). In cases when two batches of drug or filler were used in a tablet batch a weighed average of the t-values was used.

When evaluating the influence of drug and filler data on the flow properties of the powder mixture, 20 batches were included. The number of batches was reduced to 10 when the influence of drug and filler data on the tableting performance, based on tablet weight variation and tablet machine speed during commercial tablet production, was evaluated (Table 6).

Multivariate Data Analysis

The experimental data from the drug, filler, and tablet matrices were evaluated by principal component analysis or PCA (12). As a result of PCA, a model describing the systematic variation in the data by fewer variables than in the original data set is obtained. For each experiment the t-values (t1 and t2) describe the position of the experimental point projected down to a model. Hence, t-values can be used to relate experiments to each other. The loading plot can give information of how much each variable contributes to the model.

Projection to latent structures by means of partial least squares (PLS) is a statistical method to relate multivariate descriptor data sets to multivariate response data sets (13). R^2Y is the fraction of the sum of squares of the dependent variable(s) that can be explained. Q^2 is the fraction of the total variation of the dependent variable(s) that can be predicted.

Table 5

Powder Mixture for Tablets

Batch	bind	lubr	glid	inter	Slope	konso40	1kon	lodp	rhp	DRU/FIL	FILt1	FILt2	DRUt1	DRUt2
40	1.8	0.6	0	2.029	0.357	16.135	5	8.62	74	0.642	0.19001	−1.6364	−9.8652	−0.4237
41	1.8	0.6	0	1.269	0.323	14.042	5	8.2	76	0.642	−1.7016	−3.6497	−2.1538	−2.5048
42	1.8	0.6	0	1.433	0.253	11.319	5	8.13	86	0.642	−6.2331	−0.41142	1.3624	−2.6375
802	2.2	0.8	0.5	−0.35	0.169	6.384	5	10.91	30	0.2655	1.817	3.0435	−1.2894	−1.317
803	2.2	0.8	0.5	−0.45	0.188	7.028	5	10.7	32	0.2645	1.786	2.9887	−1.6179	5.0222
804	2.2	0.8	0.5	−3.26	0.206	4.984	20	10.7	34	0.262	2.2187	1.6644	−0.1214	−2.8006
805	2.2	0.8	0.5	−0.75	0.1	3.283	10	10. 3	26	0.2583	2.2187	1.6644	2.1329	−0.5456
812	2.2	0.8	0.5	−0.88	0.104	3.381	20	10.53	40	0.2645	1.008	0.439	1.916	−2.2699
813	2.2	0.8	0.5			1.841	40	10.65	45	0.2645	0.80024	0.54508	2.4471	0.081
814	2.2	0.8	0.5			2.38	40	10.59	47	0.2645	0.80024	0.54508	2.7356	2.1055
815	2.2	0.8	0.5	−1.36	0.107	2.989	20	10.75	46	0.2645	−1.7475	3.281	2.7356	2.1055
821	2.2	0.8	0.5	−0.36	0.153	5.922	5	10.71	40	0.2617	−2.6105	4.2073	0.929	0.2695
823	2.2	0.8	0.5	−0.59	0.165	5.985	5	10.02	41	0.2613	0.2395	−1.7534	−0.5142	−0.211
824	2.2	0.8	0.5	−0.7	0.153	5.453	10	10	62	0.2604	0.24551	−1.7798	0.3237	−0.8117

bind	percentage of binder
lubr	percentage of lubricant
glid	percentage of glidant
inter	intercept of the failure function (kPa)
slope	slope of the failure function
konso40	strength at 40 kPa consolidation stress (kPa)
lkon	lowest consolidation stress to give a coherent plug (kPa)
lodp	loss on drying (%)
rhp	relative humidity (%)
DRU/FIL	ratio of drug/filler
FILt1	score, t1 of filler
FILt2	score, t2 of filler
DRUt1	score, t1 of drug
DRUt2	score, t2 of drug

Table 6

Powder Mixtures of Commercial Formulation; Tableting Performance[a] and Flow Properties

Batch	Tableting Performance	Tablet Machine Speed (tabl/hr)	Ikon (kPa)
802	Poor	—	5
803	Poor	—	5
804	Medium	110 000	20
805	Good	130 000	10
812	Medium	77 000	20
813	Good	130 000	40
814	Good	130 000	40
815	Good	130 000	40
821	Poor	—	5
823	Poor	—	5
824	—[b]	—	10

[a]Based on tablet weight variation and tablet machine speed during commercial tablet production.
[b]Not tabletted during similar conditions as the preceding batches.

PCA and PLS were performed by using SIMCA-P (graphical software for multivariate modelling, version 8.0, Umetrics AB, Box 7960, SE-90719 Umeå, Sweden) after unit variance scaling and mean centering.

RESULTS AND DISCUSSION

Uniaxial Tester

The failure function curves are summarized in Fig. 3, and the areas enclosing the FF curves of drug, filler, and powder mixture are marked. Some FF curves cross each other within each area. It is obvious that, although there is a variation between batches, the FF curves of the active ingredient are located in an area in the upper part of the figure, separated from the filler and powder mixture for tablets. Consequently, the active ingredient has poor flow properties, as higher failure stresses are required for breaking the powder bed.

Three measurements were made at each consolidation stress and the variation in f_c-values, expressed as coefficient of variation, is summarized in Table 7. A contribution from the variation in actual consolidation stress, which corresponds to a 1.5% coefficient of variation at the most, is included in the variation in f_c-values. The variation is larger at the low consolidation stress with the powder mixture and the filler compared with the cohesive drug. At 40 kPa, a consolidation stress resulting in higher f_c-values, the coefficient of variation in f_c-values is lower.

The FF curves of the filler are located in an area below the active ingredient. However, the areas with the FF curves of the filler and the powder mixture partly overlap. Consequently, the filler has better flow properties than the active ingredient, but generally the powder mixture has a better flowability than the filler. The reason for that is the other three excipients constituting only 3.5% of the formulation, (see Table 1). Of these three excipients, the binder/disintegrant, glidant, and lubricant have values of the lowest applied consolidation stress to form a coherent plug of >80, 80, and 5 kPa, respectively, which means that the first two excipients have very good flow properties compared with the lubricant, which is cohesive. Obviously, the binder/disintegrant and glidant contribute most to the improved flow properties of the formulation.

The requirement for getting powders to flow is that their strength is less than the load on them. This means that the powders flow at loads below the lowest applied consolidation stress to give a coherent plug. Consequently, a material with a low value of lowest applied consolidation stress to give a coherent plug has poorer flow properties than a material with a higher value.

With all batches of active ingredient and filler, the lowest applied consolidation stress to give a coherent plug was 5 kPa. The drug is a very cohesive powder with a small particle size: as a rule >90% w/w is smaller than 32 μm (see Table 3). Less cohesive behavior characterizes the filler, where generally approximately 20–40 w/w% is smaller than 32 μm and approximately 90 w/w% is smaller than 125 μm (see Table 4). However, with the powder mixture batches there was a variation in the value of the lowest applied consolidation stress to give a coherent plug (Ikon), 5–40 kPa. With the poor batches—802, 803, 821, and 823—(see Tables 5 and 6), this value was 5 kPa, but with the medium ones—804 and 812—it was 20 kPa, and with three of the good batches—813–815—it was 40 kPa. The exception was 805, with a good tableting performance, but Ikon = 10 kPa. Because of this exception, for which no explanation has been found, it was not possible to discriminate unambiguously

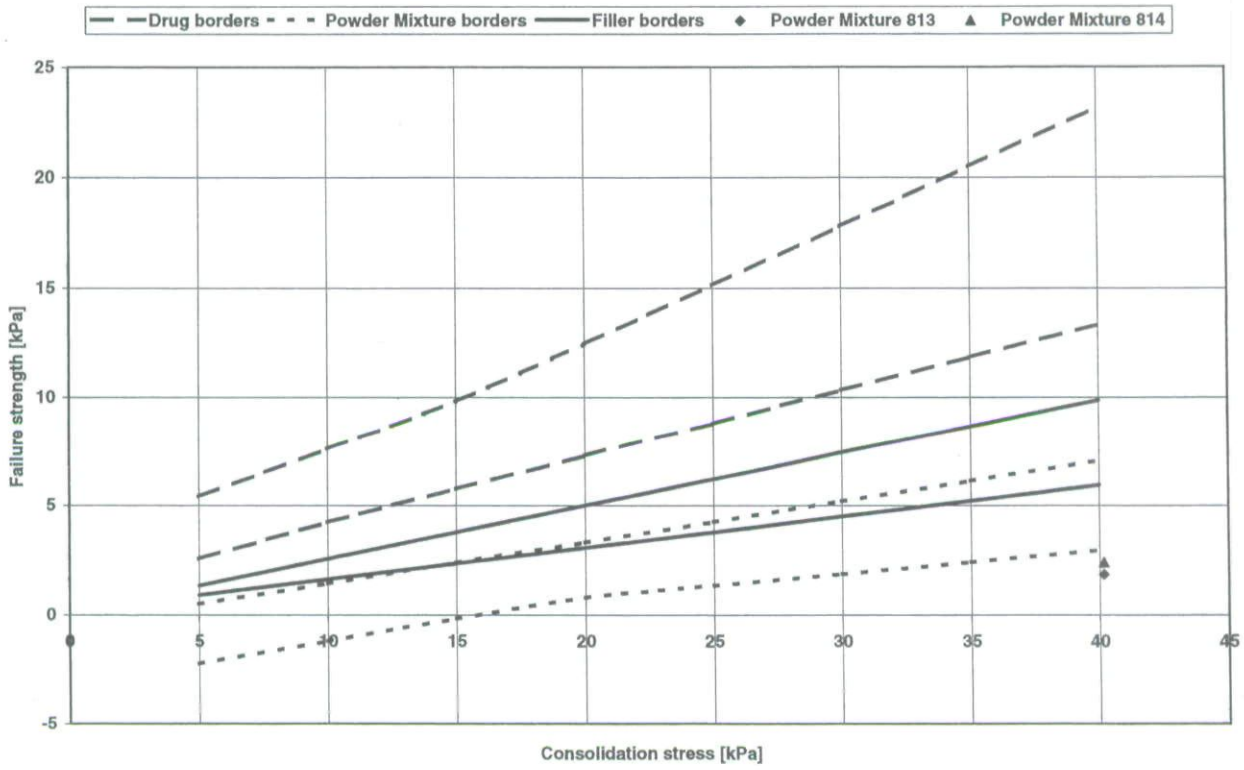

Figure 3. Uniaxial failure functions measured for drug, filler, and powder mixture batches: *x*-axis, consolidation stress, kPa; *y*-axis, compressive strength, kPa.

Table 7

Variation in f_c-Values (the Strength of the Powder) at 5 and 40 kPa Consolidation Stresses, Given by the Coefficient of Variation, i.e., the Standard Deviation as a Percentage of the Mean, Here of Series of Three Parallel Measurements

	Range of coefficients of variation for all the measurements, %	
Powder type	Consolidation Stress 5 kPa	Consolidation Stress 40 kPa
Drug	2–13	1–6
Filler	3–22	1–10
Powder mixture	5–30	0.2–9

between good and medium tableting performance based on the Ikon value, although the discrimination of poor from medium and good was without any exceptions. With Ikon values of 5 kPa the tableting performance was poor, whereas for Ikon values of 10 kPa or higher, it was medium or good. In Fig. 3 the poor batches were in the upper part of the area of the powder mixture, whereas the medium and good batches were in the lower part. It is to be observed that with the good batches 813–814 no FF curves were obtained, as coherent plugs were not formed until 40 kPa.

The flow properties of a powder are defined by the failure function. Consequently, a low value of the intercept and the slope characterizes a material with good flow properties (Fig. 3).

The influence of varying ratios of drug to filler and the other excipients is demonstrated in Fig. 4. A rank order correlation between proportion of drug and flow properties is obvious. A steeper FF curve is obtained with increasing proportions of active ingredient, but the highest proportion has far better flow properties than the drug itself. Consequently, lower proportions of the cohesive drug in combination with the other excipients improved the flow properties of the filler as the FF curves of batches 3 and 4 were less steep. Filler and excipients, batch 2, did not form a coherent plug at

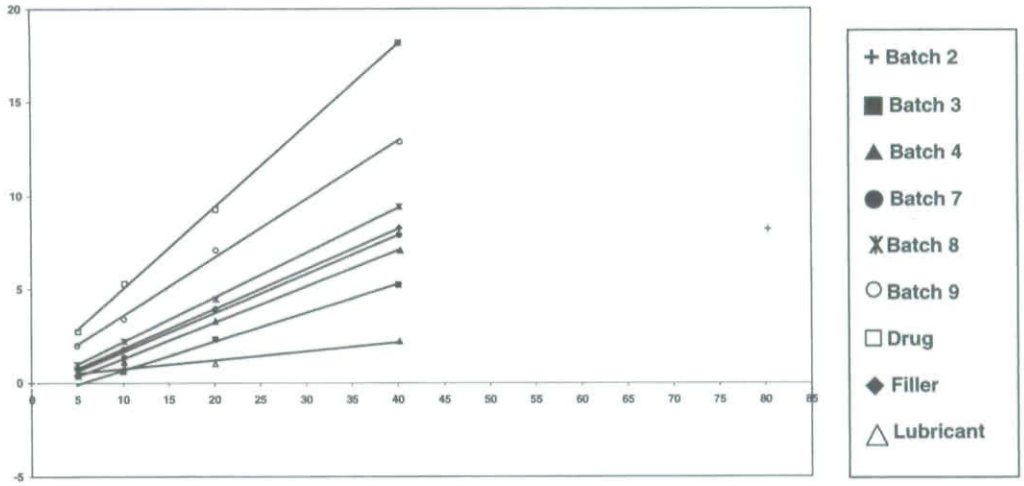

Figure 4. Uniaxial failure functions of mixtures with increasing contents of drug (see Table 2), and of drug, filler, and lubricant: *x*-axis, consolidation stress, kPa; *y*-axis, compressive strength, kPa.

40 kPa, but at 80 kPa, indicating the importance of the other excipients.

Attempts to correlate in a univariate way the flow property parameters of the powder mixture with particle size data or flow property data of included drug and filler batches failed. Due to the complexity of the processes involving particulate systems, there are no reliable quantitative relationships between primary particle properties such as particle size and distribution, shape, etc., and secondary properties such as failure properties (i.e., flow properties) or bulk density (14).

Tableting performance—based on tablet weight variation and tablet machine speed during commercial tablet production—was attempted to correlate with uniaxial tester parameters of the powder mixture. Good performance was obtained when the strength of the bed consolidated at 40 kPa was less than 3.3 kPa.

Multivariate Data Analysis

As the attempts to correlate univariately the flow property parameters of the powder mixtures with particle size data and flow property data of included drug and filler batches failed, a multivariate approach was applied.

The multivariate approach was applied separately on the drug matrix and filler matrix. Then the multivariate approach was applied on the powder mixtures with both flow property data and tableting performance data.

PCA of the filler matrix resulted in a good model explaining 62% of the variance by two components. The loading plot (Fig. 5) indicates that the strength of the powder plug consolidated at 40 kPa (bkon) and the slope (bslo) are positively correlated to some particle size variables—e.g., the percentage <125 μm (etth) and <32 μm (tret), and the specific surface from the air permeametric measurement (sfyt)—and air humidity in connection with the unaxial tester measurements (rhp). This means that poor flow indicated by higher strength of powder plug consolidated at 40 kPa and steeper slope are connected with filler of smaller particle size. It is also obvious that the strength of the powder plug consolidated at 40 kPa and the slope are negatively correlated inter alia to bulk densities (bude, tade), BET surface area, and loss on drying. Consequently, poor flow is connected with filler of lower bulk density. The BET surface area also includes cracks in the particles and is less informative regarding flow properties than the "outer" surface from air permeatry. An influence from loss on drying is expected as the failure properties of powders are affected by humidity. It is unexpected that the intercept (bint) is not correlated with the other uniaxial cell variables as they characterize the failure function.

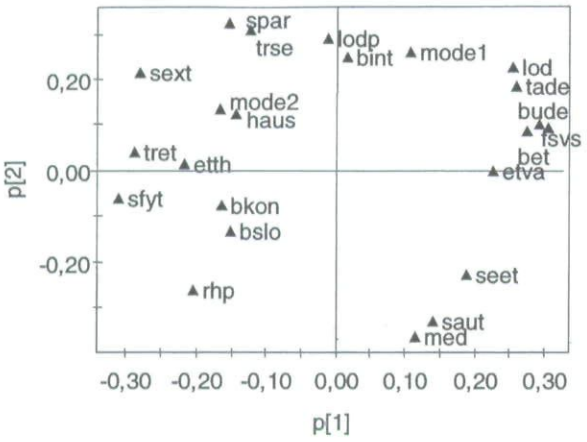

Figure 5. Loading plot of filler data: *x*-axis, principal component No. 1; *y*-axis, principal component No. 2. Variable symbols are explained in Table 4.

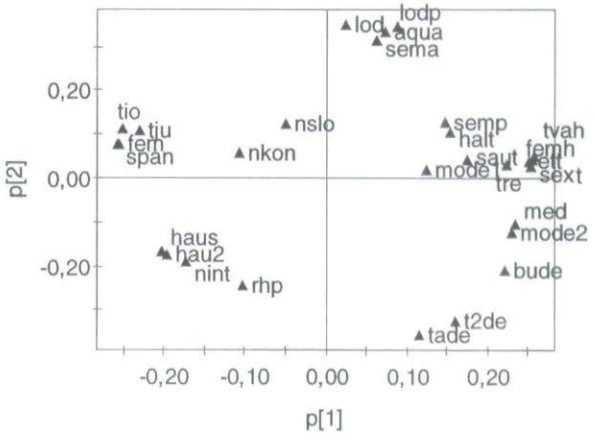

Figure 6. Loading plot of drug data: *x*-axis, principal component No. 1; *y*-axis, principal component No. 2. Variable symbols are explained in Table 3.

A good PCA model of active ingredient data explaining 63% of the variance by two components was established. From the loading plot (Fig. 6) it can be concluded that the strength of the powder plug consolidated at 40 kPa (nkon) and the slope (nslo) are positively correlated to laser diffraction particle size variables—percentages <5.2 μm (fem), <9.5 μm (tio), and <20.9 μm (tju), and specific surface (span). This means that poor flow indicated by higher strength of the powder plug consolidated at 40 kPa and steeper slope is obtained with fine particle size material. In addition, the strength of the powder bed consolidated at 40 kPa and the slope are negatively correlated to bulk densities—aerated bulk density (bude), tapped bulk density (tade, t2de)—in a similar way as the filler. The intercept (nint) is positively correlated to the other two uniaxial cell variables (nkon, nslo) but to a lower extent. This correlation is expected. There are not exactly the same variables in the filler matrix as in the drug matrix. This is the probable reason for the deviating influence of the intercept in Figs 5 and 6.

When the flow properties of the powder mixture were evaluated, an excellent PCA model was obtained, explaining 72% of the variance by two components. The three uniaxial tester variables—strength of the powder bed consolidated at 40 kPa (konso40), the slope, and the intercept (inter)—are positively correlated to the ratio of drug to filler (DRU/FIL) and the relative humidity (rhp) according to the loading plot (Fig. 7). The influence of the uniaxial tester variables on the ratio of drug to filler

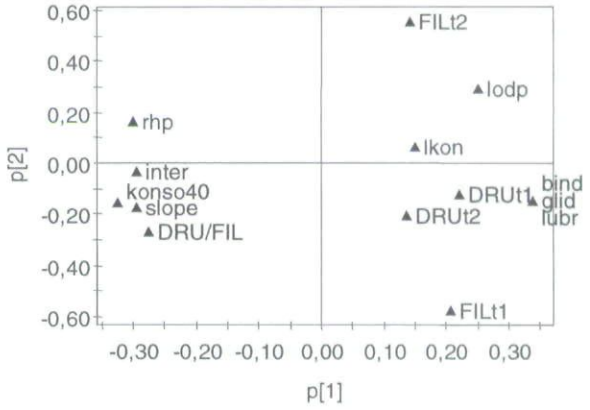

Figure 7. Loading plot of flow property data of the powder mixture: *x*-axis, principal component No. 1; *y*-axis, principal component No. 2. Variable symbols are explained in Table 5.

was also in accordance to the findings in Fig. 4. In addition, the failure properties of powders are affected by humidity. There is a negative correlation between the three uniaxial tester variables (konso40, slope, inter) and the fourth uniaxial tester variable, the lowest applied consolidation stress to give a coherent plug (lkon). The three uniaxial tester variables (konso40, slope, inter) are also negatively correlated to the t2-value of drug (DRUt2), t1-value of drug (DRUt1), binder concentration (bind), glidant concentration (glid), lubricant concentration (lubr), loss on drying (lodp), and to a certain extent to the

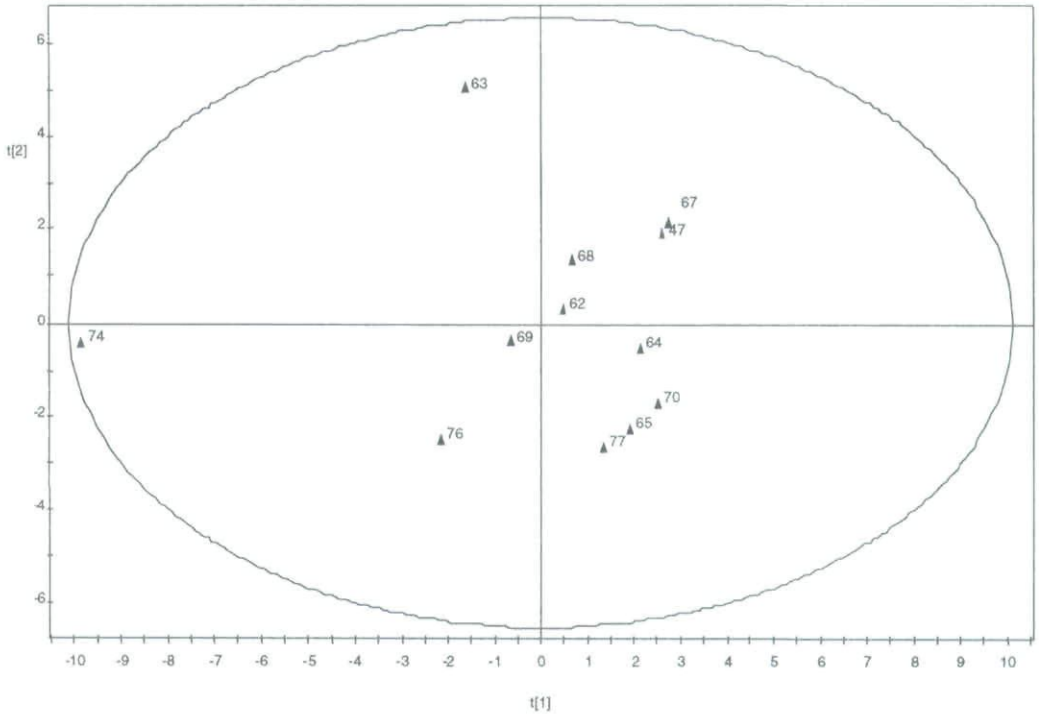

Figure 8. Score plot of drug data: *x*-axis, principal component No. 1; *y*-axis, principal component No. 2. The batch numbers are those given in Table 3.

t2 value of filler (FILt2) and t1-value of filler (FILt1). This means that low values of strength of powder bed consolidated at 40 kPa, slope, and intercept are connected with high values of lowest consolidation stress to give a coherent plug, and higher concentrations of binder, glidant, and lubricant (within the investigated space), i.e., factors facilitating flow. From the loading plot (Fig. 6) and the score plot (Fig. 8) of the drug it can be concluded that high t1-values represent high values of, for example, percentages <250 μm (tvah), <500 μm (femh), <125 μm (etth), and <63 μm (sext), and median diameter (med) and mode of the second distribution (mode2), and also represent low values of percentages <5.3 μm (fem), <9.5 μm (tio), and <20.9 μm (tju) and specific surface (span). In addition, it is obvious that high t2-values represent high values of, for example, loss on drying (lod, lodp) and water content, and also represent low values of, for example, tapped bulk density (tade, t2de). Consequently, coarser drug with higher water content indicates a better flow of the powder mixture. The influence of coarser drug is expected, and an influence of humidity on failure properties of powders is expected, too.

The tableting performance of the powder mixture was calculated on 10 batches. A good PCA model explained 63% of the variance by two significant components. From Fig. 9 it is obvious that the lowest consolidation stress to give a coherent plug (lkon) is negatively correlated to slope and the strength of the powder bed at 40 kPa consolidation stress (konso40), which is in concordance with Fig. 7, and to a certain extent to the intercept (inter). The tableting performance (tabl)—high value means good performance—is positively correlated to lowest consolidation stress to give a coherent plug (lkon). This was expected as good flow properties of the powder mixture is a condition for high tableting performance,—i.e., low tablet weight variation and high speed of the tablet machine—and good flow properties are characterized by high values of the lowest consolidation stress to give a coherent plug. The influence from the relative humidity (rhp) is contrary to Fig. 7 and there is also a negative correlation between the t1-values of drug (DRUt1) and

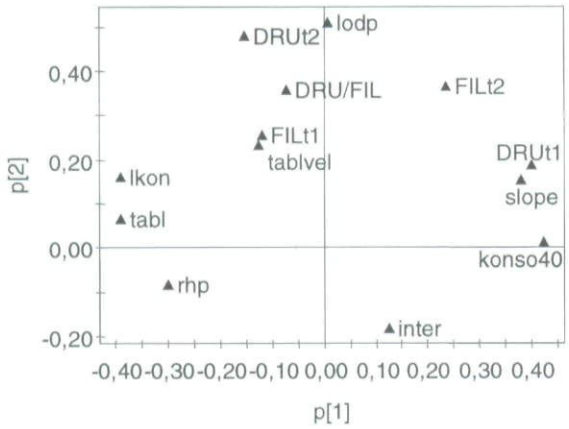

Figure 9. Loading plot of tableting data of the powder mixture: *x*-axis, principal component No. 1; *y*-axis, principal component No. 2; tabl, tableting performance; tablvel, tablet machine speed (tabl/hr). The other variable symbols are explained in Table 5.

the lowest consolidation stress to give a coherent plug (lkon). The main difference in the data set of Fig. 7 compared with Fig. 9 is the exclusion of batches 40–42 of Table 5 with deviating relative humidity values, and concentrations of binder/disintegrant, lubricant, and glidant. The tablet machine speed (tablvel) is only available for six batches, and consequently suffers from some uncertainty. It is to be noted that the ratio DRU/FIL in Fig. 9 varies very little compared with the conditions in Fig. 7.

A PLS model of predicting the tableting performance was significant ($R^2Y = 0.82$ and $Q^2 = 0.62$).

CONCLUSIONS

The failure functions of powder mixtures, drug, and filler were determined from the measurements with the uniaxial tester.

The active ingredient was more cohesive than the filler, which was somewhat more cohesive than the powder mixture. There was a variation between batches of drug, filler, and powder mixture. An overlap between filler and powder mixture occurred. The flowability of the powder mixture was improved by the binder, glidant, and lubricant, constituting altogether 3.5 w/w% of the commercial formulation.

The failure function discriminated powder mixtures with poor flowability from mixtures with medium or good flowability.

PCA of powder mixture data indicated positive correlation between the three uniaxial tester variables, i.e., slope, intercept, and strength of powder consolidated at 40 kPa. These three variables were negatively correlated with the fourth flow variable, lowest consolidation stress, to give a coherent plug. The four flow variables were influenced by the relative humidity during the measurement, drug and filler properties, and the concentrations of binder, glidant, and lubricant. Good flow properties of the powder mixture were related to active ingredient of coarser particle size and higher water content, and higher concentrations of binder, glidant, and lubricant.

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REFERENCES

1. Nelson, E. Measurement of the repose angle of a tablet granulation, J. Am. Pharm. Assoc. Sci. Ed. **1955**, *44*, 435–437.
2. Hausner, H.H. Friction conditions in a mass of metal powder, Int. J. Powder Metall. **1967**, *3*, 7–13.
3. Gold, G.; Duvall, R.N.; Palermo, B.T. Powder flow studies I: instrumentation and applications. J Pharm. Sci. **1966**, *55*, 1133–1136.
4. Williams, J.C.; Birks, A.H. The preparation of powder specimens for shear cell testing. Rheol. Acta. **1965**, *4*, 170–180.
5. Kaye, B.H.; Gratton-Liitmatainen, J.; Faddis, N. Studying the avalanching behavior of a powder in a rotating disc. Part. Syst. Charact. **1995**, *12*, 232–236.
6. Podczeck, F. Rheological studies of physical properties of powder used in capsule filling. Pharm. Technol. Eur. **1999**, *11*(9), 16–24 and **1999**, *11*(10), 34–42.
7. Maltby, L.P. Investigation of the behaviour of powders under and after consolidation, Dr. Ing. Thesis NTH/TMIH, Porsgrunn (1993).
8. Enstad, G. News on the development of the uniaxial tester. Postec Newsletter **1998**, No. 16, 17–18.
9. *European Pharmacopoeia*, 2. 9. 15. Apparent volume, 3rd edn, Council of Europe, Strasbourg, France, 1997; 141–142.

10. Amidon, G.E. Report and recommendation of the USP advisory panel on physical test methods—functionality. I. General chapter on particle characterization by optical microscopy. Pharmacopeial Forum. **1992**, *18*, 4089–4091.
11. Gabrielsson, J.; Nyström, Å.; Lundstedt, T. Multivariate methods in developing an evolutionary strategy for tablet formulation. Drug. Dev. Ind. Pharm. **2000**, *26*, 275–296.
12. Wold, S. Pattern recognition by means of disjoint principal components model. Pattern Recognition **1976**, *8*, 127–139.
13. Carlson, R.; Hansson, L.; Lundstedt, T. Optimization in organic synthesis. Strategies when the desired reaction is accompanied by parasitic side reactions. Acta Chem. Scand. **1986**, *B40*, 442–452.
14. Svarovsky, L. Powder Testing Guide: Methods of Measuring Physical Properties of Bulk Powders. Elsevier: London, 1987; 11.