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Evaluation of the properties of microcrystalline and microfine cellulose powders

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Summary

A comparison of a range of microcrystalline (MCC) and microfine (MFC) celluloses from different manufacturers has been undertaken. Tests included those associated with the powder (e.g., bulk properties, particle density, particle size range, sliding friction and swelling), those associated with tablet formation (e.g., Heckel, Kawakita and force-displacement curve evaluation) and those associated with the formed tablets (e.g., mechanical strength and disintegration). Measures of bulk properties differentiated between the MCC and MFC products. Similar grades within these types were not always equivalent and divergences were not associated with particle size range. All the products possessed similar values for sliding friction. The MCC products generally had lower values for the mean yield pressure than the MFC products, although one MCC (Heweten®10) had an atypical higher value than other MCCs. The approach of Kawakita and Lüdde (1970/71) (*Powder Technol.*, 4 (1970/1971) 61–68) however, appeared insensitive to differences in the compressibility of the products. Treatment of the force-displacement curves by multivariate analysis of variance suggested that all the products were distinctly different. The same statistical approach applied to the relationship between mechanical strength and tabletting pressure, however, suggested that the products could be divided into three groups. The first group contained all the MCC products except one (Heweten®12). The second group contained one MCC product (Heweten®12) plus three MFC products, and the third group consisted of the remaining MFC products. The tablets produced at a constant force disintegrated in different times. These differences were not associated with the swelling properties of the cellulose products. Short disintegration times were often associated with tablets with poor mechanical properties. The results clearly indicate that care must be taken in changing from one cellulose product to another in an optimized tablet formulation.

Introduction

Cellulose powders are one of the most important types of excipients used in tabletting, especially for direct compression. There are different grades of cellulose. The microcrystalline celluloses being distinguishable from the microfine grades. Products of the microcrystalline type are produced from native cellulose by acid hydrolysis. The hydrolysis product can be transformed into products suitable for pharmaceutical use by milling followed by spray drying. These products are characterized by high crystallinity of about

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60–80% (Hüttenrauch and Keiner, 1976; Doelker et al., 1987a; Padmadisastra and Gonda, 1989). The manufacturing process used by Heweten® – a microcrystalline cellulose powder of the former East Germany – was produced by a different process (Magister et al., 1980). To reduce the costs the hydrolysis products were only milled and screened. The degree of crystallinity for such products was about 30–50% (Voigt and Bornschein, 1987). In general, acid hydrolysis mainly destroys the amorphous areas of the cellulose. The result is a cellulose product of higher crystallinity and lower molecularity than the microfine cellulose product (Blaschek, 1990). Microfine celluloses represent excipients which are produced by milling of purified cellulose. Disaggregated microfine celluloses are manufactured by clearing of sediment. Microfine celluloses have a degree of crystallinity of about 15–45% (Doelker et al., 1987a; Voigt and Bornschein, 1987; Blaschek, 1990). The degree of crystallinity influences various properties including the compactibility and the adsorption of water. These could influence the flowability and the drug stability. In the region of amorphous cellulose, a fraction of adsorbed water can be bound strongly, e.g., by hydrogen bonding to hydroxyl groups in each repeating sugar unit in the cellulose. It is suggested, that approx. 3% water is strongly bound water (Ahlneck and Alderborn, 1988). The

TABLE 1

Sources of cellulose products and their classification

Type	Cellulose product	Manufacturer	Classification
MCC	Avicel® PH 101	FMC Corp., American Viscose Division, Markus Hood, U.S.A.	Standard (1)
	Serva 0.038	Serva Feinbiochemica, Heidelberg, Germany	similar to (1)
	Sanaq® 101 L	Pharma Trans Sanaq AG, Switzerland	similar to (1)
	Heweten® 10	Zellstoff- und Papierfabrik Weißenborn, Germany [a]	similar to (1)
	Heweten® 12	Zellstoff- und Papierfabrik Weißenborn, Germany [a]	('Avicel PH 102')
	Serva 0.019	Serva Feinbiochemica, Heidelberg, Germany	('Avicel PH 105')
MFC	Elcema® P 050	Degussa AG, Frankfurt/M., Germany	
	Elcema® P 100	Degussa AG, Frankfurt/M., Germany	
	Elcema® F 150	Degussa AG, Frankfurt/M., Germany	standard (2)
	Vitacel® F 120	Rettenmaier & Sons, Ellwangen-Holzmühle, Germany	similar to (2)
	Elcema® G 250	Degussa AG, Frankfurt/M., Germany	standard (3)
	Vitacel® A 300	Rettenmaier & Sons, Ellwangen-Holzmühle, Germany	similar to (3)
	Vitacel® M 80	Rettenmaier & Sons, Ellwangen-Holzmühle, Germany	

MCC, microcrystalline cellulose; MFC, microfine cellulose.

[a] Now produced by Rettenmaier & Sons, Ellwangen-Holzmühle, Germany.

remaining water is present in both the amorphous region and at the surface of the particles and is less tightly bound. Microcrystalline celluloses are mesoporous substances (pore size 1.6–100 nm) (Stanley-Wood et al., 1990).

A series of microcrystalline and microfine products have been studied. The celluloses are compared in their powder and compaction properties such as friction, swelling and compactibility. Table 1 defines the sources of the cellulose products and summarizes, which samples are supposed to be similar in their behaviour and which products should be clearly different. The aim of the work was to test whether pharmaceutical characterization methods are able to reflect the material differences, and to detect similarities in the pharmaceutical properties of the cellulose products applying multivariate mathematical methods.

Materials and Methods

Materials

Details are provided in Table 1.

Sliding friction

400 mg of the substance were compressed by an eccentric tablet press (Mühlenbau Wittenberg, Germany) until a handleable compact was formed. The surfaces of the compact must still clearly show the particle structure. The test system consisted of a variable sloping plane of polished stainless steel. The compact was positioned on the top of the sloping plane. The angle of inclination was increased until the compact just began to slide. The sliding friction coefficient was calculated using the height and the horizontal distance between top and bottom of the sloping plane.

Tabletting

20 single weighed samples (300.0 mg) were stored for 7 days in a desiccator at a relative humidity of 58% and room temperature (18–22°C). The desiccator was filled with 29.86% sodium hydroxide solution. The relative humidity was measured with a hair hygrometer. The tablets were pressed from these samples with an eccentric tablet press (KA, Spremberger Maschinenbau and Gießereien, Spremberg, Germany), instrumented with a piezoelectric measuring cell (PK 1000-1, Meßgerätewerk Zwönitz, Germany). The displacement of the upper punch was registered with a displacement arm, which uses a strain gauge (HLW Wegaufnehmer WWH 501, RFT Meßelektronik Dresden, Germany). Tablets were produced at a speed of 1 min^{-1}. Flat face punches of 11 mm diameter were used, and the force-displacement curves were registrated using an *x-y* recorder (endim 620-02, Meßapparatewerk Schlotheim, Germany). The tabletting force was varied between 0.2 and 10.5 kN. The die was thoroughly cleaned after each measurement.

Tablet height

The tablet height (± 0.001 mm) was measured using a micrometer calliper (Feinmeßzeugfabrik Suhl, Germany).

Diametral crushing strength

The diametral crushing strength was tested using an Erweka crushing strength tester (TBH-28, Erweka Apparatebau GmbH, Heusenstamm, Germany).

Disintegration time

The disintegration time was determined for 10 single tablets using the Erweka disintegration tester (Erweka Apparatebau GmbH, Heusenstamm, Germany) in distilled water of 37 ± 1°C.

True density

The substances were dried over 6 h at a temperature of 110°C. The determination was made by the liquid displacement method in glass pycnometers (100 ml) using 1 g substance and saturated solutions of the celluloses in *n*-heptane at a temperature of 20°C. The densities of the saturated solutions were measured with the Mohr-Westphal balance (Wissenschaftlicher Apparatebau Johannes Hammer, Leipzig, Germany). The observations were made in triplicate.

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 ± 0.1 ml of substance were filled into the measuring cylinder, the volume was read and the mass determined by weighing. The cylinder was closed and then tapped manually until the volume did not change. The volume was read again. The densities were calculated from the bulk and tapped volume and the powder mass.

Particle size range

10 mg substance were suspended in 1–2 drops of paraffin oil, the suspension was distributed on a slide and the Feret's diameter was observed under a microscope (Amplival, Carl Zeiss Jena, Germany). 10 fields were examined and at least three samples were used to identify the minimum and the maximum diameter.

Swelling volume

Graduated test tubes of 20 ml (degree of graduation: 0.1 ml) were used. 500 ± 0.001 mg substance were added to 10.0 ml distilled water, suspended and fixed in a test tube rack. The powder volume was determined after 60 min and then at 1 h intervals until the volume was constant. The experiments were carried out in triplicate.

Calculation

Results were analysed by ANOVA/MANOVA: Program MVD, Institute of Mathematics of the Academy of Science, Berlin, (ESER 1040, Martin-Luther-University Halle-Wittenberg).

Analysis of the values was according to Heckel (1961) and Kawakita and Lüdde (1970/1971); for force-displacement curves by simple regression analysis; BASIC programs were used (KC 85/3, written by scientists and students of the Institute of Pharmaceutical Technology, Martin-Luther-University Halle-Wittenberg).

Results and Discussion

The characteristics of the cellulose powders such as particle size range, bulk and true density, Hausner's ratio and the sliding friction are listed in Table 2.

The bulk volume of a powder determines the filling accuracy of the die together with other factors, e.g., flowability, cohesion, adhesion or internal friction. The value for the bulk volume should be as high as possible, provided that the upper limit given by the volume of the die is not exceeded. A suitable bulk volume was found to be 2.0–4.0 $cm^3\ g^{-1}$ (Podczeck and Wenzel, 1990) for the tablet press used in the experiments. All the microcrystalline celluloses show bulk volumes within the given limits, whereas all microfine samples, except the granulated products Elce-

TABLE 2

Powder characteristics of microcrystalline and microfine celluloses

Cellulose product	V_b (ml g^{-1})	H	ρ_w (g cm^{-3})	PSI (μm)	μ_s
Avicel® PH101	3.04	1.32	1.54	1–120	0.28
Serva® 0.038 (PH101)	3.67	1.43	1.53	1–120	0.33
Serva® 0.019 (PH105)	3.58	1.61	1.52	1–100	0.35
Sanaq® 101L	3.75	1.56	1.54	1–130	0.31
Heweten® 10	3.00	1.45	1.60	1–200	0.32
Heweten® 12	2.46	1.45	1.47	40–100	0.28
Elcema® P050	4.24	1.69	1.48	1– 50	0.37
Elcema® P100	4.35	2.00	1.47	1–100	0.27
Elcema® F150	4.62	1.67	1.50	1–150	0.36
Elcema® G250	2.09	1.16	1.50	90–250	0.34
Vitacel® M80	4.84	1.89	1.51	1–150	0.29
Vitacel® F120	5.08	1.85	1.49	1–120	0.29
Vitacel® A300	2.88	1.85	1.51	80–500	0.34

V_b, bulk volume; H, Hausner's ratio; ρ_w, true density; PSI, particle size range; μ_s, sliding friction coefficient ($\bar{x}$; $n = 3$).

ma®G 250 and Vitacel®A 300, have high bulk volumes well over the upper limit.

Wells (1988) provides rules to make a judgement as to the value of Hausner's ratio which gives an indication of flowability. In the range between 1.25 and 1.50 for Hausner's ratio observed for microcrystalline celluloses, the flowability can be improved by adding a lubricant, whereas for the microfine powders, except the granulated products, it appears to be unhelpful to add a lubricant.

One important factor that influences the flowability is the sliding friction of a substance. Sliding friction occurs in all the flow processes of powders and granules, e.g., in the filled hopper and the dies of a tablet press. The friction resistance between powder particles or between hopper wall and powder particles tends to oppose gravitional downward flow (Chowhan and Yang, 1983). Material-dependent disturbance of the flow process (Leuenberger and Zimmermann, 1976; Staniforth and Rees, 1982) can be attributed among other things to an increased sliding friction between the particles and the hopper wall.

One method of determinating the powder friction is to compress the powder with low force, so that cohesion between the particles occurs, but the surfaces of the compact formed clearly show different particles and therefore they approximate to the surface properties of these particles. These compacts can be tested on a sloping plane for their slide properties (Ertel and Carstensen, 1988). Using this technique differences were not detected between any of the materials.

The particle size range proved to be the more important characteristics of the size than a mean particle size value, associated with tablet formation (Podczeck, 1992), and hence is presented here. The values reflect the philosophy of the production. The granulated products Elcema®G 250 and Vitacel®A 300 do not have any fine particles. Heweten®12 is a sieve fraction of Heweten®10. To improve the flowability, the fine particles are removed and the size range is decreased.

The true densities of microcrystalline cellulose products are slightly greater than those of microfine products. Hüttenrauch and Keiner (1988) explained the differences in density in terms of the degree of crystallinity.

Regarding similar cellulose products, it must be concluded that the bulk properties such as bulk volume and Hausner's ratio show differences between batches of different manufacturers. Therefore, in an optimized powder formulation, one cellulose product cannot easily be re-

TABLE 3

Compressibility and compactibility of cellulose powders

Cellulose product	Higuchi plot		Heckel plot		Kawakita	
	m	*n*	K_p (MPa)	*A*	*a* (%)	*b*
Avicel®PH101	82.4	2.1	68.1	0.624	60.5	0.020
Serva® 0.038	66.7	24.4	74.8	0.790	53.4	0.019
Serva® 0.019	44.8	32.2	53.4	0.745	62.0	0.040
Sanaq®101L	75.6	0.6	74.2	0.738	67.3	0.019
Heweten®10	61.2	5.8	93.3	0.825	63.9	0.018
Heweten®12	79.2	−48.4	58.5	0.728	59.0	0.017
Elcema®P050	31.7	−19.1	125.3	1.220	67.4	0.021
Elcema®P100	36.1	−20.5	86.5	0.800	68.7	0.021
Elcema®F150	53.9	−19.2	88.6	0.824	66.9	0.018
Elcema®G250	14.2	−9.9	122.1	1.025	51.8	0.018
Vitacel®M80	55.5	−16.8	90.4	0.830	62.5	0.017
Vitacel®F120	59.2	−18.2	92.7	0.869	73.6	0.020
Vitacel®A300	19.8	−12.1	119.6	0.996	61.1	0.019

m, slope of the Higuchi plot; *n*, intercept of the Higuchi plot; K_p, mean yield pressure (Heckel); *A*, constant (Heckel); *a*, *b*, constants of the Kawakita expression.

placed by a product from another source. A reoptimization procedure could be necessary.

Table 3 summarizes the results obtained using model equations describing the compressibility and compactibility of the celluloses. Numerous papers on the compression of powders discuss their compressibility, i.e., the ability of a powder to decrease in volume under compression stress. One model describes the proportionality between the reduction in density with pressure and pore fraction (Heckel, 1961):

$$\frac{dD}{dP} = k \cdot (1 - D) \quad (1)$$

where D is the relative density and P the tabletting pressure.

In general, the integrated equation is used:

$$\ln\left(\frac{1}{1-D}\right) = k \cdot P + \ln\left(\frac{1}{1-D_0}\right) \quad (2)$$

where D_0 is the relative density of the loose powder.

In this linear equation the log term on the right-hand side in parentheses is normally replaced by the constant A:

$$A = \ln\left(\frac{1}{1-D_0}\right) \quad (3)$$

The reciprocal value of the slope of Eqn 2 ($K_p = 1/k$) represents the mean yield pressure by which a substance resists the deformation process. The value A describes the movement of the power particles at the beginning of the compression. The constant is a measure of densification due to the particles slipping over each other in a rearrangement, which mainly depends on size and shape, but also on hardness of the particles. This constant is considered to be a doubtful value, and it strongly depends on the range of pressure of the investigation (Watt, 1988). A series of extrinsic factors influences the shape and slope of the plot. Therefore, uniequivocal statements are possible only by ensuring reproduceble experimental conditions (Humbert-Dróz et al., 1982). The role of intrinsic factors has also been discussed (Alderborn et al., 1988). For related compounds, the relative mass of the molecules also seems to influence the results (Al-Angari et al., 1985). Paronen and Juslin (1983) differentiate between the 'tablet-in-die' and the 'ejected-tablet' method. The mean yield pressure K_p, calculated from the ejected-tablet method, reflects the proportion between plastic flow and fragmentation, and is the method of choice, if the influence of different factors at the predominant deformation mechanisms of a material are to be studied. Mean yield pressures below 80 MPa will be regarded as an indication of mainly plastic flow (York, 1992). The higher the mean yield pressure, the more brittle is a material (Humbert-Dróz et al., 1983).

The microcrystalline celluloses are deformed by mainly plastic flow, since the mean yield pressures are lower than 80 MPa. However, Heweten®10 appears to be more brittle because of its mean yield pressure of 93 MPa. A reason for this could be that the product consists of large, unwieldy particles, which have a fibre structure (Magister and George, 1980). Mashadi and Newton (1987) also reported that Avicel®PH 101, which should be similar to Heweten®10, was able to behave like a brittle material under special conditions. All microfine products are also deformed by fragmentation. Especially the very fine particles of Elcema®P 050 and the granulated products Elcema®G 250 and Vitacel®A 300 have high mean yield pressure values. Roberts and Rowe (1987) found that for brittle materials there is an increase in K_p with increase in particle size. This is in accordance with the values of the granulated products described in this article, but is contradictory to the values of Elcema®P 050.

The particle size distribution influences the value of the Heckel constant A. This effect is clearly shown for the granulated products and for the extremely fine Elcema®P 050. The microcrystalline products except Heweten®10 demonstrate lower values of A than the microfine celluloses. For microcrystalline celluloses, therefore, the reorientation seems to play a less important role in the densification process than for microfine celluloses.

A further model equation of the compression process is described by Kawakita and Lüdde (1970/1971):

$$\frac{V_0 - V}{V_0} = \frac{a \cdot b \cdot c}{1 + b \cdot P} \quad (4)$$

where V_0 is the initial powder volume, V denotes the powder volume under applied pressure and P is the compaction pressure.

The constant a $[(V_0 - V_\infty)/V_0]$ describes the maximal possible relative decrease of the initial bulk volume to the true volume of the powder compact using pressure. The constant b $[(V_0 - V)/(P \cdot V_0 - P \cdot V_\infty)]$ is a characteristic of a substance and its reciprocal value is a measure of the resistance which a substance has against the deformation (Lüdde and Kawakita, 1966). A partial relation exists between the constants a and b and the mechanical properties of the tablets made from pure substances (Podczeck and Wenzel, 1989).

Analysis based on the model of Kawakita and Lüdde (1970/1971) does not show very great differences in the compressibility of the cellulose products. This approach seems to be insensitive to differences in particle size or shape of substances.

Much more important for an industrial production of tablets is the obtaining of tablets of adequate strength than adequate deformation and volume reduction mechanisms (Leuenberger and Rohera, 1986). There are numerous equations which describe the dependence of the tablet strength on the tablet pressure used. None has a theoretical basis. The Higuchi equation is one such equation:

$$\sigma_T = m \cdot \ln P + n \quad (5)$$

where σ_T is tablet strength and P compaction pressure.

Here, the dependence of the strength on the compaction pressure is considered to be exponential. The constant m is a measure of the increase in strength depending on the pressure used. The greater the value of m, the more sensitively does the powder react to fluctuations in consolidation pressure.

Fig. 1 shows some of the Higuchi plots for the substances. The celluloses can be subdivided into three groups. In a multivariate analysis of variance (MANOVA), the curves can be differentiated in slope and intercept using every single point of curve. The three groups suggested were shown to be significantly different ($F = 61.93$;

TABLE 4

Force-displacement curves of cellulose products (part 1)

Cellulose product	E_{max} (J)	E_2 (J)	E_3 (J)	Vb (N J^{-1})
Avicel® PH101	16.64 ± 0.63	5.40 ± 0.16	0.94 ± 0.09	10.14 ± 0.33
Serva® 0.038	19.07 ± 0.77	6.32 ± 0.67	0.67 ± 0.08	8.26 ± 0.31
Serva® 0.019	16.40 ± 0.27	5.91 ± 0.25	0.63 ± 0.06	5.85 ± 0.52
Sanaq® 101L	17.20 ± 0.76	5.46 ± 0.13	0.64 ± 0.05	11.07 ± 1.00
Heweten® 10	12.12 ± 0.35	4.57 ± 0.12	0.54 ± 0.15	10.70 ± 0.74
Heweten® 12	10.23 ± 0.16	3.66 ± 0.09	1.29 ± 0.08	9.39 ± 2.34
Elcema® P050	12.19 ± 0.96	3.56 ± 0.04	1.29 ± 0.05	4.66 ± 0.42
Elcema® P100	13.31 ± 0.74	3.58 ± 0.08	1.30 ± 0.07	5.48 ± 0.66
Elcema® F150	15.23 ± 0.61	4.00 ± 0.09	1.12 ± 0.06	8.34 ± 0.52
Elcema® G250	10.04 ± 0.18	2.95 ± 0.05	1.24 ± 0.07	2.50 ± 0.10
Vitacel® M80	15.05 ± 0.41	4.02 ± 0.08	1.23 ± 0.06	8.54 ± 0.82
Vitacel® F120	15.75 ± 0.77	4.24 ± 0.13	1.13 ± 0.07	8.14 ± 1.50
Vitacel® A300	10.69 ± 0.94	3.19 ± 0.34	1.15 ± 0.05	3.57 ± 0.38

E_{max}, ΔE_0-UT-M (model constant); E_2, formation energy of the compact; E_3, elastic recovery energy; Vb, compressibility ($\bar{x} \pm s$; $n = 5$).

$f_1 = 2$; $f_2 = 9$; $p = 2 \times 10^{-12}$). The first group includes all microcrystalline products except Heweten®12. The second group consists of Heweten®12, Vitacel®F 120, Vitacel®M 80 and Elcema®F 150, while the third includes the fine powders and the granules. If the cellulose product has to be changed in a tablet formulation, in terms of tablet strength it should be by an exchange with a cellulose powder of the same group.

In Tables 4 and 5 the values obtained by recording force-displacement curves (F-D curves) are listed. The use of F-D curves (compression force vs punch displacement profile) allows the calculation of the work involved during tablet compaction. The methods of obtaining F-D curves, the definition of the areas under the curves plotted and the interpretation of the energies calculated vary in the literature (Çelik, 1992). The recording method used in this work is in accordance with Stamm and Mathis (1976). The interpretation of the areas under the curves is based on theoretical considerations described by Wenzel and Kala (1984). The formation energy of the compact (E_2) includes the energy consumed by plastic flow and/or fragmentation of the particles, and a large part of the energy that is lost by processes such as friction. The elastic recovery energy (E_3) is a measure of the work which a tablet does by expansion, when the upper punch has passed the lowest point and its direction of movement is changed. The value of E_3 depends on the rate of the elastic deformation processes and the whole deformation of the particles. E_3 is not an absolute value, since its magnitude is greatly influenced by the tablet speed. In general, the energies E_2 and E_3 are not considered separately from each other, and often the following numbers are used:

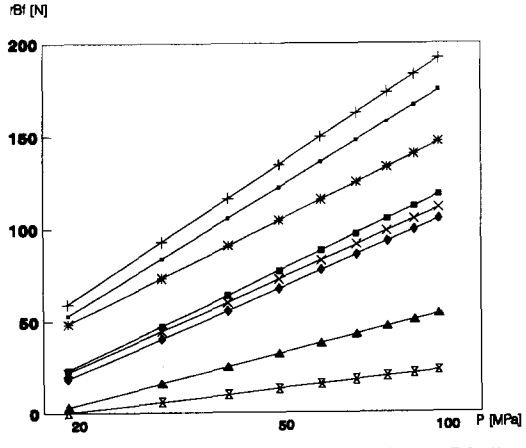

Fig. 1. Higuchi plots of chosen cellulose products: rBf, diametral crushing strength; P, tabletting force. (+) Avicel PH101; (●) Sanaq L101; (*) Heweten 10; (■) Vitacel F120; (x) Vitacel M80; (♦) Elcema F150; (▲) Elcema P050; (⧖) Elcema G250.

TABLE 5

Force-displacement curves of cellulose products (part 2)

Cellulose product	E_2 (%)	E_3 (%)	PL (%)
Avicel®PH101	32.4±0.9	5.7±0.6	85.1±1.4
Serva® 0.038	33.2±3.4	3.5±0.3	90.3±1.2
Serva® 0.019	36.0±1.2	3.8±0.4	90.4±1.2
Sanaq®101L	31.8±0.6	3.7±0.3	89.5±0.7
Heweten®10	37.7±1.2	4.5±1.2	89.1±2.6
Heweten®12	35.8±1.0	12.6±0.7	73.9±1.5
Elcema®P050	29.3±2.6	10.6±0.7	73.3±0.9
Elcema®P100	26.9±1.2	9.8±0.9	73.4±1.5
Elcema®F150	26.3±0.6	7.3±0.4	78.2±1.0
Elcema®G250	29.4±0.8	12.4±0.5	70.4±1.3
Vitacel®M80	26.7±0.9	8.2±0.2	76.6±0.9
Vitacel®F120	26.8±1.6	7.2±0.5	78.9±1.3
Vitacel®A300	29.8±1.0	10.8±0.5	73.4±1.2

PL, plasticity; E_2, formation energy of the compact; E_3, elastic recovery energy ($\bar{x} \pm s$; $n = 5$).

$$\mathrm{Pl} = \frac{E_2(\%)}{E_2(\%) + E_3(\%)} \tag{6}$$

$$\mathrm{Vb} = \frac{\mathrm{rBf}(N) \cdot \mathrm{Ew(g)}}{E_2(\mathrm{J})} \tag{7}$$

where Pl is plasticity, Vb compressibility, rBf diametral crushing strength and Ew sample mass.

The plasticity describes the ratio between reversible and irreversible deformation processes during tabletting (Stamm and Mathis, 1976). The compressibility provides a clue as to which way the energy applied is translated into mechanical strength of the tablet (Wenzel and Kala, 1984). However, the ratio between the energy really used for the deformation and that lost within E_2

is unknown and is certainly a substance-dependent value. Because of this fact and the possibility that different kinds of bonds, which accumulate different amounts of energy, can be formed, the value Vb is also not an absolute criterion for making judgements about tablet strength.

The E_2 values of the microcrystalline cellulose products are well above those of the microfine cellulose samples, however, the elastic recovery energy E_3 is in most cases lower. This could be due to the different degree of crystallinity. The relative value of E_3 of Heweten®12 is similar to the granulated products (Elcema®G 250, Vitacel®A 300). This could be due to the absence of the fine powder particles. Comparing the relative values of E_2 and E_3 as well as the plasticity of the microfine cellulose's, the products, which were suggested to be similar, show similar values. Comparing the microcrystalline celluloses, however, no similarity can be detected. In particular, the Serva product and Heweten®10, which should be similar to Avicel®PH 101, appear to be quite different. Therefore, the results were also tested using the MANOVA by regarding each individual cellulose product. Here, the MANOVA uses the multivariate description of the products by the independent parameters of the F-D curves listed in Tables 4 and 5. One advantage of the MANOVA procedure is that necessary variables can be detected and dispensable variables can be excluded. Finally, only those variables which are necessary to differentiate the cellulose products are included in the test. Variables which mainly include information that is also included in other parameters are regarded as being dispensable. So, the MANOVA procedure excluded the E_{max} values before the final significance test was made. There are significant differences between each of the individual cellulose products ($F = 15.2$; $f_1 = \infty$; $f_2 = 46$; $p = 1 \times 10^{-74}$). The similarities suggested (cf. Table 1) do not appear to exist, and the F-D curve model appears to be very sensitive at detecting different behaviour in the compression process.

Table 6 includes the values of the tablet properties when the tablets were made using a pressure of 100 MPa. In general, the microcrystalline cellulose powders provide compacts, which are stronger than those of microfine celluloses. The greater plasticity of microcrystalline cellulose is thought to result in the formation of strong hydrogen bonds during tabletting (Bangudu and

TABLE 6

Tablet properties and swelling volume of cellulose products

Cellulose product	rBf [a] (N)	Z [a] (s)	h [a] (mm)	QV (ml g^{-1})	RZ (%)
Avicel®PH101	182 ± 3	216 ± 46	2.324 ± 0.006	4.37	43.8
Serva®0.038	172 ± 11	192 ± 54	2.326 ± 0.002	4.67	27.2
Serva®0.019	138 ± 11	2412 ± 117	2.321 ± 0.004	5.14	43.6
Sanaq®101L	200 ± 17	986 ± 79	2.319 ± 0.004	4.93	31.5
Heweten®10	163 ± 9	768 ± 104	2.306 ± 0.002	4.12	37.3
Heweten®12	115 ± 23	196 ± 57	2.334 ± 0.002	3.13	27.2
Elcema®P050	55 ± 5	> 14400	2.406 ± 0.010	5.80	36.8
Elcema®P100	66 ± 6	> 14400	2.432 ± 0.006	6.13	40.9
Elcema®F150	111 ± 8	> 14400	2.455 ± 0.006	6.93	50.0
Elcema®G250	25 ± 1	69 ± 1	2.485 ± 0.004	3.80	81.8
Vitacel®M80	114 ± 11	> 14400	2.451 ± 0.005	6.10	26.0
Vitacel®F120	115 ± 22	> 14400	2.446 ± 0.004	6.43	26.6
Vitacel®A300	37 ± 2	108 ± 19	2.491 ± 0.013	5.80	101.4

rBf, diametral crushing strength; Z, disintegration time; h, tablet thickness; QV, swelling volume; RZ, relative increase on swelling.
[a] Tabletting force 10.0 ± 0.1 kN; sample weight 300.0 mg; $\bar{x} \pm s$; $n = 5$.

Pilpel, 1985). However, comparing the products similar to Avicel®PH 101, only Sanaq®101 L gives tablets which are as strong as those of the original products. The pretreatment of the microfine products Elcema®F 150 and Vitacel®F 120 and M 80 (Nürnberg and Schenk, 1988) also provides strong tablets. Microfine celluloses, which were supposed to be similar (cf. Table 1), give tablets of similar strength. Regarding the disintegration time of microcrystalline cellulose products, no similarity can be discerned. The tablets made from microfine cellulose disintegrate far slower than those made from microcrystalline powders. The short disintegration time of Elcema®G 250 and Vitacel®A 300 tablets is a result of the unsatisfactory tablet strength.

Table 6 also includes the swelling volume of the powder samples in water. The relative value given (RZ) is calculated on the basis of the bulk volume. All microcrystalline and microfine powders swell when placed in water. However, there is no similarity between the products which are purchased as similar to each other (cf. Table 1). There is also no relationship between the swelling and the disintegration time. Pesonen et al. (1988) claimed that Avicel®PH 101 did not swell in water, and that the particle form did not change. This is in contrast to the results presented in Table 6, but could explain the fact that a relationship between swelling and disintegration time is not apparent.

Baehr and Führer (1989, 1990) found that microcrystalline and microfine celluloses are different physicochemically and that samples, purchased as similar to an original product, are even dissimilar in terms of their physicochemical behaviour. These differences also result in different pharmaceutical properties as presented in this article. Doelker et al. (1987b) have also reported that great differences in packing and tabletting properties occur between microcrystalline cellulose products obtained from various manufacturers. They were able to demonstrate that the licenced products were not of the same quality as those obtained from the original product supplied by FMC Corporation. The present work confirms these findings for a further set of microcrystalline cellulose products.

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