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Multivariate analysis approach for correlations between material properties and tablet tensile strength of microcrystalline cellulose

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In this study we applied statistical multivariate analysis techniques to establish correlations between material properties and tablet tensile strength (TS) of microcrystalline cellulose (MCC) with different types and manufacturers. There were sixteen MCC samples included in this analysis described by 22 material parameters. For data analysis, principal component analysis (PCA) was used to model and evaluate the various relationships between the material properties and TS. Furthermore, partial least squares regression (PLS) analysis was performed to quantify the relationships between the material properties and TS and to predict the most influential MCC parameters contributing to the compactibility. The results showed that the moisture content, hygroscopicity and crystallinity did not exhibit significant impact on TS. The turgidity, maximum water uptake, degree of polymerization and molecular weight presented a strong positive influence on TS, while the density property, bulk and tap density, exhibited an obvious negative impact. The present work demonstrated that multivariate data analysis techniques (PCA and PLS) are useful for interpreting complex relations between 22 material properties and the tabletting properties of MCC. Furthermore, the method can be used for material classification.

1. Introduction

A considerable amount of work has been devoted to the effects produced by material properties and the mechanical characterization of powders used in pharmaceutical tablets and capsules. The source of fascination is the diversity of material properties and their high sensitivity to mechanical characterization. For instance, it is reported that the specific surface area is the most influential factor on the breaking strength of tablets, rather than crystallinity, particle size, particle shape of the starting material and the compactibility (Pesonen and Paronen 1986). The moisture content also affects mechanical strength and flowability of the material, leading to lower tensile strength of tablets, with water molecules acting as a plasticizer (>5%). It is important to separately observe the effects of each material parameter on the tablet properties. However, these parameters are usually interrelated in a way that when studying the influence of one parameter, the variations of other related parameters need to be taken into account, including different grades and manufacturers of the material. Taking microcrystalline cellulose (MCC) as an example, the decrease of contact area for bonding is accompanied by an increase of particle size of MCC products, resulting in lower tensile strength of the tablets (Doelker 1993). Suzuki and Nakagami concluded that compactibility parameters of pulverized MCC (Avicel PH 101) decreased when the degree of crystallinity became smaller and the bonding strength and tablet tensile strength peaked in the range of 3.3–5.6% moisture for MCC (Avicel PH 102) (Suzuki and Nakagami 1999; Sun 2008). Since the effect of each material property on tabletting behavior was studied separately and partially, a much more reasonable methodology for better understanding the correlations is desired. Therefore, techniques of multivariate analysis appear to be useful to investigate the correlations among the variables qualitatively and quantitatively.

To approach multivariate problems various projection methods are applied. The so-called principal component analysis (PCA) method offers convenient tools for modeling and over-viewing the correlation structure of a multivariate data set. PCA is used for searching trends, dominating variables, groups and outliers among the data. Another projection method, so-called partial least squares regression (PLS) analysis, is used to look for relationships among two types of variables, i.e. x and y variables, providing information on the importance of each variable on the selected y. The results of analyses are evaluated on the bases of two goodness-of-fit parameters: R2 describes how much of the variation is explained by the model, while Q2 describes the predictive power of the model. For a reasonable model Q2 values larger than 0.5 are expected. Another criterion is that the R2 and the Q2 values should not deviate too much. A detailed description of PCA and PLS algorithms used by the software can be found in the literature (Eriksson et al. 2001). Nowadays, the potentials provided by multivariate data analysis techniques have been most intensively utilized in areas such as pharmacology, meteorology, environmental studies and process automation. However examples related to materials science problems are rare (Ikeda et al. 2008; Imamura et al. 2008).

Cellulose, the most abundant biopolymer, gives strength and stiffness to plant fibres. Microcrystalline cellulose (MCC) are

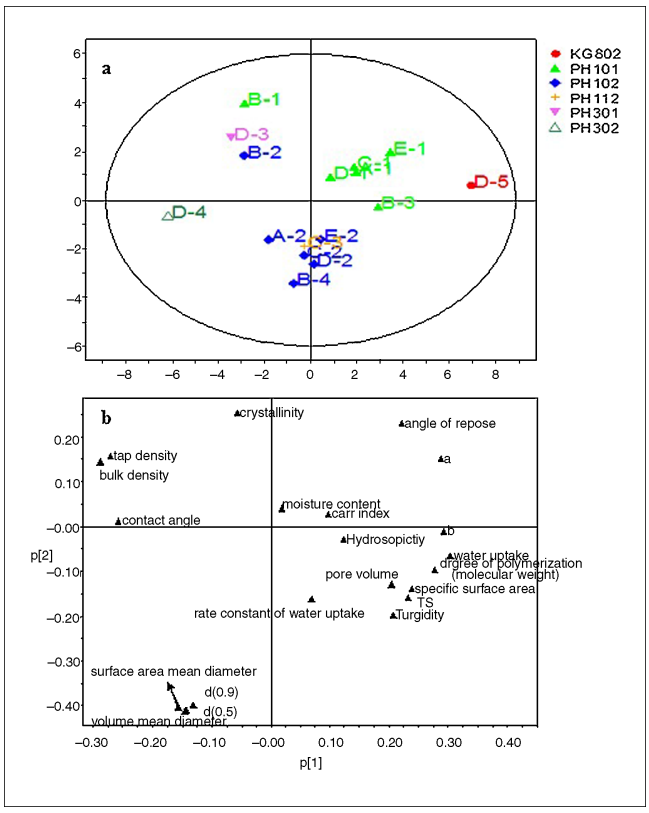

Fig. 1: PCA (a) score plot and (b) loading plot for all the MCC samples

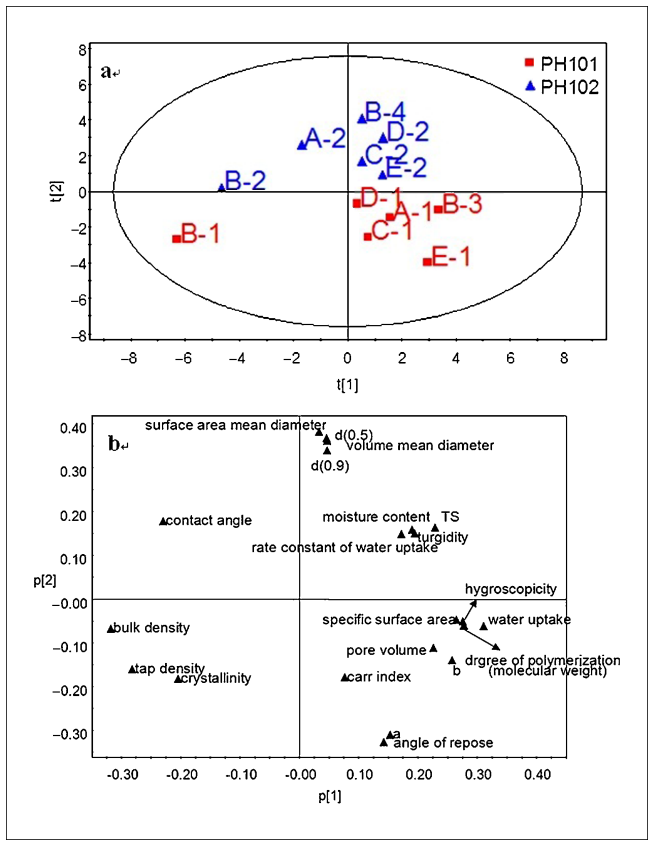

Fig. 2: PCA (a) score plot and (b) loading plot for the PH101 and PH102 MCC samples

particles of hydrolyzed cellulose consisting of a very large mount of cellulose microcrystals together with amorphous areas. Due to their good mechanical performance at relatively low weight and pressure, including flowability, excellent compactibility, great hygroscopicity, and so on, MCC are being increasingly used for direct compression tabletting, especially in the tablets production of Chinese Traditional Medicine (Wu et al. 2001; Zhu et al. 2008).

The different types of MCC exhibit different properties, for example moisture contents and particle sizes, affecting the compactibility and compressibility (Landin et al. 1993; Bhimte and Tayade 2007; Doelker et al. 1995). The aims of this present work are to establish a meaningful and applicable quantitative methodology by using PCA and PLS regressions (Moropoulou et al. 2003; Harju et al. 2002; Haware et al. 2009) to (1) investigate the correlation between material properties of MCC and mechanical properties of tablets, which has been deduced from measurements of TS; (2) obtain physical property classification of materials by examining sixteen MCC samples of different types and manufacturers.

2. Investigations and results

The data of material properties used in the present analysis were determined by methods aforementioned and shown in Tables 1, 2 and 3 for multivariate analysis.

2.1. PCA analysis

Data analysis was started by performing PCA for all of the samples. Since, all of the samples are located inside of the ellipse that defines the boundary of the 95% confidence region of the model, Fig. 1a shows that no outliers are detected in the data set and the samples do not form obvious clusters inside the ellipse. At the same time, overall inspection of the loading plot of Fig. 1b reveals that most of the 22 variables, except the moisture content, crystallinity and hygroscopicity, are important as all of them are located relatively far from the origin of the plot. Especially the turgidity, maximum water uptake, degree of polymerization and molecular weight are situated close to each other and TS. The results indicated the strong positive correlations existing among them. In fact, an increase of DP resulted in a better compactibility and greater water absorption, which agreed with the previous report (Shlieout et al. 2002). Furthermore, the sample density values, including bulk and tap density, are both found at the greatest distance, suggesting that its bulk and tap density are strong negatively correlation with TS.

PCA was also carried out for only PH101 and PH102. As shown in the score plot of Fig. 2a, PH101 and PH102 were separated by the t[2] axis, i.e. PC2. Further interpretation from the loading plot (Fig. 2b) was that particle size was the most influential factor among the PC2. Therefore, PH101 and PH102 could be divided by particle size, which is in accordance with the classification of PH101 and PH102. Angle of repose and 'a' were also found significantly different between PH101 and PH102, which revealed that PH102 has better flowability and lower compressibility than that of PH101.

2.2. PLS regression

To model the relation between material properties and the value of TS, PLS regression was performed by two PCs (R2X = 0.721, R2Y = 0.91 and Q2 = 0.727). In the case of PCA, no outliers were diagnosed as all the observations were found within the ellipse of 95% confidence. The PLS coefficient diagram given in Fig. 3 revealed the distinct impact (positive or negative) of material properties on TS. As indicated from the data of PCA, turgidity, maximum water uptake, DP and molecular weight present strong positive influence on TS, whereas the density properties bulk and

Table 1: Material properties and tablet tensile strength (TS) of MCC (n = 3)

	Type	ρ_{bulk} (g/ml)	ρ_{tap} (g/ml)	CI (%)	DP	M	DC (%)
A-1	PH101	0.319±0.005	0.469 ± 0.008	32 ± 0.01	215.2 ± 0.4	34855 ± 69	56.2
A-2	PH102	0.352 ± 0.01	0.518 ± 0.014	32 ± 0.01	189.5 ± 0.6	30701 ± 105	54
B-1	PH101	0.415 ± 0.01	0.611 ± 0.014	32 ± 0.00	198.2 ± 0.6	32107 ± 104	65.7
B-2	PH102	0.357 ± 0.008	0.525 ± 0.011	32 ± 0.01	202.5 ± 0.1	32803 ± 14	67.4
B-3	PH101	0.319 ± 0.002	0.469 ± 0.002	32 ± 0.00	266.7 ± 0.9	43210 ± 142	50.0
B-4	PH102	0.314 ± 0.001	0.461 ± 0.001	32 ± 0.00	221.7 ± 0.6	35908 ± 101	53.8
C-1	PH101	0.334 ± 0.002	0.491 ± 0.004	32 ± 0.01	224.7 ± 0.6	36402 ± 91	54.9
C-2	PH102	0.336 ± 0.002	0.494 ± 0.003	32 ± 0.01	225.2 ± 0.4	36484 ± 68	48.4
C-3	PH112	0.343 ± 0.006	0.505 ± 0.009	32 ± 0.00	214.8±0.3	34803 ± 48	54.6
D-1	PH101	0.334 ± 0.001	0.491 ± 0.002	32 ± 0.01	227.3 ± 0.2	36824 ± 35	52.4
D-2	PH102	0.323 ± 0.003	0.440 ± 0.008	26.67 ± 1.16	233.0 ± 0.4	37748 ± 57	54.4
D-3	PH301	0.408 ± 0.01	0.557 ± 0.005	26.8 ± 1.06	158.6 ± 0.2	25693 ± 29	51.6
D-4	PH302	0.446 ± 0.007	0.655 ± 0.01	32 ± 0.01	155.1 ± 0.3	25118 ± 42	53.6
D-5	KG802	0.261 ± 0.001	0.383 ± 0.001	32 ± 0.01	257.5 ± 0.9	41713 ± 143	51.6
E-1	PH101	0.303 ± 0.009	0.499 ± 0.02	39.19 ± 1.05	239.2 ± 0.5	38748 ± 75	64.5
E-2	PH102	0.314 ± 0.003	0.505 ± 0.004	37.86 ± 0.23	238.8 ± 0.5	38680 ± 80	56.6

Table 2: Material properties and tablet tensile strength (TS) of MCC (n = 3)

	Type	Surface area mean diameter (μm)	Volume mean diameter (μm)	d50 (μm)	d90 (μm)	Specific surface area (m^2/g)	Pore volume (cm^3/g)	Water uptake (ml/g)	Rate constant of water uptake ($ml \cdot s^{-0.5}$)
A-1	PH101	39.344	78.477	64.108	160.549	1.0538 ± 0.0360	0.0041 ± 0.0001	3.6068 ± 0.0298	0.2326 ± 0.0077
A-2	PH102	74.476	125.946	113.189	228.802	1.1952 ± 0.0194	0.0048 ± 0.0004	2.9528 ± 0.0181	0.2658 ± 0.0155
B-1	PH101	35.276	67.523	55.393	135.657	0.6626 ± 0.0052	0.0037 ± 0.0002	2.6613 ± 0.1432	0.1120 ± 0.0112
B-2	PH102	49.499	90.532	77.274	180.581	0.5971 ± 0.0088	0.0033 ± 0.0000	2.8712 ± 0.0781	0.2294 ± 0.0051
B-3	PH101	47.551	82.517	71.515	157.144	1.0552 ± 0.0031	0.0051 ± 0.0002	3.5231 ± 0.0714	0.2865 ± 0.0215
B-4	PH102	92.587	146.506	138.021	249.838	0.9519 ± 0.0075	0.0043 ± 0.0001	3.2209 ± 0.0497	0.2388 ± 0.0211
C-1	PH101	39.002	71.285	60.061	142.526	1.2649 ± 0.0110	0.0069 ± 0.0002	3.3825 ± 0.2044	0.1878 ± 0.0081
C-2	PH102	70.896	136.03	126.825	252.903	0.9800 ± 0.0077	0.0059 ± 0.0002	3.3977 ± 0.1374	0.2112 ± 0.0104
C-3	PH112	63.632	129.572	119.55	246.155	1.0374 ± 0.0128	0.0061 ± 0.0001	3.3581 ± 0.3060	0.3914 ± 0.0208
D-1	PH101	44.207	70.33	62.212	130.047	0.9997 ± 0.0129	0.0049 ± 0.0001	3.1094 ± 0.0709	0.3293 ± 0.0234
D-2	PH102	73.696	132.143	122.035	240.551	1.1603 ± 0.0050	0.0052 ± 0.0001	3.2630 ± 0.1784	0.2377 ± 0.0112
D-3	PH301	45.149	73.77	66.2	134.826	0.5888 ± 0.0058	0.0027 ± 0.0000	2.7680 ± 0.1605	0.3056 ± 0.0149
D-4	PH302	78.075	139.716	130.596	248.712	0.6399 ± 0.0028	0.0040 ± 0.0001	2.3916 ± 0.2492	0.2596 ± 0.0172
D-5	KG802	30.085	58.208	47.95	115.714	1.2232 ± 0.0992	0.0057 ± 0.0002	4.2952 ± 0.2821	0.3427 ± 0.0120
E-1	PH101	35.413	74.528	58.726	154.137	1.4813 ± 0.0803	0.0070 ± 0.0004	3.4924 ± 0.0130	0.2014 ± 0.0099
E-2	PH102	64.007	131.678	117.661	255.996	1.3395 ± 0.1097	0.0057 ± 0.0003	3.1147 ± 0.1939	0.2906 ± 0.0170

Table 3: Material properties and tablet tensile strength (TS) of MCC (n = 3)

	Type	Hygroscopicity (%)	Moisture content (%)	Angle of repose (°)	Turgidity (ml/g)	CA (°)	a	b	TS (MPa)
A-1	PH101	7.35 ± 0.13	4.45 ± 0.07	41.95 ± 1.55	3.88 ± 0.2	72.5 ± 1.1	0.8736	0.26	1.1475 ± 0.034
A-2	PH102	6.33 ± 0.37	4.72 ± 0.16	32.3 ± 1.21	3.56 ± 0.08	72.4 ± 0.8	0.8446	0.1753	0.8851 ± 0.05
B-1	PH101	5.58 ± 0.05	3.33 ± 0.17	38.6 ± 1.85	3.04 ± 0.06	78.0 ± 0.9	0.8567	0.1874	0.7046 ± 0.0337
B-2	PH102	5.25 ± 0.05	4.05 ± 0.27	33.63 ± 1.09	3.1 ± 0.03	82.1 ± 0.4	0.8518	0.1821	0.8092 ± 0.0362
B-3	PH101	6.94 ± 0.13	4.15 ± 0.18	38.6 ± 1.85	3.78 ± 0.13	70.9 ± 2.0	0.8669	0.3169	1.2697 ± 0.0533
B-4	PH102	5.69 ± 0.05	4.58 ± 0.07	32.23 ± 2.31	3.79 ± 0.11	76.8 ± 2.2	0.8489	0.2503	1.4783 ± 0.059
C-1	PH101	6.13 ± 0.49	3.80 ± 0.10	40.9 ± 0.87	3.38 ± 0.07	70.5 ± 2.3	0.8684	0.2613	1.0849 ± 0.0802
C-2	PH102	6.55 ± 0.23	4.10 ± 0.09	35.5 ± 1.04	3.35 ± 0.15	72.2 ± 2.4	0.8524	0.2626	0.9451 ± 0.0205
C-3	PH112	6.72 ± 0.47	1.93 ± 0.07	36.7 ± 0	3.34 ± 0.15	68.2 ± 2.4	0.8524	0.2328	0.7409 ± 0.0198
D-1	PH101	6.4 ± 0.25	4.76 ± 0.14	35.5 ± 1.04	3.42 ± 0.13	72.9 ± 1.2	0.8705	0.1857	1.1745 ± 0.0671
D-2	PH102	7.3 ± 0.42	4.32 ± 0.15	35.63 ± 1.1	3.54 ± 0.05	78.4 ± 1.4	0.8484	0.2236	1.513 ± 0.0362
D-3	PH301	7.5 ± 0.12	5.47 ± 0.23	37.5 ± 1.04	2.92 ± 0.08	77.4 ± 0.3	0.8488	0.1344	0.7402 ± 0.0348
D-4	PH302	7.1 ± 0.16	4.38 ± 0.25	33.63 ± 1.1	3.2 ± 0.05	82.4 ± 0.6	0.8288	0.1081	0.5397 ± 0.0124
D-5	KG802	7.72 ± 0.06	4.74 ± 0.17	41.95 ± 1.55	3.85 ± 0.08	67.2 ± 1.0	0.9032	0.4991	1.5516 ± 0.0641
E-1	PH101	7.31 ± 0.17	4.56 ± 0.12	32.3 ± 1.21	3.18 ± 0.03	67.6 ± 0.4	0.8689	0.3236	1.04 ± 0.0521
E-2	PH102	7.0 ± 0.07	4.67 ± 0.10	38.6 ± 1.85	3.24 ± 0.09	76.2 ± 0.8	0.8597	0.2093	0.9758 ± 0.0623

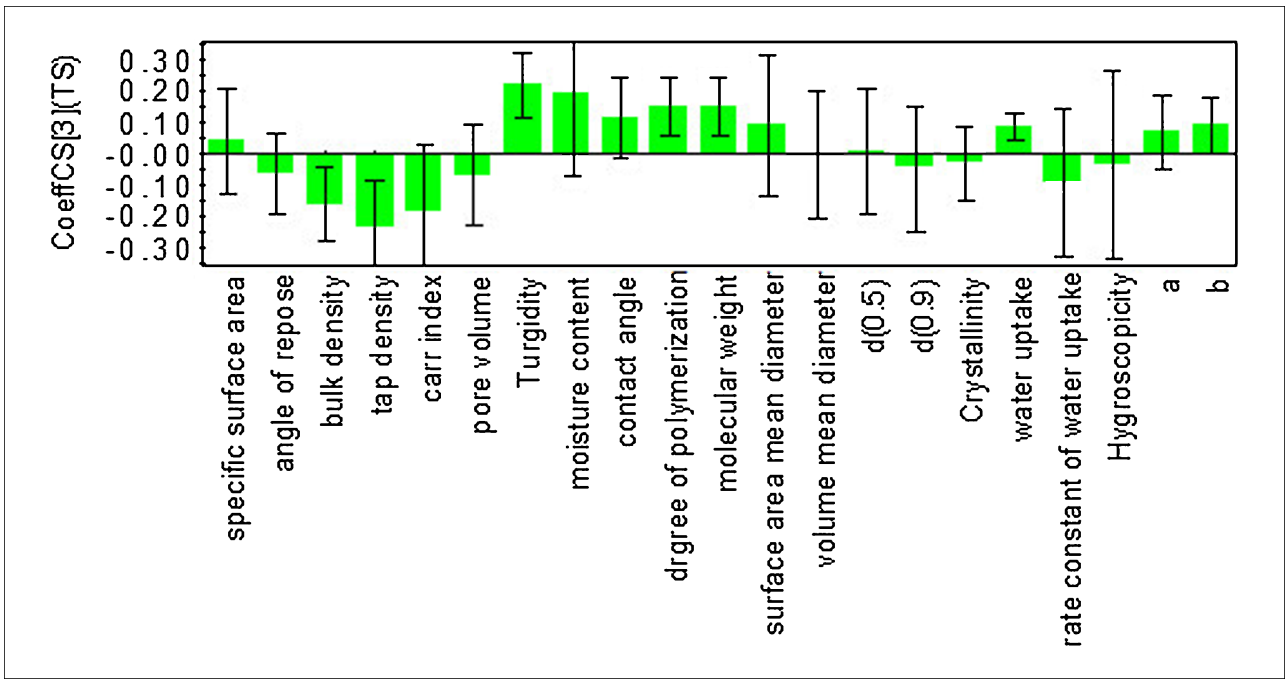

Fig. 3: Coefficient diagram for TS of MCC. For each parameter the 95% confidence interval is indicated

tap density, exhibit obvious negative impacts on TS, which can be demonstrated in the VIP diagram of Fig. 4. Furthermore, a, b and contact angle are also shown to have a strong positive impact on TS. All of the samples fall to a satisfactory manner on the diagonal, $r = 0.9539$ (Fig. 5). Therefore, the relationships between material properties of MCC samples and the value of TS have been successfully constructed by the means of employed multivariate data analysis techniques.

3. Discussion

MCC is a widely used tabletting excipient. In terms of tabletting technology, the material is described as a binder/filler, for it is usually added to enhance the compactibility. Although the preparation of MCC and their physical properties have been reported, the mechanical properties of tablets pressed from MCC with the different grades and manufacturers have not been studied.

It was reported that under a common pressure, table tensile strength was optimum at intermediate water content, jumped at approximately 3.3% water and then decreased gradually. It was reported that moisture in MCC (>5%, w/w) lead to poorer tabletability (Sun 2008). Since all of the samples under research were equilibrated to get maximum moisture below 5% (w/w), there was less correlation between moisture content and TS in this paper.

DP and molecular weight displays a high correlation to TS (0.741, $P = 0.001$) deduced by PCA, can be explained by that DP and molecular weight have a remarkable influence on the physicochemical properties of the cellulose materials, and on

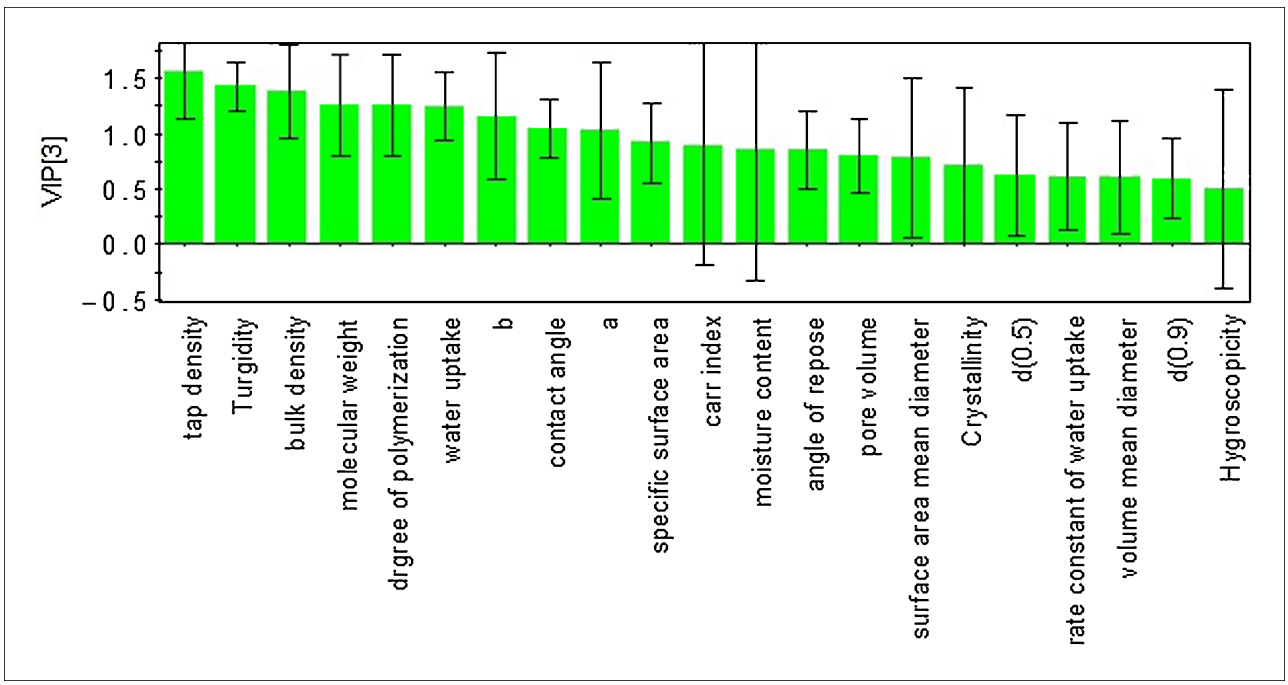

Fig. 4: Relative importence of variables in the PLS regression analysis of TS of MCC

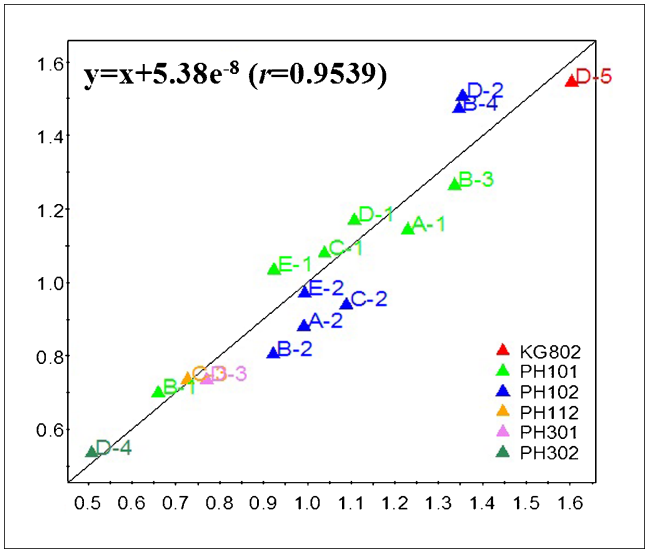

Fig. 5: Observed versus predicted plot for TS of MCC

the behavior of these materials consequently during compression. DP of MCC is the average number of glucose units in a molecule, and it is proportional to the molecular weight. With the increased DP and molecular weight, the bonding strength of hydrogen bridges increased intra- and intermolecularly (Suzuki and Nakagami 1999).

Density of MCC reflects its porosity, which is an important factor of the application for MCC. TS decreased with increased bulk density and tap density, whose Pearson correlation coefficients were (–0.811, P = 0.0001) and (–0.885. P = 0.0001) in relation to TS. It could be explained that MCC with lower density has a higher surface roughness, which contributes to mechanical interlocking during formation. Therefore, the higher density contributes to the weaker mechanical property. Meanwhile, DP displays a high correlation to bulk density and tap density, whose Pearson correlation coefficients were (–0.875, P = 0.0001) and (–0.794, P = 0.0001), respectively. The results here were confirmed by the previous report that MCC particles of DP 244 and 299, consisting of agglomerations of small MCC particles or fibers, undergo fragmentation during compression. It leads to an increase of the secondary binding points and higher mechanical strength of tablets (Shlieout et al. 2002). Bulk density and tap density decreased, accompanied by an increase of DP and lead to an increase of TS.

Similarly, turgidity and maximum water uptake increased with the increment in DP. Parameter a and b, as compression descriptors, have good positive relation with TS, for that the TS of tablets was partly determined by the compressibility (Wu et al. 2001).

The present work has demonstrated that multivariate data analysis techniques (PCA and PLS) are useful for interpreting complex relations between the material properties and the tabletting properties of MCC. For the 16 MCC samples with different grades and manufacturers, the correlation between material properties and compactibility was successfully modeled to predict the values of TS on the bases of material properties only and to elucidate contributions of each material property. Several properties including turgidity, maximum water uptake, degree of polymerization, molecular weight, bulk and tap density were found to be the most influential factors on TS. In addition, we observed that PH101 and PH102 could be obviously distinguished by particle size, angle of repose and value of a, which indicated that PH102 had better flowability and lower compressibility than those of PH101 in line of the general knowledge.

4. Experimental

4.1. Materials

All the chemicals used in this research were of standard pharmaceutical grade. Sixteen MCC samples of different types were obtained from different manufacturers at home and abroad. MCC PH101 samples were purchased from Anhui Shanhe Pharmceutical Exipients Co., Ltd (A-1, China), Shandong Liaocheng E Hua Pharmaceutical Co., Ltd (B-1, B-3, China), JRS Pharma Ltd (C-1, Germany), Asahi Kasei Corp. (D-1, Japan) and ISP Inc. (E-1, USA), respectively. MCC PH102 samples were purchased from Anhui Shanhe Pharmceutical Exipients Co., Ltd (A-2, China), Shandong Liaocheng E Hua Pharmaceutical Co., Ltd (B-2, B-4, China), JRS Pharma Ltd (C-2, Germany), Asahi Kasei Corp. (D-2, Japan) and ISP Inc. (E-2, USA) respectively. MCC PH112 sample was purchased from JRS Pharma Ltd (C-3, Germany). MCC PH301, PH302 and KG802 samples were purchased from Asahi Kasei Corp. (D-3, D-4, D-5, Japan). Cupriethylenediamine hydroxide was from Sigma-Aldrich (USA). All other chemicals and solvents were of at least analytical grade.

4.2. Properties of MCC samples

4.2.1. Bulk and tap density

An appropriate amount of sample was poured into a 25 ml graduate cylinder and tapped to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density according to the relationship: mass/volume. For tap density, the cylinder was tapped until no further change in volume. The volume of the sample was then read and used in the calculation. Each sample was tested in triplicates.

Density of MCC indicates its porosity, which is an important factor in the application of MCC. The Carr index (CI) was determined form bulk and tapped densities according to Eq. (1) as an indication of the flowability of a powder (Ghorab and Adeyeye 2007).

$$CI = \frac{\text{Tap density} - \text{Bulk density}}{\text{Tap density}} \times 100 \quad (1)$$

The value of CI above 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

4.2.2. Degree of polymerization (DP) and molecular weight

The DP was determined by measuring the viscosity for the harmonized pharmacopoeia regulations (Kumar and Kothari 1999). All experiments were performed at 25 ± 0.5 °C using the Ubbelohde viscometer (Shanghai Liangjing Glass Instrument Factory, China) with cupriethylenediamine hydroxide as the solvent. Since the measurement deals with an ideally viscous liquidity (Newtonian fluidity) in the solution, the viscosity was determined by one point measurement with a capillary-type viscosimeter. Each sample was tested in triplicate. The measured flow time was multiplied by the apparatus constant to a kinematic viscosity. By dividing the true by the blank value of the kinematic viscosity, the relative viscosity is obtained. Then the intrinsic viscosity ($[\eta]_c$) is determined by interpolation using the intrinsic viscosity tablet and DP is calculated by Eq. (2).

$$DP = \frac{95[\eta]_c}{m\left[(100-b)/100\right]} \quad (2)$$

where m is the mass in grams of the substance to be examined and b the loss on drying as a percentage.

Due to the degree of polymerization (DP) represents the number of anhydrous dextrose associated in MCC molecule, the average molecular weight (M) was calculated by Eq. (3).

$$M = 162 * DP \quad (3)$$

4.2.3. Degree of crystallinity

Powder X-ray diffraction was performed using a D8 ADVANCE diffractometer (Beuker-axs Corporation, Germany), with monochromatic Cu Kα radiation (λ=1.5408 Å), voltage 40 kV, current 40 mA and 2θ over a 5–65° range. Diffraction patterns of MCC samples were determined. Each sample was tested in triplicates. The degree of crystallinity (DC %) was calculated by Eq. (4) (Nelson and O'Connor 1964).

$$DC\ \% = (I_{002} - I_{am})/I_{002} \quad (4)$$

Where I_{002} is the diffractogram height at the position of the 002 peak (2θ=22.6°) and I_{am} the height of amorphous am background (2θ = 16.5°).

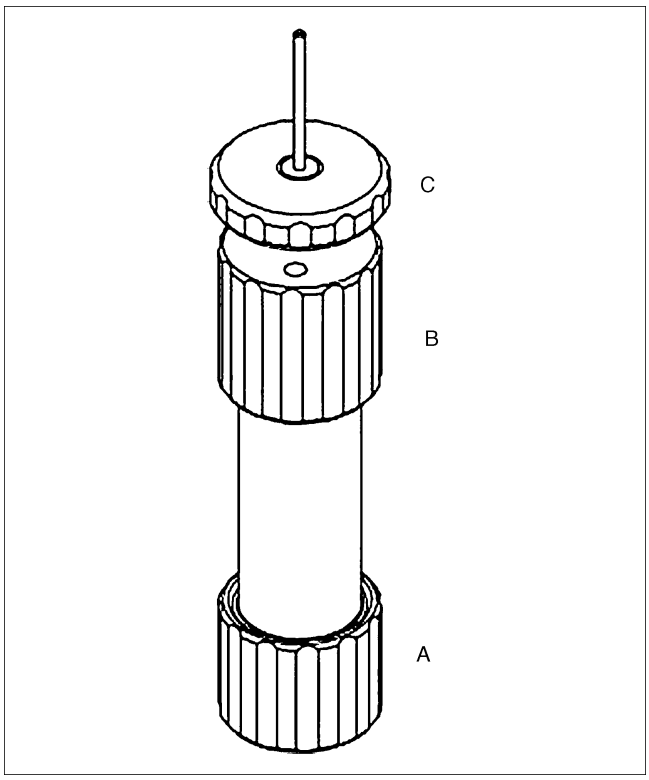

Fig. 6: Sample holder Fh 11

4.2.4. Particle size analysis

Particle size analysis of MCC samples were examined by dry-powder techniques using a laser diffraction particle size analyser (Malvern 2000, Malvern, UK). Each sample was tested in triplicates. Surface area mean diameter, volume mean diameter, d50 and d 90 were determined.

4.2.5. Surface area and pore volume

Surface area and pore volume of different grades of MCC were determined by nitrogen adsorption technique using TriStar3000 surface area and pore volume analyser (Micromeritics Instrument Corp., USA). Each sample was tested in triplicates. Moisture was removed from the samples prior to the surface area measurement by nitrogen flow at 55 °C overnight using FlowPrep 060 degasser (Micromeritics Instrument Corp., USA)

4.2.6. Maximum water uptake and rate constant of water uptake

The maximum water uptake and rate constant of water uptake were determined by the experimental apparatus shown in Fig. 6. Each sample was tested in triplicate.
This apparatus can instantly response to quality changes over time. The FH 11 (DCAT 11, Data Physics, Germany) is a special options holder to determine the wetting behavior of adsorbing materials like powders, pigments, fibers and fiber bundles. Firstly, put a filter paper into the bottom screw cap A to prevent the small holes from cloging. Then, place 200 mg dried sample weighed pricisely into the holder as homogeneous as possible. After the balance is tared, the increasing mass of the sample in the process of water absorption is calculated as a function of time. The holder was then lowered to the liquid surface of the reservoir, until the holder bottom touched the liquid surface. Then the changes of samples were recorded, when the final height was reached. The rate constant of water uptake was calculated according to Eq. (5), which could be simplified to Eq. (6).

$$V^2 = (2dr\cos\theta/K_0\eta)t \tag{5}$$

where V is the amount of water uptake (ml/g) at time t, d the average aperture, r the surface tension of liquid, θ the contact angel of solid/liquid interface, K_0 the shape constant of aperture, η the viscosity of liquid and t the elapsed time (s).

$$V^2 = Kt^2 \tag{6}$$

where V is the amount of water uptake (ml/g) at time t, K denotes the rate constant of water uptake and t the elapsed time (s). Fluid absorption dynamics equation of MCC was obtained by regressing fluid absorption (V^2) of MCC, usage amount less than 90%, to corresponding time (t).

4.2.7. Hygroscopicity

Hygroscopicity was measured following the procedures published (Chinese Pharmacopoeia, 2010). Each sample was tested in triplicate.

4.2.8. Moisture content

Moisture content of the sample was determined with an MA45 infrared dryer (Sartorius, Germany). Infrared rays enable the evaporation of bound and unbound moisture. Mass change was measured and water content was expressed as percentage of the total mass until 105 °C. Measurement was terminated when weight loss was less than 0.1% in 50 s. Each sample was tested in triplicate.

4.2.9. Angle of repose

The static angle of repose was measured by GTB Granulate Flow Testers (Erweka GmbH, Germany). Each sample was tested in triplicates.

4.2.10. Turgidity

Turgidity was measured following the procedures published (Chinese Pharmacopoeia, 2010). The vacuum drying sample of 2 g was weighed for each measurement. Each sample was tested in triplicates. Turgidity was calculated by Eq. (7):

$$S = \frac{V}{W} \tag{7}$$

Where S is the turgidity, V the volume after dilatation and W the weight of the dried material.

4.2.11. Contact angle measurement

The Contact angle (CA) was determined by using the DCAT 11 dynamic contact angle tensiometer (Data Physics, Germany) (Bachmann et al. 2003; Goebel et al. 2004). Each sample was tested in triplicates.

4.2.12. Tablet preparation

Tablets were compressed from powder with the Model TRD8 rotary tabletting machine (Erweka GmbH, Germany). The tablet machine was equipped with a pair of instrumented flat-face punches with a diameter of 10 mm. The rotation speed of the tablet press was kept at 10 rpm. The target maximum compression pressure was used at 2 KN and the compression pressure at 25.48 MPa. After compaction, with the tablet weight at 190 ± 3.97 mg, the tablets were stored for 24 h in desiccators at 28.7 °C and a relative humidity of 29%.The compression behavior was studied using the Kawakita equation Eqs. (8) and (9).

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \tag{8}$$

$$C = \left[\frac{V_0 - V}{V_0}\right] \tag{9}$$

where P is the applied pressure, a the maximum volume available for reduction under pressure, b the constant inversely related to the yield strength of the particles, C the degree of volume reduction, V the volume of compact at pressure P and V_0 the initial apparent volume of powder, respectively.
Diameter and thickness of the tablets obtained from different compression force were measured after 24 h using a micrometer. Each sample was tested in triplicates. The same tablets were used to measure the load necessary to cause fracture with a YD-20 tablet hardness tester (Tianjin TDTF Technology Co., Ltd, China). The tensile strength (TS) was calculated by Eq. (10) (Qunaibi et al. 2009).

$$TS = \frac{2P}{\pi Dt} \tag{10}$$

where P is the hardness of the tablet, D the tablet diameter and t tablet thickness.

4.3. Statistical analysis

The multivariate data analysis was carried out using SIMCA-P 12.0 software (Umetrics, Sweden). Data are presented as mean±S.D. To ascertain reproducibility, each experiment was conducted three times.

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References

Appendix XIXJ (2010) Chinese Pharmacopoeia (1st ed.), Beijing: Chemical Industry Press, p. 200.

Bachmann J, Woche SK, Goebel MO, Kirkham MB, Horton R (2003) Extended methodology for determining wetting properties of porous media. Water Resour Res 39: 1353–1366.

Bhimte NA, Tayade PT (2007) Evaluation of microcrystalline cellulose prepared from sisal fibers as a tablet excipient. AAPS PharmSciTech 8: 1–7.

Doelker E (1993) Comparative compaction properties of various microcrystalline cellulose and generic products. Drug Dev Ind Pharm 19: 2399–2471.

Doelker E, Massuelle D, Veuillez F, Humbert-Droz P (1995) Morphological, packing, flow and tabletting properties of new Avicel types. Drug Dev Ind Pharm 21: 643–661.

Eriksson L, Johansson E, Kettaneh-Wold N, Wold S (2001) Multi-and megavariate data analysis: principles and applications. Umeå: Umetrics.

Ghorab MK, Adeyeye MC (2007) High shear mixing granulation of ibuprofen and β-cyclodextrin: effects of process variables on ibuprofen dissolution. AAPS PharmSciTech 8: 1–9.

Goebel MO, Bachmann J, Woche SK, Fischer W, Horton R (2004) Water potential and aggregate size effects on contact angle and surface energy. Soil Sci Soc Am J 68: 383–393.

Harju M, Andersson PL, Haglund P, Tysklind M (2002) Multivariate physicochemical characterization and quantitative structure-property relationship modeling of polybrominated diphenyl ethers. Chemosphere 47: 375–384.

Haware RV, Tho I, Bauer-Brandl A (2009) Multivariate analysis of relationships between material properties, process parameters and tablet tensile strength for α-lactose monohydrates. Eur J Pharm Biopharm 73: 424–431.

Ikeda H, Tsukamoto H, Sugimoto A, Sawa A, Crabtree BL, Byrd HJ, Murakami T, Mishima HK, Kihira K (2008) Clinical significance of topical instillation technique in Japanese glaucoma patients. Pharmazie 63: 81–85.

Imamura N, Mizoguchi T, Yamauchi H, Karppinen M (2008) Multivariate data analysis approach to understand magnetic properties of perovskite manganese oxides. J Solid State Chem 181: 1195–1203.

Kumar V, Kothari SH (1999) Effect of compressional force on the crystallinity of directly compressible cellulose excipients. Int J Pharm 177: 173–182.

Landin M, Martínez-Pacheco R, Gómez-Amoza JL, Souto C, Concheiro A, Rowe RC (1993) Effect of batch variation and source of pulp on the properties of microcrystalline cellulose. Int J Pharm 91: 133–141.

Moropoulou A, Polikreti K, Bakolas A, Michailidis P (2003) Correlation of physicochemical and mechanical properties of historical mortars and classification by multivariate statistics. Cem Concr Res 33: 891–898.

Nelson ML, O'Connor RT (1964) Relation of certain infrared bands to cellulose crystallinity and crystal lattice type. Part II. A new infrared ratio for estimation of crystallinity in cellulose I and II. J Appl Polym Sci 8: 1325–1341.

Pesonen T, Paronen P (1986) Evaluation of a new cellulose material as binding agent for direct compression of tablets. Drug Dev Ind Pharm 12: 2091–2111.

Qunaibi EA, Disi AM, Taha MO (2009) Phenytoin enhances collagenization in excision wounds and tensile strength in incision wounds. Pharmazie 64: 584–586.

Shlieout G, Arnold K, Müller G (2002) Powder and mechanical properties of microcrystalline cellulose with different degrees of polymerization. AAPS PharmSciTech 3: 11.

Sun CC (2008) Mechanism of moisture induced variation in true density and compaction properties microcrystalline cellulose. Int J Pharm 346: 93–101.

Suzuki T, Nakagami H (1999) Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets. Eur J Pharm Biopharm 47: 225–230.

Wu JS, Ho HO, Sheu MT (2001) A statistical design to evaluate the influence of manufacturing factors on the material properties and functionalities of microcrystalline cellulose. Eur J Pharm Sci 12: 417–425.

Zhu L, Feng Y, Xu DS, Ruan KP, Yang Y (2008) Correlation with physical properties of mixture of herbal extracts and microcrystalline cellulose and tensile strength of formed tablets. Chin J Pharm 39: 349–351.