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A statistical design to evaluate the influence of manufacturing factors and material properties on the mechanical performances of microcrystalline cellulose

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Abstract

In this study, a statistical experimental design was used to evaluate the effects of manufacturing factors and material properties on the mechanical performances of microcrystalline cellulose (MCC) products for the purpose of optimizing mechanical performances and reducing source variations affecting tablet strength of MCC. Results demonstrated that only fracture toughness and sensitivity to compaction speed among mechanical performances were affected by the manufacturing factors; however, the use of manufacturing factors to predict the mechanical performances was poor. On the other hand, the critical stress intensity factor, fracture toughness, and sensitivity to compaction speed can be quantitatively predicted by material properties examined in this study. Meanwhile, the cohesive energy density (CED), degree of crystallinity, crystallinity index, and shape index may serve as important material properties for controlling the mechanical performances of MCC. In conclusion, although the MCC products with high fracture toughness and low sensitivity to compaction speed could be optimally obtained, it was not possible to manipulate manufacturing factors to directly control the exact mechanical performances of MCC products. Instead, material properties of MCC products might potentially be used to precisely predict their mechanical performances. The influence of source variations of MCC products on the strength of tablets might be reduced by regulation of their CED, degree of crystallinity, crystallinity index, and shape index.

Keywords: Microcrystalline cellulose; Molecular-related property; Particle morphology; Mechanical parameter; Compactibility; Compressibility

1. Introduction

Microcrystalline cellulose (MCC) is a widely used excipient in direct compression formulations. Source and batch variations have been reported to affect the material properties and tablet strength of MCC [1,2]. Reduction in the influence of source variation of MCC on tablet strength has been attempted by the process of harmonization. For excipients used in direct compression, both compactibility and compressibility determine the strength of tablets. The compactibility of tablets originates from the intermolecular attraction between particles. The attractive forces of a material can be represented by its cohesive energy density (CED). The CED has been used to estimate Young's modulus of a variety of pharmaceutical powders [3]. Meanwhile, several mechanical parameters, including Young's modulus (E), critical stress intensity factor (K_{IC}), and fracture toughness (FT), have been successfully used to probe the mechanical properties and fracture mechanics of pharmaceutical powders [4]. As a result, the tensile strength of compacts was reported to represent the synergism of these mechanical parameters [5].

The compressibility describes the deformability of materials. For polymer excipients, compressibility is related to the aggregation state of the polymer chains. A polymer solid with disordered polymer chains is mechanically weak and has a higher tendency to deform plastically [6]. Since the plastic deformation process is a function of time, the compressibility of a material deformed plastically is influenced by the speed of compaction [7]. The sensitivity of changing compressibility to compaction speed might produce the problem of the deterioration in strength of tablets when the formulation designer switches from a low-speed formulation phase to high-speed large-scale production. In summary, the influence of source variation on tablet strength of an excipient deformed plastically is closely

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linked to its mechanical performances (mechanical parameters and sensitivity to compaction speed).

Industrially, MCC is generally manufactured by mineral acid hydrolysis. The hydrolysis conditions have been reported to affect the particle shape, the crystallinity, and the molecular weight of MCC [8]. It has been proposed that the irregular shapes of particles provide mechanical interlocking to strengthen MCC compacts [9]. On the other hand, the aggregation state of a polymer chain and the molecular weight remarkably influence the viscoelasticity of semicrystalline polymers [10,11]. Further, changes of the aggregation state of a polymer chain might alter the molar volume and result in a change of its CED [12], thus changing the intermolecular attraction between particles. Meanwhile, being a semicrystalline polymer, the viscoelastic behavior of the amorphous portion of MCC molecules might be responsive to the sensitivity of changing compressibility to compaction speed as well [13]. Therefore, it is interesting to explore how the material properties (particle morphology and molecular-related properties) of MCC affect its mechanical performances. Furthermore, the correlation constructed between manufacturing factors and mechanical performances is useful for manufacturers to optimize the mechanical performances of MCC products. It is also desirable to find the key material properties that control the mechanical performances of individual excipients. Only then, can reduction in source variations affecting the strength of tablets be made by the control of manufacturing factors and regulation of key material properties. However, no work has been detail reported on these matters.

In this study, the main object is to statistically evaluate the effects of manufacturing factors and material properties on the mechanical performances of MCC products. Manufacturing conditions could then be optimized to engineer MCC products with desired mechanical performances. On the other hand, the key material properties that control the mechanical performances of MCC products were possibly deduced as a practical way to regulate the qualities of MCC products for minimizing the source variation.

2. Experimental design

A three-factor, five-level central composite design was used. This design is useful for exploring quadratic response surfaces and constructing a second-order polynomial model, thus helping to optimize a process using a small number of experimental runs. The design consists of replicated center points and the set of points lying at each edge of the multidimensional cube that defines the region of interest. A central composite design is made rotatable by the choice of ϕ. The value of ϕ for a design with three factors is 1.68179. The independent variables and their corresponding real and orthogonal values in the central composite design are listed in Table 1. The model constructed is as follows: $Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_1 X_2 + b_5 X_2 X_3 + b_6 X_1 X_3 + b_7 X_1^2 + b_8 X_2^2 + b_9 X_3^2 + E$, where b_0 to b_9 are the regression coefficients; X_1, X_2, and X_3 are the factors studied; Y is the measured response; and E is the error term. The stepwise multiple regression method is a combination of forward and backward regressions and is used to eliminate non-significant terms from polynomial equations. In this study, the α-values for both forward and backward regression processes are designated as 0.1. The polynomial equations and response surface plots were obtained with the statistical package, Design-Expert 5 (State-Ease, USA).

Table 1
Independent variables and their corresponding real and orthogonal values in the central composite design

Independent variable	Level				
	−1.68179	−1	0	1	1.68179
(X_1) Concentration of HCl (N)	2.16	2.50	3.00	3.50	3.84
(X_2) Temperature (°C)	73	77	83	89	93
(X_3) Duration of hydrolysis (min)	43.2	50.0	60.0	70.0	76.8

3. Materials and methods

3.1. Materials and sample preparations

Wood pulp, Temalfa 94 (lot no. 61398), was obtained from Tembec (Canada). In preliminary studies, the extreme values assigned to the independent variables were first checked to establish that MCC could be prepared under these conditions. The 20 experiments designed to test the effect of three hydrolysis factors are shown in Table 2. A total of 300 g of wood pulp was used for each experiment. After hydrolysis, the hydrolyzed product was washed with distilled water until the pH value of the washing solution was near neutral, and no white precipitation appeared with the addition of a 0.1 N $AgNO_3$ solution. Next, the hydrolyzed product was centrifuged to eliminate water. The wet mass was then forced through a 1.19-mm sieve and oven-dried for 12 h at 60 ± 1°C. The dried granules were milled and screened through a series of sieves with different-sized openings (355, 150, 125, 88, 75, 60, and 25 μm) to control the particle size distribution of the MCC products to the same range as Avicel PH 102 (the mean particle size lying at 10% of normal distribution [d10] is not more than 45 μm, the mean particle size lying at 50% of normal distribution [d50] is in the range of 75–95 μm; and the mean particle size lying at 90% of normal distribution [d90] is not less than 140 μm). The obtained MCC products were stored for at least 7 days at a relative humidity of 40% before any test. The water content was controlled at 3–5% (w/w) and measured using an

Table 2
Three-factor central composite design: variables, their levels, and matrix and data of the response

Run	Independent variable			Response (mechanical performances)			
	X_1	X_2	X_3	E (GPa)[a]	K_{IC} (MPa $m^{1/2}$)[a]	FT (N m^{-1})[a]	Sensitivity to compaction speed[b] ($\times 10^{-3}$)
1	−1	−1	−1	10.87 ± 0.99	0.860 ± 0.024	151.5 ± 3.2	3.37 ± 1.17
2	−1	1	1	12.43 ± 1.31	0.750 ± 0.063	105.9 ± 13.9	2.81 ± 0.50
3	1	−1	1	8.77 ± 1.17	0.613 ± 0.049	83.4 ± 12.8	2.06 ± 0.17
4	1	1	−1	8.95 ± 0.89	0.853 ± 0.081	119.8 ± 21.9	2.87 ± 0.58
5	0	0	0	9.57 ± 0.76	0.604 ± 0.019	112.4 ± 19.7	2.68 ± 0.95
6	0	0	0	8.79 ± 0.79	0.829 ± 0.119	114.7 ± 23.8	2.62 ± 0.45
7	−1	−1	1	7.70 ± 0.15	0.685 ± 0.043	130.7 ± 19.4	2.45 ± 0.14
8	−1	1	−1	8.51 ± 0.60	0.927 ± 0.137	179.3 ± 44.7	2.03 ± 0.11
9	1	−1	−1	9.63 ± 0.82	0.645 ± 0.064	89.1 ± 10.5	3.02 ± 1.16
10	1	1	1	6.37 ± 0.47	0.477 ± 0.018	58.5 ± 6.5	2.19 ± 1.07
11	0	0	0	10.43 ± 0.51	0.781 ± 0.178	165.4 ± 54.0	2.79 ± 0.24
12	0	0	0	7.85 ± 0.54	0.572 ± 0.028	95.6 ± 14.3	2.23 ± 0.53
13	1.68179	0	0	8.24 ± 0.26	0.629 ± 0.068	93.8 ± 19.0	2.24 ± 0.78
14	−1.68179	0	0	8.61 ± 0.27	0.574 ± 0.027	99.0 ± 12.4	2.09 ± 0.54
15	0	1.68179	0	8.98 ± 0.64	0.445 ± 0.029	63.7 ± 11.0	2.73 ± 0.46
16	0	−1.68179	0	10.44 ± 1.15	0.620 ± 0.019	115.7 ± 16.5	2.43 ± 0.51
17	0	0	1.68179	8.21 ± 0.39	0.532 ± 0.036	67.5 ± 7.7	3.00 ± 0.14
18	0	0	−1.68179	11.34 ± 0.84	0.558 ± 0.060	96.7 ± 11.2	2.62 ± 0.29
19	0	0	0	9.36 ± 0.30	0.487 ± 0.054	82.5 ± 8.8	2.54 ± 0.71
20	0	0	0	8.49 ± 0.20	0.584 ± 0.072	97.1 ± 7.7	3.26 ± 1.18

[a] Variation is indicated as ± S.E.
[b] All values are the mean ± S.D. of three determinations.

OHAUS moisture determination balance (Model MB200, OHAUS, USA).

3.2. Measurement of molecular-related properties

3.2.1. Degree of polymerization (DP)

The DP was determined according to National Formulary XVIII. The kinematic viscosities of the MCC solution and solvent (1.0 M cupriethylenediamine hydroxide solution) were measured with a Wells-Brookfield plate viscometer (Model DV-II + , USA).

3.2.2. Degree of crystallinity

Powder X-ray diffraction measurements were carried out at room temperature on a Shimadzu X-ray diffractometer (Model XD-5, Japan) using monochromatic CuKα radiation and a scan rate of 4°/2θ per minute over the range of 4–50°/2θ. According to Nelson and O'Connor [14], the degree of crystallinity was calculated as follows:

$$\%\,\text{Degree of crystallinity} = (I_{002} - I_{\text{am}})/I_{002} \times 100; \qquad (1)$$

where I_{002} = the diffractogram height at the position of the 002 peak ($2\theta = 22.6°$); and I_{am} is the height of amorphous background ($2\theta = 19°$).

3.2.3. Crystallinity index

The crystallinity index was determined from the solid-state ^{13}C CP/MAS nuclear magnetic resonance spectra and was calculated as described by Ek et al. [15]. The measurements were performed on a Bruker MXL 300 spectrometer operating at 75.47 MHz with spinning at 4.5 kHz using a double air-bearing probe and ZrO_2 rotors. The instrumental parameters were: 3 ms contact time, and 2048 data points filled to 4096 K. The chemical shift scale was referenced to the methyl group in adamantane located at 14.0396 ppm. The number of scans on each spectrum was 10,000.

3.2.4. True density and cohesive energy density (CED)

The true density was measured using a nitrogen-air pycnometer (Model PYC-G100A-1, PMI, USA). The CED of MCC products was calculated from true density as described by Roberts and Rowe [12]. The average of three determinations was reported.

3.3. Measurement of particle morphology

The image of particles was collected using an image analyzer (Microtek, Model MRS-600ZS, Taiwan). The software package, Image-Pro Plus 1.0 (Media Cybernetics, USA), was used to obtain all dimensions of particles. The shape index and the surface roughness were calculated as described by Iida et al. [8] and Podczeck and Newton [16]. At least 150 particles were analyzed for each MCC product. The surface roughness was calculated as follows:

$$\text{Surface roughness} = (2\pi r_e)/(P_m f); \qquad (2)$$

where r_e = arithmetic mean of the distances between the center of gravity and the perimeter for an angle of 5° between the measurements; P_m = perimeter of the particle outline; and f is a correction factor to minimize the effect of ellipticity on the surface roughness [$f = 1.008 - 0.231 \times (1 - (\text{breadth of the particle}/\text{length of the particle}))$] [16]. A perfect sphere has a surface roughness value of 1.00, and increasing surface roughness leads to values smaller than 1.00. The shape index was calculated as follows:

$$\text{Shape index} = (4\pi A)/P_m^2; \tag{3}$$

where A is the projected area of a particle. Theoretically, only a circle can have a shape index of 1.00. For other irregular figures, the value is smaller than 1.00.

3.4. Measurement of mechanical performances

All mechanical properties and sensitivity to compaction speed were determined using a three-point beam bending test on a dynamic mechanical analyzer (Perkin Elmer, Model DMA 7e, USA). Beams were prepared by compacting the powders in a rectangular die, 25 mm in length and 5 mm in breadth. The thickness of the beams was controlled at 2 mm by the design of the depth of the upper punch. Since all beams were compressed to a constant thickness of 2 mm, porosity could be varied by changing the weight of powder placed in the die cavity.

3.4.1. Mechanical properties

All mechanical properties are influenced by the solid fraction of beams. By using Spriggs equation [17], they were compared at zero porosity by extrapolating the plot of measured mechanical strength vs. porosity to zero. In order to cover a range of porosities, 18 beams of each MCC product were tested. Young's modulus (E) was obtained by stressing beams to fracture at a frequency of 1 Hz. The maximum Young's modulus was recorded. The critical stress intensity factor (K_{IC}) was determined and calculated as described by Roberts et al. [18]. Fracture toughness (FT) was determined and calculated as described by Mashadi and Newton [4].

3.4.2. Sensitivity to compaction speed

Beams with a porosity of 0.21 were prepared. The damping of beams was measured using a frequency scan on a dynamic mechanical analyzer beginning at a frequency of 1 Hz and ending at 16 Hz. The graphs of damping vs. frequency were plotted, and the sensitivity to compaction speed was defined as the slope multiplied by −1. The average of three beams was reported.

3.5. Statistical methods

3.5.1. Pearson correlation analysis

Pearson correlation measures the closeness of a linear relationship between two variables. If one variable can be expressed exactly as a linear function of another variable, then the correlation is 1 or −1, depending on whether the two variables are directly or inversely related. A correlation of zero means that each variable has no linear predictive ability for the other.

3.5.2. Canonical correlation analysis

Canonical correlation analysis is used to examine the linear relationships between a set of independent variables (X) and a set of more than one dependent variable (Y) [19]. It is especially useful when the dependent or criterion variables are moderately intercorrelated. The technique consists of finding one linear combination of the X variables, say

$$U = a_1 X_1 + a_2 X_2 + a_3 X_3 + \cdots \tag{4}$$

and one linear combinations of the Y variables, say

$$V = b_1 Y_1 + b_2 Y_2 + b_3 Y_3 + \cdots \tag{5}$$

U and V are called the canonical variables of the X's and Y's, respectively. For any particular choice of coefficients, the a's and the b's, the values of U and V can be computed for each individual in the sample (20 runs for this study). The resulting correlation between U and V is called the first canonical correlation and is dependent on the choice of the a's and the b's. In canonical correlation analysis, the values of the a and b coefficients are selected to express the best correlations between U and V. Multivariate tests based on several approximate F statistics including Wilks' Lambda test, Hotelling–Lawley Trace test, and Roy's Greatest Root test, are used to determine whether the first canonical correlation is significant.

The SAS System for Windows 6.12 edition (SAS Institute, USA) was used to carry out all statistical tests in this study, and $P < 0.05$ was considered to be statistically significant for all statistical tests.

4. Results and discussion

Measurements of mechanical performances of MCC products manufactured according to this statistical experimental design were conducted, and results are shown in Table 2. Young's modulus (E) describes the stiffness of a material and originates from the dependence of the energy of interaction between molecules and their distance of separation. The critical stress intensity factor (K_{IC}) describes the state of stress around an unstable crack or flaw in a material and is an indication of the stress required to produce propagation of a crack. Thus, it is a measure of the brittleness of materials as reflected by the resistance of a material to cracking via tensile stresses acting normal to the crack wall. Fracture toughness (FT) is an estimate of the energy necessary for crack propagation.

For amorphous materials, the extent of deformation is sensitive to compaction speed. Compaction at low speed

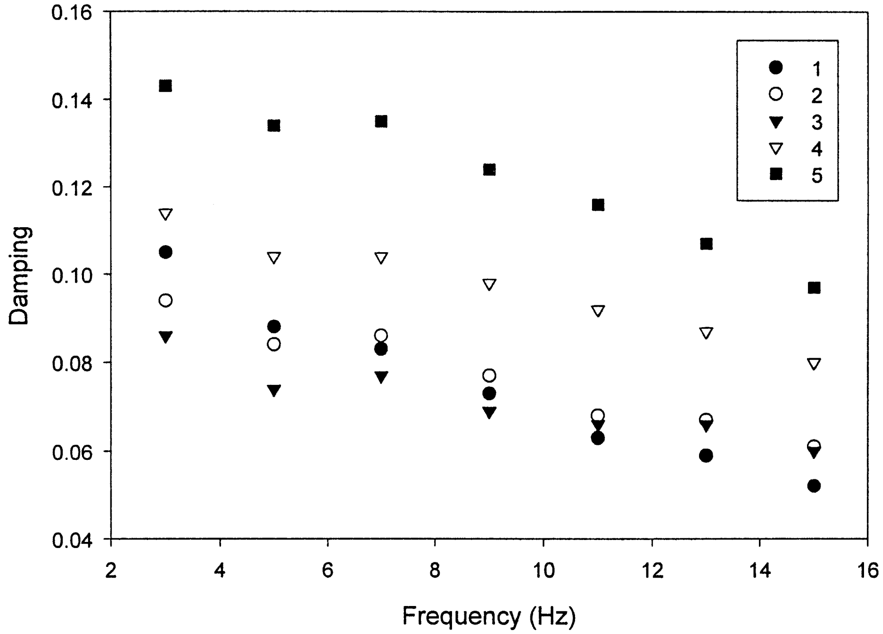

Fig. 1. Damping of beams produced from MCC vs. the frequency of deformation (numbers refer to MCC products obtained from runs 1 to 5 of experimental design as listed in Table 2).

results in the formation of tablets with low porosity, since deformation is dominated by the viscous component, which is irreversible. Compaction at high speed produces tablets with higher porosity and lower strength, because of an increase of elasticity of materials [13]. MCC is a semicrystalline polymer, therefore, the amorphous portion of the MCC molecule might possess viscoelasticity and be sensitive to tableting speed. Damping has been used to measure

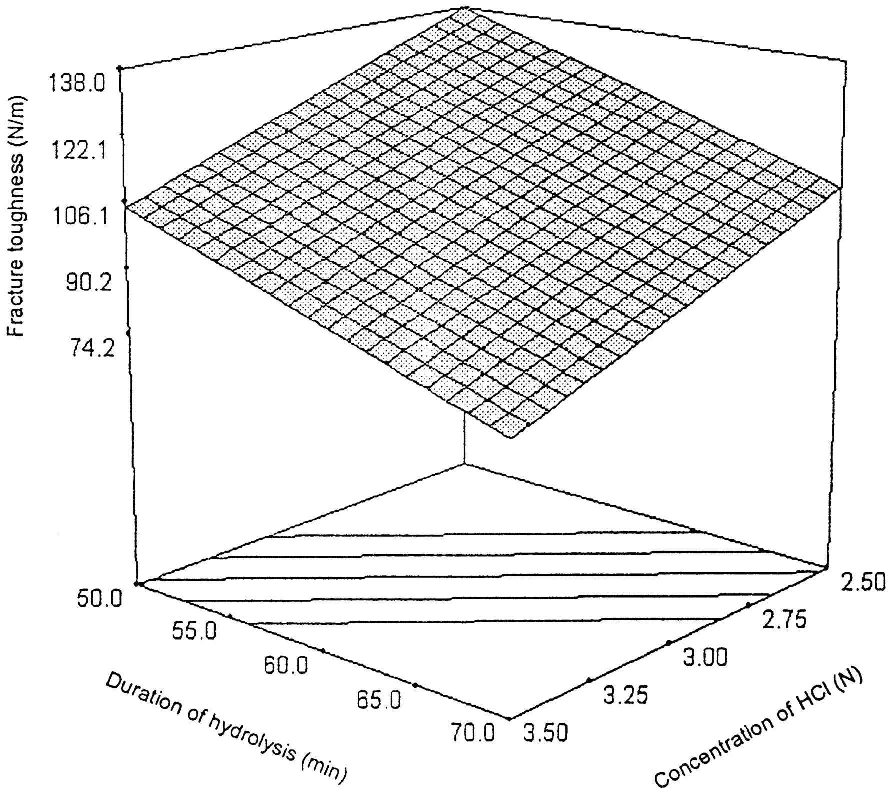

Fig. 2. Response surface plot showing the effect of HCl concentration (X_1) and duration of hydrolysis (X_3) on the fracture toughness of MCC products.

the viscoelasticity of a material [20]. The lower the damping value, the less of a tendency there is for a material to deform irreversibly. Therefore, damping of beams produced from MCC decreases with an increase of deformation frequency as shown in Fig. 1. Meanwhile, at a definite frequency of deformation, damping remains constant as the porosity of MCC compacts falls below 0.4 [21]. Thus, sensitivity of changing compressibility to compaction speed of MCC products is simulated by the sensitivity of changing damping values to deformation frequency of the beams with a porosity of 0.21.

The stepwise multiple regression of these mechanical performances with respect to hydrolysis factors (X_1, X_2, and X_3) based on a central composite design of 20 experi-

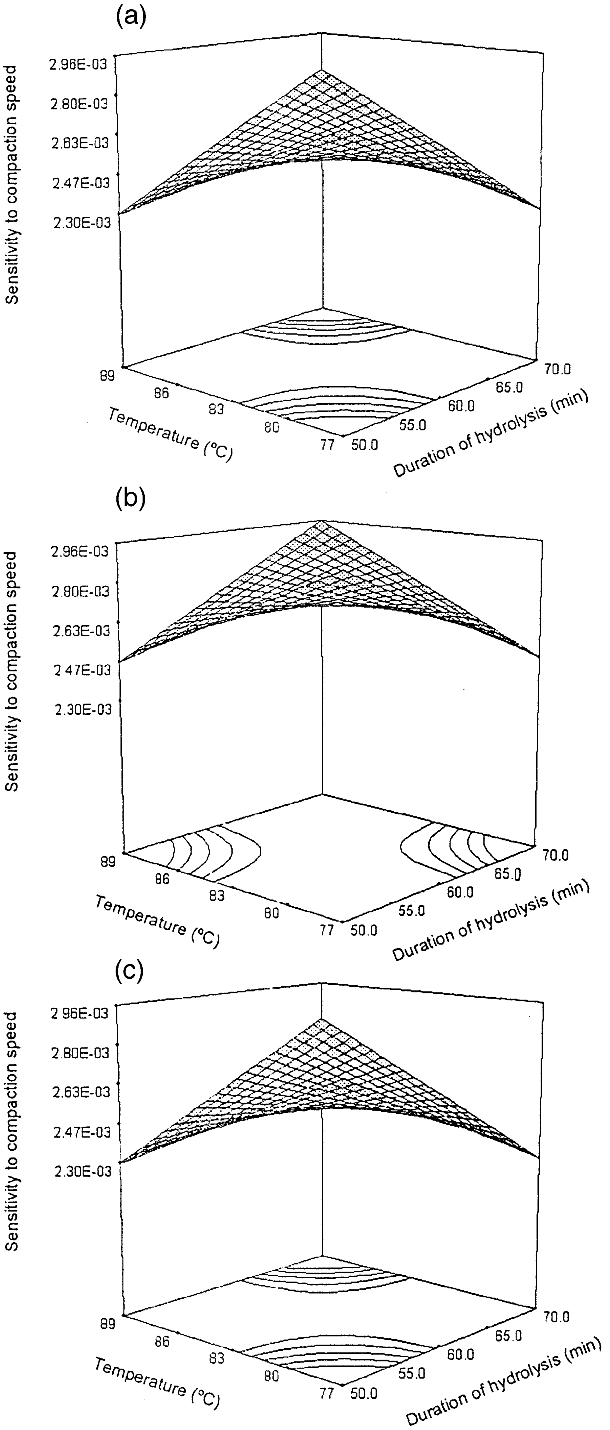

Fig. 3. Response surface plot showing the effect of temperature (X_2) and duration of hydrolysis (X_3) on the sensitivity to compaction speed of MCC products at three HCl concentrations: (a) 2.50 N, (b) 3.00 N, and (c) 3.50 N.

mental sets was only able to generate two second-order polynomial equations for fracture toughness (FT) and sensitivity to compaction speed.

$$\mathrm{FT} = 106.11 - 16.51 X_1 - 15.39 X_3, \quad (\mathrm{R}^2 = 0.3598); \tag{6}$$

$$\text{Sensitivity to compaction speed} = 0.002717 - 0.0001679 X_1^2 + 0.0002457 X_2 X_3, \quad (R^2 = 0.3091). \tag{7}$$

The results show that FT and sensitivity to compaction speed are significantly affected by the hydrolysis factors ($P < 0.05$). According to Eq. (6), FT was independent of temperature (X_2). Fig. 2 shows the effect of HCl concentration (X_1) and duration of hydrolysis (X_3) on FT at a fixed temperature (83°C). The fracture toughness decreased with increasing HCl concentration and duration of hydrolysis. On the other hand, Fig. 3 shows the effect of temperature (X_2) and duration of hydrolysis (X_3) on sensitivity to compaction speed at low, medium, and high concentrations of HCl (2.50, 3.00, and 3.50 N, respectively). Either increasing temperature for a short duration or lowering temperature with prolonged hydrolysis would result in a decrease of sensitivity to compaction speed of MCC products irregardless of what level of HCl concentration was used. Based on these two quantitative equations, a MCC product with high fracture toughness and low sensitivity to compaction speed could be optimally obtained by hydrolysis at high temperature (89°C), short duration (50 min), and low level of HCl (2.50 N). However, the R^2 values of these two polynomial equations are quite low, which means that the predicted precision of FT and sensitivity to compaction speed by these hydrolysis factors are poor. Results also demonstrate that E and K_{IC} depend on none of the selected variables. This means that neither the stiffness nor brittleness of MCC products are affected by these hydrolysis factors.

Since the use of manufacturing factors to predict the mechanical performances was poor, it was thought that material properties of MCC instead might possibly be correlated with mechanical performances to some extent and might be useful to predict the mechanical performances of MCC products. Material properties of MCC are divided into molecular-related properties and particle morphology. Table 3 shows the average experimental results of these material properties of MCC products. The degree of polymerization (DP) of MCC is the average number of glucose units in a molecule, which is proportional to the molecular mass. The degree of crystallinity was calculated from the X-ray diffractogram. This parameter describes the regularity of the arrangement of polymer chains. The crystallinity index was calculated from NMR spectra by dividing the intensity of the crystalline C4 peak (89 ppm) by the sum of the crystalline and amorphous C4 (84 ppm) intensities. This index indicates the extent of hydrogen bonding between glucose units of the MCC molecule, since the $\mathrm{O_3{-}H \cdots O_5'}$ intramolecular hydrogen bonding makes the C4 carbon peaks shift toward a lower magnetic field [22]. The CED was calculated from the true density. Denser molecules of the same chemical structure of MCCs result in a higher value of CED, thus indicating higher

Table 3
Molecular-related properties and particle morphology of MCC products

Run	Degree of polymerization (DP)[a]	Degree of crystallinity (%)	Crystallinity index (%)	Cohesive energy density (CED, MPa)[a]	Surface roughness[b]	Shape index[b]
1	241.02 ± 0.78	67.8	56.9	926.36 ± 3.68	0.86 ± 0.12	0.59 ± 0.19
2	191.18 ± 0.92	74.2	57.8	928.79 ± 4.95	0.90 ± 0.09	0.73 ± 0.14
3	206.54 ± 0.81	79.3	61.2	921.32 ± 2.77	0.88 ± 0.06	0.69 ± 0.11
4	187.75 ± 1.73	74.8	59.4	934.96 ± 10.28	0.88 ± 0.06	0.68 ± 0.11
5	195.78 ± 1.67	73.2	70.8	917.36 ± 6.43	0.89 ± 0.07	0.70 ± 0.14
6	206.92 ± 0.63	74.1	64.0	925.88 ± 11.12	0.88 ± 0.08	0.69 ± 0.15
7	236.17 ± 1.27	77.5	58.5	910.14 ± 1.22	0.83 ± 0.09	0.59 ± 0.14
8	200.56 ± 0.06	77.9	64.7	924.80 ± 2.61	0.87 ± 0.06	0.68 ± 0.12
9	205.43 ± 0.90	79.1	64.3	928.40 ± 9.34	0.88 ± 0.08	0.69 ± 0.14
10	188.21 ± 0.94	77.1	65.3	925.82 ± 2.45	1.01 ± 0.10	0.90 ± 0.17
11	207.44 ± 0.90	75.4	65.6	933.59 ± 2.13	0.88 ± 0.07	0.69 ± 0.13
12	199.16 ± 0.86	75.0	67.8	910.82 ± 3.95	0.88 ± 0.09	0.67 ± 0.15
13	193.71 ± 0.04	78.3	67.0	917.55 ± 7.87	0.88 ± 0.07	0.70 ± 0.13
14	229.47 ± 0.67	76.7	65.0	907.71 ± 5.59	0.87 ± 0.07	0.65 ± 0.14
15	189.57 ± 0.95	76.7	62.7	917.11 ± 4.83	0.87 ± 0.06	0.70 ± 0.10
16	247.31 ± 1.17	79.2	65.8	922.36 ± 10.04	0.85 ± 0.10	0.59 ± 0.17
17	195.37 ± 1.59	77.1	64.2	921.84 ± 6.56	0.88 ± 0.11	0.70 ± 0.17
18	206.14 ± 1.41	75.9	66.0	922.79 ± 6.15	0.87 ± 0.09	0.65 ± 0.13
19	197.90 ± 2.49	71.7	68.5	925.19 ± 6.27	0.88 ± 0.09	0.69 ± 0.13
20	199.14 ± 0.03	76.3	71.2	920.37 ± 1.79	0.88 ± 0.10	0.68 ± 0.14

[a] All values are the mean ± S.D. of three determinations.
[b] All values are the mean ± S.D. of 150 determinations.

Table 4
Correlation matrix of material properties and mechanical performances of MCC products

Variable	DP	Crystallinity index	Degree of crystallinity	CED	Surface roughness	Shape index	*E*	K_{IC}	FT	Sensitivity to compaction speed
DP	1	−0.27035 (0.2490)	−0.0628 (0.7924)	−0.2783 (0.2349)	−0.5511* (0.0118)	−0.7162* (0.0004)	0.2068 (0.3817)	0.2063 (0.3828)	0.4026 (0.0784)	0.0087 (0.9709)
Crystallinity index		1	0.1584 (0.5048)	−0.2348 (0.3190)	0.1898 (0.4228)	0.2053 (0.3852)	−0.2558 (0.2763)	−0.4683* (0.0373)	−0.2236 (0.3433)	−0.1542 (0.5162)
Degree of crystallinity			1	−0.2120 (0.3696)	0.0128 (0.9573)	0.1352 (0.5698)	−0.3617 (0.1171)	−0.2585 (0.2712)	−0.2546 (0.2787)	−0.4839* (0.0306)
CED				1	0.2739 (0.2426)	0.2689 (0.2517)	0.4062 (0.0756)	0.4683* (0.0373)	0.2570 (0.2741)	0.4263 (0.0609)
Surface roughness					1	0.9531* (0.0001)	−0.3234 (0.1643)	−0.3043 (0.1921)	−0.4357 (0.0549)	−0.1252 (0.5989)
Shape index						1	−0.3705 (0.1078)	−0.3019 (0.1957)	−0.4606* (0.0410)	−0.2106 (0.3728)
E							1	0.2917 (0.2121)	0.3143 (0.1772)	0.4240 (0.0625)
K_{IC}								1	0.8518* (0.0001)	0.1571 (0.5084)
FT									1	0.0620 (0.7950)
Sensitivity to compaction speed										1

Figures in parentheses indicate *P* values.

$^{*}P < 0.05$.

attractive forces between molecules [12]. On the other hand, particle morphology was described by the shape index and surface roughness. The shape index represents the regularity of particle shape, and the parameter of surface roughness describes the degree of roughness of particle surfaces.

The relationships between these molecular or particle features and mechanical performances were deduced by Pearson correlation analysis. Further, the canonical correlation analysis was employed to examine the key material properties for controlling mechanical performances of MCC products as described by Bohidar and Bohidar [23]. The correlation matrix for the Pearson correlation analysis is shown in Table 4. K_{IC} shows a moderate correlation to CED $(0.4683, \ P = 0.0373)$. As expected, an increase in intermolecular attraction enhances resistance of MCCs to cracking. Further, K_{IC} also shows a moderate correlation to the crystallinity index $(-0.4683, \ P = 0.0373)$. When the extent of intramolecular hydrogen bonding increases, K_{IC} of MCC decreases. This might be explained by the intramolecular hydrogen bonding confining the polymer chains to a specified aggregation state, thus reducing the free polymer chains able to participate in the intermolecular hydrogen bonding between particles. Since hydrogen bonding is the strongest attractive force among the intermolecular forces, the decrease in intermolecular hydrogen bonding between particles is accompanied by a decrease in mechanical strength of beams. FT displays a moderate correlation to shape index $(-0.4606, \ P = 0.0410)$. When particles of MCC become irregular, FT increases. This might be explained by the irregular particles providing a greater extent of mechanical interlocking, and the energy necessary for crack propagation being larger than that in symmetrical ones. The sensitivity to compaction speed has a moderate correlation with degree of crystallinity $(-0.4839, \ P = 0.0306)$. This result demonstrates that an increase in the amorphous portion of MCC molecules is accompanied by increasing sensitivity of changing compressibility to compaction speed of these polymer solids.

The key material properties of MCC products were evaluated by canonical correlation analysis. The independent variables (X) are material properties (degree of crystallinity, crystallinity index, CED, and shape index). Since the DP and surface roughness correlated to none of the mechanical performances (as shown in Table 4), these two material properties were excluded from the canonical correlation analysis. The dependent variables (Y) are mechanical performances. The first canonical correlation is 0.8917, which is statistically significant based on approximate F statistics of Wilks' Lambda test $(P = 0.0132)$, Hotelling–Lawley Trace test $(P = 0.0020)$, and Roy's Greatest Root test $(P = 0.0001)$. Standardized coefficients and the correlation of the canonical variables with the original variables for the first canonical correlation are shown in Table 5. Considering the coefficients of X-set variables, the CED is the highest contributor to the X's canonical variable. This shows that the attractive force between molecules is the most important material property controlling the mechanical performances of MCC products. The correlation between CED and its canonical variable is moderate (0.6750). At the same time, the degree of crystallinity, crystallinity index, and shape index also present a moderate correlation to their canonical variables $(-0.5540, \ -0.4786$, and -0.4601, respectively). This means that the degree of crystallinity, crystallinity index, and shape index also serve as important material properties controlling the mechanical performances of MCC. All mechanical performances show a moderate correlation to their respective canonical variables. This means that all mechanical performances are well controlled by these material properties of MCC products examined.

Table 5
Canonical correlation analysis of material properties and mechanical performances of MCC products

Variable	Standardized coefficients	Correlation
Material property (X variable)		
Degree of crystallinity	−0.2958	−0.5540
Crystallinity index	−0.1370	−0.4786
Cohesive energy density	0.7389	0.6750
Shape index	−0.5907	−0.4601
Mechanical property (Y variable)		
Young's modulus	0.3965	0.7413
Critical stress intensity factor	0.5458	0.7458
Fracture toughness	0.0212	0.6369
Sensitivity to compaction speed	0.4218	0.6770

5. Conclusions

Among the mechanical performances of MCC products, only fracture toughness and sensitivity to compaction speed were affected by the manufacturing factors. However, the manufacturing factors cannot be used to precisely predict mechanical performances. Nevertheless, a MCC product with high fracture toughness and low sensitivity to compaction speed could be optimally obtained by hydrolysis at high temperature (89°C), of short duration (50 min), and with a low level of HCl (2.50 N). Pearson correlation analysis revealed that the critical stress intensity factor, fracture toughness, and sensitivity to compaction speed of MCC products can be quantitatively predicted by material properties examined in this study. Thus, MCC products with optimized mechanical performances might be obtained by the selection of adequate material properties. The CED, representing the attractive forces between molecules, was found to be the key material property of MCC products controlling their mechanical performances. In addition, the degree of crystallinity, crystallinity index, and shape index may also serve as important properties for controlling the mechanical performances of MCC. Therefore, the influence of source variations of MCC products on the strength of tablets might be reduced by regulation of their CED, degree of crystallinity, crystallinity index, and shape index.

List of symbols

A	projected area of a particle
CED	cohesive energy density
DP	degree of polymerization
E	Young's modulus
F	Fisher's F distribution
f	a correction factor defined in Eq. (2)
FT	fracture toughness
I_{002}	the X-ray diffractogram height at the position of the 002 peak of MCC products
I_{am}	the X-ray diffractogram height of amorphous background of MCC products
K_{IC}	critical stress intensity factor
P	probability
P_m	perimeter of a particle outline
R^2	squared multiple correlation coefficient
r_e	arithmetic mean of the distances between the center of gravity and the perimeter of a particle
U	canonical variable of the independent variables
V	canonical variable of the dependent variables
X	independent variable
Y	dependent variable

Greek letters

α	critical value of probability used in the stepwise multiple regression
ϕ	value for rotatability of the central composite design

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References

[1] M. Landin, R. Martinez-Pacheco, J.L. Gomez-Amoza, C. Souto, A. Concheiro, R.C. Rowe, Int. J. Pharm. 91 (1993) 133.
[2] M. Whiteman, R.J. Yarwood, Powder Technol. 54 (1988) 71.
[3] R.J. Roberts, R.C. Rowe, Powder Technol. 65 (1991) 139.
[4] A.B. Mashadi, J.M. Newton, J. Pharm. Pharmacol. 39 (1987) 961.
[5] R.J. Roberts, R.C. Rowe, P. York, Int. J. Pharm. 125 (1995) 157.
[6] A. Martin, Physical Pharmacy, 4th edn., Lea & Febiger, Philadelphia, PA, 1993, pp. 575–581.
[7] R.J. Roberts, R.C. Rowe, J. Pharm. Pharmacol. 37 (1985) 377.
[8] K. Iida, K. Aoki, K. Danjo, A. Otsuka, C.Y. Chen, E. Horisawa, Chem. Pharm. Bull. 45 (1997) 217.
[9] C. Nyström, G. Alderborn, M. Duberg, P.G. Karehill, Drug Dev. Ind. Pharm. 19 (1993) 2143.
[10] S. Manabe, K. Kamide, Polym. J. 16 (1984) 375.
[11] J.E. Mark, A. Eisenberg, W.W. Graessley, L. Mandelkern, E.T. Samulski, J.L. Koenig, G.D. Wignall, Physical Properties of Polymers, 2nd edn., American Chemical Society, Washington, DC, 1993, pp. 194–195.
[12] R.J. Roberts, R.C. Rowe, Int. J. Pharm. 99 (1993) 157.
[13] K.V.V. Maarschalk, H. Vromans, G.K. Bolhuis, C.F. Lerk, Eur. J. Pharm. Biopharm. 42 (1996) 49.
[14] M.L. Nelson, R.T. O'Connor, J. Appl. Polym. Sci. 8 (1964) 1325.
[15] R. Ek, G. Alderborn, C. Nyström, Int. J. Pharm. 111 (1994) 43.
[16] F. Podczeck, J.M. Newton, Int. J. Pharm. 124 (1995) 253.
[17] R.M. Spriggs, J. Am. Ceram. Soc. 44 (1961) 628.
[18] R.J. Roberts, R.C. Rowe, P. York, Int. J. Pharm. 91 (1993) 173.
[19] A.A. Afifi, V. Clark, Computer-Aided Multivariate Analysis, 2nd edn., Van Nostrand Reinhold, New York, 1990, pp. 252–256.
[20] D.Q.M. Craig, F.A. Johnson, Thermochim. Acta 248 (1995) 97.
[21] G.W. Radebaugh, S.R. Babu, J.N. Bondi, Int. J. Pharm. 57 (1989) 95.
[22] K. Kamide, K. Okajima, K. Kowsaka, T. Matsui, Polym. J. 17 (1985) 701.
[23] N.R. Bohidar, N.R. Bohidar, Drug Dev. Ind. Pharm. 20 (1994) 2165.