Assessment of Processing and Polymorphic Form Effect on the Powder and Tableting Properties of Microcrystalline Celluloses I and II

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Microcrystalline cellulose I (MCCI) is an excipient used as a diluent, disintegrant, glidant and binder for the production of pharmaceutical tablets. In this work, microcrystalline cellulose II (MCCII) was obtained from cotton fibers by basic treatment with 7.5 N NaOH followed by an acid hydrolysis. MCCI and MCCII materials were processed by wet granulation, dry granulation and spray drying. Either the polymorphic form or processing had no effects on the particle morphology or particle size. However, MCCII powders had a higher porosity, less packing tendency, degree of crystallinity, degree of polymerization and density, but a faster disintegration than MCCI. The tensile strength of MCCI was highly affected by the wet and dry granulation processes. Most of the resulting powder and tableting properties were dependent on the polymorphic form of cellulose, rather than on the processing employed.

Key words microcrystalline cellulose II; spray drying; wet granulation; dry granulation

Cellulose is the most abundant polymer in nature composed of glucose units connected through a β-1,4 glycosidic linkage. The polymer chains of this polymer braid together and forms microfibrils in the plants cell wall. Microcrystalline cellulose I (MCCI) is produced by acid hydrolysis of wood pulp.[1] During this process the amorphous regions of the microfibrils are eliminated leaving the most crystalline parts intact.[2] The resulting product is usually washed and spray-dried to get a powder which is classified according to the resulting size, density and moisture content. MCCI is widely used as a pharmaceutical aid for compression of tablets and processes, such as wet and dry granulation and pelletization, respectively. It has a good compressibility, compactibility, lubricity and it is used as a binder, filler and has a good loading capacity for drugs.[3—5]

MCCII is produced by mercerization of MCCI and is the most stable allomorph of cellulose.[1] It is also useful for direct compression, shows less crystallinity and higher density compared to MCCI and disintegrates quickly regardless of the compression force used.[6] MCCII presents an antiparallel arrangement of the conformation of the chains, while MCCI exhibits a parallel chain arrangement. It is reported that the transformation of MCCI to MCCII is carried out without complete loss of the crystalline order.[1] MCCII is useful in the design and development of formulations of rapidly disintegrating tablets.[6] The aim of this study was to evaluate the powder and tableting properties of MCCII produced from cotton and processed by spray drying, wet granulation and dry granulation and compared these properties with those of commercial MCCI treated under the same conditions.

Experimental

Materials MCCI (Novacel PH-101, lot 6N608C, Avicel PH-102, lot c0909048 and Avicel PH-2000, lot 70637) was donated by FMC Biopolymers, Philadelphia, PA, U.S.A. MCCII was obtained from cotton (lot H-111489, JGB, Columbia). Sodium hydroxide (lot 58051305C) and concentrated hydrochloric acid (37%, lot k40039517) were obtained from Carlo Erba, and Merck, respectively.

Methods. Preparation of Microcrystalline Cellulose II (MCCII) Approximately, 150 g of cotton was added to a round bottom flask containing 1800 ml of 2 N HCl. The acid hydrolysis was then conducted for 2 h at 105 °C in a heating mantle (EM0500/CMK4, Electrothermal, U.S.A.). The residue thus obtained was then washed with distilled water until reaching a pH from 5 to 7. This product was soaked for 72 h in a 7.5 N solution of sodium hydroxide at room temperature with periodic stirring. After 72 h the resulting cake was filtered and washed with distilled water until reaching a pH from 5 to 7.

Dry Granulation of MCCII An amount of slurry equivalent to *ca.* 50 g of dry sample was tray-dried at room temperature until reaching a moisture content of less than 10%. This sample was then sequentially sieved through a 6 (3350 μm), 10 (2000 μm), 24 (711 μm), 40 (425 μm) and 100 (150 μm) mesh using an oscillating granulator (Riddhi Pharma Machinery, Gulabnagar, India).

Wet Granulation of MCCII An amount of slurry equivalent to *ca.* 50 g of dry sample was sequentially passed through a 6 (3350 μm), 10 (2000 μm), 24 (711 μm), 40 (425 μm) and 100 (150 μm) mesh using an oscillating granulator (Riddhi Pharma Machinery, Gulabnagar, India) when the moisture content was *ca.* 60, 50, 40, 30 and 20%, respectively. The final powder was dried on a fluid bed drier (Leflu, Indemeg LTDA) for 15 min at 50 °C.

Spray Drying of MCCII Aqueous dispersions of MCCII of about 3% w/v were prepared in a homogenizer (JK-T18, Ultraturrax, Taquara, Brazil) for 5 min at 10000 rpm. The dispersions were then spray-dried on a Buchi mini spray-drier (B-290, Zurich, Switzerland). The operating conditions were: inlet temperature of 194 °C, outlet temperature of 66 °C, drying air velocity of 35 m^3/h, flow rate of 5 ml/min, atomizing pressure of 180 kPa and a nozzle diameter of 800 μm.

Wet Granulation of MCCI About 200 ml of distilled water was added to 100 g of MCCI and mixed manually until a wet mass was obtained. The wet mass was granulated on an oscillating granulator (Riddhi Pharma Machinery, Gulabnagar, India) as described under "wet granulation of MCCII."

Dry Granulation of MCCI About 100 g of MCCI was directly granulated on an oscillating granulator (Riddhi Pharma Machinery, Gulabnagar, India) as described under "dry granulation of MCCII."

Spray Drying of MCCI About 100 g of MCCI was used as obtained from the manufacturer without any further processing since these products come as spray-dried materials.

Principal Component Analysis (PCA) This type of multivariate analysis was used to identify patterns and relationships among the data. PCA transforms the original data solely in terms of the two main eigenvectors or axes which are perpendicular to each other. The software Minitab (v.15, Minitab, Inc, State College, PA, U.S.A.) was used for data processing.

Powder X-Ray Difractograms (XRD) Characterization XRD were obtained over a 5 to 45° 2θ range using a Siemens difractometer (Model D5000, Siemens Energy and Automation, Inc., Madison, WI, U.S.A.), equipped with a monochromatic Cu$K\alpha$ (α_1=1.5460 Å, α_2=1.54438 Å) X-ray radiation. The step width was 0.020° 2θ/min with a time constant of 0.5 s. The Difrac® plus Eva software, version 2.0 (Siemens Energy and Automatization, Inc., Madison, WI, U.S.A.) was used for calculation of the areas by using the following equation (Rabek, 1980):

$$DC = I_C / (I_C + I_A) \cdot 100\% \quad (1)$$

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Where I_C is the sum of the areas of all crystalline peaks, and I_A is the area of a diffuse halo due to the amorphous region.

Powder Properties The optical microphotographs were taken on an optical microscope (BM-180, Boeco, Germany) coupled with a digital camera (S8000fd, Fujifilm Corp., Japan). The true density was determined on a helium picnometer (AccuPyc II 1340, Micromeritics, U.S.A.) with *ca.* 2 g of sample. The bulk density was determined by the ratio of 100 g of sample divided the measured volume. The tap density was measured directly from the final volume of the tapped sample from the AUTO-TAP analyzer (AT-2, Quantachrome instruments, U.S.A.). The Carr's index was obtained from the equation:

$$\varepsilon = \left[1 - \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}}\right] \cdot 100\% \quad (2)$$

Where, ρ_{tap} and ρ_{bulk} are the tap and bulk densities, respectively. Porosity (ε) of the powder was determined from the equation:

$$\varepsilon = \left[1 - \frac{\rho_{bulk}}{\rho_{true}}\right] \cdot 100\% \quad (3)$$

Where ε, $\rho_{bulk,}$ and ρ_{true} are the porosity, bulk density and true density of the powder, respectively.

The degree of polymerization (DP) was obtained by the intrinsic viscosity method [η] at 25±0.5 °C using a Canon-Fenske capillary viscometer (cell size 50) and Cupriethylendiamine hydroxide (CUEN) as solvent.[7] The DP was found by the relationship:

$$DP = 190 \cdot [\eta] \quad (4)$$

The compressibility of the powder was obtained by applying the Kawakita equation[8]:

$$N / ((V_i - V_0) / V_t) = N / a + 1 / ab \quad (5)$$

Where, N is the tap number, V_i the initial volume and V_t the volume at the respective tap number. The constant "a" is related to the total volume reduction for the powder bed (compressibility index) and the constant "b" is related to the resistant forces (friction/cohesion) to compression.[9]

Particle Size Samples were fractionated on a ROTAP sieve shaker (RX29, W.S. Tyler Co., Mentor, OH, U.S.A.) using stainless steel 420, 250, 180,125 105, 75 μm sieves, stacked together in the order written (Fisher Scientific Co., Pittsburgh, PA, U.S.A.). Approximately 50 g of the sample was shaken for 30 min followed by weighting the fractions retained in each sieve. The geometric mean diameter, d_g, and particle size distribution were determined from the log-normal distribution plot constructed between the sieve mean diameter and cumulative percent frequency using the Minitab software (v.15, Minitab, Inc., State College, PA, U.S.A.).

Preparation of Compacts Compacts weighting *ca.* 500 mg were made on a rotary tablet press having eight stations (Lefly, Riddi Pharma Machinery, India) coupled with a 13 mm flat-faced tooling. The compression force was adjusted so the resulting compacts have a solid fraction of *ca.* 0.7.

Disintegration Time The USP/NP method was employed. Briefly, a Hanson disintegrator (39-133-115, Hanson Research Corporation, Northridge, CA, U.S.A.) was used with water maintained at 37±2 °C and 30 strokes/min.[10]

Compact Tensile Strength It was determined on a Vankel hardness tester (UK 200, VANKEL, Manasquan, NJ, U.S.A.). Each compact was placed between the platens and the crushing force was then measured. The radial tensile strength (TS) values were obtained according to the Fell and Newton equation[11]:

$$TS = \frac{2F}{\pi Dt} \quad (6)$$

Where, F is the breaking force (N) needed to break the compact into two halves, D is the diameter of the compact (mm), and t is the compact thickness (mm).

Swelling Studies (Swelling Values) The swelling value is expressed as the ratio of the expanded volume of the powder after placing water and the initial sample weight. It was determined as reported previously by Edge and collaborators.[12] Briefly, approximately 500 mg of the powder was vigorously dispersed in a 10 ml graduate cylinder filled with 10 ml of distilled water at room temperature and the increase in volume of the powder was measured with time.

Water Uptake Rate It was determined according to the reported procedure Zhao and Ausburger min minor modifications.[13] Briefly, a funnel (diameter 6 cm), attached to a Tygon tubing at the stem, was placed on an analytical balance (Model, HT220E, Shinko Denshi Co., Japan) with the help of a tripod stand. The Tygon tubing was long enough to deliver water into a collecting vessel placed next to the balance. A Whatman filter paper (diameter 90 mm) was wetted with distilled water and placed in the funnel. An accurately weighed sample of the test material (*ca.* 500 mg) was then added and the weight of the stand, funnel, wetted filter paper, powder, and the tygon tube, was measured altoguether. Ten milliliters (10 ml) of distilled water was then poured into the funnel and the change in weight as a function of time was then recorded.

Results and Discussion

Table 1 shows the results of the tests suggested by the British Pharmacopoeia for microcrystalline cellulose. Although these tests were designed for MCCI, results demonstrated that MCCII as obtained from cotton also complies with the pharmacopoeia requirements. This means that the MCCII allomorph of cellulose could potentially get the acceptance as a pharmaceutical excipient.

The powder XRD of MCCI obtained from the different sources and the commercial products (Novacel PH-101, Avicel PH-102 and Avicel PH-200) are shown in Fig. 1. It is well known that cellulose I exhibits a parallel arrangement of the chains.[1] Thus, MCCI materials displayed the following characteristic diffraction peaks due to the cellulose I lattice at 14.8, 16.3 and 22.4° 2θ, corresponding to the 1$\bar{1}$0, 110 and 200 reflections, respectively.[6] A shoulder at 20.4° 2θ has also been also identified in some cellulose I excipients.[15] On the contrary, MCCII materials showed crystalline peaks at 12, 20 and 22° 2θ corresponding to the 110, 110 and 200 reflections, respectively, confirming the presence of the cellulose II lattice.[16]

The morphology of the powders is shown in Fig. 2. Independent of the process used and the cellulose type all samples showed from an elongated to a fibrous shape. Further, particles of MCCI samples such as Avicel PH-102 and Avicel PH-200 presented an aggregated morphology. The original long fibers of cotton (the source for MCCII) are chopped down into smaller ones during the hydrolysis and granulation steps, especially when they passed through the smaller mesh (150 μm). Further, MCCI is a spray dried material derived from softwood sources. Either processing or the polymorphic form did no caused major morphological differences between MCCI and MCCII. Most of the spray dried MCCI products still keep the prevalent fibrous and elongated shape morphology after processed by wet or dry granulation.

The particle size diameters and the particle size distribu-

Table 1. Compliance of MCCII with the British Pharmacopoeia Specifications[14]

Test	Specification	Result
Identification	A violet-blue color is form with $ZnCl_2$	Passed
Acidity or alkalinity	pH of 5—7.5	7.15
Ether-soluble substances	Max. 0.05%	0.001%
Water soluble substances	Max. 0.2%	0.005%
Starch and dextrins	No blue or reddish brown color is produced	Passed
Heavy metals	Max. 10 ppb	0.1 ppb
Organic impurities	No red color is produced	Passed
Loss on drying	Max. 6%	3.2%
Sulphated ash	Max. 0.1%	0.01%

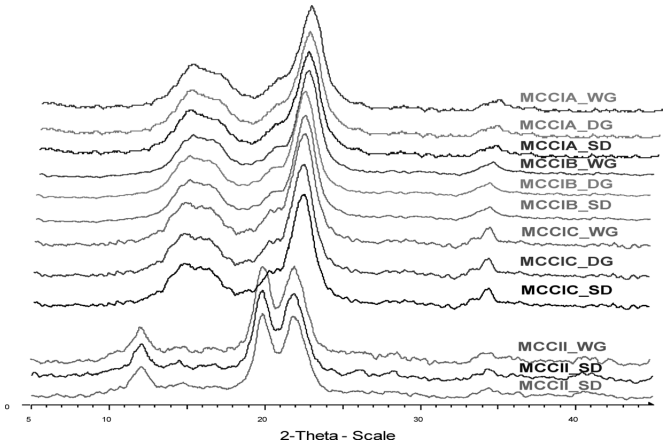

Fig. 1. Powder X-Rays Difractograms of MCCI (Novacel PH-101, Avicel PH-102 and Avicel PH-200) and MCCII Processed by Wet (WG) and Dry Granulations (DG) and Spray Drying (SD), Respectively

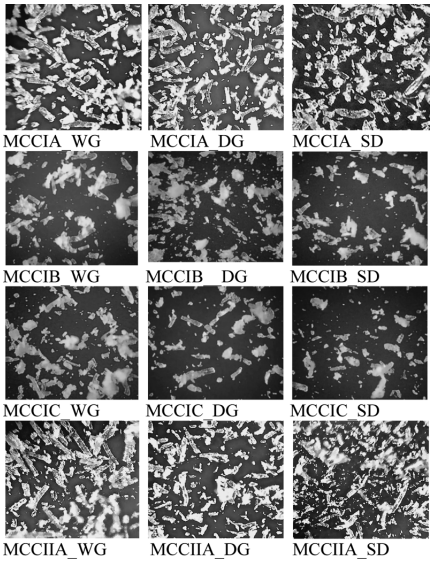

Fig. 2. Optical Microphotographies of MCCI (Novacel PH-101, Avicel PH-102 and Avicel PH-200) and MCCII Processed by Wet (WG) and Dry Granulations (DG) and Spray Drying (SD)

tion are shown in Table 1 and Fig. 3, respectively. Most of the distributions of the cellulosic materials were narrow and positively skewed. However, MCCIC_SD, MCCIC_DG, MCCIB_SD and MCCIB_DG showed the widest distribution of particle size. Particle size depended on the process employed rather than on the polymorphic form of cellulose. The wet granulation process slightly increased the particle size of MCCII, probably due to the high affinity of this material for water. On the contrary, the wet and dry granulation processes reduced the particle size for Avicel PH-102 and Avicel PH-200 which initially showed high particle sizes.

The acid mediated degradation of the large molecular weight cellulose obtained from cotton with a DP of *ca.* 1370 leads to a reduction of the DP to *ca.* 73—78 for MCCII. Lin and collaborators reported values of DP for cotton linter of 1565.[17] During the acid hydrolysis step, the acid mainly attacks the glycosidic bonds located on the less ordered surface of the microfibrils since they are more accessible than the glycosidic bonds located in the ordered regions of the microfibrils of cellulose. For this reason, the hydrolysis kinetic is initially fast and then slows down and levels off when most of the amorphous regions are hydrolyzed.[1] The larger values of DP obtained for MCCI are due to the presence of the less accessible regions of this allomorph during the hydrolysis step.

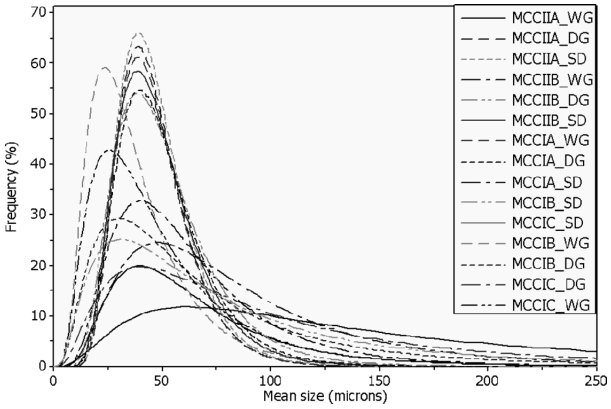

Fig. 3. Particle Size Distribution for MCCI and MCCII Processed by Spray Drying, Wet and Dry Granulations, Respectively

Results also demonstrated that processing and the polymorphic form had a strong effect on the bulk density, voluminosity and hence, on the Carr's index. Likewise, the degree of volume reduction (given by the compressibility index) and packing tendency of MCCI and MCCII was comparable and it was not affected by the process employed. In most cases, for the same process, values of bulk and tap density of MCCI were larger than those of MCCII indicating a better particle packing for MCCI. Since voluminosity is the reciprocal of the bulk density, the MCCI data of voluminosity for the same process were smaller than those of MCCII. Further, for the same process, values of true density of MCCI were slightly larger than those of MCCII. This means that MCCI had a higher molecular packing than MCCII. These values were reflected on the values of porosity obtained. In this case, for the same process MCCII had larger values than MCCI. The antiparallel arrangement of the chains encountered for MCCII might render a wider spacing between the crystals of the chains allowing for a larger mobility. This is reflected on the larger powder porosity values obtained for MCCII.

The process of granulation had a negative effect only on the tensile strength of the compacts made from Novacel PH-101. This effect might be related with the strain hardening or hornification. In other words, this material becomes less plastic after wet of dry granulation.[18] Other studies suggested that both work of hardening and large particle sizes, which are generated after dry granulation might be the cause for the loss of compactibility.[19] The work of hardening establishes that during dry or wet granulation a great amount of defects in the particles and entanglement of new dislocations occurs while being deformed plastically. These defects hardens particles and makes plastic deformation more difficult for a subsequent compaction process.[20,21] MCCII on the contrary, showed smaller tensile strength values than MCCI since it is a less plastic material.[6,22] MCCII compacts also showed faster disintegration times than MCCI. Perhaps, the fact of having a larger porosity, water uptake rate and swelling value

Table 2. Matrix Used for the Principal Component Analysis of MCCI

CT	A	A	A	B	B	B	C	C	C
PR	WG	DG	SD	WG	DG	SD	WG	DG	SD
DG (μm), $n=1$	42	53.3	41.9	42.4	75.7	92.8	55.4	113.2	187.5
C, $n=1$	0.4	0.3	0.3	0.4	0.3	0.4	0.4	0.4	0.4
DP, $n=1$	218.2	232.7	221.6	223.4	225.4	226.3	220.5	227.6	229.4
DC (%), $n=1$	73.4	70.1	75.2	72.8	74.6	72.1	76.1	74.3	75.1
P	0.76	0.81	0.77	0.77	0.77	0.77	0.75	0.75	0.77
BD (g/cc), $n=3$	0.38±0.00	0.31±0.00	0.36±0.01	0.36±0.01	0.36±0.01	0.37±0.01	0.39±0.01	0.35±0.00	0.37±0.00
TD (g/cc), $n=3$	0.49±0.01	0.41±0.00	0.47±0.01	0.58±0.01	0.50±0.01	0.49±0.03	0.48±0.01	0.47±0.00	0.52±0.00
CI (%), $n=3$	25.3±1.0	23.5±0.8	29.9±0.9	37.6±1.5	29±0.88	27.4±0.6	19.5±1.6	26.6±0.5	28.8±0.7
V (cc), $n=3$	2.7±0.0	3.2±0.0	2.6±0.0	2.8±0.1	2.81±0.1	2.8±0.2	2.6±0.1	2.9±0.1	2.7±0.1
D (g/cc), $n=3$	1.57±0.00	1.60±0.00	1.58±0.00	1.58±0.00	1.58±0.00	1.58±0.00	1.57±0.00	1.57±0.00	1.581±0.00
TS (Mpa), $n=3$	0.08±0.01	0.05±0.02	0.12±0.01	0.18±0.02	0.23±0.02	0.22±0.01	0.17±0.01	0.18±0.01	0.18±0.02
DT (s), $n=3$	535.0±17.5	293.2±59.0	236.3±2.9	1141±113	1257±118	1461±459	1275±60	1390±37	1437±67
WUR (ml/s), $n=1$	0.31	0.35	0.32	0.31	0.39	0.32	0.31	0.26	0.29
SV, $n=3$	0.7±0.0	0.8±0.0	0.8±0.0	0.6±0.0	0.6±0.0	0.8±0.0	0.6±0.0	0.5±0.0	0.9±0.0

WG wet granulation, DG dry granulation, SD spray drying, A, Novacel PH-101; B, Avicel PH-102; C, Avicel PH-200; P porosity, DG geometric mean diameter, C compressibility index, DP degree of polymerization, DC degree of crystallinity, BD bulk density, TD tap density, V voluminosity, D true density, TS compact tensile strength, DT compact disintegration time, WUR water uptake rate, SV swelling value.

Table 3. Matrix Used for the Principal Component Analysis of MCCII

PR	WG	DG	SD	WG	DG	SD
CT	MCCII	MCCII	MCCII	MCCII	MCCII	MCCII
Lot	A	A	A	B	B	B
DG (μm), $n=1$	61.2	44.4	42.3	54.8	47.7	45.8
C, $n=1$	0.4	0.2	0.3	0.4	0.2	0.3
DP, $n=1$	73.5	77.3	76.8	74.8	77.3	72.4
DC (%), $n=1$	66.1	64.3	60.2	62.4	63.1	64.3
P	0.79	0.80	0.78	0.80	0.82	0.79
BD (g/cc), $n=3$	0.32±0.00	0.28±0.00	0.34±0.00	0.31±0.00	0.27±0.00	0.33±0.00
TD (g/cc), $n=3$	0.43±0.00	0.37±0.00	0.51±0.00	0.42±0.00	0.36±0.00	0.50±0.00
CI (%), $n=3$	23.7±0.2	24.1±0.0	34.3±0.6	25.0±0.0	24.0±0.0	34.0±0.0
V (cc), $n=3$	3.1±0.1	3.5±0.0	3.0±0.0	3.2±0.0	3.7±0.0	3.0±0.0
D (g/cc), $n=3$	1.56±0.00	1.57±0.00	1.56±0.00	1.57±0.00	1.58±0.00	1.58±0.00
TS (Mpa), $n=3$	0.11±0.00	0.17±0.00	0.11±0.04	0.10±0.00	0.13±0.00	0.10±0.00
DT (s), $n=3$	29.7±0.6	45.3±5.5	21.0±2.0	20.3±0.6	30.7±0.8	18.3±2.4
WUR (ml/s), $n=1$	0.45±0.00	0.44±0.00	0.46±0.00	0.45±0.00	0.45±0.00	0.46±0.00
SV(ml/g), $n=3$	1.1	1.3	1.2	1.2	1.2	1.1

WG wet granulation, DG dry granulation, SD spray drying, A, Lot 1; B, Lot 2; P porosity, DG geometric mean diameter, C compressibility index, DP degree of polymerization, DC degree of crystallinity, BD bulk density, TD tap density, V voluminosity, D true density, TS compact tensile strength, DT compact disintegration time, WUR water uptake rate, SV swelling value.

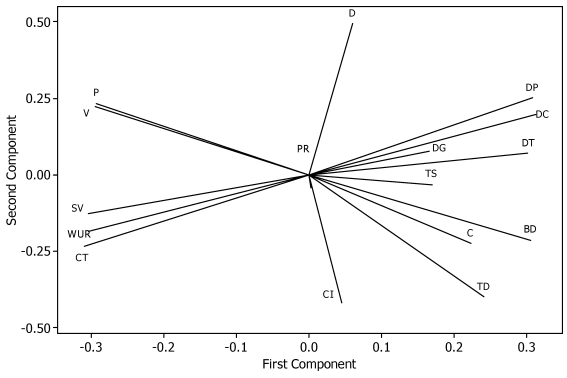

Fig. 4. Principal Component Analysis Showing the Relationship among the Variables Studied

and a less degree of crystallinity than MCCII might play an important role in disintegration for MCCII.

The loading plot of measured properties is shown in Fig. 4. The lines show the projections of the original powder properties on to the PC1 and PC2 using the coordinate scales on the X and Y axis, respectively. The numbers on the axis are in arbitrary units. The cellulose type had a major influence on the degree of polymerization, degree of crystallinity, disintegration time, and a minor influence on the packing tendency and bulk and tap densities. This indicates that these properties depended mainly on the polymorphic form of cellulose (MCCI and MCCII) rather than on processing. Further, in most cases except for voluminosity, swelling value, water sorption rate and porosity the former properties were lower in value for MCCI than for MCCII. On the contrary, processing only had a slight effect on the true density and Carr's index of cellulosic excipients.

Conclusion

Particle morphology and particle size were not affected by either the polymorphic form of MCC, or the process employed. In general, MCCII powders had a higher porosity, less degree of packing, lower degree of crystallinity, lower degree of polymerization and density, but a faster disintegration than MCCI. The tensile strength of MCCI was highly affected by the wet and dry granulation processes. Most of the

resulting powder and tableting properties were dependent on the polymorphic form of MCC, rather than on processing. It is important to select the right polymorphic form of MCC before formulating a drug in a solid dosage form since it could affect the overall powder and tableting properties of the mixture.

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