Evaluation of Microcrystalline Cellulose Prepared From Sisal Fibers as a Tablet Excipient: A Technical Note

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Nitin A. Bhimte[1] and Pralhad T. Tayade[2]

[1]Department of Pharmaceutics, The Bombay College of Pharmacy, Kalina, Santacruz (E), Mumbai 400 098, India
[2]Yadaogaon Tasgaonkar Institue of Pharmacy, Karjat, India

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INTRODUCTION

Microcrystalline cellulose (MCC), introduced in the early 1960s, is regarded as the best excipient for direct compression tableting.[1-3] Several reports have described various methods of preparing pharmaceutical-grade MCC from absorbent cotton[4-6]; however, there is a constant search for new sources of MCC because of the high cost of commercially available products. Traditionally, MCC has been prepared from bamboo,[1,3] wood pulp,[4] and viscose rayon.[5] Attempts have also been made to produce MCC from other sources such as newsprint waste,[7] hosiery waste,[8] and corncobs,[9] as well as from fast-growing plants including *Sesbania sesban, S roxburghii,* and *Crotalaria juncea*.[10] The particle size distribution, packing, and flow properties of MCC, as well as the tableting[11] and disintegration characteristics,[12] are well documented. Attempts have also been made to understand the mechanism of the disintegration action of MCC in tablets.[12]

Earlier, MCC was prepared from wood pulp and cotton linters. The other agrowaste materials mentioned above used for preparing MCC are also used for other products such as pulp and paper. Sisal (*Agavae sisalana Perrine)* fiber is one such cellulosic source, which is abundantly available and not regularly used for manufacturing costly cellulosic products. For a long time, sisal fiber has been used to prepare ropes and cordages as well as coarse textile materials such as netting and matting, but its use for preparing costly cellulosic products would be of great advantage. Because the process is simple and economical, cottage units in small-scale sectors may be set up to recycle sisal fibers into industrially important MCC.

In the present study, an attempt has been made to evaluate the MCC prepared from sisal fibers and to examine its feasibility as a tablet diluent or disintegrant. This product was evaluated with reference to the pioneer product Avicel PH-102, the Indian products Flocel-102 and Ranq-102, and a fine-powder MCC from a local source. The types of cellulose were evaluated for moisture content and for packing properties in terms of bulk density, tapped density, true density, and porosity. Flow properties included the battery of tests suggested by Carr, which includes angle of repose, angle of spatula, percentage compressibility, and cohesion or uniformity coefficient.[13,14] Particle size and size distribution of the cellulose were evaluated by laser diffractometry. Scanning electron microscopy was used to study the particle morphology. The crystallinity index for all cellulose types was calculated from the data of x-ray diffraction analysis. The tablets were prepared using each type of cellulose as a diluent and disintegrant separately, for the model drug captopril. Tablets were also prepared with MCC in conjugation with a carrageenan (GP-379 NF), to study the effect of MCC on the release profile of these tablets. Tablets were evaluated for crushing strength, thickness, disintegration time, and dissolution profile. The prepared tablets were also compared with existing marketed tablets (Aceten 25 mg) for disintegration time and dissolution time profile.

Corresponding Author: Pralhad T. Tayade, Yadaogaon Tasgaonkar Institue of Pharmacy, Karjat, India. Tel: 91-22-26670871; Fax: 91-22-26670816; E-mail: pralhadtayade@yahoo.com

MATERIALS AND METHODS

Materials

The 4 samples of microcrystalline cellulose were used as received from the suppliers: Avicel PH-102 (FMC Corp, Philadelphia, PA), Flocel-102 and Ranq 102 (Gujarat Microwax Ltd, Gujarat, India), and a pharmaceutical-grade fine-powder MCC was generously donated by Ajanta Pharma Ltd (Mumbai, India). The sisal fibers were obtained from Khadi and Village Industries Commission (Mumbai, India). Captopril was a gift sample from Wockhardt Ltd (Mumbai, India). One *i*-carrageenan, GP-370 NF, was generously donated by FMC Corp. Marketed captopril tablets (Aceten 25 mg) were used for comparison of disintegration time and dissolution time profile with that of prepared tablets. All other chemicals and reagents used were of analytical grade. For convenience, all MCC samples were termed as follows: Avicel PH-102, Flocel-102, a fine-powder MCC (AJ), Ranq-102, and MCC from sisal fibers (MCC-SI).

Preparation of Microcrystalline Cellulose From Sisal Fibers

Sisal fibers (120 g) were extracted with a boiled ethanol-benzene mixture for 6 to 8 hours, so that the siphoning from the extractor was not less than 4 times per hour. After extraction with the ethanol-benzene mixture, the excess solvent was removed by suction, and the thimble as well as the material in it was washed with ethanol to remove traces of benzene. The sisal fibers were extracted again with 95% ethanol for 4 hours until the alcohol siphoned was colorless.

The sample from the thimble was transferred to a Buchner funnel, and the excess solvent was removed by suction. The material was washed several times with distilled water to remove traces of ethanol. The sample was finally allowed to air dry thoroughly. The proximate analysis of this material gave the following results: ash content (0.25%), α-cellulose (93.00%), lignin (0.06%), and moisture content (5.95%) by weight.

This material was washed several times with distilled water until it became acid free, and then was kiered in an autoclave using a solid:liquor ratio of 1:20 with 2% sodium hydroxide solution for 3 hours. The resultant product was washed thoroughly with water followed by 0.1% acetic acid. The pulp thus obtained was bleached with sodium chlorite ($NaClO_2$) and buffer solution to get a maximum brightness. The process of 3-stage bleaching was performed as follows:

- Stage 1—Bleached with water, buffer solution, and sodium chlorite.
- Stage 2—Thirty minutes after stage 1, bleached with buffer solution and sodium chlorite solution.
- Stage 3—Thirty minutes after stage 2, bleached with buffer solution and sodium chlorite solution.

This material was then treated with 0.3% sodium metabisulphite for 45 minutes to remove chlorine from pulp. This bleached pulp was then treated with 17.5% sodium hydroxide solution with constant stirring for 90 minutes to get pure α-cellulose. The α-cellulose thus obtained was hydrolyzed by 2 N HCl, keeping the solid:liquor ratio of 1:20 and refluxing at 105ºC ± 2ºC for 15 minutes. After hydrolysis, the material was washed thoroughly with water and then treated with 1% ammonium hydroxide solution followed by washing with distilled water, and then air dried. This final material was MCC, obtained as dried cake, which was powdered and stored until further evaluation.

Determination of Micromeritic Properties of Cellulose

Measurement of Bulk Density, Tapped Density, and Percentage Porosity of Microcrystalline Cellulose

The bulk and tapped densities were measured in a 50-mL graduated measuring cylinder as a measure of packability of the MCC powders. The sample contained in the measuring cylinder was tapped mechanically by means of a constant-velocity rotating cam with the change in its initial bulk density to a final tapped density when it attained its most stable form (ie, unchanging arrangement). The porosity was calculated from the values of the bulk and tapped density using the following formula:

$$\%\ Porosity = \left(1 - \frac{True\ Volume}{Bulk\ Volume}\right) \bullet 100 \qquad (1)$$

True density was determined by pycnometer using water displacement method. Each experiment was performed in triplicate.

Particle Size and Size Distribution

The particle size analysis was performed by laser diffractometry (Malvern Particle Mastersizer S, Version 3.00, Malvern Instruments Ltd, Malvern, UK). The medium used was isopropyl alcohol. The beam length was 2.4 mm. The obscuration for all samples was kept in between 15% and 20%.

Flow Properties of Cellulose

A battery of tests described by Carr was performed to determine flowability indices for the MCC powders.[13,14] In brief, the angle of repose was determined by using a fixed-base cone method, and the angle of spatula was determined by measuring the angle of powder on a spatula lifted from a powder bed and averaging that number with the angle of powder remaining on the spatula after it falls from a set height. Uniformity coefficient, obtained by the sieve analysis of the sample, is a numerical value arrived at by dividing the width of the sieve opening that will pass 60% of the sample by the width of sieve opening that will pass just 10% of the sample. Percentage compressibility was determined using the following formula:

$$\%\ Compressibility = \left(\frac{Tapped\ Density\ -\ Bulk\ Density}{Tapped\ Density}\right) \bullet 100 \qquad (2)$$

The values obtained for these 4 parameters were converted into index numbers using Carr's table.[6,7] All above experiments were done in triplicate.

Powder X-ray Diffractometry

Powder x-ray diffraction patterns of all the MCC samples were recorded on a Jeol JDX-8030 x-ray diffractometer using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a current of 25 mA (Jeol Ltd, Tokyo, Japan). The scanning

rate employed was 1° min^{-1} over 10° to 40° 2θ (diffraction angle) range. The crystallinity index was determined for all MCC samples by Segal's formula[15]:

$$\%\ Crystallinity\ Index = \left(\frac{I_{020} - I_{am}}{I_{020}}\right) \bullet 100 \qquad (3)$$

where, I_{020} = Intensity at 22.5° and I_{am} = Lowest 2θ value near 18°.

Moisture Content Determination

A specimen sample weighing ~2 g (A), for each MCC, was kept at 105°C for 8 hours, and then weighed again (B).[16] The moisture content was calculated using the following formula:

$$Moisture\ Content = \left(\frac{A - B}{A}\right) \bullet 100 \qquad (4)$$

The experiment was performed in triplicate to check the reproducibility of results.

Scanning Electron Microscopy

Particle morphology of all the MCC samples was studied by using PHILIPS XL-30 scanning electron microscope (SEM) (Philips FEI quanta200, FEI, Hillsboro, OR). The samples were mounted on a specimen stub with double-sided adhesive tape and subjected to gold sputter coating to render them electrically conductive.

Tablet Preparation and Evaluation

Tablets using MCC as a diluent and as a disintegrant were prepared separately on a 16-station single-rotary machine (GMC, Mumbai, India), manually using a 9-mm standard concave punch for the model drug, captopril. The crushing strength of all the tablets was maintained at 30 to 40 N because there was variation in the compaction force required to produce a tablet, and it was impossible to maintain the same compression force for all MCC tablets. Crushing strength of the tablets was measured by the Erweka crushing strength tester (Erweka, GmbH, Ottostrasse, Germany). As a diluent, the MCC concentration was 50% wt/wt, which was mixed thoroughly with dicalcium phosphate to get the final diluent concentration of 82% wt/wt. As a disintegrant, the MCC was used at a concentration of 10% wt/wt. The materials were added by using the method of serial dilution and then tumble mixing in an airtight polyethylene bag for 30 minutes before compression (average tablet weight, 250 ± 5 mg).

Modified release tablets were prepared by mixing MCCs and carrageenan (GP-379). MCC was mixed thoroughly with carrageenan (GP-379 NF) in 3 different proportions (1:0.5, 1:1, and 1:1.5). The tablets were checked for crushing strength, disintegration time, and in vitro drug release using a USP-24 dissolution tester (Electrolab, Mumbai, India) with the paddle rotating at 50 rpm in 0.1 N HCl as dissolution medium at 37.7°C ± 2°C. The amount of drug released was determined spectrophotometrically at 206 nm (Shimadzu UV spectrophotometer 160A, Shimadzu Corp, Kyoto, Japan). The disintegration time and drug release profile of the prepared tablets was compared with existing commercial tablets of captopril. The batch size consisted of 50 tablets.

Results and Discussion

Physicochemical Characterization

There was no comparable difference in the x-ray diffraction pattern of all cellulose samples. The diffraction pattern appeared the same as shown in Figure 1. The crystallinity index calculated by Segal's formula was also approximately the same for all samples except for Ranq-102, which showed a crystallinity index as high as 70%. The crystallinity index of all other samples was found to be around 60%.

In the SEM photomicrographs of the cellulose, it can be seen that the particles of Avicel-102 appeared small and plate shaped. The particle size of Ranq-102 and Flocel-102 is very large in comparison with other samples. These samples contain a good amount of angular, fibrous particles along with a few plate-like structures. The particles of MCC fine powder appeared as a mixture of plate-shaped particles and thread-like structures tending to form aggregates. MCC from sisal fibers appeared as long thread-like fibers. This difference must be because of processing of the samples. The difference in the morphology of the particles was evident in the packing and flow characteristics of the material.

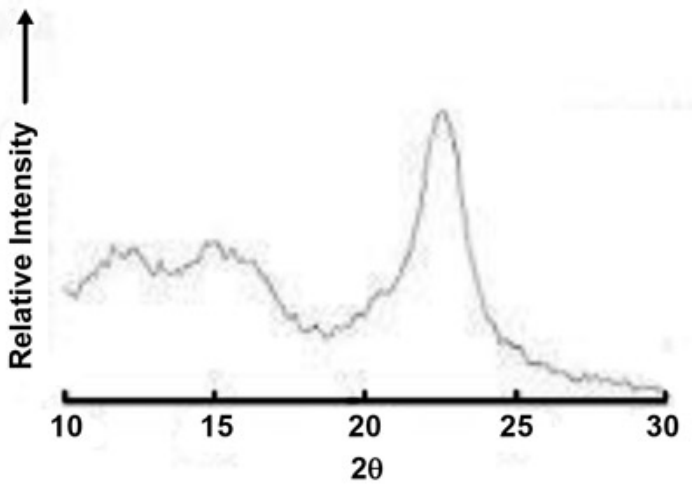

Figure 1. X-ray diffraction pattern of all MCC samples.

Table 1. Micromeritic Properties of Various Cellulose Types*

Sample Name	Bulk Density, g/mL	Tapped Density, g/mL	True Density, g/mL	Porosity, %	Moisture Content, %	Mean Volume Diameter, μm
Avicel	0.325 ± 0.05	0.440 ± 0.05	1.322 ± 0.07	26.00 ± 2.00	3.96 ± 0.65	130.82
Flocel	0.321 ± 0.04	0.406 ± 0.04	1.350 ± 0.08	24.70 ± 3.25	4.27 ± 0.75	153.00
MCC(AJ)	0.312 ± 0.05	0.431 ± 0.03	1.372 ± 0.09	27.66 ± 2.35	5.06 ± 0.65	62.17
Ranq	0.303 ± 0.06	0.385 ± 0.04	1.331 ± 0.08	22.00 ± 3.32	4.91 ± 0.69	117.93
MCC-SI	0.238 ± 0.06	0.333 ± 0.04	1.314 ± 0.09	29.33 ± 3.25	4.27 ± 0.72	115.99

* MCC indicates microcrystalline cellulose; MCC (AJ), a fine powder MCC; and MCC-SI, MCC from sisal fibers. All values represent mean ± SD (n = 3).

Moisture Content and Micromeritic Properties of Cellulose

The most variable attribute in the powder characterization was particle size distribution. Table 1 shows the mean particle size in terms of mean volume diameter of particles. The size distribution pattern for all MCC samples was different. Flocel-102 showed the particles with larger size followed by Ranq-102. Pharmaceutical-grade fine powder MCC and MCC prepared from sisal fibers were similar with respect to particle size. Avicel-102 satisfactorily fit a log normal distribution (R^2 = 0.9278) and Flocel-102 also showed an acceptable log normal distribution (R^2 = 0.9471). In contrast, the other cellulose samples did not show good log normal distribution of particle size (R^2 < 0.890; sisal fiber MCC showed R^2 = 0.872). Table 1 shows the moisture content of MCC samples. Moisture content for each sample was found to be around 5% wt/wt, and no value exceeded 7% wt/wt (limits of US Pharmacopeia/National Formulary [USP/NF]-24/19). The moisture sorption of the cellulose is related to the crystallinity of the MCC powders,[17] and the low values of moisture content are indicative of higher crystallinity.

All MCCs exhibit low bulk and tap densities as tabulated in Table 1, and this is in accordance with the reported literature.[11,18-20] The lowest values were observed for the MCC prepared from sisal fibers; however, the difference in the packing properties was found for all the samples as shown in Table 1. This difference in the packing properties of the products is probably because of the difference in particle size distribution and particle shape.

Particle shape should have been a critical determinant in the density determination, as all the MCC samples except sisal fiber MCC were spherical as depicted in Figure 2. The MCC prepared from sisal appeared fibrous. Bulk density for all other samples of MCC was found to be lower than Avicel-102. There was no comparable difference in true density for all samples as shown in Table 1. The consequences of particle shape were also reflected in the porosity as there is considerable difference in the porosity values of all the cellulose types as given in Table 1. The lower porosity values were found for the materials having bigger particle size such as for Flocel-102 and Ranq-102.

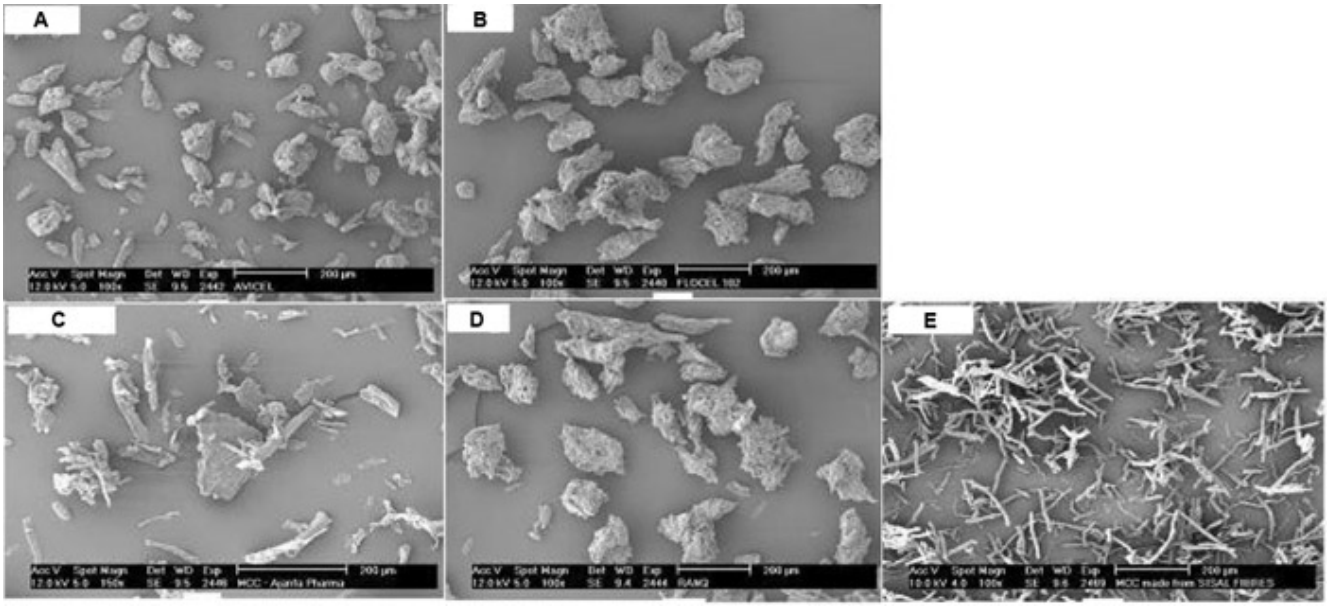

Figure 2. Scanning electron microscope photomicrographs of MCC samples: (A) Avicel; (B) Flocel; (C) a fine powder MCC, MCC (AJ); (D) Ranq; and (E) MCC from sisal fibers, MCC-SI.

Table 2. Carr's Battery of Tests to Evaluate Flow Properties of Powders

Degree of Flowability	Flowability Index	Angle of Repose (°)	Compressibility (%)	Angle of Spatula (°)	Uniformity No.
Excellent	90-100	25-30	5-10	25-31	1-5
Good	80-89	31-35	11-15	32-38	6-8
Fair	70-79	36-40	16-20	39-45	9-12
Passable	60-69	41-45	21-25	46-60	13-17
Poor	40-59	46-55	26-31	61-76	18-22
Very poor	20-39	56-65	32-37	76-90	23-35
Very very Poor	0-19	66-90	>38	>91	>36

Flow Properties of Cellulose

Flow characteristics of the pharmaceutical excipients are of major concern with respect to the handling and compaction of the powder materials, especially for directly compressible excipients. The angle of repose gives a qualitative assessment of internal and cohesive frictions. An angle up to 40° indicates reasonable flow potential and those with an angle greater than 50° exhibit poor flow or absent flow. Angle of repose measurements are sensitive to moisture content and may provide a means of monitoring batch-to-batch differences.

Compressibility is calculated from bulk density and tapped bulk density. Compressibility value of 20% and above indicates a powder that is not free flowing and that has a tendency to create bridges in the hopper. Materials with compressibilities of 40% to 50% are particularly difficult to discharge from the hopper.

Cohesion is a descriptive measure of interparticle forces based on the behavior of the material during sieving. It is an apparent cohesive force existing on the surface of the fine particles that are composed of millions of atoms or molecules.[13] Powders with a higher cohesion percentage do not flow well, and care must be taken in designing factors, hoppers, and other handling equipment.[13]

Angle of spatula gives a relative angle of internal friction of the material and a large number indicates poor flowability.

Flowability was determined using Carr flowability table[13,14] (Table 2). The values obtained for angle of spatula, angle of repose, compressibility, and cohesion are converted into index numbers using this table. These index numbers are then totaled to give a flowability index. High numbers (80-100) indicate that bridge-braking measures are unnecessary. Numbers below 60 indicate that flowability is poor, and vibration or special apparatus and techniques may be required to get the material to flow through a hopper.[21] The results obtained are tabulated in Table 3, and it showed that the overall flow does not depend on 1 or 2 aspects of flow. As seen from the data, a "good sample" may have poor percentage compressibility or poor angle of spatula, and the data obtained was in agreement with the work done by Carr.

The difference in the flow properties can be attributed to the difference in the moisture content (which affects cohesiveness), particle shape, and particle size distribution as reflected in the packing properties.[11] No sample was found to be excellent in terms of flow properties. Avicel-102 and Flocel-102 were found to be "good." Surprisingly, Flocel-102 received more points than Avicel-102. Ranq-102 was found to be "fair," and the fine-powder MCC sample and MCC from sisal fibers were found to be poor flowing. These findings could be attributed to the characteristic particle shape of the cellulose. The angle of repose and angle of spatula were also found to be poor for these samples. Uniformity of cohesion was good for almost all samples of MCC. Avicel-102 was found best in this respect.

Evaluation of Tablets Prepared Using Different Cellulose Types

There were variations in the force necessary to compact the various mixtures, especially when MCC was used as a diluent. This type of variation in the force was not prominent when the MCC was used as a disintegrant.

A possible effect of the moisture content of the powders on strength cannot be excluded,[3,19,21,22] although its importance

Table 3. Evaluation of MCC According to Carr*[13,14]

Samples	Angle of Repose, °	% Compressibility	Angle of Spatula, °	Uniformity No.	Flowability Index
Avicel	30.00 ± 2.0	26 ± 1	38.00 ± 2.5	1.41	82.0
Flocel	27.78 ± 1.25	24 ± 1	35.63 ± 2.6	1.60	85.0
MCC(AJ)	61.92 ± 3.10	28 ± 2	52.50 ± 4.6	1.60	59.0
Ranq	39.70 ± 1.58	21 ± 2	52.91 ± 3.5	1.13	74.5
MCC-SI	65.20 ± 3.20	18 ± 1	51.00 ± 3.0	2.00	56.0

* MCC(AJ) indicates a fine powder microcrystalline cellulose; MCC-SI, MCC from sisal fibers.

Table 4. Evaluation of Tablets Made From MCC*

	MCC as a Diluent		MCC as a Disintegrant	
Sample	Thickness, mm	Disintegration Time, s	Thickness, mm	Disintegration Time, min
Avicel	3.3 ± 0.2	18 ± 2	3.0 ± 0.2	4.27 ± 0.5
Flocel	3.4 ± 0.2	16 ± 2	3.0 ± 0.2	4.13 ± 0.5
MCC(AJ)	3.3 ± 0.2	35 ± 4	2.9 ± 0.2	11.3 ± 1.2
Ranq	3.5 ± 0.2	22 ± 3	2.8 ± 0.2	11.0 ± 1.1
MCC-SI	3.5 ± 0.2	23 ± 3	3.1 ± 0.2	6.6 ± 1.0

* MCC indicates microcrystalline cellulose; MCC (AJ), a fine powder MCC; MCC-SI, MCC from sisal fibers.

must be limited when we consider the figures of water content given in Table 1. This variation in the force can be attributed to the internal structures of the particles, although it has been demonstrated that the mechanical strength of the compacts was not related to the crystallinity of the starting materials.[18] We have confirmed the same by determining the crystallinity of the materials and its effect while compacting it. The role played by the morphology of the particles, therefore, could also be excluded.[19] Structure differences are nevertheless quite conceivable if reference is made to possible variations in the processing conditions during the manufacture of MCC that involves hydrolysis of wood cellulose, intensive shearing of the slurry, and spray drying.[11]

Because there was a variation in the compaction force needed to compress the tablet blends, tablets have been compressed by keeping the crushing strength constant for all the samples (30-40 N). This procedure led to little variation in the thickness of the tablets, as shown in Table 4. The disintegration time (DT) did not vary significantly. The disintegration time of the tablets made from sisal fiber MCC as a diluent was similar to the tablets made from the commercial pharmaceutical-grade MCC sample and was comparable to commercial tablets; however, variation in the disintegration time of the tablets was found when MCC was used as tablet disintegrant. There was no comparable difference in the DT of the tablets made from Avicel-102 and Flocel-102, but the tablets made from Ranq-102 showed high DT. It was difficult to say why there was difference in the DT, because although MCC is a widely used tablet excipient, the data on its disintegration properties are scanty. Some have attributed this difference to the liquid penetration[3,12] and some have attributed it to the pressure,[23] where the material was found relatively ineffective as a disintegrant in an insoluble direct compression system. MCC appeared, however, to be a useful complementary disintegrating agent. The disintegration time of the tablets of a cation-exchange resin was reduced in the presence of MCC.[12] Another reason has also been reported,[24] where tablets containing MCC and cornstarch showed a shorter disintegration time than those containing the disintegrating agent alone. There it was suggested that MCC accelerated the water penetration and thus swelling of the cornstarch, so this difference in the disintegration properties between all MCCs could be attributed to the liquid-penetration capacity. This behavior was thought to be caused by a difference in the widening of the pores during penetration.[12] The in vitro release profile of the captopril tablets containing MCC as a diluent and as a disintegrant are shown in Figure 3. As a diluent, the release profile of the tablets made from sisal fiber MCC was very much similar to that of other commercial MCC samples. As a disintegrant, the tablets made from sisal fiber MCC took a longer time to release the

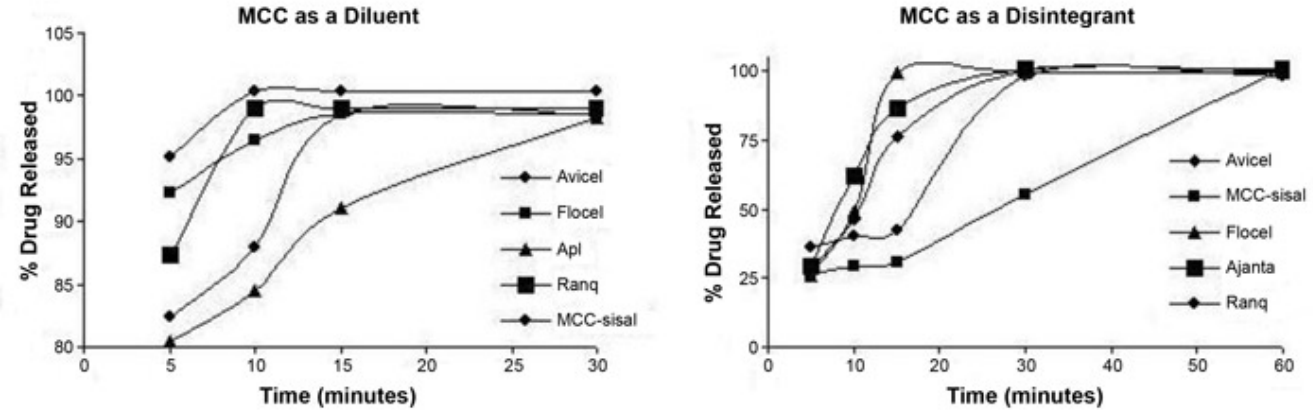

Figure 3. Dissolution time-release profile of the tablets made from MCC as a diluent and disintegrant. Apl. indicates Ajanta Pharmaceutical Limited.

drug. This difference in the delay may be attributed to the difference in the liquid-penetration capacity of the cellulose sample. The release profile of the tablets prepared with sisal fiber MCC was comparable to other tablets and was faster than commercial tablets.

In the case of tablets prepared with MCC and carrageenan, the tablets of sisal fiber MCC showed a similar release profile to tablets of other commercial MCCs in all 3 proportions used (1:0.5, 1:1, and 1:1.5, data not shown). The drug release was most sustained in the tablets prepared with 1:1.5 proportions. The above data suggest that MCC prepared with sisal fibers is completely miscible with sustained-release vehicles and could be used as an adjuvant in controlled-release formulations.

CONCLUSION

The above data demonstrated that MCC derived from sisal fibers could be an industrially feasible alternative for currently used MCCs as diluent and disintegrant for both immediate-release as well as sustained-release oral solid dosage forms.

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