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Tableting properties of microcrystalline cellulose obtained from wheat straw measured with a single punch bench top tablet press

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ABSTRACT

The objective of this work was to study the relation between the manufacturing conditions of microcrystalline cellulose (MCC), its physicochemical properties and its tableting behavior. Two different preparation procedures were used to produce MCC from wheat straw, utilizing an acid hydrolysis method, either using only sulfuric acid or combination of sulfuric and hydrochloric acid. The tableting behavior of obtained MCC samples and mixtures of MCC with ibuprofen was studied using a dynamic powder compaction analyzer. It was observed that some of the obtained MCC samples showed better flowing properties than commercially available Vivapur[®] PH101 and also very high values of tensile strength, solid fraction and elastic recovery. This can be linked with its good compaction behavior, but on the other hand it can cause problems with the disintegration of the tablets. In mixtures with ibuprofen, MCC samples showed lower values of tensile strength, while on the other hand elastic recovery did not seem to be much affected, still exhibiting very high values. According to the obtained results, it can be concluded that MCC obtained from the agricultural waste could have satisfactory properties for tablet preparation by the direct compression method. Further studies are needed to optimize process conditions in order to achieve better physicochemical characteristics, especially in terms of elastic recovery.

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1. Introduction

Today, tablets are considered by far the most widespread dosage forms as they offer advantages for both manufacturers and consumers, such as easy administration and precise dosing, high physicochemical stability, suitability for modification of drug release, cheap large scale production, etc. Due to its simplicity, the lowest number of processing steps and avoidance of contact of the mixture with heat and/or water, direct compression is

preferable method of tablet production. However, the production of tablets by direct compression can often be a complex process, since only a few raw materials inherently possess those properties which are necessary for the production of tablets of satisfactory quality by this method (Armstrong, 2007a). When formulating direct compression tablets, the choice of the direct compression filler is extremely critical. It must meet certain requirements, such as good binding functionality and powder flowability, a well-designed particle size distribution, compatibility with other excipients or drugs and the ability to carry high amounts of active ingredient (Bolhuis and Chowhan, 1996). In general, direct compression fillers are commonly occurring materials whose properties have been modified using well-known processes such as spray drying, wet granulation, etc. in such a way to give the flowability and compressibility demanded by the direct compression process. Since filler usually makes the major part of the tablet formulation, the quality and performance of tablets directly depend on the flowability, compressibility and compactibility of the filler (Armstrong, 2007b).

Microcrystalline cellulose (MCC) was introduced as a binder for direct compression in 1964 by the FMC Corporation (Albers et al.,

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2006). Since then, for more than 50 years, MCC has been recognized as one of the most useful direct compression binders, due to its outstanding binding properties (Bolhuis and Armstrong, 2006; Carlin, 2008). It is available in a wide range of particle sizes and from various sources. Hence, it must be pointed out that the substitution of one brand of MCC by another must be approached with great attention (Armstrong, 2007b). If raw materials are not properly controlled, many problems can occur, such as poor flowability and inconsistent tablet weight, unsatisfactory tablet strength, lack of content uniformity or segregation and dissolution failure (Friedman, 2011; Hentzschel et al., 2012; Ilic et al., 2013; McCormick, 2005; Patel et al., 2006). However, due to the high prices of commercially available products, there is growing interest for new sources of MCC.

The increasing environmental awareness currently has pushed towards the development of new types of green bio-based and degradable materials from natural sources for various applications. Wheat straw is an example of an agro-industrial by-product that requires new end uses, since it is considered as the most important type of agriculture residue in the EU as 144 million tons accumulate each year. Only a small percentage is used in applications such as animal feed and bedding, construction of mud houses, energy production, and the majority of the straw generated is left on the field to decompose (Panthapulakkal and Sain, 2015). Since wheat straw is rich in lignocellulosic mass, there is a great demand for efficient exploitation of cellulose and its use in various industries, among others in pharmaceutical industry.

It is well known that the morphology, physicochemical properties and mechanical characteristics of MCC exhibit variations according to the origin of the raw material and the extraction process. Up to date, a great number of studies is available where an attempt has been made to produce MCC from various sources, usually utilizing an acid hydrolysis method for its production (Shlieout et al., 2002; Battista and Smith, 1962; Adel et al., 2011; El-Sakhawy and Hassan, 2007; Håkansson and Ahlgren, 2005). However, only a few studies attempted to find a relation between the manufacturing conditions of MCC with its physicochemical properties, which proves to strongly influence tablet quality (Shlieout et al., 2002; El-Sakhawy and Hassan, 2007; Wu et al., 2001; Krstić et al., 2018; Pachau et al., 2019).

The aim of this work was to study the feasibility of using MCC produced from agricultural waste, as filler for tablet production by direct compression. Two different procedures for MCC production have been examined, a single-step and two-step acid hydrolysis, while drying using supercritical carbon dioxide has been utilized to determine whether it had an influence on the final quality of the product. In order to evaluate performances of the obtained MCC samples as direct compression fillers, samples were tested by a dynamic powder compaction analyzer (Gamlen D-series), with comparative testing of commercially available samples of MCC. Additionally, feasibility of tablet production by direct compression using MCC and a drug with poor tableting properties was evaluated by compressing mixtures with MCC and different amounts of ibuprofen.

2. Materials and methods

2.1. Materials

Wheat straws were collected from a farm in Resnik, Serbia. Hexane, methanol, hydrochloric acid, as well as sulfuric acid were obtained from Sigma-Aldrich (Tokyo, Japan). Sodium hydroxide was purchased from Fisher Scientific (Loughborough, United Kingdom), sodium chlorite from Acros Organics (Geel, Belgium), ethanol absolute from Zorka Pharma (Sabac, Serbia) and ibuprofen

from Fagron B.V. (Rotterdam, The Netherlands). Commercially available MCC (Vivapur® PH101 (JRS Pharma GmbH & Co. KG, Rosenberg, Germany)) was used for comparison with prepared MCC samples. All chemicals were of analytical grade and were used as received, without any further processing.

2.2. Methods

2.2.1. Pre-treatment of wheat straw

The wheat straws (20 g) were milled in a cutting mill (SM-450, M.R.C. Scientific Instruments, Israel) to approximately 250–500 µm in size, followed by purification with hexane and methanol for 6 h using a Soxhlet apparatus in order to remove extractives (dewaxing). The process of delignification (removing lignin and hemicellulose) was performed with a 2% (w/w) sodium hydroxide solution for 2 h after which the pulp was subjected to bleaching using a 0.7% (w/w) sodium chlorite solution for 1 h. Both processes were performed using wheat straws in a liquid ratio of 1:20. In order to obtain white raw cellulose pulp, the bleaching process was carried out twice under the same conditions and washed with deionized water until pH of 7 was reached.

2.2.2. Production of MCC

In order to obtain MCC with tableting characteristics very much alike the commercial MCC, raw cellulose was treated in two different procedures (Fig. 1). Both procedure 1 and 2 were carried out using only one chemical method (acid hydrolysis). In procedure 1, bleached cellulose pulp was treated with 64% wt. sulfuric acid (H₂SO₄) for 1 h (sample A1) and 2 h (sample A2), respectively. The process was carried out on a magnetic stirrer (RCT standard, IKA, Germany) at 40 °C, under continuous stirring (400 rpm). The hydrolysis was stopped by adding ten-fold deionized water to the reaction mixture. Procedure 2 represents a slightly more complicated method of obtaining the MCC compared to procedure 1. Briefly, cellulose pulp was first treated with 2,5 N hydrochloric acid during 1 h, after which it was filtered with deionized water until neutral pH was reached. The aqueous suspension was freeze dried (ALPHA 1–2 LDplus, Martin Christ, Germany) for 48 h. Freeze drying was first carried out at a temperature of –40 °C and pressure of 0,12 mbar (main drying), after which the sample was subjected to

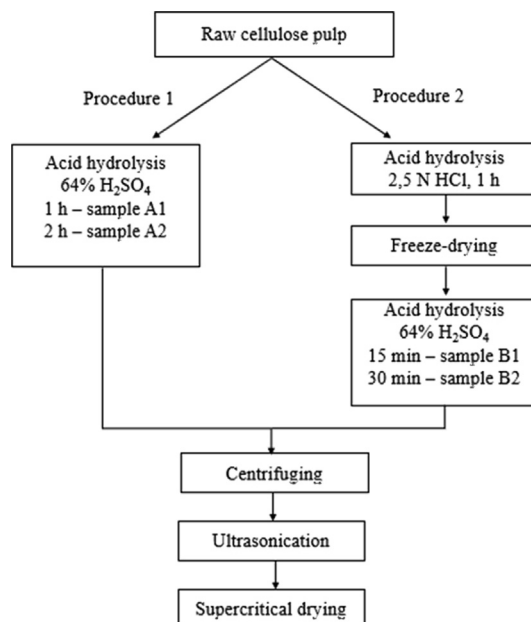


Fig. 1. Preparation scheme of MCC samples from wheat straw.

final drying ($-52\text{ }^{\circ}\text{C}$ and $0,001\text{ mbar}$). Afterwards, the obtained powder was exposed to $64\% \text{ H}_2\text{SO}_4$, during 15 min (sample B1) or 30 min (sample B2). Subsequently, all samples were centrifuged at 5000 rpm (MPW56, MPW Med. instruments, Poland). Centrifuging was repeatedly done until the neutral pH was reached. The resulting mixture was then ultrasonicated (Bandelin Sonorex RK 102 H, BANDELIN electronic GmbH & Co KG, Germany) for 5 min, in order to break potentially present MCC aggregates.

2.2.3. Supercritical CO_2 drying of MCC

In this work, supercritical drying was performed in a semi-batch Autoclave Engineers Screening System (Autoclave Engineers Group, USA), assisted by the use of CO_2 as the supercritical fluid. This system is intended for small laboratory research runs with the maximum operating pressure of 35 MPa at $238\text{ }^{\circ}\text{C}$. It consists of CO_2 bottle with siphon, cryostat, high pressure liquid pump, extractor vessel with electric heater and separator vessel (Milovanovic et al., 2013). Since supercritical CO_2 has very poor affinity to water (Liebner et al., 2010), dehydration of aqueous MCC suspensions was performed with a series of ethanol solutions (20, 40, 60, 80 and 100%), until water was completely replaced with absolute ethanol. So obtained ethanol suspensions were placed in an autoclave and subjected to the CO_2 at the pressure and temperature above its critical point (20 MPa , $40\text{ }^{\circ}\text{C}$) (Rusmirović et al., 2017). The process itself involved two types of drying, static and dynamic. Firstly, static drying was performed for 1 h, in order to achieve saturation of the supercritical solvent with absolute ethanol. Afterwards, the samples were exposed to the continuous scCO_2 flow during 2 h, under the same conditions (20 MPa , $40\text{ }^{\circ}\text{C}$). After dynamic drying was completed, the system was depressurized slowly (1 MPa/min). Dried MCC samples were further characterized and compared with commercially available MCC (Vivapur[®] PH101).

2.2.4. Scanning electron microscopy (SEM)

The surface morphology of the MCC particles was examined using scanning electron microscopy (SEM) (JSM-6610LV, JEOL, Japan) with a 20 kV acceleration voltage. In order to avoid charging, all samples were coated with gold (LEICA SCD005 sputter coater) prior to analysis. Photomicrographs were taken at various magnifications ($500\times$, $10,000\times$ and $35,000\times$).

2.2.5. Particle size and particle size distribution

Particle size analysis was performed using a laser diffraction analyzer, Malvern[®] Mastersizer 2000 (Malvern Instruments, UK). A small amount of samples was dispersed in deionized water and the suspension was sonicated for 3 min before delivering to the optical unit at a speed of 2000 rpm. The obscuration for all samples was kept between 9 and 15% during analysis. Volume particle size distribution (PSD) of each sample was measured in triplicates.

2.2.6. Powder densities and flow properties

The true density (ρ_{true}) of each sample, as well as that of the commercially available MCC, was measured using a gas displacement pycnometer (Accupyc 1330, Micromeritics, Norcross, Ga., USA). After loading into the sample cell, samples were subjected to the helium, which was used as the pressurized gas for the measurements. The experiments were performed in triplicate at $25\text{ }^{\circ}\text{C}$, using the cell with the 85% filling ratio and all samples were weighed prior to analysis.

On the other hand, bulk (ρ_{bulk}) and tapped (ρ_{tapped}) densities were measured according to the European Pharmacopoeia (Ph. Eur. 10.0) recommendations [General Chapter <2.9.34>] (European Pharmacopoeia 10th edition, 2019). Bulk density was obtained simply by adding a known mass of powder to 10 ml graduated cylinder, after which the density was calculated as ratio

mass/volume. Tapped density was obtained by mechanically tapping a graduated measuring cylinder containing the powder sample, using volumeter (StaV 2003, J. Engelsmann AG, Ludwigshafen, Germany).

Flowability and compressibility of the powders were evaluated in terms of Hausner ratio (HR) and Carr index (CI), using the Eq. (1), and Eq. (2), respectively as below (Ph. Eur. 10.0):

$$\text{Hausner ratio} = \text{tapped density/bulk density} \quad (1)$$

$$\text{Carr index (\%)} = 100 \times (\text{tapped density} - \text{bulk density})/\text{tapped density} \quad (2)$$

2.2.7. Tableting properties

In order to compare the functional properties important for tableting of MCC isolated from wheat residues, as well as commercially available MCC, it was necessary to define the parameters which will allow these powders to be compared. With the intention of investigating the impact of addition of an active ingredient to the tableting properties of the isolated MCC, compacts with 10 and 40% of ibuprofen were also prepared and examined.

Tableting properties, such as net compression work, elastic recovery and tablet tensile strength (TS) were determined from the data measured by a dynamic powder compaction analyzer, Gamlen Tablet Press D-series (Gamlen Tableting Ltd., UK). A powder sample of $30 \pm 1\text{ mg}$ was manually loaded into the die and compacted directly into tablet at fixed speed (60 mm/min) using a flat round upper punch with a diameter of 6 mm. The compression process was performed at five different pressures (34.69, 69.39, 104.09, 138.78, 173.48 MPa) and all measurements were repeated three times. The process itself can be divided into three phases: compression (powder sample is compressed into tablet), detachment (tablet is detached from die base) and ejection phase (tablet is ejected into ejection cavity). Supporting software (Gamlen TP Controller Version 3.26) was used to record compression, detachment and ejection profiles by measuring upper punch force and displacement.

Net work of compression (J) indicates the material's compressibility, as well as type of deformation tablets are subjected to. It is described as the difference between the total compression work and elastic work, both measured using areas of rectangles of the force-displacement curve. While the total compression work represents the area under the force-displacement curve during the compression phase, the elastic work is obtained during the elastic recovery of the material.

Elastic recovery, which indicates the expansion of a tablet after the ejection, was calculated indirectly using the Eq. (3):

$$\text{Elastic recovery (\%)} = ((h_0 - h_{\text{max}})/h_{\text{max}}) \times 100 \quad (3)$$

where h_0 and h_{max} represent the difference between the base position of the punch and the positions of the punch when the compression load has its minimum (h_0) and maximum value (h_{max}).

The compact solid fraction was calculated according to the following Eq. (4):

$$\text{Solid fraction} = \text{compact density/true density} \quad (4)$$

Tablet tensile strength was conducted from the tablet hardness (F), tablet thickness (h) and diameter (D) according to the Eq. (5) as below (Fell and Newton, 1970):

$$\text{Tablet tensile strength} = 2 \times F/\pi \times h \times D \quad (5)$$

While tablet thickness was measured using a calliper, tablet hardness and diameter were obtained using a hardness tester (Erweka TBH 125D, Erweka, Heusenstamm, Germany).

3. Results and discussion

3.1. Scanning electron microscopy

The morphology of the freeze-dried microcellulose samples was visualized by SEM and presented in Fig. 2a-f. Fig. 2a and b shows SEM photomicrographs of the samples A1 and A2 that were obtained using only sulfuric acid. As it can be seen from these images, both samples exhibit long, rod-shaped particles. Although sample A2 was subjected to sulfuric acid for longer time (2 h compared to sample A1 where hydrolysis was carried out for 1 h) it can clearly be seen that there is no significant difference in the particle morphology and size between these two samples.

SEM micrographs of Vivapur® PH101, available in the product documentation (JRS Pharma 2020) showed similar particle morphology like samples A1 and A2.

On the other hand, when cellulose fibers are subjected to two-step hydrolysis - firstly using hydrochloric acid and then with sulfuric acid, the loss of fibrous structure can certainly be observed. Fig. 2c and d represents sample B1 with irregular-shaped particles with smooth surface. Although with irregular shapes, these microparticles appear as defined and well separated. As hydrolysis time is further increased, microparticles become less defined and appear as flakes, which tend to form aggregates, as seen in Fig. 2e and f, representing sample B2. From these SEM images it can be clearly observed that the inclusion of an additional

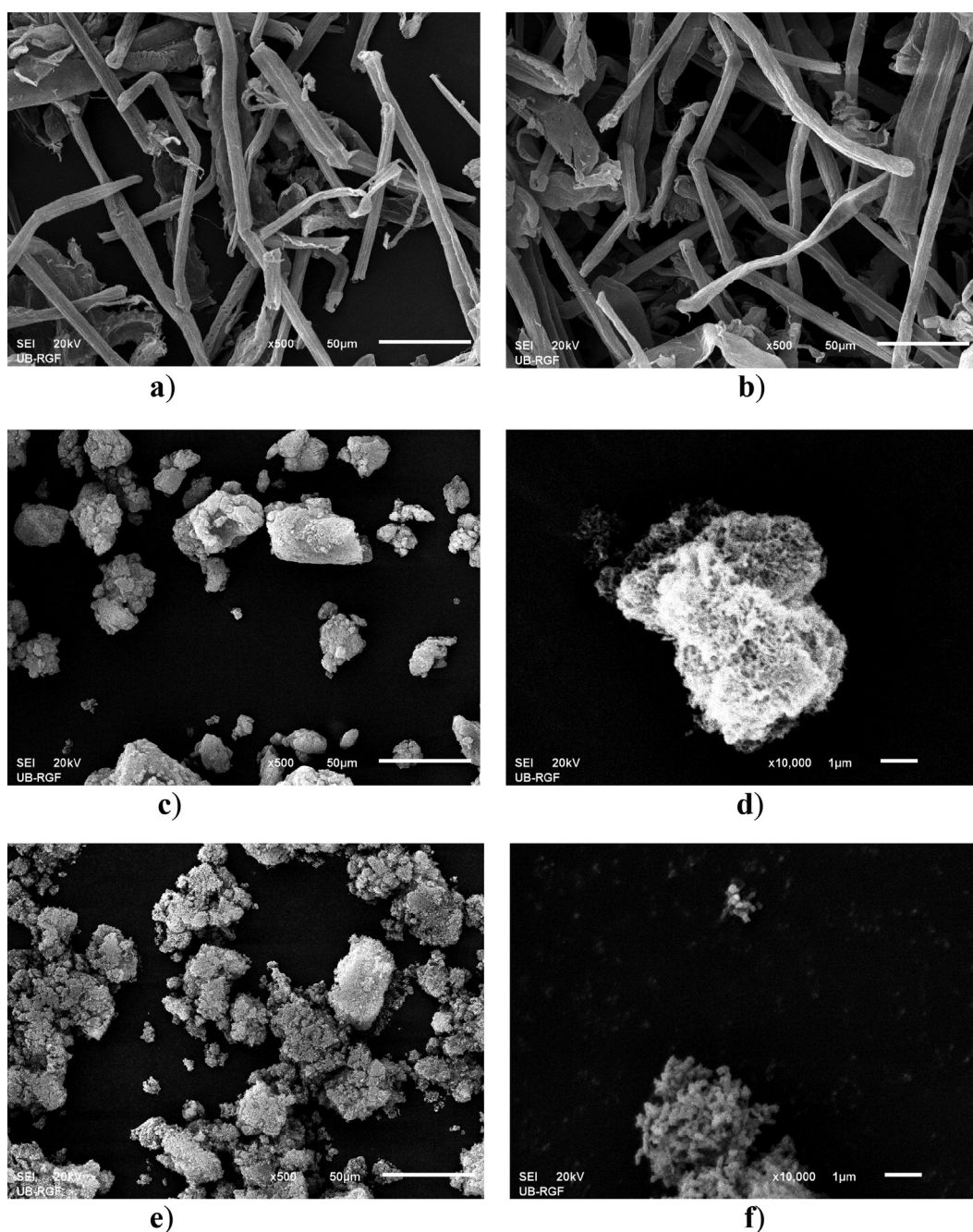


Fig. 2. Scanning electron micrograph of samples (a) A1; (b) A2; (c, d) B1 and (e, f) B2.

hydrolysis step with hydrochloric acid led to evident difference in size and shape of cellulose particles from fiber-like particles to smaller irregularly shaped particles. Fiber-like particles like those obtained using single-step hydrolysis with sulfuric acid are very unfavorable for powder flowability due to the high contact area between particles which increases powder cohesiveness.

3.2. Particle size and particle size distribution

The effects of the different approaches in preparation of the MCC samples on their PSD are presented in Fig. 3 and Table 1. It can be seen that the size distribution pattern for samples A1 and A2 (Fig. 3a and b) are very much alike, with both exhibiting right-skewed distribution with shoulders on the right side. Unlike sample A2, sample A1 showed a slightly higher peak at the end of the tail. This is probably due to the stronger aggregation of the particles, caused by incomplete reaction during hydrolysis. However, both samples showed the major particle size distribution between 5 and 65 μm , with mass median diameters being 31.52 μm for sample A1 and 28.87 μm for sample A2. Although sample B1 showed slightly smaller mass median diameter (26.35 μm) compared to the samples A1 and A2, its curve showed left-skewed distribution with long left tail, indicating higher volume of smaller particles.

The narrowest distribution of all samples was observed for sample B2 (Fig. 3d), with mass median diameter being much smaller

than the other samples (12.17 μm). Hence, it is noticeable that the production method used for the preparation of MCC samples, and also the hydrolysis time has a significant effect on the breakdown of cellulose chains and their agglomeration. Procedure 2, which includes combined treatment with hydrochloric and sulfuric acid, gave smaller and more uniform particles. These results are in accordance with the results shown by scanning electron microscopy.

3.3. Powder flow properties

Table 2 reports the values of true density, as well as CI and HR, which were used as flowability indicators in the present research. As seen from the table, none of the samples exhibited free flowing properties according to the criteria given in the European Pharmacopoeia (European Pharmacopoeia 10th edition, 2019). The lowest CI and HR values were observed for sample B1, indicating fair flow of the particles, while sample B2 showed passable flow with its CI and HR values higher than the sample B1. On the other hand, flow of samples A1 and A2 was rated as very poor. Based on their high CI values it can be assumed that both samples A1 and A2 are highly compressible powders. This is an expected consequence of the rod-like particle morphology of these samples which causes dense packing of particles during tapping. Furthermore, their high HR values, which were greater than 1.4 corresponds to the cohesive nature of these two samples. The results obtained by bulk and

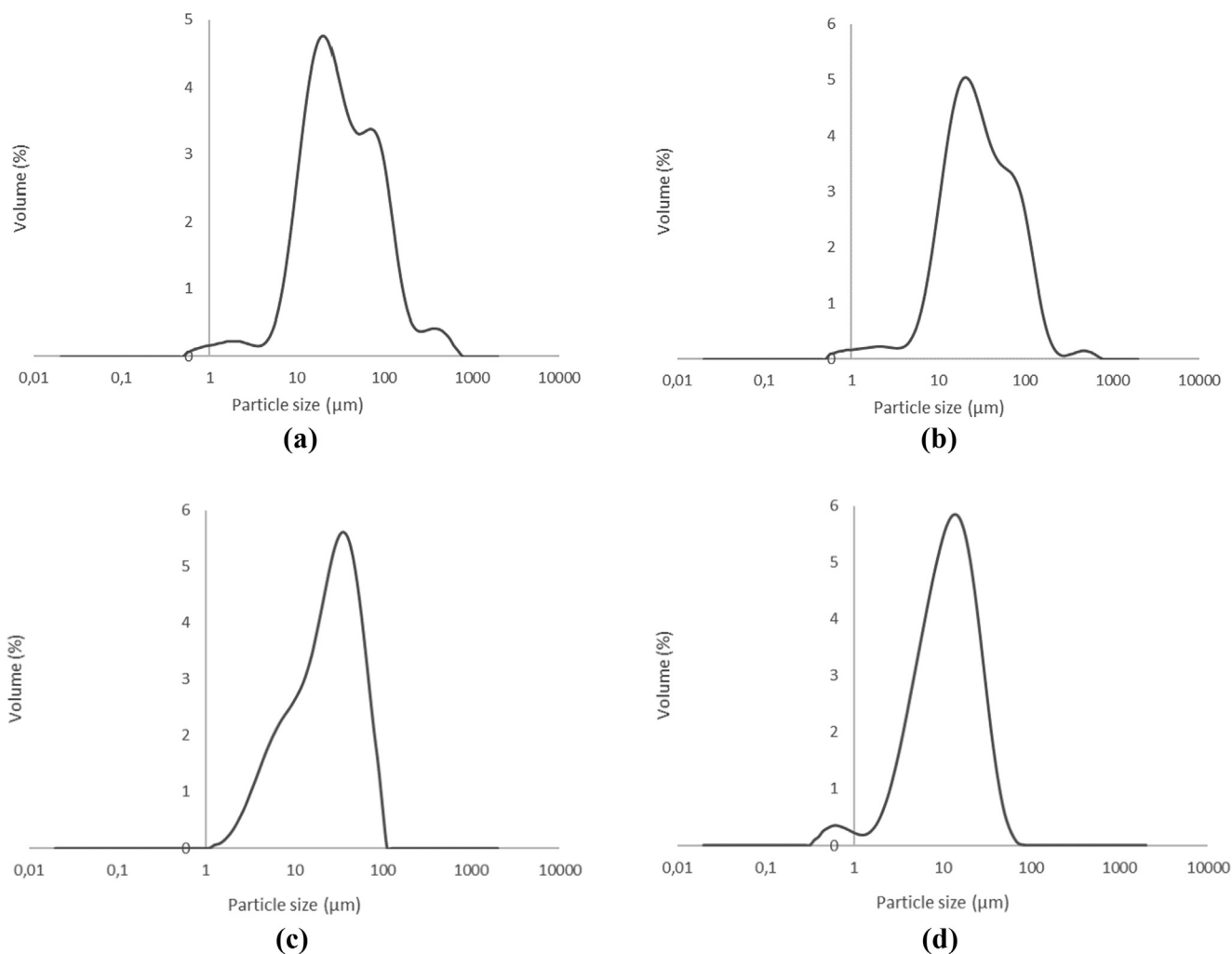


Fig. 3. Particle size distribution of samples (a) A1; (b) A2; (c) B1 and (d) B2.

Table 1
Particle size of analyzed samples.

MCC sample	D (v, 0.1) (μm)	D (v, 0.5) (μm)	D (v, 0.9) (μm)	SPAN
A1	10.23	31.25	123.83	3.64
A2	9.81	28.87	102.48	3.21
B1	5.83	26.35	64.48	2.23
B2	3.83	12.17	29.65	2.12

Table 2
Density and flowability characteristics of analyzed samples.

MCC sample	True density (g/cm ³)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr index (%)	Hausner ratio
A1	1.63 ± 0.01	0.063 ± 0.003	0.093 ± 0.004	32.33 ± 0.15	1.48 ± 0.00
A2	1.58 ± 0.01	0.076 ± 0.001	0.111 ± 0.001	31.84 ± 0.59	1.47 ± 0.01
B1	1.68 ± 0.04	0.152 ± 0.001	0.187 ± 0.001	18.57 ± 0.96	1.23 ± 0.01
B2	1.66 ± 0.03	0.149 ± 0.002	0.195 ± 0.004	23.54 ± 0.69	1.31 ± 0.01
Vivapur® PH101	1.56*	0.331 ± 0.017	0.466 ± 0.016	28.83 ± 2.30	1.41 ± 0.05

(±standard deviation).

*from the reference Choi et al., 2010.

tapped density are in accordance with their particle morphology, as observed by SEM. Samples A1 and A2 have a rod-like morphology with high contact area between the particles which makes powder more cohesive and hinders powder flow. On the other hand, two step hydrolysis procedure breaks long cellulose fibers to smaller particles, with lower contact area, making better flowability of samples B1 and B2. Flowability of Vivapur® PH101 was similar to samples A1 and A2, which is expected due to similar particle morphology.

3.4. Tableting properties

The present study was performed at a range of compaction pressures in order to investigate the main tableting properties of the samples, found to be relevant for their potential application as direct compression fillers.

The ability of the material to absorb work during the compression process has a significant effect on the tablet characteristics. As stated above, one such parameter that indicates the compressibility of materials is work of compression, shown in Table 3. For all investigated powders, it is noticeable that work of compression is proportional to the applied compaction pressure, with some minor exceptions. Relatively high work of compression is typical for MCC samples, as this material is deformed by plastic deformation, which is energy-demanding process (Haware et al., 2009). Sample A1 and A2 showed almost identical compressibility, with the compression work increasing proportionally with the increase in compaction pressures applied, ranging from 34.69 MPa to 138.78 MPa. With further rise in compression pressure beyond 138.78 MPa, no extra work was consumed during the compression of sample A2. Such behavior of the sample A2 was very similar to the observed behavior of commercial MCC, with both samples reaching a plateau as the higher compaction

pressures were applied. Substantially higher values of the compression work were observed during the compression of the samples B1 and B2. This may be a consequence of the lower particle size of these samples which increases interparticle bonding and therefore resistance to applied compaction pressure. This observation is in direct correlation with the determined values for CI, whereby B1 and B2 had higher values in comparison to A1 and A2 samples. Based on the obtained results, it can clearly be seen that the lowest compression work was consumed during the compression of the commercial MCC. Considering that the material is more compressible when less work is utilized for the compression process, it can be concluded that Vivapur® PH101 showed the best compressibility. On the contrary, the least compressible sample was sample B2. However, although compression of samples B1 and B2 consumes more energy, low particle size with higher specific surface area of this sample should result in tablets with higher tensile strength.

MCC is an excipient known for its viscoelastic behavior (Thoores et al., 2014). Elastic recovery is a parameter that indicates the disruptive forces acting after the process of compression and its values are presented in Table 4. The obtained data show that elastic recovery follows the same trend as work of compression. As the applied compaction pressure is increased, almost identical increase in elastic recovery was observed for the samples A1, B1 and B2. On the other hand, once again sample A2 showed the most similar behavior to the commercial MCC, as both did not show further increase in elastic recovery at the highest compaction pressure applied in this study. However, it is important to note that all investigated samples, including Vivapur® PH101, showed extensive elastic recovery values, going as high as 80.93% (measured value for the sample A1 at the compaction pressure of 173.48 MPa). Although the observed in die elastic recovery was high, all prepared tablets show high tensile strength (see further)

Table 3
Work of compression of the tested samples.

Compaction pressure (MPa)	Work of compression * 10 ⁻² (N*m)				
	A1	A2	B1	B2	Vivapur® PH101
34.69	46.0 ± 1.8	38.9 ± 0.5	44.9 ± 0.6	54.9 ± 2.7	26.7 ± 0.3
69.39	64.1 ± 1.3	59.9 ± 1.3	68.0 ± 10.1	81.2 ± 1.5	47.9 ± 1.2
104.09	77.0 ± 2.6	74.6 ± 0.3	94.4 ± 2.0	106.0 ± 0.7	63.2 ± 2.2
138.78	87.7 ± 2.2	84.2 ± 1.8	108.0 ± 1.1	119.0 ± 1.1	74.5 ± 2.5
173.48	96.3 ± 0.3	84.1 ± 1.3	117.6 ± 1.0	125.6 ± 3.1	75.0 ± 1.9

(±standard deviation).

Table 4
Elastic work and elastic recovery of the tested samples.

Compaction pressure (MPa)	Elastic Work * 10 ⁻² (N*m)					Elastic Recovery (%)				
	A1	A2	B1	B2	Vivapur® PH101	A1	A2	B1	B2	Vivapur® PH101
34.69	3.3 ± 0.4	3.5 ± 0.0	2.8 ± 0.0	2.4 ± 0.1	3.5 ± 0.0	28.5 ± 0.7	28.5 ± 0.9	21.3 ± 0.3	20.8 ± 1.1	25.9 ± 0.6
69.39	9.9 ± 0.0	9.9 ± 0.1	8.2 ± 0.0	7.8 ± 0.1	9.7 ± 0.1	40.8 ± 0.8	39.9 ± 1.3	32.8 ± 0.5	35.5 ± 0.9	37.9 ± 1.4
104.09	20 ± 0.0	20.0 ± 0.3	17.5 ± 0.3	17.0 ± 0.2	19.5 ± 0.2	53.7 ± 1.6	51.5 ± 0.1	45.8 ± 1.5	45.6 ± 0.3	50.3 ± 2.2
138.78	32.8 ± 0.2	32.6 ± 0.1	30.0 ± 0.2	30.0 ± 0.1	32.1 ± 0.2	66.7 ± 1.7	65.6 ± 1.3	59.3 ± 1.2	59.4 ± 1.6	64.0 ± 3.5
173.48	48.0 ± 0.2	32.5 ± 0.5	46.4 ± 0.3	45.8 ± 0.6	32.4 ± 0.2	80.9 ± 0.7	64.9 ± 1.5	74.3 ± 0.5	74.4 ± 1.0	64.0 ± 2.3

(±standard deviation).

and there was no appearance of tablet capping and lamination, which are common consequences of elastic relaxation. Due to the low bulk density, the amount of MCC that can be accommodated in the die cavity was limited to 30 mg, and the good compressibility of the material under applied compression pressure resulted in tablet with a very low thickness. Therefore, even a small increase in tablet thickness after completion of the compression process will be large relative to the tablet thickness at maximum compression pressure.

The values of solid fraction and tablet tensile strength, as the most important indicators of compactibility of the materials are presented in Fig. 4. All samples showed an increase in the values of the solid fraction with the rising compaction pressures. There are some differences in the trends of changes in the solid fraction upon increase in the compaction pressure. Commercial MCC (Vivapur® PH101) and the sample A2 have the highest solid fraction

upon application of the lowest compaction pressure, followed by the lowest relative increase in solid fraction for these two samples with further rise in compression pressure. This is related to their different mechanism of consolidation, in comparison to other samples, which could previously be seen during the analysis of the work of compression. The highest solid fraction achieved by compression of samples A2 and Vivapur® PH101 at lowest compression pressure is consequence elongated rod-like particle morphology. These elongated particles are not prone to rearrangement upon applied pressure, which limits material densification upon pressure. The linear relationship between solid fraction and compression pressure for these two samples ($R^2 > 0.99$) proved linear decrease of tablet porosity under applied pressure. Tablets with the highest solid fraction (i.e. the lowest porosity) were obtained with compression of samples B1 and B2 at all applied compression pressures above 104 MPa, due to the lowest particle size of these samples which resulted in the closest particles packing. These samples initially exhibit lower solid fraction (i.e. higher porosity), as particles are not closely packed before compression. As particles of these samples are more prone to rearrangement, tablet solid fraction rises faster under applied pressure giving at the end of compression tablets with higher solid fraction, i.e. lower porosity. More intensive particle rearrangement of these samples, with simultaneous formation and breakage of interparticle bonds cause that there was no linear relationship between solid fraction and compression pressure, over the whole range of compression pressures applied. High solid fractions observed when these samples were compressed in the upper range of compression pressures tested may indicate on possible problems with disintegration of prepared tablets, due to difficult penetration of water between closely packed particles.

It is significant to point out that the tensile strength values of all samples were above 1.7 MPa, regardless of the applied compaction pressure. This implies that tablets made from the investigated samples were mechanically strong enough to enable successful commercial manufacturing as well as the following distribution (Pitt and Heasley, 2013). High mechanical strength of tablets made of MCC is attributed to plastic deformation of the material and hydrogen bonds formation between adjacent particles (Haware et al., 2009). Furthermore, introduction of sulfate groups using sulfuric acid in the preparation procedure further increases tablet tensile strength through polar-polar interactions between MCC particles (El-Sakhawy and Hassan, 2007). Considerably higher values of tensile strength were observed for the samples B1 and B2, ranging from 3.8 ± 0.6 MPa to 6.0 ± 0.3 MPa, irrespective of the applied compaction pressure. As previous characterization techniques show, application of repeated acid hydrolysis in the preparation of these samples resulted in smaller size irregularly shaped particles. This enables formation of stronger interparticle bonds and therefore resulted in tablets of higher tensile strength. The same trend of increasing tablet tensile strength with decreasing particle size was demonstrated by compression of different grades of MCC by Haware et al. (2010). Observed high tensile strengths are

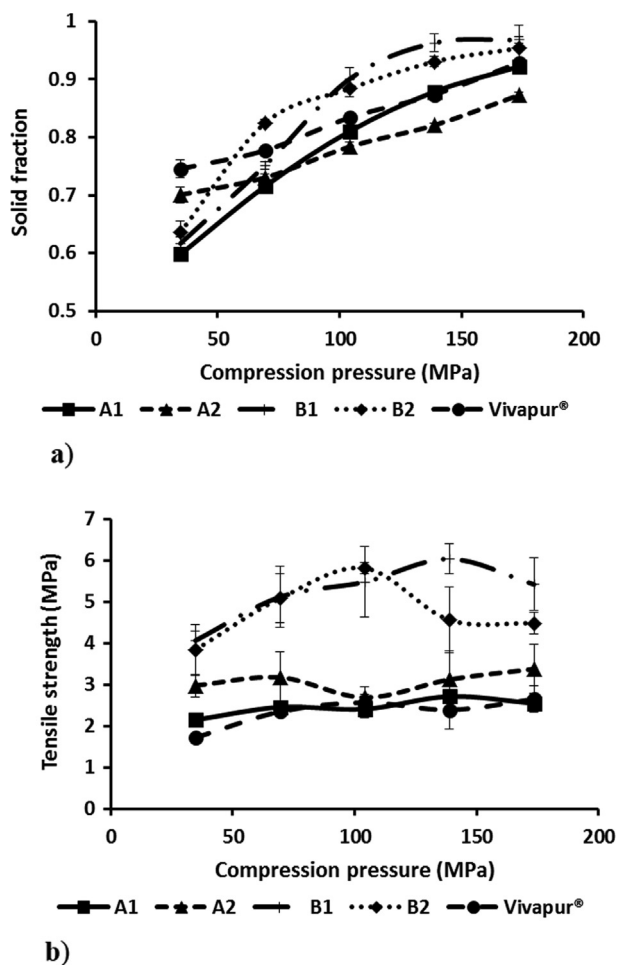


Fig. 4. Compressibility (a) and (b) tableability profiles of the samples.

Table 5

Work of compression of the samples prepared with ibuprofen.

Compaction pressure (MPa)	Work of compression * 10 ⁻² (N*m)							
	Compacts with 10% ibuprofen				Compacts with 40% ibuprofen			
	A1	A2	B1	B2	A1	A2	B1	B2
34.69	34.4 ± 1.9	32.9 ± 1.5	51.3 ± 2.2	48.6 ± 1.2	28.3 ± 1.0	26.1 ± 0.2	35.0 ± 2.0	32.3 ± 5.9
69.39	52.5 ± 0.9	52.1 ± 0.8	86.2 ± 5.7	77.0 ± 2.1	42.5 ± 0.5	40.3 ± 0.2	61.0 ± 2.4	58.9 ± 5.3
104.09	65.9 ± 3.2	65.4 ± 1.9	99.4 ± 2.6	93.2 ± 2.0	52.1 ± 1.5	49.5 ± 1.0	71.6 ± 1.9	73.1 ± 2.0
138.78	74.6 ± 1.2	68.9 ± 1.9	112.3 ± 1.5	106.7 ± 2.8	58.3 ± 1.2	56.7 ± 0.4	80.3 ± 4.6	78.6 ± 1.9
173.48	79.3 ± 2.7	77.6 ± 1.2	108.8 ± 2.9	116.1 ± 2.3	58.7 ± 0.7	61.5 ± 1.6	87.2 ± 0.8	80.9 ± 2.4

(±standard deviation).

Table 6

Tablet tensile strength of the samples prepared with ibuprofen.

Compaction pressure (MPa)	Tablet tensile strength (MPa)							
	Compacts with 10% ibuprofen				Compacts with 40% ibuprofen			
	A1	A2	B1	B2	A1	A2	B1	B2
34.69	2.0 ± 0.0	1.8 ± 0.2	3.6 ± 0.5	2.9 ± 0.4	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.2	1.4 ± 0.2
69.39	2.1 ± 0.5	1.9 ± 0.4	3.9 ± 0.3	3.4 ± 0.4	2.0 ± 0.2	1.8 ± 0.1	1.9 ± 0.4	1.7 ± 0.2
104.09	2.4 ± 0.1	2.6 ± 0.7	3.3 ± 0.8	3.8 ± 0.2	2.2 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.7 ± 0.1
138.78	2.4 ± 0.3	2.4 ± 0.3	3.9 ± 0.1	3.4 ± 0.6	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.3	1.9 ± 0.4
173.48	2.1 ± 0.2	2.4 ± 0.3	2.8 ± 0.4	2.6 ± 0.3	2.0 ± 0.1	2.0 ± 0.1	2.1 ± 0.3	2.0 ± 0.4

(±standard deviation).

in agreement with slightly lower values of elastic recovery found for samples B1 and B2. Such higher values of tensile strength were also described by Wu et al. (Wu et al., 2001), where tensile strength for MCC obtained from wood pulp was ranging from 4.48 to 6.42 MPa, measured under similar compaction pressures. Furthermore, it is important to note that upon increase in compression pressure, tablet tensile strength varied less in the case of samples prepared in this study, compared to a similar study (Krstić et al., 2018), where MCC was as well isolated from wheat straw. Huge variations in tablet tensile strength upon increase in compression pressure, reported in the reference (Krstić et al., 2018), is disadvantageous for tableting, as common variations in compression pressure during tablets production process can lead to unacceptable variations in tablet properties. Additionally, it is important to emphasize that sufficiently high values of tensile strength were observed even for tablets with lower solid fraction. Therefore it is possible to achieve tablets with desired mechanical properties to withstand production process and handling as well as high porosity, which is important for tablets disintegration upon contact with an aqueous medium. It is evident from the Fig. 4b, that sample A1 exhibits almost an equal tableting profile as commercial grade MCC, Vivapur® PH101.

In order to evaluate the behavior of the obtained samples in the presence of a model drug, compacts of the isolated MCC have been prepared with ibuprofen. As seen in Table 5, addition of 10% of ibuprofen slightly lowered the values of work of compression for all samples, except sample B1, wherein the compaction work values at lower compression pressures were slightly higher compared to pure sample (Table 3). It can clearly be seen that significantly lower work was consumed on compression of ibuprofen itself. Also, lower work of compaction is spent during compression of samples with higher loads of ibuprofen (40%), indicating that ibuprofen has a strong influence in decreasing the work needed for the compression process.

Addition of ibuprofen to the MCC samples seems to have the strongest influence on tablet tensile strength (Table 6). When mixed with 40% ibuprofen, all samples showed significantly lower values of tensile strength, in some cases going below the recommended 1.7 MPa (Pitt and Heasley, 2013). However, with

selection of the appropriate compression pressure, tablets of acceptable mechanical strength can be prepared, indicating that obtained MCC samples show satisfactory dilution capacity.

4. Conclusions

In this study, four samples of MCC were obtained from wheat straw utilizing two different procedures of an acid hydrolysis method and varying the duration of the process itself. The results revealed significant size reduction of the biomaterial, with evident difference in shape and particle morphology. Combined treatment with hydrochloric and sulfuric acid resulted in samples with smaller and more uniform particles, which upon compression gave tablets with higher tensile strength and lower porosity. Samples prepared using only sulfuric acid exhibited larger rod-like particles and showed similar tableting behavior as commercially available MCC. Even though all samples exhibited extensive values of elastic recovery, which are unfavorable, this can be linked with the testing conditions. From our findings, we can conclude that MCC obtained from the agricultural waste could have satisfactory properties for tablet preparation by the direct compression method. According to the obtained results, advantage should be given to preparation process of MCC based on two-step hydrolysis with sulfuric and hydrochloric acid. Samples obtained by this process showed better flowability and high tensile strength when compressed even with very low compression pressure. Further studies are needed to optimize both the conditions used in the acid hydrolysis method (such as time, concentration of acid, type of acid) as well as additional techniques used in the production process in order to further improve the tableting properties of the material.

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CRedit authorship contribution statement

Jovana Krivokapić: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Jasna Ivanović:** Conceptualization, Methodology, Writing - review & editing. **Jelena Djuriš:** Conceptualization, Methodology, Software, Formal analysis, Writing - review & editing, Supervision. **Djordje Medarević:** Conceptualization, Methodology, Software, Validation, Data curation, Writing - review & editing, Visualization, Supervision. **Zorica Potpara:** Conceptualization, Writing - review & editing. **Zoran Maksimović:** Conceptualization, Resources, Writing - review & editing. **Svetlana Ibrić:** Conceptualization, Resources, Writing - review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare no conflict of interest.

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