LIGNOCELLULOSIC BIOMASS AS A SOURCE OF MICROCRYSTALLINE CELLULOSE – CHEMICAL AND TECHNOLOGICAL CHARACTERIZATION AND FUTURE PERSPECTIVES

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Dedicated to Acad. Bogdan C. Simionescu
on the occasion of his 70th anniversary

In this paper, agricultural waste (corn stover and wheat straw) was used for isolation of microcrystalline cellulose (MCC). Lignocellulosic biomass is widely available and applying smart technologies to valorise it will have a double benefit through environmental protection and achieving high-performance materials for targeted applications. The obtained MCC showed excellent features in terms of purity, physical-chemical properties and safety, as well. The methods applied for characterizing the materials were as follows: FT-IR, SEM, ICP-AAE and IC. Then, tablets were made by the compression method, using the isolated and purified MCC, as well as its commercially available counterpart. Excellent technological characteristics were confirmed by testing material compaction, compactibility, compressibility and drug release. This was one of the first tests in which Gamlen Tableting D was applied, especially in the case of using biomass, in the first phase, with prospects of application at a large scale, particularly, in the pharmaceutical industry.

Keywords: microcrystalline cellulose, corn stover, wheat straw, compactibility, compressibility, employment of agricultural residues

INTRODUCTION

It has been estimated that as much as 140 billion metric tons of biomass are generated every year from agriculture worldwide. Equivalent to approximately 50 billion tons of oil, this volume of agricultural biomass waste (in the form of residual stalks, straw, leaves, roots, husk, nut or seed shells, waste wood and animal husbandry waste) can be converted to an enormous amount of energy and raw materials. Biomass wastes can substantially displace fossil fuel, reduce emissions of greenhouse gases and provide renewable energy. On the other hand, as a raw material, biomass waste has an attractive potential for both large-scale industries and community-level enterprises.[1]

Widely available, renewable and virtually free, waste biomass has already become an interesting and important resource in many developed and developing countries.

However, although there is an emerging trend in the utilization of biomass conversion technologies, agricultural biomass is, at least in Serbia, still largely underutilized and left to rot or openly burned in the fields – which is common

practice, resulting in air pollution and posing risk to human and ecological health.[1,2]

Waste generation comes hand-in-hand with increasing population, prosperity and urbanization, while remaining as a major challenge for communities to collect, recycle, treat and dispose it. A cornerstone of sustainable development is the establishment of affordable, effective and truly sustainable waste management practices.[2] The use of organic waste in order to obtain useful products is of great importance to the environment. In recent literature, different treatment methods of agricultural waste have been reported. Corn stalks, rice straw, wheat straw and dhaincha have been efficiently fractionated to cellulose, hemicelluloses and lignin by formic acid/peroxyformic acid/H_2O_2 and the obtained product was characterized using FTIR, TEM, TGA and XRD.[3] Zhong *et al.*[4] proposed tetra-α-butylammonium hydroxide for extraction of cellulose from wheat straw and a procedure for recycling this solvent and its reuse for the same purpose. García *et al.*[5] applied a cold alkaline extraction to obtain hemicellulose derivatives from wheat straw. The solid fraction was further treated with NaOH-anthraquinone to get cellulose pulp, which was used for preparation of paper sheets. Fan *et al.*[6] applied microwave irradiation for both isolation of crude cellulose from rice straw and its conversion into MCC by partial hydrolysis. After making a comparison with traditional heating methods, similar results were obtained under milder conditions and MW irradiation. However, microwave irradiation has the advantage of shorter treatment time and lower temperature required for the mentioned procedures. It is obvious that waste management is one of the major environmental issues in many countries where mid- and/or long-term plans for solving organic waste problems are already implemented in legislation and practice as well. In Serbia, the National Waste Management Strategy 2010-2019 proposes several methods of waste management practices, such as the decrease of waste at sources, re-use, recycling, composting, anaerobic digestion, incineration and other waste treatment procedures. This framework seems to be flexible enough to include some other innovative approaches to the problem of organic solid waste, such as considering it as a suitable and inexpensive source of various raw materials for the pharmaceutical and chemical industries.[7]

Microcrystalline cellulose (MCC) is purified, partially depolymerized cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant material, with mineral acids.[8] It was discovered in 1955 by Battista and Smith and first commercialized under the brand name Avicel®. It can be obtained commercially from wood, as well as from a number of various non-woody lignocellulosic materials (*e.g.* cotton linters stalks and rags, soybean husk, corn cob and stover, coconut shells, rice husk, sugar cane bagasse, wheat straw *etc.*).[9] Within the European Union and Switzerland, MCC is also specified as E 460 in lists of substances that are permitted to be used as food additives, and is considered as a versatile and valuable additive in the pharmaceutical industry (as binder in various solid dosage forms of medicines and dietary supplements, *e.g.* tablets by direct compression), in the food industry (as anticaking agent, thickener, texturizer, emulsifier, bulking agent and fat substitute), as well as in the cosmetic industry (as filler due to its superior dry binding properties).[8,9]

Bearing in mind the importance of MCC in the pharmaceutical and related industries, we applied a set of common laboratory procedures for extraction and pharmaceutical quality/health safety assessment of MCC produced from corn stover and wheat straw, which had been collected as waste from crop fields in Serbia. The main objective of this paper is, therefore, to investigate the possibility of application of this compound isolated from biomass in the pharmaceutical industry.

EXPERIMENTAL
Chemicals and reagents
In the extraction process, hexane (Carlo Erba Reagenti SpA, Rodano (MI), Italy), methanol (Zorka Pharma, Serbia), sodium hydroxide (Centrohem d.o.o., Serbia), 0.7% sodium chlorite (Acros Organics, Belgium), glacial acetic acid (Lach-Ner s.r.o., Czech Republic), 2.5 M hydrochloric acid (Zorka Pharma, Serbia) were used as solvents. Ibuprofen was used as a model drug (Ph. Eur. 9.0.). Commercially available microcrystalline cellulose (Vivapur® (JRS PHARMA, Germany)) was used for comparison with the obtained products. Sodium hydroxide (JT Baker, USA) and potassium hydrogen phosphate (Merck, USA) were used for dissolution. According to USEPA Method 3015A, 65% (v/v) nitric acid (Merck, USA) and 30% (v/v) solution of H_2O_2 (Zorka Pharma, Serbia) were used as solvents.

Samples and isolation of microcrystalline cellulose
Lignocellulosic biomass (corn and straw) was collected from the fields located at 44°44'12.98" N and 20°25'13.01" E of Belgrade – Resnik (Serbia). The

samples are firstly purified, then dried at room temperature and crushed to the consistency of coarse powder. The starting materials (~20 g) were first sieved to achieve uniform particle size of 250-500 μm. The plant material was successively defatted by continuous extraction with hexane and methanol in an all-glass Soxhlet apparatus, until exhausted, 6 h with each solvent at its boiling temperature.

The material was then subjected to delignification by alkaline treatment and bleaching, as described by Panyasiri et al.[10] In brief, the defatted plant material was treated with 2% (w/v) aqueous sodium hydroxide (NaOH) solution using a fiber to liquor ratio of 1:20 for 2 h at the boiling temperature of the mixture, under constant stirring on a magnetic stirrer and reflux. The delignified plant material was washed thoroughly with distilled water until a colourless supernatant was produced, filtered and dried in an oven at 50 °C to constant weight. The residue (crude α-cellulose) was then bleached with a 20 times higher quantity of 1% (w/v) aqueous sodium chlorite (NaClO$_2$) solution at pH = 4, obtained by the addition of glacial acetic acid. The procedure was repeated twice. The bleached mixture was cooled down to room temperature and then washed with water to a neutral reaction.

The mixture was subsequently subjected to hydrolysis, as described by Achor et al.,[11] using a 2.5 M solution of HCl at the boiling point for 15 min, then transferred into a vessel containing a three times higher amount of cold tap water and left overnight to settle. After rinsing with water to a neutral pH, the resulting microcrystalline cellulose was dried in an oven at 50 °C until constant weight was achieved.

Characterization of microcrystalline cellulose
Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR spectra of isolated and commercially available microcrystalline celluloses were obtained using a Perkin Elmer Spectrum One FT-IR spectrometer coupled to a horizontal Golden Gate MKII single-reflective ATR system (Specac, 214 Kent, UK), equipped with a Zy-Se lens and associated with the appropriate software.

Scanning Electron Microscopy (SEM)

The shape and surface characteristics of the isolated and commercially available MCCs were analyzed by a scanning electron microscope (JOEL JSM-6390LV, USA), under vacuum conditions and at a voltage of 30 kV. Samples were mounted on the aluminium stub and photomicrographs of the powders were taken. Before that, a thin layer of gold was applied over the samples to make them electrically conductive, using a cool sputter coater (BAL-TEC SCD 005, Switzerland) for 100 seconds at a current of 30 mA.

Analysis of metals and metalloids by Inductively Coupled Plasma Atomic Emission Spectrometry

Samples of microcrystalline cellulose isolated from corn and straw were prepared by microwave digestion,

in accordance with the method recommended by the Environmental Protection Agency.[12] The determination of Fe, Mn, Pb, Cd, Hg and As was performed using Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES), in accordance with the recommendations of a previously described method,[13] on an iCAP 6500 Duo instrument (Thermo Scientific, United Kingdom). The iTeva software was used to process data. The operating parameters of the instrument are given in Table 1.

The concentrations of the analyzed elements were determined by external calibration, using the Multi-Emission Standard (ICP, AccuStandard) for the analysis of Fe, Mn, Pb, Cd and As, and for the Hg single standard (Mercury Atomic Absorption Standard – AA, AccuStandard). As a control standard, the Laboratory Performance Check Standard, Plasma Emission Standard (ICP), AccuStandard was used.

Working solutions were produced by suitable dilution of a corresponding stock solution with 2.5% nitric acid (HNO$_3$).

Emission intensity was measured at wavelengths given in Table 2. Table 2 also presents the results of the regression-correlation analysis and the most important validation parameters of the applied method.

Analysis of representative anionic species by Ion Chromatography

In accordance with the recommendations of the published method, the amount of sulphate and chloride in the isolated and commercially available microcrystalline celluloses was determined by Ion Chromatography.[14]

The ionic chromatograph Dionex Model IC (DX 300), with a Spectra System autosampler, Spectra-Physics AS 3000, a Dionex AGP1 gradient pump and a Dionex CDM 3 conductometric detector, were used. The suppression column ASRS 300, 4 mm, and the analytical AS 9-HC, 4 x 250 mm, were utilized. The mobile phase was 9 mM Na$_2$CO$_3$, with a flow rate of 1.0 mL/min, with an injection volume of 10 μL. The detection limits were as follows: 0.05 mg/L for chlorides and 0.05 mg/L for sulphates.

Characterization of microcrystalline cellulose as pharmaceutical excipient

In the preliminary phase of characterizing the microcrystalline cellulose powder, flowability, bulk and tapped density, Carr's index and Hausner's ratio were assessed. The procedures of these tests are presented elsewhere (Ph. Eur. 9.0).

Determination of true density using a helium pycnometer

The samples were first dried for 24 h at 130 °C. After drying, they were transferred to a vacuum desiccator, with CaCl$_2$ and silica gel, for cooling. Immediately after the transfer, the samples were vacuumed for 4 h.

Table 1

Equipment and experimental parameters for analysis of metals and metalloids by Inductively Coupled Plasma Atomic Emission Spectrometry

RF power	1150 W
Nebulizer	Sea Spray
Spray chamber	Glass cyclonic
Peristaltic pump speed	50 rpm
Argon flow and pressure for the nebulizer	0.4 L/min/26 MPa
Flow of argon for cooling	14 L/min
Auxiliary flow of argon	0.5 L/min

Table 2

Emission wavelengths of the analyzed elements, as well as the results and validation parameters of their regression-correlation analysis

Element	λ, nm	y = ax + b	R^2	RSD, %	LOD, ppb	LOQ, ppb
Fe	259.94	y = 29862x + 128	0.9997	4.0	0.7	2.0
Pb	220.35	y = 2666x + 14	0.9993	2.0	8.0	27.0
Mn	257.61	y = 113990x + 721	0.9997	0.6	0.2	1.0
Cd	228.80	y = 29188x + 244	0.9996	1.3	0.7	2.0
Hg	184.95	y = 1175x + 12	0.9996	1.3	5.0	18.0
As	189.04	y = 1044x + 8	0.9998	2.0	21.0	69.0

Density measurements were performed by an ATC Pycnomatic (Thermo, Italy) at 20.00 ± 0.01 °C. An average density was calculated from five consecutive measurements of each individual cellulose sample. The measurement was repeated in five series under the same conditions and the corresponding standard deviation was calculated.

Tensile strength

Firstly, the measurements of weight, thickness and crushing strength of the flat-faced tablets were done (Erweka tablet hardness tester TBH125D, Germany). Then, the breaking force was converted into tensile strength according to Newton's equation (Eq. (1)):[15]

$$\sigma = \frac{2F}{\pi dh}$$

(1)

where: σ – radial tensile strength (N/cm); F – maximal force (N); d – tablet diameter (cm).

Simulation of material compaction, determination of compactibility and compressibility

For evaluating the compression behavior of the materials, a Gamlen Tablet Press benchtop single-punch tablet press was used.[16]

The weight of the compression powder was kept constant (25 mg), as well as the tablet diameter (6 mm) and the rate of compression of the tablet (60 mm/min). Tablets were compressed at a load of 100, 300 and 500 kg. Ten tablets were made and their weight, thickness, diameter and breaking strength were measured afterwards. In the analysis of tablet compression, it was observed that the mass, diameter, thickness and hardness of the tablets, for the same compression force, were very close. Based on those measurements, Heckel's curves for the MCC isolated from corn, straw and the commercial one were constructed.

The compression model, proposed by Leuenberger, combines the parameters of compressibility and compactibility. Using the Heckel equation (Eq. (2)) and the general equation of the Leuenberger curve (Eq. (5)), the compactibility and compressibility coefficients were calculated:

$$\ln(\frac{1}{1-D}) = k\sigma_d + A$$

(2)

where D is the relative density of the compact in the matrix at the compression pressure σ_d, and A is the slope and the cutoff (*i.e.*, the regression coefficients) of the linear part of the curve. The relative density D gives information about the part of the solid fraction in the powder column (Eq. (3)):

$$D = \frac{\rho_a}{\rho_t}$$

(3)

where ρ_a is the apparent density (which is calculated by dividing the mass with the volume of the powder column) and ρ_t is the true material density (which is measured by the helium pycnometer).

The mean yield pressure (σ_y, MPa) was calculated according to Eq. (4):

$$\sigma_y = \frac{1}{k}$$

(4)

where k is the Heckel parameter (MPa^{-1}).

The equation of the Leuenberger's curve (Eq. (5)) is presented below:

$$\sigma_T = \sigma_{Tmax} - (1 - e^{-\gamma\sigma_d D})$$

(5)

where: σ_T – the radial tensile strength, σ_{Tmax} – the maximum tensile strength, γ – the parameter called the compressibility, σ_d – the compression pressure, and D – the relative density.

Dimensional changes and elastic recovery during compaction

For determining the dimensional changes of tablets during compression, extremely precise measurement of the position of the piston rods is required. Measurement of the dimensional changes from the minimum thickness of the tablet during compaction, tablet thickness at zero pressure while the tablet is still in the die, to the thickness of the tablet upon ejection from the die, was carried out using the data obtained from the Gamlen Tableting D series simulator.

The work of compression and the elastic work were calculated as the surface below the curve of the piston position as a function of the applied force during compression, or the elastic recovery of the tablet after removal from the device matrix. The total area was obtained using the trapezoid method. The width and height of the trapeze were taken as the difference between two successive points of the piston position of the matrix and the corresponding value of the applied force.

In-die elastic recovery (Eq. (6)) at the end of the decompression phase was calculated using the Armstrong and Haines-Nutt method, from the dynamic compression profile obtained by the compaction simulator:[17]

$$In - die\ elastic\ recovery\ (\%) = \frac{H_a - H_b}{H_b} \times 100 \qquad (6)$$

where in-die elastic recovery is expressed in percentage (%); Ha is the height of the tablet at the end of the decompression phase (mm); Hb is the minimum tablet height at the maximum pressure force (mm).

The ejection work was calculated as the area below the curve of the piston position as a function of the applied force, at the stage of ejecting the tablet from the matrix. The detachment work represents the surface under the same curve, but in the phase of removing the tablet from the bottom surface of the device matrix.

Tablet compression

Tablets were prepared by the direct compression method. Flat-faced punches with a diameter of 13 mm were used to compress the tablet mass, using an eccentric tablet machine (EKO Korsch, Germany). Tablet weight was set to 500 mg. Tablets were prepared with ibuprofen and microcrystalline cellulose with a % mass ratio of 20-80. Both the microcrystalline cellulose obtained from corn and straw and the commercially available one were used.

Disintegration time

Disintegration testing was performed on a disintegration test apparatus on six tablets at 37 °C in 900 mL distilled water in accordance with Ph. Jug. V.

In vitro dissolution studies

Dissolution studies were performed in the paddle apparatus (Erweka DT 600, Germany) at 50 rpm using 900 mL of USP phosphate buffer of pH 6.8 as a dissolution medium. Dissolution medium samples were withdrawn at predetermined time intervals (30, 60, 90 and 120 min). Then, they were appropriately diluted and analyzed by UV spectrophotometry (Evolution 300 spectrophotometer, Thermo Fisher Scientific, USA) to determine the percentage of drug released. The ibuprofen dissolution rate profiles from the tablets were compared by calculating the difference (f_1) and the similarity factor (f_2).[18]

RESULTS AND DISCUSSION

In this work, microcrystalline cellulose (MCC) was obtained from lignocellulosic biomass (corn stover and wheat straw). The extraction yields of MCC from the stover and the straw were of 40% and 36%, respectively. In comparison with similar studies, a significantly higher yield was achieved, whereby the cellulose was almost completely isolated from the straw and the stover on the basis of literature data.[15] When we are talking about corn, the result of the isolation process is better than in the case of the straw, namely of 40.05%. Other authors (Suvachittanont and Ratanapan) obtained a lower yield of microcrystalline cellulose from corn, compared to ours (27%).[16] In their study, the starting material was only corn cob, while we used the other parts of the corn stover, except the cobs, which can explain the higher yield we obtained.

FT-IR spectra for both samples and commercially available microcrystalline celluloses were recorded and presented in Figure 1.

Despite some small differences, the FT-IR spectra of the MCC samples exhibit all the characteristics of pure microcrystalline cellulose. Typical absorption peaks of cellulose were observed at 1430, 1158, 1109, 1025, 1000 and 970 cm^{-1}.[21] The peaks at 3331-3333 cm^{-1} are assigned to stretching of the –H bond of the –OH group. The peaks at 2884 cm^{-1} for Vivapur® and 2890 cm^{-1} for our samples are attributed to C–H stretching. The bands at 1428 and 1313 cm^{-1} in the Vivapur® spectrum and at 1429 and 1316 cm^{-1} in the spectrum of our obtained products were attributed to the asymmetric –CH$_2$ bending and wagging. The peak associated to the –C–O–C– stretch of the β-1,4-glycosidic linkage in cellulose was observed at 1160 cm^{-1} for all the samples.[22]

For observing the shape and surface of cellulosic fibers, Scanning Electron Microscopy

(SEM) was applied. Comparing the detailed micrographs (Fig. 2), it can be concluded that the fibers of microcrystalline cellulose obtained from straw and corn were longer and more irregular than the spherically shaped fibers of commercial microcrystalline cellulose. Upon further careful analysis of the obtained SEM micrographs of the microcrystalline cellulose from straw and corn, besides long fibers, some spherical forms were observed. Incomplete hydrolysis might be responsible for the diverse shapes. Also, by comparing the obtained SEM micrographs with those from the literature, it is obvious that the shape of cellulosic fibers before the hydrolysis process is quite similar.[23]
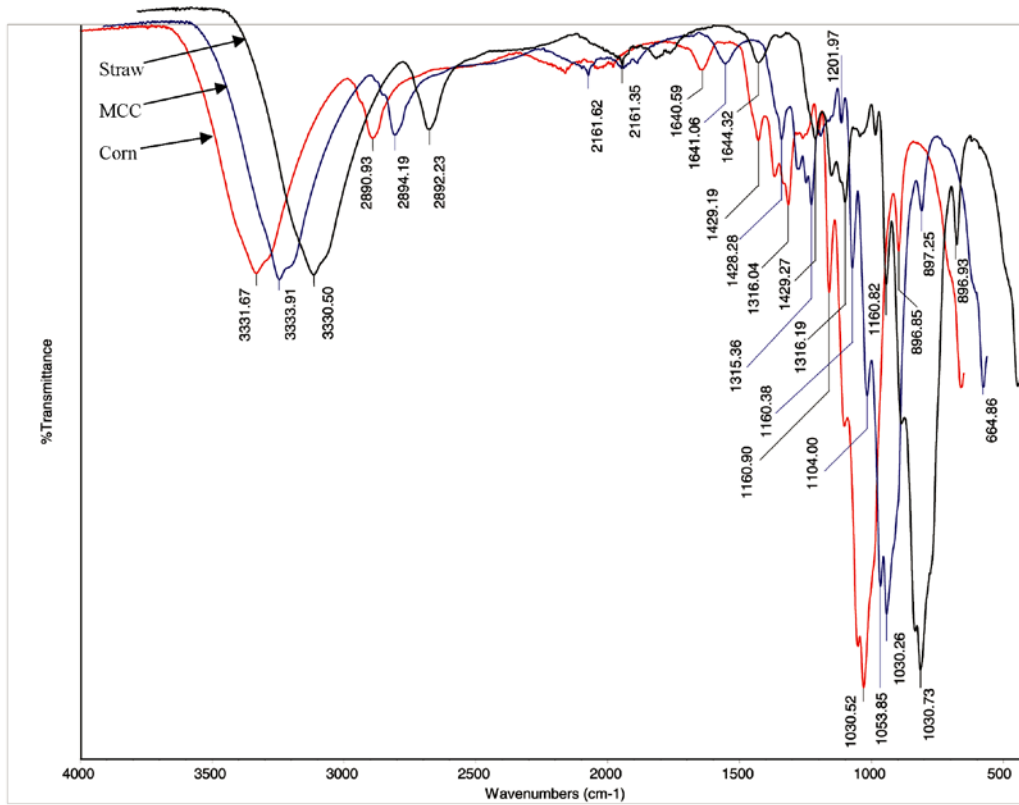
Figure 1: FT-IR spectra of commercially available microcrystalline cellulose, microcrystalline cellulose from straw and microcrystalline cellulose from corn
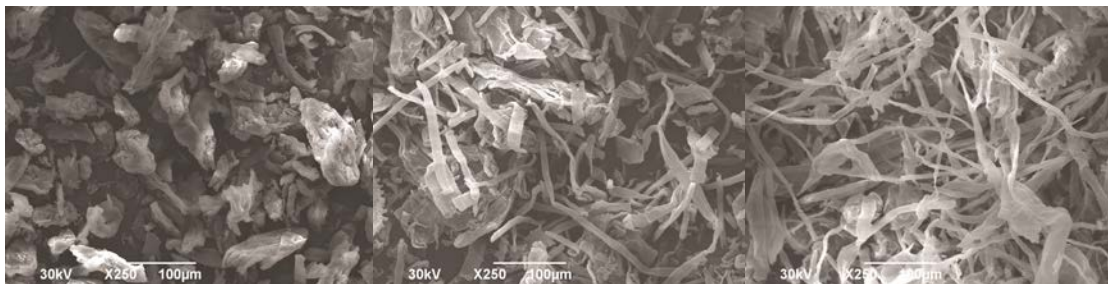
Figure 2: SEM images of commercially available microcrystalline cellulose (left), microcrystalline cellulose isolated from corn (center) and from straw (right)

Table 3
Presence of metals, metalloids and anions (mg/kg)

Element/anion	Concentration (mg/kg)	
	Corn	Straw
Lead (Pb)	6.41	1.79
Iron (Fe)	148.5	55.4
Manganese (Mn)	2.14	4.29
Cadmium (Cd)	<0.1	<0.1
Mercury (Hg)	<0.05	<0.05
Arsenic (As)	<0.9	<0.9
Sulfates (SO_4^{2-})	464	530
Chlorides (Cl^-)	116	456

Microcrystalline cellulose is widely used in oral pharmaceutical and food products and is generally considered as a relatively non-toxic material, since it is not systematically absorbed after oral administration. Despite its low toxic potential, it is necessary to determine the concentration of certain significant metals, metalloids and anions present in MCC, in order to assess the safety of its application and to meet the requirements for quality defined in the Ph. Eur. 9.0. The maximum permissible concentration of heavy metals is up to 10 ppm, thus, according to the obtained results (Table 3), it can be concluded that the straw and corn-based samples are safe for human use.

The permitted concentrations for iron, manganese and anions are not defined in the official pharmacopoeias, so additional tests should be carried out in order to prevent potentially high concentrations of individual elements in the sample. These values indicate the possible pollution of the soil in the area where the material was collected. The iron and manganese may come from groundwater, for example, from weathering of iron and manganese bearing minerals and rocks. Industrial effluents, acid-mine drainage, sewage and landfill leachate may also contribute to the content of iron and manganese in local groundwater.[24] Only a few studies have been devoted to the investigation of the presence of acidic anion species in biomass used for obtaining microcrystalline cellulose.

Powder characterization

In this part, the isolated MCC and the commercially available one (Vivapur®) were subjected to several preliminary tests. The measurements of the flow and bulk density were used for calculation of Carr's index and Hausner's ratio (Table 4).

From the obtained results, it can be concluded that the flow is not significantly different between the MCCs from straw and corn, but in comparison with that of the commercial sample, it was lower. This result is due to the different particle size and shape of the isolated MCC and commercial MCC.

The true density of MCC from corn and straw, as well as of that commercially available excipients, was determined using the helium pycnometer. The obtained values (1.551 g/cm³, 1.620 g/cm³ and 1.604 g/cm³, respectively) do not differ significantly and are within a range reported in the literature, *i.e.* from 1.512 to 1.668 g/cm³.[25]

It is important to point out that the characterization of excipients defines the deformation properties, which depends on the nature of the excipients. For example, the behavior of any crystalline material is dependent on the crystallite size and shape. Microcrystalline cellulose usually deforms plastically, but it also exhibits a certain degree of elasticity.[26]

According to Heckel's equation (Eq. (2)), the linear part of the curve (value of A), is related to the densification of the powder and the rearrangement of the particles during the loading of the matrix – before applying any compression force. The slope of the curve (k) is a measure of the plasticity of a material, which means that the increase in the slope of Heckel's curve for a material increases its plasticity. The mean yield pressure (σ_y) is calculated as the reciprocal value of the slope (k). The value of σ_y also reflects the compressive characteristics of the material and the lower the value, the greater the plastic deformation.[27,28] Typical materials with plastic deformation have yield pressures reported to be in the range of 40-135 MPa, whereas materials that deform mainly by fragmentation have higher yield pressures, ranging from 340 to 430 MPa.[29]

Table 4
Results of the preliminary phase of microcrystalline cellulose characterization

Excipients	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Flowability (categories)	Flowability (g/s)
MCC from straw	0.056	0.11	50.02	2.002	very poor	0.04
MCC from corn	0.085	0.17	50	2	very poor	0.28
MCC (Vivapur®)	0.335	0.48	30	1.42	poor	2.38

Table 5
Parameters of Heckel's and Leuenberger's curves

Excipients	Heckel's equation				Leuenberger's equation		
	k (10^{-3} MPa^{-1})	A	σ_y (MPa)	R^2	σ_{Tmax} (MPa)	γ (MPa^{-1})	R^2
MCC from corn	0.0056	0.6389	178.57	0.9673	10.8031	0.0408	0.9324
MCC from straw	0.009	0.528	111.11	1.000	9.6727	0.009	0.9616
MCC (Vivapur®)	0.0143	0.392	69.93	0.8529	10.2332	0.0664	0.9004

According to Roberts and Rowe,[29] commercially available excipients and MCC from straw are deformed plastically during compression, while the MCC from corn showed brittle fracture rather than plastic deformation (Table 5). Also, due to their slightly lower k values, the MCCs from corn and straw exhibit plastic deformation with fragmentation during compression as well.

The correlation plot between compressive pressure and tablet porosity for the formulations with commercial MCC and MCC from corn and straw (Fig. 3a) shows no significant changes in the porosity of the system, which indicates that plastic deformation is predominant through the compression process of the microcrystalline cellulose tablets rather than brittle fracture.

The dependence of the tensile strength on the compression pressure is presented in Figure 3b, and the results were used for the calculation of Leuenberger's equation. The compression model suggested by Leuenberger and used here for further analysis of compressibility and compactibility is presented in Figure 4.

There is a positive correlation between the mechanical strength of the tablets and the number of established connections between the particles. The relative reduction in the number of bonds between the particles is proportional to the increase in compression pressure and the relative density change. The relation of the breaking stretching force (σ_T) and the tensile strength can be considered a measure of the strength of the compactor (Eq. (5)). It is also a measure of compactness, σ_{Tmax}, the ability of the material to become compact with sufficient strength at a certain pressure.[27] Materials with low σ_{Tmax} show relatively poor compactibility, even when a high compression pressure is applied. On the other hand, a high γ value shows that the maximal tensile strength could be achieved at low compression pressure.[30]
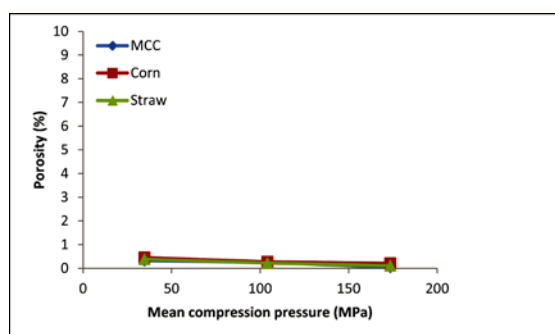
a)
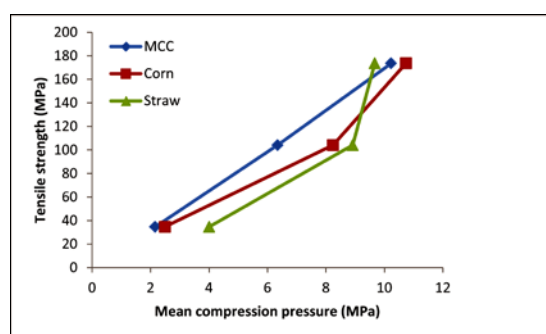
b)

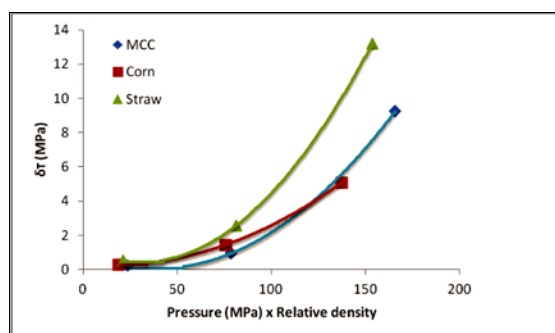Figure 3: Percentage of porosity (V/V) (a) and tensile strength (b) of tablets compressed at different pressures

Figure 4: Tensile strength of corn, straw and commercial MCC according to Leuenberger's equation

Figure 5: Tabletability of different MCC powders

It was noted that the compactibility of the microcrystalline cellulose obtained from corn and that of the commercially available microcrystalline cellulose are approximately equal to or slightly higher than 10 (the limit value between plastic deformation and brittle fracture), while that of the straw MCC is close to 10. It means that all the materials exhibit the same type of deformation – plastic. Based on the value of the compressibility (γ), which is large (10^{-2}), we found that these materials achieve tensile strength relatively fast with the increase of the applied compression force.

The dependence of the tensile strength on the compression pressure in tableting is shown in Figure 5. With increasing the compression pressure, changes in the tensile strength are visible for all three materials. It increases up to 120 MPa. Further increase in the compression pressure does not affect the tensile strength. This trend is confirmed for the MCC from straw and for the commercial one, while with regard to the MCC from corn, further increase of the compression pressure leads to a slight increase in tensile strength. It can be pointed out that, for similar values of compression pressure, compressed tablets of satisfactory mechanical properties can be obtained from all these materials.

The degree of packing of MCC with increasing compression force is presented in Figure 6. The work required for compression is the sum of the work needed to rearrange the particles, for deformation and for fragmentation. For all the materials, the compression force increases the work of compression, which can indicate that compact parts pass through the integration and/or fragmentation at the micro-level after compression. In addition, such specific behavior
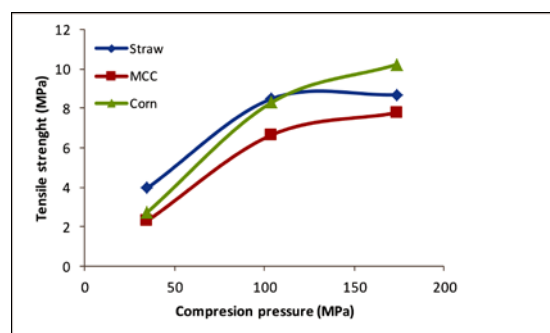
influences the resulting elastic recovery profiles (Fig. 7).

The dependence of elastic work on compression force is shown in Figure 8 and similar behavior is noticed for all the materials. When the pressure increases, more and more primary particles are fragmented into smaller particles, which have greater resistance to deformation, exhibiting an elastic character in that way.[28] Since in-die elastic recovery refers to the amount of potential energy during the compression and its release during the decompression phase, it can be concluded that commercial excipients preserve a greater amount of energy than the MCC from corn and straw. These results can be attributed to the differences in the fiber structure and the type of deformation.[31]

In order to verify the necessity of using lubricants in the manufacture of tablets, the parameters related to the work of compression required to remove or eject the tablet from the matrix of the simulation device were calculated. At a higher compression pressure, a greater force is required to eject the tablet from the device matrix (Fig. 9).

A slightly higher pressure is needed to eject the tablets made using commercial excipients than those made from the corn and straw MCC. The increase in the compression pressure does not significantly affect the detachment stress of the corn and straw MCC tablets from the bottom of the device matrix, as shown in Figure 10.

We also noticed that the tablets made from commercial excipients could stick to the bottom of the matrix at higher values of compression pressure. So in these cases, it is necessary to use lubricants. In the case of the direct compression method for the production of tablets, a lubricant

may be used in small amounts, or it may be omitted from the formulation when the obtained materials have satisfactory characteristics, even

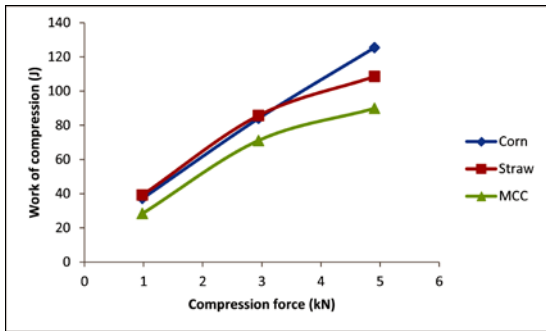slightly better than those of the commercial ones.[16]

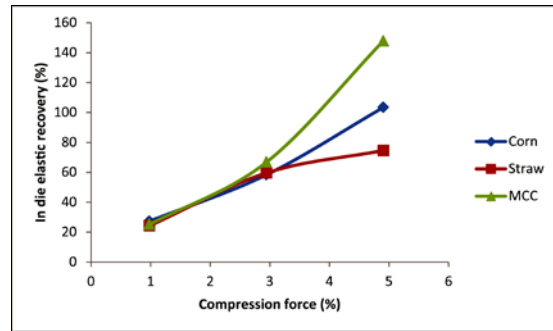Figure 6: Compression work of different MCC powders as a function of compression force
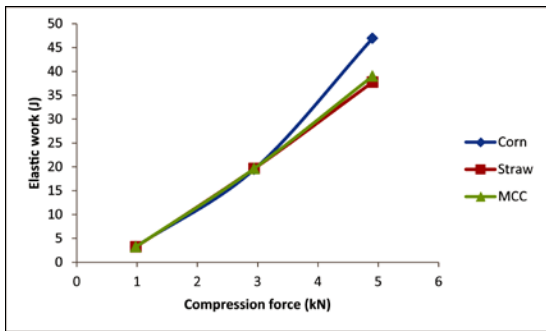

Figure 7: In-die elastic recovery (%)

Figure 8: Elastic work of different MCC powders as a function of compression force
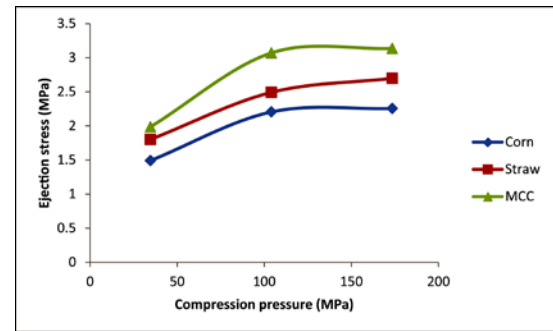

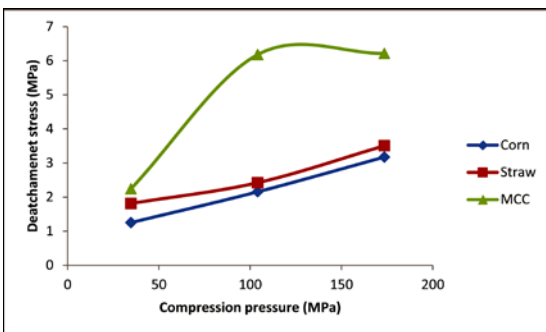Figure 9: Ejection stress of different MCC powders

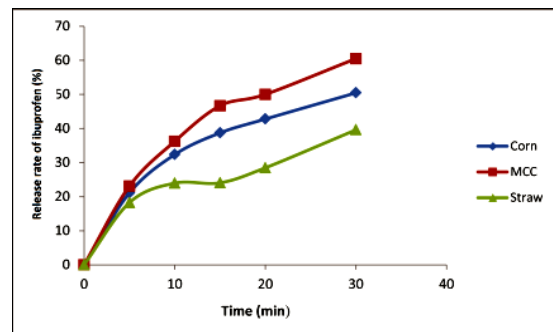Figure 10: Detachment stress of different MCC powders

Figure 11: Dissolution profiles of tablets prepared from different MCC powders

The disintegration behaviour and the dissolution rate of the tablets were investigated. To this end, tablets containing straw and corn MCC, as well as commercial MCC, as excipient, and ibuprofen as an active ingredient were tested. It was found that the tablets based on commercial MCC disintegrated in 1 min, while those made from both straw and corn MCC needed 3 min for

disintegration. Such a difference is not significant from the biopharmaceutical point of view. The highest dissolution rate was achieved for the tablets made from commercial MCC as excipient (Fig. 11).

The obtained results were used for calculating the factors of similarity (f_2) and difference (f_1), which showed that there is no significant

difference between the dissolution rate of commercial MCC and that of the MCC isolated from corn ($f_2 = 58.9\%$). The same conclusion can be drawn with regard to the dissolution rate of the MCCs from straw and corn ($f_2 = 51\%$). On the other hand, a significant difference is noticed between commercial MCC and the one isolated from straw ($f_2 = 37.43\%$).

CONCLUSION

In this study, microcrystalline cellulose (MCC) was successfully isolated from lignocellulosic biomass (corn stover and wheat straw). The extraction yields of MCC from stover and straw were of 40% and 36%, respectively. The isolated microcrystalline cellulose was subjected to chemical and technological characterization. Firstly, its structure was confirmed by FT-IR spectroscopy, while the shape and surface characteristics of the particles were analysed by SEM. Based on a comparison of the micrographs, it appeared that, after the hydrolysis, the microcrystalline cellulose fibers obtained from straw and corn were longer and more irregular than the more spherically shaped fibers of commercial microcrystalline cellulose, although they looked quite similar before this chemical process. The safety of the obtained product was extensively tested by the quantification of selected heavy metals, metalloids and anions, using ICP-AES and IC, respectively. According to the obtained results, the content of heavy metals was below the maximum permissible concentration of 10 ppm. Thus, the straw and corn-based samples were confirmed to be safe for human use from the chemical point of view. For the first time, a systematic technological characterization was done with the basic objective to examine the possibilities of pharmaceutical application of the developed material. After preliminary testing of flowability, bulk and tapped density, the technological characterisation of the tablets made from the isolated and commercial MCCs was performed, including the simulation of material compaction, and the determination of compactibility and compressibility. It was noted that the compactibility of the microcrystalline cellulose obtained from corn and that of the commercially available one are close to or slightly higher than 10. The large compressibility (10^{-2}) shows that these materials achieve tensile strength relatively fast with an increase in the applied compression force, exhibiting satisfactory mechanical properties. Also, tests were carried out to investigate the disintegration behaviour and the dissolution rate of the tablets containing straw, corn and commercial MCC as excipient and ibuprofen as active ingredient. No significant difference, from the biopharmaceutical point of view, among the tested materials was found. The obtained results demonstrated the satisfactory characteristics of the isolated MCC, opening the perspective of implementing the methodology presented in this work for large-scale production.

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