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# Microcrystalline Cellulose: The Inexhaustible Treasure for Pharmaceutical Industry

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**Abstract** Microcrystalline cellulose (MCC) is pure partially depolymerized cellulose synthesized from α-cellulose precursor. The MCC can be synthesized by different processes such as reactive extrusion, enzyme mediated, steam explosion and acid hydrolysis. The later process can be done using mineral acids such as $H_2SO_4$, HCl and HBr as well as ionic liquids. The role of these reagents is to destroy the amorphous regions remaining the crystalline domains. The MCC is a valuable additive in pharmaceutical, food, cosmetic and other industries. The MCC is one of the most important tableting excipients due to its outstanding dry binding properties of tablets for direct compression. Different properties of MCC are measured to qualify its suitability for such utilization, namely particle size, density, compressibility index, angle of repose, powder porosity, hydration swelling capacity, moisture sorption capacity, moisture content, crystallinity index, crystallite size and mechanical properties such as hardness and tensile strength. Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are also important to predict the thermal behavior of the MCC upon heat stresses. The degree of polymerization (DP) of the MCC is typically less than 400, while that for nanocrystalline cellulose is more than 400 extending to several thousands of (1→4)-β-d-glucopyranose units. The MCC particles with size lower than 5µm must not be more than 10% of the total particles. There are several types of the MCC, namely PHs 101, 102, 103, 105, 112, 113, 200, 301 and 302 based on the particle size and subsequent utilization.

***Keywords:*** *microcrystalline cellulose, dry granulation, wet granulation, XRD, FTIR, XRD, TGA, DTA, MSDS*

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## 1. Introduction

### 1.1. Microcrystalline Cellulose (MCC) Difinition

MCC is purified, partially depolymerized cellulose synthesized by acid-hydrolysis of alpha cellulose ($I_\beta$-allomorph). It was discovered in 1955 by O. A. Battista and P. A. Smith and was first commercialized under the brand name Avicel® [1]. In 1962, they reported its preparation scheme by the American Viscose Company of microcrystalline cellulose, hence the origin of the product name "Avicel". In 1964 FMC, Corporation introduced Avicel® PH to the pharmaceutical industry as an ingredient for direct compression tableting where the "PH" designation indicates that the product is suitable for pharmaceutical use [1,2]. The MCC was first registered in the supplement to the National Formulary, twelfth edition, in 1966 [3].

### 1.2. Raw Precursor

MCC can be obtained commercially from wood [4] as well as non-woody lignocellulosic materials such as cotton linters [5], cotton stalks [4], cotton rags [5], soybean husk [5], corn cob [7], water hyacinth [8], coconut shells [9], rice husk [4,10], sugar cane bagasse [4,10,11,12,13,14], jute [15], ramie [16], fibers and straw of flax [17], wheat straw [18], sorghum stalks [19], sisal fibers [20] and coconut shells [9]. Seed flosses extracted from mature pods of milkweed (*Calotropis procera*) shrubs and kapok (*Ceiba pentandra*) trees are additional cellulosic resources. Except for cotton floss due to its high purity of alpha cellulose, most seed flosses must be treated to remove impurities such as lignin, pectin, wax as reported by Hindi [21].

Cellulose is the most abundant natural polymer on earth with an annual biomass production of about50 billion tons [22]. Cellulose consists of linear chains of β-1,4-D anhydro-glucopyranose units. In wood, cellulose chains are packed in layers held together by cross-linking hydrogen bonds [23] within a polymeric matrix of lignin, hemicelluloses and pectin [24]. Woods differ considerably in chemical composition (allocations of cellulose, hemicelluloses and lignin in cell wall) and structural organization, i.e., regions which are relatively more crystalline or amorphous according to softwoods (evergreen conifer) and hardwoods termed as deciduous broadleaf [23,25]. The amorphous regions are more susceptible to partial depolymerization by acid hydrolysis resulting in shorter and more crystalline fragments such as the MCC [23,26].

## 1.3. Industrial Applications

The MCC is a valuable additive in pharmaceutical as a binder for tablets by direct compression (DC) and in vitamin supplements, in food as an anticaking, thickener, texturizer, emulsifier and bulking agent as well as a fat substitute and in cosmetic as a filler [5,19] due to its superior dry binding properties [23]. The DC remains the most economical technique to produce large batches of tablets although its efficiency is directly impacted by the raw material attributes [23]. It is also used in plaque assays for counting viruses, as an alternative to carboxymethyl cellulose [27]**.** Another applications of the MCC such as paints, paper and nonwoven textiles, oils field services, medicine and composites because of its properties such as high strength, flexibility and aspect ratio [28,29].

## 1.4. Synthesis

The MCC can be synthesized by different processes such as reactive extrusion process, enzyme mediated process [18], the steam explosion process and acid hydrolysis process [4,5]. The acid hydrolysis process (Figure 1) is preferred due to its shorter reaction duration comparing to the other processes. Furthermore, it can be applied by a continuous process rather than a batch-type process and it consumes limited quantity of acid and can produce fine particles of the MCC [5].

The synthesis procedure of the MCC reported by Ohwoavworhua *et al*. [30] and applied with slight modification by Ohwoavworhua *et al*. [19] can be concluded as follow: A 50 g quantity of the α-cellulose was hydrolyzed with 0.8 l of 2.5 N hydrochloric acid at a boiling temperature of 105° for 15 min. The fraction passing through 710 µm sieve was obtained and stored at room temperature in a desiccator.

**Drying of the MCC**

There are different techniques can be used for drying of the MCC, namely freeze-drying (lyophilization) using liquid nitrogen, fluid-bed drying, hot air oven drying and desiccation with silica-gel to less than 5% (w/w) water content [31]. MCC is commonly dried by spray-drying the neutralized slurry obtained from the hydrolysis process. By varying spray drying conditions, it can be manipulating the degree of agglomeration and moisture content. Smaller particle sizes below 50 µm can be obtained by further milling MCC [22].

**Characterization of the MCC**

There are many different techniques can be used to characterize the MCC such as infrared spectroscopy (FTIR), X-ray diffraction (XRD), thermogravimetric analysis (TGA), differential thermal analysis (DTA) or differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR), atomic force spectroscopy (AFM), scanning electron microscopy (SEM), transmission electron microscopy (TEM), hi-resolution transmission electron microscopy (Hi-TEM).

**Physicochemical Properties of MCC**

The organoleptic characteristic, identification tests, solubility and presence of organic impurities such as starch, dextrin and water-soluble substances can be done according to credit procedures such as the British Pharmacopoeia (BP) specifications [32]. The pH determination of the supernant obtained by shaking 2 g of the MCC powder with 100 ml of deionized water for 5 minutes [30]. Total ash content in the MCC can be determined by weighing the residue remained after combustion at 550° until all the carbon is eliminated [30].

Different properties of MCC synthesized from many cellulosic precursors were evaluated by several investigators. The MCC of sugar cane and Avicel powders were evaluated for particle size analysis [33], density and compressibility index [20,30,34], angle of repose [35], powder porosity [30], hydration [36] and swelling capacity [30], moisture sorption capacity and moisture content [34].

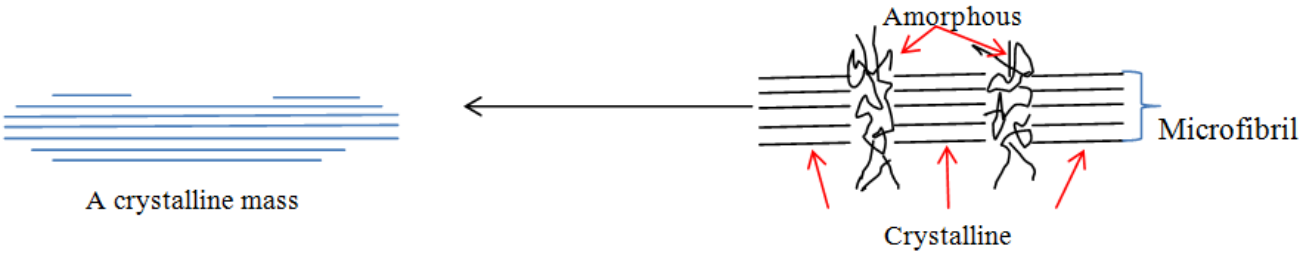


**Figure 1.** Effect of acid hydrolysis on destroying the amorphous domains of a cellulosic microfibril

**Table 1. Hydrolysis reagents (acid type and concentration), liquor to cellulose ratio (L/C), hydrolysis conditions and yield of microcrystalline cellulose (MCC-Y)**

| Hydrolysis reagent | | L/C (vol./wt) | Hydrolysis condition | | MCC-Y % | Reference |
|---|---|---|---|---|---|---|
| Type | Conc. | | Temperature ($^0$C) | Duration (minute) | | |
| HCl | 2N | 10:1 | 105 | 15 | n.f[1]. | [5] |
| HCl | 2N | 10:1 | 45 | 15 | n.f[1]. | [4] |
| HCl | 2.5N | 20:1 | 85 | 90 | 80 | [5] |
| HCl | 2.5N | 62.5:1 | 105 | 15 | 19 | [4] |
| HCl | 2N | 10:1<br>20:1 | n.f[1]. | 45-60 | n.f[1]. | [7] |

[1]Not defined.

For particle size analysis, it can be determined using a sieve shaker, containing standard sieves arranged in a descending order according to their opening size. About 20 grams of the MCC powder is placed on the top sieve and shaking for 5 min. The weight of MCC retained on each sieve is determined. The average diameter can be calculated as reported by Ansel *et al.* [33] using the following equation: Average diameter of the MCC particles = [∑ (% retained)×(mean aperture)]/100. The real density ($D_r$) of cellulose powders can be determined by the xylene displacement method [34] and computed according to the following Equation: $D_r$ = [w/{(a+w)-b}×SG], where w represents weight of powder, SG represents specific gravity of xylene, a represents sum weights of bottle and solvent and b represents the sum weights of bottle, solvent and the MCC powder [19].

For the moisture content (MC) determination, about 2 g of the MCC sample was weighed (A) and oven-dried at 105-C for 8 hours, and then weighed again (B). The MC was calculated using the following formula: [(A-B)/A] ×100 [37].

**Spectroscopic Studies of the MCC**

The optical microscope (10X, 40X or 100 X magnifications) can be used for speculating hydrolysis progress as well as preliminary assessment of the MCC particles.

Scanning electron microscopy (SEM) and/or transmission electron microscopy (TEM) study (Table 2) is widely used to character the MCC particles. Before SEM examination, all samples are sputtered with a 15 nm thick gold layer (JEOL JFC- 1600 Auto Fine Coater) in a vacuum chamber. For the SEM imaging, it can be done by Field Emmision SEM device such as JEOL, JSM-7600F [20], while TEM imaging can be applied by such TEM-1011 JEOL, Japan.

For X-ray differaction (XRD), the wide angle X-ray diffraction spectra of the MCC can be recorded on a proper X-ray differactometer such as a XRD 7000 Shimadzu diffractometer (Japan). The system has a rotating anode generator with a copper target and wide angle powder goniometer. The generator must be operated at 30 KV and 30 mA. All the experiments should be performed in the reflection mode at a scan speed of 4° /min in steps of 0.05°. All samples are scanned in 2θ range varying from 4° to 30°.

The crystallinity index of the MCC can be determined by using the following equation:

$Ic=[(I_{002}-I_{am})/(I_{002})]x100$ [20], where $I_{002}$ represents the intensity of crystalline peak arising from and alpha-cellulose while $I_{am}$ is the crystallographic plane arising from remained amorphous cellulose plus amorphous impurities (lignin and pectin).

Crystallite size (CS) is the mean diameter of the crystal and can be calculated by the Scherrer equation as follows [38,39,40]:

$$CS = (57.3k\lambda)/(\beta\cos\theta)$$

Where k is the shape factor of the crystal (0.94), λ is the wave length of X-ray incident upon the crystal (0.1542 nm), β is the full width at half maximum (FWHM) of the crystalline peak corresponding to the crystallographic plane 002, and θ is the Bragg angle corresponding to the (002) plane. A factor of 57.3 was used to convert β from degrees to radians.

**Lattice Spacing (LS)**

The *d*-spacings is calculated using the Bragg equation as follows:

$$d = n\lambda / 2\sin\theta$$

Where n is an ordinal number with a value of 1 for diffractions with the strongest intensity [40,41], λ is the wavelength of X-rays incident on the crystal (0.1542 nm), and θ is the Bragg angle corresponding to the (002) plane.

The crystal and molecular structure together with the hydrogen-bonding system in cellulose $I_\beta$ can be determined using synchrotron and neutron diffraction data recorded from oriented fibrous samples prepared by aligning cellulose microcrystals [42].

**Table 2. Types of the commercial microcrystalline cellulose [1]**

| MCC Type | Particle Size (micron) | Utilization |
|---|---|---|
| PH 101 | 50 | It is most widely used for direct compression tableting, wet granulation, spheronization and in capsule filling processes. |
| PH 102 | 100 | It is used as the PH-101 but its larger particle size improves flow of fine powders. |
| PH 103 | 50 | It has the same particle size as PH-101 with lower moisture content (3%), so it is used for moisture sensitive pharmaceutical active ingredients. |
| PH 105 | Less than 50 | It has the smallest particle size. It is the most compressible of the PH products. It is useful in direct compression for granular or crystalline materials. It can be mixed with PH-101 or PH-102 to obtain specific flow and compression characteristics. It has applications in roller compaction. It is poorly flowable by itself. cannot determine neat compressibility. |
| PH 112 | 100 | It has the same particle size as PH-102. It has lower moisture content (1.5%). It is used for high moisture sensitive pharmaceutical active ingredients. |
| PH 113 | 50 | It has the same particle size as PH-101. It has lower moisture content (1.5%). It is used for high moisture sensitive pharmaceutical active ingredients. |
| PH 200 | 180 | It has a large particle size with increased flowability. It is used to reduce weight variation and to improve content uniformity in direct compression formulations and in wet granulation formulations. |
| PH 301 | 50 | It has the same particle size as PH-101 but denser providing more flowability and tablet weight uniformity. Useful for making smaller tablets and in capsule filling excipient. |
| PH 302 | 90 | |

**Thermal Analyses**

There are different types of the thermal analyses of the MCC (Table 2), namely thermogravimetric analysis (TGA) which measures weight changes, differential thermal analysis (DTA) that measures exothermic and endothermic reactions, differential scanning calorimetry (DSC) which measures the heat required to raise the sample temperature. In addition, thermal conductivity (TC) is frequently used to measure ability to transmit heat across the MCC sample. Furthermore, thermo-mechanical analysis (TMA) is useful to measure dimensional changes due to altering temperature. For the composites reinforced by the MCC, dynamic mechanical thermal analysis (DMTA) is used to investigate viscoelastic properties of polymers. The thermal behavior of the MCC can be predicted by TGA, DTA or DSC using a Seiko &star 6300 analyzer. Heating scans from 30 up to 550°C at 20°C/min in nitrogen atmosphere are performed for each sample [43].

In conclusion, parameters and techniques used to characterize microcrystalline cellulose (MCC), namely crystallinity index [4,5,7,20] and crystallite size [4,7] determined by X-ray differaction, Fourier transform infrared spectrometry [4,5], thermogravimetric analysis [4,5], differential thermogravimetric analysis [4,5], differential thermal analysis [44], differential scanning calorimetry [44], scanning electron microscopy [4,7,20], transmission electron microscopy (TEM), viscosity measurement [4], particle size and particle size distribution [4,19,20], true density [4,19], tensile strength [4], hardness [4], wet granulation [4], hydration capacity [19], swelling capacity [19], moisture sorption capacity [19] and compressibility [19,20].

**Table 3. USA Standard Mesh, analogous hole diameter and models of the MCC based on their particle size**

| US Mesh | Hole diameter (µm) | Models of sieved MCC |
|---|---|---|
| 35 | 500 | |
| 40 | 400 | |
| 45 | 354 | |
| 50 | 297 | - |
| 60 | 250 | |
| 70 | 210 | |
| 80 | 177 | PH 200 |
| 100 | 149 | |
| 120 | 125 | - |
| 140 | 105 | PH 102, PH 112 |
| 170 | 88 | PH 302 |
| 200 | 74 | |
| 230 | 63 | - |
| 270 | 53 | PHs 101,103, 113, 301 |
| 325 | 44 | |
| 400 | 37 | |
| 450 | 32 | PH 105 |
| 500 | 25 | |
| 635 | 20 | |

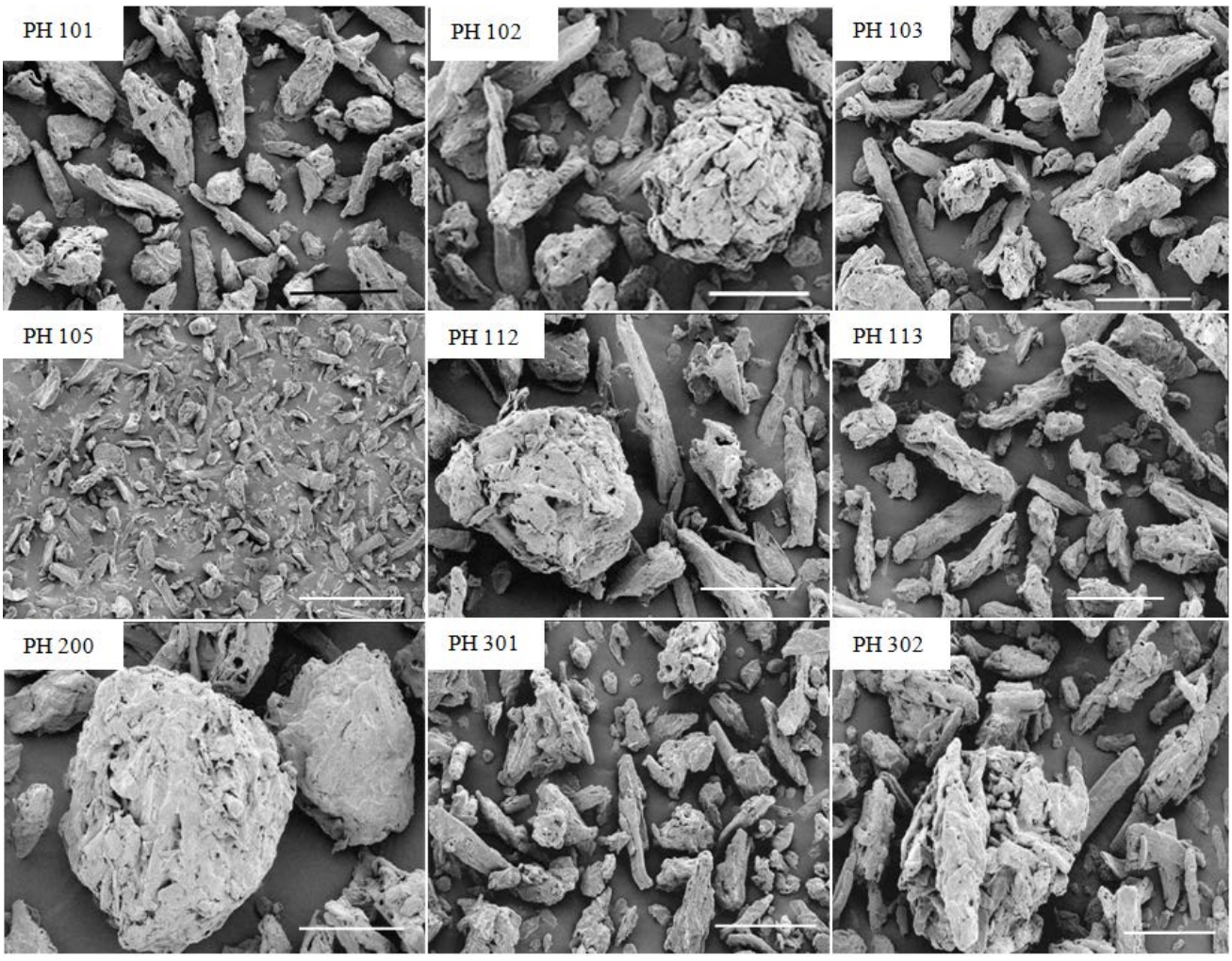


**Figure 2.** SEM micrographs of microcrystalline cellulose (MCC) models with a scale bar of 100 µm [1]

The MCC is most widely used for direct compression tableting, wet granulation and extrusion spheronization, for partition chromatography, as a reference material in characterization of microcrystalline cellulose (MCC) using powder X-ray diffraction and Fourier transform infrared spectroscopy, to evaluate crystallinity index and spectral analysis of cellulose using XRD and solid-state $^{13}C$ NMR, as used in preparation of phosphoric acid-swollen cellulose for enzyme assay using HPLC, and in capsule filling processes, especially those employing tamping or other means of consolidation as part of the process. The MCC model '102' has a median particle size of about 100 μm. It has similar compression properties to that for 101 but its larger particle size improves flow of fine powders [26,45]. So, it is widely used for direct compression tableting, wet granulation and spheronization and in capsule filling processes. However due to the low bulk density of MCC, its mass flow is less than that of other common and denser excipients such as direct compression grades of lactose or dibasic calcium phosphates [2,46,47,48]. Furthermore, lubricant sensitivity is sometimes used as a functional test to evaluate MCCs synthesized from several sources [1]. In addition, carrying capacity is another test of the MCC used in pharmaceutical industry that measures the amount of a drug substance [1].

**Avicel® RC/CL**

If a food grade sodium carboxymethylcellulose is added to the microcrystalline cellulose, with additional wet attrition before drying, a colloidal microcrystalline cellulose is produced termed as Avicel® RC/CL which can function as a suspending agent, emulsion stabilizer, etc [1].

**The Tableting Characteristics of MCC-Models**

According to Reier [1], the MCC can be directly compressed alone without addition of a lubricant at humidities below 55%. On the other hand, above this moisture level, some formulas face sticking texture can be arisen. In formulations, lubrication is always necessary, although the MCC has been termed as an antiadherent material and reduction in lubricant concentration may be obtained in some formulations.

The MCC has a lubricant sensitivity in which its compressibility may be reduced when mixed with other material such as magnesium stearate. Particle size of the MCC also influences the lubricant sensitivity. Avicel PH-200 (180 microns) is more sensitive to lubricant than is Avicel PH-101 (50 microns) due to the same concentration of lubricant more efficiently covers the larger particle size of the PH-200 than the smaller particle size of the PH-101 particles with larger particle surface area [1].

Compactability is affected by the porosity of the MCC particles. Really, PH-101, PH-102, and PH-200 have about the same neat compressibility even though their mean particle size varies from 50 to 180 microns while PH-301 (50 microns) and PH-302 (90 microns) are more dense and less compressible or compactable [1].

**Table 4. Material safety data sheet (MSDS) of the microcrystalline cellulose (MCC)**

| | |
|---|---|
| Product name | Avicel® PH Microcrystalline Cellulose |
| Chemical family | Carbohydrate |
| Synonyms | Microcrystalline cellulose (INCI name): MCC, cellulose gel |
| Alternate names | Avicel PH 101, 102, 103, 105, 112, 113, 200, 200 NLM, 301, 302, Avicel® RC/CL |
| Odor | Odorless |
| Appearance | White, free-flowing powder |
| Moisture content (%) | Typically 1 - 5 % water, by weight |
| pH (In solution) | 5.0 - 7.0 (11% solids dispersion) |
| Solubility in water (% wt/wt) | Insoluble |
| Specific gravity | 0.2 - 0.5 g/cc |
| Explosive properties | St-1 |
| Minimum ignition temperature | 420°C |
| Stability and reactivity | Stable |
| Emergency overview | Powder becomes slippery when wet and its accumulation may form fire. |
| Potential health effects | No significant health hazard |
| Eye and skin | Non-irritating for eyes and skins of rabbit and guinea pig |
| Dermal LD50 | > 2,000 mg/kg (rabbit) |
| Oral LD50 | > 5,000 mg/kg (rat) |
| Inhalation LC50 (rat) | > 5.05 mg/l Maximum attainable concentration-zero mortality |
| Overexposure's acute effects | It has low oral, dermal and inhalation toxicity as well as non-irritating and non-sensitizing to skin. |
| Overexposure's chronic effects | Inert dust and nontoxic to the lung and negative in the ames mutagenicity assay and caused no chromosome damage |
| Carcinogenicity | Not listed |
| First aid treatments | Flush eye with plenty of water, wash skin with plenty of soap and water, never give anything by mouth to an unconscious person and if breathing difficulty obtain medical attention |
| Ecological results | The MCC is inherently biodegradable in soil. It biodegrades in soil at a rate comparable to starch. |

**Table 5. Permissible exposure limits (PEL) of the MCC-dust in some countries [49]**

| Country | PEL (mg/m³) | Notes |
|---|---|---|
| Australia (TWA)[1] | 10 | - |
| Belgium (TWA)[1] | 10 | Inhalable dust |
| China (STEL)[2] | 25 | - |
| China (TWA)[1] | 10 | - |
| Hong Kong (TWA)[1] | 10 | - |
| Ireland (TWA)[1] | 10 | Inhalable dust |
| Korea (TWA)[1] | 10 | - |
| New Zealand (TWA)[1] | 10 | Respirable dust with no asbestos and <1% free silica |
| Singapore (PEL)[3] | 10 | - |
| Switzerland (TWA)[1] | 3 | Respirable dust |
| United Kingdom (STEL)[2] | 10 | Total inhalable dust |
| United Kingdom (TWA)[1] | 10 | Total inhalable dust |
| United Kingdom (TWA)[1] | 4 | Respirable dust |

[1] TWA: Time-weighted average, [2] STEL: Short-term exposure limits and [3] PEL: Permissible exposure limit.

**Benefits of MCC in wet granulation**

Wetting MCC with water followed by drying and compression revealed to tablets with lower hardness than that for dry compression [1]. In addition, the wet granulation reduces the density of the agglomerated particles thereby decreasing their internal surface area, but also can cause some adhesion between particle agglomerates, reducing external surface area resulting in less particle interlocking and hydrogen bonding. The use of Avicel PH-101 or PH-102 in wet granulation formulations as 5-20% of the formulation can offer the following functionalities [1]:

1. The MCC rapidly adsorb water distributing it through the mixture.
2. It decreases sensitivity to water content, wet screening and localized overwetting due to its large surface area and adsorptive capacity.
3. It increases drying efficiency.
4. It controls color mottling and drug content uniformity.
5. Tablets compressed from granulations containing MCC are harder at the same compression stresses and less friable than those compressed without it.

**The MCC as a Spheronizing Agent**

The extrusion-spheronization process aims to present drugs in sphere-shaped tablets. Extrudates that are plastic, but without rigidity, tend to agglomerate into very large spherical balls. The mass to be extruded must be

1. Cohesive and deformable enough to flow through the die without sticking and able to retain its shape after extrusion
2. Plastic so that it can be rolled into spheres in the spheronizer but non-cohesive so that each sphere remains discrete.

The MCC is an excellent extrusion-spheronization aid, especially Avicel PH-101 that acting as a molecular sponge for the water added to the formulation, altering the rheological properties of the wet mass, enhancing the tensile strength of the wet mass through autoadhesion.

**The material safety data sheet (MSDS) of the MCC**

The material safety data sheet **(**MSDS**)** of the MCC is presented in Table 5 [49].

# 2. Conclusion

- MCC is purified, partially depolymerized cellulose synthesized by acid-hydrolysis of alpha cellulose ($I_{\beta}$-allomorph).
- MCC can be obtained from lignocellulosic materials such as wood, cotton linters, cotton stalks, cotton rags, soybean husk, corn cob, water hyacinth, coconut shells, rice husk, sugar cane bagasse, jute, ramie, fibers and straw of flax, wheat straw, sorghum stalks, sisal fibers, coconut shells and seed flosses of *Calotropis procera* and *Ceiba pentandra*.
- The MCC is a valuable additive in pharmaceutical as a binder for tablets by direct compression (DC) and in vitamin supplements, in food as an anticaking, thickener, texturizer, emulsifier and bulking agent as well as a fat substitute and in cosmetic as filler due to its superior dry binding properties**.**
- The MCC can be synthesized by different processes such as reactive extrusion process, enzyme mediated process, the steam explosion process and acid hydrolysis process.
- The acid hydrolysis process is preferred due to its shorter reaction duration comparing to the other processes.
- MCC Drying can be done by freeze-drying (lyophilization), fluid-bed drying, hot air oven drying and desiccation with silica-gel to less than 5% (w/w) water content.
- MCC is commonly dried by spray-drying the neutralized slurry obtained from the hydrolysis process.
- There are many different techniques can be used to characterize the MCC such as infrared spectroscopy, X-ray diffraction, thermogravimetric analysis, differential thermal analysis or differential scanning calorimetry, nuclear magnetic resonance, atomic force spectroscopy, scanning electron microscopy, transmission electron microscopy, hi-resolution transmission electron microscopy.

- There are several types of the MCC, namely PHs 101, 102, 103, 105, 112, 113, 200, 301 and 302 based on the particle size.
- PH 101 is most widely used for direct compression tableting, wet granulation, spheronization and in capsule filling processes
- The MCC is an excellent extrusion-spheronization aid, especially PH-101 that acting as a molecular sponge for the water added to the formulation, altering the rheological properties of the wet mass, enhancing the tensile strength of the wet mass through autoadhesion.
- Avicel® RC/CL is microcrystalline cellulose mixed with sodium carboxymethylcellulose as a food grade material.

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