MICROCRYSTALLINE CELLULOSE: A BIOPOLYMER WITH DIVERSIFORM APPLICATIONS

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With characteristics, such as white color, tasteless, odorless, neutral, non-reactive, non-toxic, stable, biocompatible, and biodegradable, along with excellent compaction properties, high mechanical strength, and low density, microcrystalline cellulose (MCC) stands out as a top excipient for direct compression tablets. As the demand for renewable, eco-friendly, and non-fossil materials becomes increasingly imperative, this most abundant biopolymer on Earth is sought not only in the pharmaceutical industry, but also in the cosmetics, food, construction, and wastewater treatment sectors. This review paper highlights the importance of this substance by describing its various applications across the mentioned industrial sectors, with a focus on direct compression tablets as the most commonly used oral dosage form. Results from numerous experiments have demonstrated the benefits of MCC as a component in a variety of products, including direct compression tablets, coated spheres, topical preparations, ice cream, cocoa, fried beef patties, sausages, cement, foamed concrete, and adsorbents for heavy metals in wastewater treatment.

Keywords: microcrystalline cellulose, pharmacy, food, construction industry, wastewater treatment

INTRODUCTION

Since its introduction in the 1960s,[1-3] MCC has been considered the best excipient for the production of tablets by direct compression.[4] It was branded as Avicel® by FMC Corporation in 1964.[5] In addition to Avicel, MCC is also available on the pharmaceutical market under various brand names, including Emcocel (Edward Mendell, USA), Vivacel (JRS, USA),[6] MICROCEL (Roquette, France), CEOLUS (Asahi Kasei, Japan), and Comprecel (Mingtai, Taiwan).[7] This substance consists of purified, partially depolymerized cellulose, obtained from fibrous plant material. It is prepared by treating alpha cellulose with mineral acids.[8] The β-1,4-linked polymer of D-glucopyranose is partially depolymerized to produce a mean degree of polymerization (DP) ranging from 150 to 250, with a mean particle size ranging from 40 to 200 μm.[9] With its characteristics of being white, tasteless, odorless, neutral, non-reactive, non-toxic, stable, biocompatible, biodegradable, and having excellent compaction properties, high mechanical strength, and low density, MCC stands out as the most commonly used excipient for tableting.[10-13]

In the United States (US), specifications for MCC are provided in the Food Chemicals Codex, where it is labeled as cellulose gel. It is a carbohydrate (a fiber source insoluble in water) that is indigestible by humans and provides 0 calories. It has Generally Recognized as Safe (GRAS) status and has been used in the food industry for decades.[14] The European Regulation (EC) No 1333/2008 of the European Parliament and of the Council, dated December 16, 2008, labels it as E460(i), and it can be found in the list of food additives, among permitted emulsifiers, stabilizers, thickening and gelling agents for use '*quantum satis*' for the purpose of achieving technological benefits.[15]

Oral administration of medication is often preferred for therapeutic purposes because it is non-invasive, easy for individuals to use, and tablets are one of the most commonly used forms.[16] Tablets are solid dosage forms that contain an active pharmaceutical ingredient (API)

with or without suitable diluents, and are manufactured through compression.[17] Among all fillers for direct compression, MCC is the most widely used, offering the highest dilution potential and capacity.[18,19] In the USA, tablets are the most widely used solid dosage form[17] and account for over 80% of all dosage forms administered to humans.[20]

MCC has a wide range of uses in pharmaceutical oral forms, including as a binder/diluent in tablets and capsules, as lubricant,[21] glidant, stabilizer, suspending agent, directly compressible filler, wet granulation filler, roller compaction agent, compaction aid, extrusion agent for pellet spheronization, and for immediate, sustained, extended, and delayed release formulations. It is also used for enhancing the organoleptic properties of oral tablets.[22] It functions as an excipient, adsorbent, suspending agent, tablet and capsule diluent, and tablet disintegrant. The largest users of MCC are the pharmaceutical and food industries, as well as the construction industry.[23] This review paper aims to describe the applications of MCC in these industrial sectors, with a particular emphasis on direct compression tablets.

MCC SOURCES AND PREPARATION METHODS

Sources for MCC production can be classified into two groups: wood and non-woody lignocellulosic materials. The latter includes cotton linters, cotton stalks, cotton rags, soybean husks, corn cobs, water hyacinth, coconut shells, rice husks, sugar cane bagasse, jute, ramie, flax fibers, wheat straw, sorghum stalks, sisal fibers, and more.[24,25]

The industrial methods for MCC production include acid hydrolysis, enzymatic hydrolysis, thermal explosion, and mechanical disintegration. Acid hydrolysis is the most commonly used method due to its efficiency in terms of time and resources. In this process, the starting material undergoes acid hydrolysis (using H_2SO_4) at temperatures ranging from 25 to 55 °C under stirring. Cellulose microfibrils, due to their tightly packed crystalline structure and numerous hydrogen bonds, are resistant to acid treatment. On a molecular level, the process involves selective degradation of the less ordered regions of the cellulose polymer chains, which exposes and frees the crystalline sites, leading to the formation of crystalline aggregates. After acid hydrolysis, the resulting hydrolysate is washed with distilled water to remove acid residues, then neutralized with a 1.5 M Na_2CO_3 solution, and washed again.[13,26,27]

The pharmaceutical industry requires MCC of high brightness. Therefore, when starting materials are low-cost pulps, containing high contents of caramelized sugars, which yield lower brightness MCC, the product must undergo a neutralization or alkalization step before the bleaching stage. Hydrogen peroxide is most commonly used for bleaching.[26] As an example, Abu-Thabit *et al*., who isolated MCC from raw date seeds, began with dewaxing the starting material using 200 mL of a 2:1 chloroform solvent mixture. After the seeds were dewaxed and dried, they performed delignification for 3 hours at 90 °C with 500 mL of a 17.5% NaOH solution under stirring. This process resulted in dark brown delignified slurry, which was then filtered and washed with distilled water until the pH reached approximately 7. After 48 hours of drying at room temperature, the yellow-colored cellulosic residue underwent bleaching using a sodium hypochlorite solution at a concentration of approximately 10–15% at 80 °C for 45 minutes. The bleached MCC was then washed with distilled water until the pH reached approximately 7 and freeze-dried to a constant weight.[28]

The method of producing bacterial cellulose by cultivating microorganisms (*e.g*., *Acetobacter xylinum*), followed by acid hydrolysis to obtain MCC with average particle sizes between 70-90 μm and a degree of polymerization (DP) of 250, is less commonly used.[29] Spray drying under different conditions is another technique allowing to achieve the desired particle size and moisture content.[30]

APPLICATIONS OF MCC IN THE PHARMACEUTICAL INDUSTRY

Direct compression tablets

The earliest written records of oral tablets date back to 1843, when Brockedon invented the first hand-operated device for compressing pills.[31] Today, computerized tableting machines are capable of producing up to 500,000 tablets per hour.[32] The most cost-effective and simplest of all techniques is direct compression,[16] which involves tableting a blend of ingredients without a preliminary granulation or agglomeration process.[30] It consists of just two processing stages: 1) mixing the API with excipients, and 2) compacting the tablet powder blend into tablets.[33]

The relative compactibility of various direct compression fillers was compared using magnesium stearate and stearic acid as lubricants. The fillers tested included Avicel PH-101® (MCC), Nu-Tab® (compressible sugar), Di-Pac® (compressible sugar), anhydrous lactose, Fast-Flo lactose, Emcompress® (dicalcium phosphate), Elcema G250® (powdered cellulose), and Starch 1500® (pregelatinized starch). It was found that MCC exhibited the highest compactibility of all the substances tested, followed by Fast-Flo lactose.[34] As the best dry binder for direct compression,[19] MCC is synonymous with direct compression tableting.[35] In formulations made by direct compression, MCC is typically used as an ingredient in amounts of less than 60% (w/w).[36]

When developing a new formulation, it is important to consider that the tabletability of MCC can vary among manufacturers owing to differences in the types of pulp used as raw material in the production process.[37] *In vitro* adsorption and bioavailability can be adjusted by using specific MCC brands in formulations. There are more than twenty different MCC products available on the market.[9] There is typically a minor difference between batches from the same producer compared to those from different producers, primarily concerning particle size and specific surface area.[5] Comparing products from different manufacturers revealed significant differences in lignin content, hemicellulose sugar content and composition, the presence or absence of cellulose II, enthalpy of immersion, particle size, and flow properties.[34]

When MCC tablets are produced at higher tableting speeds, the tablet strength is reduced due to shorter exposure time to compression.[36] As a result, tablet porosity increases.[38] Additionally, capping tendencies are associated with high tableting speeds.[6] The moisture in MCC, as previously discussed, can provide lubricating and plasticizing effects.[36] The strength of the produced compacts is achieved through the mechanical interlocking of particles.[39] Additionally, due to the viscoelastic strain relief, tablets undergo expansion, with Avicel PH-101 showing the greatest expansion, which typically reaches its maximum after 72 hours. The crystallinity of MCC does not impact the tensile strength of compacts. For example, two products with significant differences in crystallinity (Avicel PH-101 and Unimac MG-100) produce compacts with almost equal tensile strength, but with toughness values more than twice as high. Softer tablets can be produced using the granular form of powdered cellulose.[36] For producing softer tablets, it is recommended to use hydrophobic lubricants (such as magnesium stearate), along with extended blend times and high blend speeds.[40] The type of MCC selected for the formulation affects tablet hardness, friability, and dissolution. For example, since Avicel PH-200 negatively impacts these characteristics, Avicel PH-102 was chosen for the formulation of 500 mg amoxicillin tablets made by direct compression.[41]

In formulations with poorly compactible APIs, such as paracetamol or ascorbic acid, MCC is used alone at concentrations of 40-50% in the final tablet mixture due to its excellent properties as a dry binder. However, for APIs with better compactibility, such as aspirin or hydrochlorothiazide, where the total API content in the tablet is lower than that of paracetamol or ascorbic acid, the tablet mixture should consist of 20-40% MCC. In these cases, additional diluents, such as lactose or dicalcium phosphate, are included to reduce production costs and improve flow properties.[36]

To improve the tableting mixture and overall performance, MCC is mixed with starch, calcium sulfate,[42] calcium carbonate,[43] dicalcium phosphate dihydrate, *β*-cyclodextrin, and lactose.[44,45] When using direct compression, blending MCC with dicalcium phosphate dihydrate or lactose results in a mixture with improved performance.[46] This combination was studied by Wells and Langridge, who concluded that a mixture of dicalcium phosphate dihydrate and Avicel PH-102 in a 9:1 ratio produces the strongest tablets.[47] A combination of dicalcium phosphate and Emcocel 90M in a 1:4 ratio results in increased compaction speed and enhanced radial strength.[48] The formulations for some tablets produced by direct compression are provided in Table 1.

MCC is also used in formulations for the sustained release of APIs. When combined with hydrophilic polymers, it forms a viscous, gelling layer in the tablet mixture. This layer slows down water penetration, thereby releasing the API from the eroded parts of the tablet.[18] For example, a sustained-release tablet containing naproxen as the API and including Avicel PH-102 in its formulation was reported to be produced by direct compression.[51] Nalluri *et al*. prepared a controlled-release tablet using Avicel PH-105 and carvedilol as the API through direct

compression.[52] The use of plant extracts as APIs is also popular. For example, a tablet formulation containing an extract from *Phyllanthus niruri* L. (meniran) and Avicel PH-102 (40-50%) was prepared by direct compression.[53] Rapidly disintegrating tablets (uncoated, weighing 220 mg, with a diameter of 8 mm), containing meclizine hydrochloride (an antiemetic agent) as the API, were formulated with a mixture of Avicel PH-102 (120 μm), Avicel PH-301 (40 μm), low-substituted hydroxypropylcellulose L-HPC11 (50 μm), L-HPC21 (40 μm), and 1% magnesium stearate.[54] Particles with a diameter greater than 15 μm contribute to a rough mouthfeel in tablets.

A formulation for rapidly disintegrating tablets containing ethenzamide and ascorbic acid as APIs, mixed with Avicel PH-102 and L-HPC, was developed. This mixture results in a tablet with a rough mouthfeel due to the particle size of the excipients used.[56]

Table 1
Formulations of direct compression tablets

Ingredient (%)/ tablet	MCC	API	Filler	Lubricant	Refs
Amphetamine sulfate	MCC 68.3%; 63.52%	Amphetamine sulfate 1.7%; 6%	Lactose 30%	Magnesium stearate 0.48%	49
Ascorbic acid	Avicel PH-101 40-50%	Ascorbic acid 50-60%	/	/	36
Aspirin	Avicel PH-101, Emcocel 50M, Emcocel 90M 69%; 29%	Aspirin 30%; 70%	/	Magnesium stearate 1%	
Aspirin	Avicel PH-101, Emcocel 90M 9%	Aspirin 60%	Lactose 30%	Magnesium stearate 1%	
Ephedrine	MCC 30%	Ephedrine hydrochloride 8%	Calcium sulfate 50%	Magnesium stearate 2%	49
Phenobarbital	Avicel PH-101, Emcocel 50M, Emcocel 90M 69%	Phenobarbital 30%	/	Magnesium stearate 1%	
Prednisone	Avicel PH-102 73.5%	Prednisone 2%	Lactose 24.5%	Magnesium stearate 1%	50
Paracetamol	Avicel PH-102 49.5%	Paracetamol 49.5%	/	Magnesium stearate 1%	67
Phenethicillin	Avicel PH-102 97%; 30%	Phenethicillin 2%; 68%	/	Magnesium stearate 1%; 2%	
Quinine tablet	MCC 33%	MCC 33%	Lactose 10%; Calcium sulfate 4.6%	Magnesium stearate 2.9 %	49
Sodium phenobarbital	MCC 63%	Sodium phenobarbital 6%	Lactose 30%	Magnesium stearate 1%	
Steroid	MCC 48%	Androstane-type steroid 40%	Lactose 10%	Magnesium stearate 2%	

Additionally, the formulation was improved by replacing Avicel PH-102 (120 μm) with the novel Avicel PH-M-06 (7 μm) to eliminate the undesirable rough mouthfeel. The preparation procedure consisted in mixing MCC and L-HPC in a V-shaped mixer for 15 minutes, then adding acetaminophen or ascorbic acid, followed by 1% magnesium stearate to produce 200 mg tablets.[57]

Avicel® CE-15, a mixture of MCC and guar gum, facilitates the production of chewable tablets with a desirable smooth and creamy mouthfeel.[18]

In summary, the performance of tablets results from the contribution of each component and the applied processes, as these factors collectively influence the manifestation of the excipient's desired functional properties.[58,59]

The USP includes a non-mandatory information chapter listing excipient properties relevant to tablet diluents like MCC. These properties are: (1) particle size and size distribution, (2) particle shape, (3) bulk/tapped/true density, (4) specific surface area, (5) crystallinity, (6) moisture content, (7) powder flow, (8) solubility (MCC is insoluble in water), and (9) compaction properties for tablet dosage forms.[60] Properties of various MCC products are provided in Table 2.

Characterizing the physical, chemical, and structural properties of excipients using process analytical technologies is a critical aspect of producing a high-quality final product. Although APIs often receive more attention, likely because excipients are perceived as less critical, variations in less uniform excipients with crystalline forms can pose risks to patients. These variations are controlled by process analytical technology. Blend uniformity of the powder mixture is crucial for tablets, as issues with blend uniformity can lead to problems with content uniformity and overall product quality. Near-infrared spectroscopy can be used to examine the formulation and process variables of the powder bed.[61] Wu *et al*. tested a formulation containing ibuprofen, MCC, and anhydrous lactose and concluded that the tendency for segregation increased as the ratio of API to MCC particle size increased. Therefore, characterizing particle size and determining the appropriate weight of MCC are crucial for selecting the optimal rotation speed, which may ensure a better blending outcome.[62]

Stability, toughness, and hygroscopicity are related to the hydroxyl groups in cellulose units and the large surface-to-volume ratio of microfibrils.[63,64] Horio *et al*. studied the effect of particle shape on MCC and concluded that spherical particles with a porous structure contribute to better compressibility, while elongated particles tend to enhance tablet hardness.[65] A higher degree of polymerization (DP) generally results in greater compressibility, compactibility, and water absorption.[37] Even low compression forces can plastically deform particles, resulting in strong compacts.[35] From the opposite perspective, there is a research that claims that there is no obvious correlation between the DP and tabletability. Thanks to its relatively low bulk density and broad particle size distribution, small amounts of MCC are able to efficiently bind other materials, especially poorly tabletable APIs.[30]

Because of low bulk density and extensive particle size apportionment, even low tabletable APIs are possible to be compressed by addition of MCC.[30] The smaller particle size and rough surface favor adsorption. After experimental testing, the most impactful characteristic of MCC affecting the breaking strength of tablets was found to be the specific surface area (which is actually 90-95% internal),[66] and it is not affected by crystallinity, particle size and shape.[67] Conversely, some research suggests that there is no clear correlation between the degree of polymerization (DP) and tabletability. Nonetheless, due to its relatively low bulk density and wide particle size distribution, even small amounts of MCC can effectively bind other materials, particularly APIs that are difficult to compact.[68]

An important property for the tableting process, the moisture content, is limited to a maximum of 7% as the accepted loss on drying.[8] Khan *et al*. proposed that moisture within the pores acts as an internal lubricant, facilitating smoother particle flow.[69] The moisture content in MCC affects its tabletability by promoting smoother particle flow.[30] According to Doelker, the moisture content is the most important parameter affecting the mechanical properties of tablets.[36] Water has a plasticizing effect and enhances surface bonding at levels of 3-5%. However, at higher moisture levels (8.2%) or lower levels (1.1%),[36] bonding is reduced, leading to decreased tabletability.[64] The breaking of hydrogen bonds was identified as the underlying mechanism. This also impacts tablets during storage, as they tend to swell and soften under high humidity conditions. Increased moisture content is associated with lower crushing strength and longer disintegration times.[6,70] Recent studies have shown that Ceolus UF-711, with its porous particles sized at 50 μm, is a more suitable grade compared to Avicel PH-101 and Avicel PH-102.[71] The features and benefits of various grades of Avicel® and CEOLUS® are detailed in Table 3.

Table 2
Properties of MCC products that affect tableting[36, 9]

MCC product	Avicel PH-101	Avicel PH-102	Avicel PH- 105	Emcocel 50M	Emcocel 90M	Unimac MG-100	Unimac MG-200	MCC type 101	Indocel 80
Mean diameter (μm)	34	53	/	35	52	31	45	30	-
True density (g/cm^3)	1.532	1.564	/	1.543	1.557	1.547	1.541	1.555	/
Degree of polymerization	167	178	/	/	/	113	/	151	212
BET surface area $(m^2g^{-1})^3$	1.22	1.12	2.45	1.27	1.25	/	/	/	/
Degree of crystallinity (%)	74.85	77.7	72.8	66.9	/	53	/	74	58
Moisture content (%)	4.7	4.9	/	5	4.6	3.7	3.8	3.5	6
Flow rate (g/s)	/	9.1	/	/	10.8	/	12	/	/
Compressibility (%)	30	26	/	/	/	/	/	/	/

Table 3
Features and benefits of various grades of Avicel[6, 69]

Avicel	Benefits and features
PH-101	Most often used for direct compression tableting
PH-102	Compression properties similar to PH-101, particles are larger than PH-101
PH-103, PH-112, PH-113	Reduced moisture content, ideal for moisture-sensitive substances
PH-105	Finest particle size; can be admixed with PH-101 or PH-102 to achieve specific flow and/or compression properties
PH-200	Large particles, increased flowability, reduces tablet weight variation, lubricant sensitive, lower carrier capacity
PH-301	Higher density than PH-101, increased flowability, greater tablet weight uniformity, the potential for making smaller tablets
PH-302	Density similar to PH-301 and particle size like PH-102. Increased flowability, greater tablet weight uniformity, for smaller tablets
CEOLUS KG	Facilitates high-dose formulation; realizes low pressure tableting; lower tablet friability; preventing sticking and capping; suitable for roller compaction; suitable for once daily tablets, bilayer tablets, MUPS tablets
CEOLUS-UF 702	Improves poorly flowable formulations; fast disintegration and dissolution with sufficient hardness; prevents segregation and over-lubrication; facilitates high-speed tableting
CEOLUS-UF 711	Optimized for tableting of poorly compactable and flowable formulations
CELPHERE	Tolerant with high stress and coating machine varieties; reduces aggregation; yields improvement in coating; stable storage stability; suitable for controlled released formulations like multiple unit pellet system
PC-10	Toler-stabilizer for moisture sensitive APIs; granulation aid; carrier for extracts; dissolution enhancer

Table 4
Volumetric and gravimetric flow rates of fillers for direct compression tableting

Filler	Grade	Poured bulk density (g/cm^3)	Gravimetric flow rate (kg/min^3)	Volumetric flow rate (L/min^3)
MCC	Avicel PH 102	0.314	1.300	4.140
Powdered cellulose	Elcema G250	0.531	1.499	2.823
Pregelatinized starch	Starch 1500	0.589	1.200	2.037
Hydrous lactose	Fast-Flo	0.650	2.200	3.385
Compressible sugar	Di-Pac	0.694	3.747	5.399
Dibasic calcium phosphate	Di-Tab	0.933	4.300	4.609

Table 5
Parameters of uncoated carbamazepine tablets made by direct compression with different fillers

Parameter	β-CD	HP β-CD	Tablettose® 100	Pearlitol® 300 DC	Emcompress® Premium	Vivapur® 102	Avicel® HFE-102	Cellactose® 80
Bulk density (g/m)	0.652	0.418	0.575	0.676	0.88	0.318	0.388	0.426
Tapped density (g/mL)	0.813	0.503	0.714	0.758	1.049	0.446	0.499	0.519
Ability to settle (mL)	18	14	14	7	10	45	26	14
Carr Index (%)	17.8	13.1	18.8	9.7	14.9	26.9	21.8	16.9
Hausner ratio	1.14	1.07	1.1	1.05	1.1	1.26	1.17	1.07
Flow time (s/100 g)	1.9	0.8	1.1	0.4	0.4	4.6	3.2	1.2
Angle of repose (°)	27.4	33.7	28.8	26.3	23.5	38.6	31.5	31.3
Martin's diameter (μm)	90	137	86	225	141	107	90	103
Moisture (%)	8.11	5.96	0.4	0.28	0.33	3.47	3.4	2.18

MCC products are known for their poor flow properties, which can lead to variations in tablet weight. Avicel PH-101 has the worst flow properties, resulting in the highest weight variation in tablets. In contrast, Avicel PH-200 stands out for its good flow properties, reducing weight variation.[36] Additionally, larger particles of Avicel PH-102, Avicel PH-302, and silicified MCC (SMCC) 90 exhibit better flowability.[4] Proslov® is a market product that contains 98% silicified MCC combined with 2% colloidal silicon dioxide.[72] With superior flow and compaction properties,[73] Proslov® enhances mixing efficiency, reduces the need for excipients, and results in lower disintegration time.[18] It also improves powder flow, tablet strength, and reduces lubricant sensitivity and the need for wet granulation.[74]

Although MCC is composed of water-soluble glucose units, it is insoluble in water due to its crystalline structure. Despite this, it has a creamy feel in the mouth.[23,75] This is due to the compact arrangement of glucose polymers in the molecule, which results in indigestibility in the upper gastrointestinal tract and partial fermentability by colonic microflora.[76,77]

Tablets with high concentrations of MCC soften when exposed to high humidity due to moisture absorption, which weakens the interparticulate hydrogen bonds. This softening is reversible and disappears once the tablets are removed from the humid environment. Table 4 provides a comparison of the relative volumetric and gravimetric flow rates of MCC and other fillers used in direct compression tableting.[78]

In practice, even the same grades of MCC produced by the same manufacturer can exhibit variability due to unavoidable intra-batch and inter-batch differences. This can lead to tablets with inconsistent properties, resulting in variations in weight, uneven distribution of the API, and unacceptable crushing strength.[79]

Conceicao *et al*. tested the characteristics of uncoated carbamazepine tablets made by direct compression using various fillers, including MCC, β-cyclodextrin (β-CD), hydroxypropyl β-cyclodextrin (HP β-CD), Tablettose® 100 (α-lactose monohydrate), Pearlitol® 300 (mannitol), Emcompress® Premium (calcium hydrogen phosphate dihydrate), Vivapur® 102 (MCC), Avicel® HFE-102 (MCC 90% w/w /mannitol 10% w/w), and Cellactose® 80 (lactose monohydrate 75% w/w /cellulose 25% w/w). The results presented in Table 5 indicate that Vivapur® 102 and Avicel® HFE-102 exhibited acceptable flow properties. While lactose monohydrate generally showed the best results, its

use is limited because of lactose intolerance in a percentage of the population.[80]

Table 6 summarizes the various applications of MCC in the pharmaceutical industry based on its concentration.

Interactions with MCC

While excipients are generally considered inert, experimental results have shown that interactions between the API and tablet excipients can affect bioavailability.[81] As MCC is used as an excipient in oral tablets, it is crucial to understand potential interactions with other constituents, especially the API. These interactions can influence the stability, solubility, release rate, dissolution, and bioavailability of the API.[82] The lipophilic surface of MCC is amorphous, allowing drug molecules to adsorb to these regions.[9] The interactions between excipients and APIs can influence the choice of the manufacturing process, whether dry mixing or using solutions of the drug and excipients. For example, when MCC is dry-mixed with alkoxyfuroic acid, decomposition occurs at a later stage.[83] The adsorption affinity of MCCs for fluphenazine dihydrochloride and promethazine hydrochloride does not impact the release of these APIs from the suspension of excipient *in vitro*.[84]

Table 6
Usages of microcrystalline cellulose[21]

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

In a rare study on this topic, it was found that steroids, including phenothiazines, antihistamines, and antibiotics, can be adsorbed onto MCC from aqueous solutions. While the adsorption of diphenhydramine, chlorpheniramine, isoniazid, and p-aminobenzoic acid was minimal, the adsorption of phenothiazine derivatives was significant, with the following order of adsorption: promazine < triflupromazine < chlorpromazine << acrinol. This trend was consistent for both MCC PH-101 and PH-301. The adsorption of these phenothiazine derivatives increased with pH and decreased with ionic strength. For acrinol, the proposed adsorption mechanism on MCC involved ion exchange, though non-electrostatic forces also played a significant role. The negatively charged surface of the MCC molecule allows ion-exchange interactions with cationic drugs, although not all cationic drugs are equally adsorbed.[85]

The presence of residues or degradation products from the manufacturing process of MCC, such as reducing sugars (*e.g*., glucose and lactose), can potentially interact with active pharmaceutical ingredients (APIs) in tablet formulations. The manufacturing process, which involves acid hydrolysis and milling, may leave behind reactive impurities like glucose, formaldehyde (HCHO), hydrogen peroxide (H2O2), and various metals (Mg, Mn, Al, Cr, Cu, Fe, Ni, Zn, Ca, and other heavy metals). These impurities can participate in chemical reactions with APIs. One significant interaction is the Maillard reaction, a major chemical reaction between reducing sugars and amine-containing drugs. This reaction can lead to tablet browning, as observed in the interaction between the amine drug Vigabatrin® and Avicel®. Discoloration was also noted in tablets containing ethane sulfonamide with MCC, highlighting the potential for visual and chemical changes due to such interactions. In summary, the presence of these residues and impurities in MCC can affect tablet stability, appearance, and potentially the efficacy of the API, emphasizing the importance of controlling these factors in tablet formulation.[86]

The interaction between diclofenac and MCC in a buffered solution demonstrates that MCC can influence the release profile of the drug. Specifically, when diclofenac is formulated with MCC, the release of the API is slower compared to formulations containing more soluble excipients like dextrose and lactose. After 8 hours, the release of diclofenac from the MCC-containing formulation is around 75%, whereas formulations with dextrose or lactose, which are more soluble, typically show faster release rates.

This slower release observed with MCC can be attributed to several factors:

- Hydrophilic nature of MCC: being hydrophilic, MCC may create a more complex gel-like structure in the tablet matrix, which can slow down the rate at which water penetrates the tablet and subsequently releases the drug;
- Matrix formation: MCC forms a matrix that can retard the diffusion of the drug out of the tablet, leading to a slower release profile. This matrix effect is particularly relevant for controlled-release formulations, where a gradual release of the API is desirable;
- Crystalline structure of MCC: the crystalline nature of MCC can contribute to its ability to control the rate of drug release. The compact structure of MCC can act as a barrier to the release of the API, compared to more soluble excipients that dissolve and release the API more quickly.

The role of MCC as a tablet excipient affects the release profile of APIs, such as diclofenac, providing a slower release compared to formulations with more soluble excipients. This characteristic can be leveraged for controlled-release applications where a gradual release of the API is beneficial.[87] Bromhexine hydrochloride exhibits greater adsorption onto the surface of Avicel-PH 101 compared to Avicel-PH 102. This difference in adsorption can be attributed to several factors related to the properties of the MCC grades:

- Particle size: Avicel-PH 101 typically has a smaller particle size compared to Avicel-PH 102. Smaller particles provide a larger surface area relative to their volume, which can enhance the adsorption of substances like bromhexine hydrochloride;
- Surface area: the increased surface area of finer particles in Avicel-PH 101 allows for more interaction with the API. This can lead to a higher degree of adsorption compared to the larger particles of Avicel-PH 102, which have a relatively smaller surface area;
- Porosity: smaller particles, such as those in Avicel-PH 101, might have higher porosity, which can further increase the adsorption capacity. The porous structure allows for more significant interaction between the MCC and the API;
- Surface characteristics: the surface properties of the MCC particles, including their texture and surface energy, can also influence adsorption. The finer particles of Avicel-PH 101 may have different surface characteristics that enhance the binding of bromhexine hydrochloride.

In summary, the increased adsorption of bromhexine hydrochloride onto Avicel-PH 101 compared to Avicel-PH 102 is primarily due to the smaller particle size of Avicel-PH 101, which provides a larger surface area and potentially higher porosity for the API to interact with.[88]

The adsorption of tacrine hydrochloride from aqueous solutions onto MCC is characterized by being fully reversible and is influenced more by the source of the MCC rather than the size of the MCC agglomerates. Here is a detailed breakdown of the factors involved:

- Reversibility: the adsorption process of tacrine hydrochloride onto MCC is fully reversible, meaning that the drug can be released from the MCC surface back into the solution, without permanent binding. This property is important for applications where controlled release of the drug is required;
- Source of MCC: softwood *vs*. hardwood – MCC derived from softwood generally has a higher adsorption capacity compared to that derived from hardwood. This difference is due to the inherent properties of the cellulose in softwood, which can have different surface chemistry and porosity;
- Ion exchange mechanism: te adsorption mechanism for tacrine hydrochloride involves ion exchange. Softwood-derived MCC tends to have more functional groups available for ion exchange, enhancing its capacity to adsorb cationic drugs like tacrine hydrochloride;
- Size of agglomerates: the size of MCC agglomerates does not significantly affect the adsorption of tacrine hydrochloride. This indicates that, while particle size might influence other properties, such as flowability and compressibility, the adsorption of tacrine hydrochloride is more dependent on the chemical nature of the MCC and its source rather than the physical size of the particles.

In summary, the adsorption of tacrine hydrochloride onto MCC is influenced by the type of MCC used, with softwood-derived MCC having a higher capacity for adsorption due to its greater ion-exchange properties. The process is reversible and is not significantly affected by the size of MCC agglomerates.[9]

The absence of interaction between Celecoxib and Avicel PH-102 when the tablet is dissolved in aqueous medium suggests the following points:

- Inertness of Avicel PH-102: Avicel PH-102 appears to be chemically inert in this context, meaning it does not chemically interact with Celecoxib under the conditions tested (*i.e*., when the tablet is dissolved in water). This inertness is beneficial for maintaining the stability and efficacy of the active pharmaceutical ingredient (API);
- Stable API release: the lack of interaction indicates that Celecoxib's release from the tablet is not affected by Avicel PH-102, which can be important for ensuring consistent bioavailability and therapeutic efficacy;
- Formulation considerations: in tablet formulations, the excipient's role is often to aid in the physical properties of the tablet, such as its hardness, disintegration, and flow characteristics. Since Avicel PH-102 does not interact with Celecoxib, it is likely being used solely for its functional properties as a binder and filler, without affecting the chemical stability of the API.
- *In vivo* relevance: while this finding is relevant for the *in vitro* dissolution studies, it is also crucial to consider how the tablet performs *in vivo*. The inertness of Avicel PH-102 towards Celecoxib in dissolution tests suggests that the formulation might also maintain Celecoxib's stability during digestion and absorption in the gastrointestinal tract.

In summary, Avicel PH-102 does not interact with Celecoxib in an aqueous medium, supporting its role as a stable excipient in tablet formulations, where chemical interaction with the API is not desired.[81]

Disintegration of tablets

Disintegration is a crucial step in the tablet dissolution process, and it involves several key mechanisms. The initial and critical step in the disintegration of tablets is the penetration of water. Water infiltrates the tablet matrix, causing it to swell and soften. This is essential for breaking down the tablet into smaller particles or granules. Once water penetrates, the tablet begins to break apart due to the mechanical forces applied. These forces disrupt the inter-particle bonds formed during tablet compression. The process often involves the rupture of the tablet's structural integrity, leading to fragmentation into smaller particles.

The choice of excipients also plays a significant role in the disintegration process. For instance, disintegrants, such as starch, croscarmellose sodium, and sodium starch glycolate, are added into tablet formulations in order to enhance the disintegration of tablets. They absorb water and swell, leading to the tablet's breakup. Meanwhile, binders like MCC help hold the tablet together, while their concentration and type can affect disintegration. Overuse of binders might hinder the disintegration process.

The size and shape of the particles used in the tablet formulation influence how well the tablet disintegrates. Smaller particles often result in faster disintegration due to their larger surface area. Also, the compression force applied during tablet compression impacts the tablet's hardness and subsequently its disintegration. High compression forces generally result in harder tablets that may take longer to disintegrate, whereas lower forces might result in faster disintegration, but potentially weaker tablets. Finally, factors like pH and temperature of the dissolution medium can also affect the disintegration process. Tablets need to disintegrate efficiently under physiological conditions for optimal drug release and absorption.

In summary, the disintegration is a complex process initiated by water penetration, which leads to the mechanical breakdown of the tablet. The effectiveness of this process depends on the formulation, including the type and concentration of excipients, as well as the compression parameters.[89] The combination of water absorption, swelling, and mechanical forces from the digestive fluids facilitates the breakdown of tablets into smaller particles, enabling the release and absorption of the API.[90]

It is known that intermolecular bonds and van der Waals forces are responsible for the cohesion in MCC tablets.[91] The disintegration mechanism is described as the interruption of particle-particle bonds, which are intermolecular forces between the cellulose fibers, disrupted by imbedded water capillaries.[92,93] Lahdenpaa *et al*. conducted experiments with 16 different mixtures of Avicel® grades PH-101, PH-102, and PH-200 compressed tablets. The results showed that higher amounts of Avicel PH-101 in the mixture resulted in tablets with greater resistance.

Conversely, increased amounts of granular Avicel PH-102 and especially Avicel PH-200 led to tablets with shorter disintegration times.[94] In addition, Avicel PH-102 is characterized by lower crushing strength and shorter disintegration time.[95]

The porosity of tablets directly affects the rate at which water and body liquids penetrate. MCC's property of fast water entry, by widening the pores, is intensified when combined with dibasic calcium phosphate dehydrate in the tablet formulation and is slowed with dextrose.[96,97] For comparison, water penetrates into MCC by capillarity faster than into potato starch,[98] because MCC increases both capillary action and diffusion transport into the tablet.[99-101] However, researchers reported that an aspirin tablet with potato starch disintegrated in a shorter time than one with MCC, attributing this difference to variations in particle sizes.[102] Mitrevej *et al.* reported that the disintegration time of MCC tablets is independent of the presence of magnesium stearate as a lubricant in the tableting mixture.[103] Shah *et al*. established a correlation between the degree of polymerization and disintegration, noting that disintegrants with a high degree of polymerization and a small number of carboxymethyl groups tend to have a low degree of disintegration, regardless of the degree of substitution.[104]

The penetration rate of the dissolution solvent is related to the tortuosity, porosity, and pore size distribution, as dissolution is based on the release of API from the tablet into the solvent medium. This process is described by the dissolution theory, which posits that smaller particles have increased surface area and greater dissolution potential. Analytical methods, such as UV–Vis/HPLC, magnetic resonance imaging (MRI), thermogravimetric analysis, infrared spectroscopy, and infrared imaging, can be used to observe this process. Factors affecting dissolution include pore volume, the presence of superdisintegrants, like croscarmellose sodium, interparticle sinter bridges, and the temperature of the dissolution medium. These factors can significantly impact the dissolution rate, potentially doubling or halving it.[101] The experiment performed by Spence *et al*. showed that the addition of MCC to a model compound in a 90:10 ratio increased the dissolution rate compared to the compound alone.[99]

The effect of food on tablet disintegration is significant and should not be minimized. Abrahamsson *et al*. studied the impact of food on the disintegration of MCC tablets containing metoprolol as the API and concluded that food significantly delays disintegration by forming a film around the tablet.[105]

Coated spheres

Probiotic

A formulation consisting of MCC, calcium-crosslinked alginate, and lactose was tested and proved suitable for protecting against gastric acid, while providing rapid release in simulated intestinal conditions. The wet powder mass included MCC, sodium alginate, and lactose in a mass ratio of 5:3:2, with the addition of 13 mL of granulation fluid per 10 g of dry ingredients (containing *L. casei* suspension with 3% w/v $CaCl_2$). This formulation offers an alternative to oral formulations with live bacterial cells, such as tablets, capsules, pellets, and microcapsules, with economic benefits due to lower production costs. It effectively protected *L. casei* cells from gastric acid and delayed their release in simulated intestinal fluid (pH 7.0).[106]

Diclofenac

The cores consisting of diclofenac-layered sugar, isomalt, and MCC were coated with Eudragit® RS30D (ERS) and Eudragit® RL30D (ERL) in ratios of 0:1, 0.5:0.5, and 1:0. This coating exhibited permeability properties similar to those of ERS and ERL. Compared to pellet cores without MCC, those containing MCC were mechanically much stronger. Dissolution tests revealed that diclofenac sodium pellets with sugar or isomalt cores showed lower sensitivity to changes in osmolality compared to pellets containing MCC.[107]

Injectable bone cement formulations

The implant-associated infections in bone substitution surgery are common. To reduce this risk, a controlled delivery system incorporating silver ions and encapsulated in CMC particles obtained by spray-drying has been developed as part of a self-setting calcium phosphate bone cement formulation. This system proved effective against *S. aureus* CIP 4.83 and *S. epidermidis* CIP 6821T infections. Additionally, the inclusion of silver-CMC microspheres in the bone cement formulation improved injectability and reduced filter-pressing during paste extrusion.[108]

Encapsulation of essential oils

The encapsulation of essential oils provides protection from losses and environmental factors. A formulation consisting of sodium caseinate (3.5% w/v), polysaccharide (0.5% w/v), and CMC (0.25% w/v) was developed for *β*-pinene encapsulation using complex coacervation. The results showed that the produced coacervates with MCC in their composition are effective for encapsulation and delivery.[109]

Topical preparations

Topical preparations provide drug availability at the desired local site and may be in the form of creams, gels, or sprays. Due to its non-irritating, inert, and non-toxic properties, MCC is used in topical preparations as a diluent and lubricant. MCC products recommended for maintaining suspension uniformity and preventing settling, while providing thixotropic viscosity and enhancing formulation stability, include Avicel® RC591, Avicel® CL-611, Viscarin® GP-109, and Viscarin® GP-209. Avicel® RC591 improves skin feel and increases emulsion stability, whereas Avicel® CL-611 is used in concentrations of 1%, 2%, 4%, and 6% in topical cream formulations, such as those containing hydrocortisone acetate as the API.[18]

OTHER AREAS OF APPLICATION

Food industry

Because it is non-toxic and possesses excellent native physicochemical properties, such as elastic modulus and high aspect ratio, MCC is used as an interfacial stabilizer in food production. It has been reported that, even without a dispersing agent, cellulose microcrystals can effectively stabilize O/W emulsions for several months through the Pickering mechanism of stabilization. In this mechanism, MCC microcrystals act as a mechanical barrier oriented to prevent oil droplet coalescence, while other substances in the system serve as dispersing and protective colloids for MCC. The colloidal MCC thickens the continuous phase between the droplets, creating a continuous three-dimensional network that stabilizes the emulsion.[23]

Ice cream

Ice cream is defined as a formulated food consisting of air cells dispersed in a continuous aqueous phase that is frozen. It contains stabilizers to increase viscosity, improve aeration, and control meltdown. MCC (cellulose gel) (E460) has been applied in foam stabilization and overrun control processes. Specifically, the addition of 0.4% or more MCC to the ice cream mixture formulation results in the formation of a gel that maintains the original texture of the frozen dessert. This is achieved by increasing resistance to heat shock, preserving the three-phase system of air–fat–water, and preventing whey separation. Additionally, MCC contributes to a reduction in fat and solids content in the range of 2 to 4%, with minimal texture loss.[110]

Cocoa beverages

Cocoa-based beverages incorporate MCC in their composition to enhance creaminess and suspension stability. The addition of MCC particles to cocoa drinks facilitates the formation of network structures with other particles in the system, which improves both creaminess and stability.[111,112]

Fried beef patties

Fried beef patties with MCC content ranging from 0.5% to 3 wt% were formulated to evaluate the impact of MCC on microstructural and functional characteristics. In this study, 10% of the ground beef was replaced with a dispersion of MCC in water. MCC's insolubility in water makes it useful as a fat replacer or substitution in food systems. The best sensory evaluation results were achieved with beef patties containing 2 wt% MCC, which were found to be juicier and to have a fat-like mouthfeel. It has been established that MCC is not suitable as a fat replacer in concentrations higher than 0.5 wt%.[113]

Sausages

To produce healthier sausages while lowering production costs, the addition of MCC in place of fat or protein was observed to improve the mechanical properties of the sausages, enhancing their firmness.[114]

Construction industry

Cement paste

Farooque *et al.* added CMC in the form of solutions (0.25%, 0.5%, and 1.5%) to ordinary Portland cement and observed improvements in acid resistance, compressive strength, water absorption resistance, porosity, and chemically bound water.[115] Celikci *et al*. advanced the use of CMC by recovering cellulose from cotton waste, synthesizing CMC through chemical modification, and incorporating it into cement

mixtures. This addition improved the properties of the cement paste by increasing hydration time and consistency, demonstrating that CMC can contribute to sustainable development by addressing industrial waste challenges.[116]

Foamed concrete

The foamed concrete is widely used in the construction industry due to its excellent properties, including light weight, good heat and sound insulation, and fire resistance. However, its mechanical performance is often limited by foam stability. CMC has been found to address this limitation effectively. When added at concentrations of 0.1%, 0.2%, 0.3%, 0.4%, and 0.5%, CMC acts as a stabilizer for foamed concrete. Its addition reduces foaming volume, water secretion rate, and average pore size, while increasing foam half-life. Additionally, properties such as dry density, water absorption, and compressive strength improve. Notably, the optimal amount of CMC for foamed concrete is 0.4%, the same concentration that is optimal for ice cream.[117]

Wastewater treatment sector

The global issue of heavy-metal pollutants in water resources is a significant concern considering their harmful effects on the environment and human health. A newly synthesized porous adsorbent, created by crosslinking oxidized MCC particles with tetrafluoroterephthalonitrile, has demonstrated excellent performance in rapidly and efficiently removing low initial concentrations (10 mg L^{-1}) of heavy metals (Pb^{2+}, Cu^{2+}, and Cd^{2+}) from aqueous solutions. This adsorbent achieved removal efficiencies of 93.2%, 87.5%, and 72.3%, respectively, within just 5 minutes, and is also reusable.[118]

To address the same issue, a further advancement involved obtaining MCC from banana fiber and subsequently preparing a nanochitosan (NCS)/sodium alginate (SA)/MCC beads for Pb^{2+} removal. The results demonstrated their potential for removing heavy metals from industrial wastewater, with two usage cycles, showing no significant decrease in loading capacity.[119]

CONCLUSION

MCC has a long history of use in pharmaceutical formulations, particularly in direct compression tablets. Its application extends significantly into the food and construction industries, leveraging its renewable and non-fossil origins, even from waste materials. With a promising future in modern pharmaceutical forms, MCC's well-established physical and chemical properties facilitate easy selection of appropriate grades. When MCC is mentioned, direct compression tablets are often the first association. In food products, MCC enhances textural, sensory, and organoleptic properties, while lowering calorie content. It serves as an economical substitute for various ingredients, including meat. In construction, MCC improves the properties of materials, and its use in wastewater treatment underscores its role in the circular economy.

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