Microcrystalline Cellulose as a Versatile Excipient in Drug Research

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ABSTRACT

Microcrystalline cellulose (MCC) has emerged as the most resourceful excipient of all times in drug research. Thanks to its profusion in terms of grades available for different needs and its physical properties that support a variety of functionality requirements especially for the most frequently used unit dosage forms. MCC can be used as a bulking agent, disintegrant, binder, lubricant, and glidant besides being a stability enhancer and a secondary suspending agent. It can be used in direct compression of most drugs and saves material, capital, equipment, and labor. Its ever increasing applications in drug research include its utility in immediate release (tablets and liquids) dosage forms, sustained release dosage forms (multiparticulates and matrix tablets), topical preparations, oral liquids, organoleptic enhancements as in chewable and mouth dissolving tablets, anti-reflux, and nutraceuticals. The review discusses these applications in sufficient detail citing examples and investigating the justifications for such functions.

Key words: Avicel, direct compression, extrusion, microcrystalline cellulose, multiparticulates, wet granulation

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INTRODUCTION

Despite many research studies being conducted in the field of drug delivery, none of them have been able to match the characteristic features and advantages offered by oral unit dosage forms such as tablets and capsules. With the advent of this form of drug delivery, the subsequent researches of betterment of this delivery system emerged, which included sophisticated machinery and superior tableting aids. These tableting aids, which we affectionately call excipients, have been an imperative part of tableting that forms the basis of delivering potent or non potent drugs in the form of such effective and patient-friendly unit dosage forms. The most basic and important excipients categories involved in tableting include diluents/bulking agents, disintegrants, binders, lubricants, and glidants and many examples of each can be cited from the oldest to the newest literature. Each of these categories of excipients has a specific proven cause for its requirement in tableting and the absence of which can cause serious consequences. Many excipients offer multiple advantages and can serve dual purposes. However, microcrystalline cellulose (MCC) is an excipient that can play the roles of almost every category listed above for tablet research. Because of this, MCC is the most versatile and user friendly excipient among numerous available. The development of MCC has made an extremely valuable tableting agent available to the pharmaceutical industry and since its introduction in late 1950s, it stands today as...
the single most important tablet excipient developed in modern times. Its incorporation in one way or the other can be seen in almost every finished unit dosage form.

MCC is derived from a special grade of purified alpha wood cellulose by severe acid hydrolysis to remove the amorphous cellulose portions, yielding particles consisting of bundle-like needle-like microcrystals.\[1\]

**RESOURCENESS OF MICROCRYSTALLINE CELLULOSE**

MCC is a white, insoluble, neutral, non reactive, free-flowing versatile excipient. Its physical, chemical, and rheological properties make it a filler of choice in a variety of pharmaceutical operations. Its categorical uses and justifications have been explained briefly.

**Filler**

Diluents, also popularly known as fillers, form a very imperative part of a tablet especially in the case of the tablets of drugs with low doses. To achieve content uniformity, a tablet size should at least be greater than 3 mm and the corresponding weight should be more than 50 mg.\[2\] The role fulfilling these requirements is played by the diluents. Lately, MCC can be considered as the most widely used diluent in the direct compression and wet granulated tablet making procedures. However, the grades may be different; the most widely pronounced grades are Avicel PH 101 and Avicel PH 102 (FMC Corporation, Princeton, NJ, US) where PH stands for the pharmaceutical grade of MCC. Avicel PH 101 is the original grade and PH 102 is a partially agglomerated product with a larger particle size distribution and slightly better fluidity but with no significant difference in the compressibility.\[3\]

**MCC as directly compressible filler:** MCC is the most compressible of all the direct compression fillers and has the highest dilution potential and capacity, which is defined as the amount of active ingredient that a diluent can successfully carry in the direct compression technique.\[4\] This can be explained on the basis of the nature of MCC particles themselves, which are held together by hydrogen bonds in the same way that a paper sheet or an ice cube is bonded. Hydrogen bonds on adjacent cellulose molecules account solely for strength and cohesiveness. MCC particles are deformed plastically under compaction forces to yield an extremely large number of clean surfaces brought in contact during this deformation forming a strong compact even under low compression forces.\[5\]

Another factor of MCC being the most favorite diluent is its low bulk density. An excipient with low bulk density and large particle size distribution will exhibit a high dilution potential on a weight basis, optimum packing density, and coverage of drug and other excipient materials.\[4\]

Avicel grades (Avicel PH-102 SCG, Avicel HFE-102, Avicel PH-200, Avicel PH-302) provide excipient solutions to many challenges of direct compression formulations including improved flow, better compressibility, and accommodation of moisture-sensitive actives.\[6\]

Overall, as direct compression filler, Avicel promotes efficient dry blending of ingredients and produces tablets with high hardness levels and low friability levels with excellent compression. It produces tablets of superior whiteness and color stability.

**MCC as wet granulation filler:** MCC is one of the very few types of filler with water insoluble yet hydrophilic properties with swelling tendencies (other examples being calcium pectinate and sodium alginate) and excellent water imbibing or wicking action. This is what makes it an excipient of choice in wet granulation procedures. Both Avicel PH 101 and PH 102 can be used advantageously as fillers in wet granulation in a recommended level of 5–15%. When used as a wet massing adjunct, the wicking action of MCC promotes rapid and even wetting of the powder mix. An advantage of its use in wet granulation is its ability to retain water, which makes the wet mass less sensitive to overwetting due to an excess of granulating fluid. The milling of the wet mass is easier due to less clogging of the screen that produces a more uniform granulation, which is readily dried and reduces case hardening. Case hardening is a phenomenon observed in incompletely dried granules. In some cases, when the granules are dried at a high temperature, the inside of the granules remain wet and the surface seems dried. The granules are often hard and resist disintegration. Under compaction forces, the granules break and deform plastically to form soft tablets due to the moisture coming out of the incompletely dried granules.\[7,8\]

The addition of Avicel PH 101 or PH 302 in wet granulation promotes rapid, even wetting as a result of the wicking action of MCC, reduced sensitivity of the wet mass to over-wetting, faster drying, fewer screen blockages or case hardenings, reduced dye migration, and faster disintegration.\[6\]

Since MCC is water insoluble, the small drug particles get
trapped between the deformed MCC particles and may delay wetting and dissolution. This must be overcome by adding portions of water soluble direct compression excipients.[4]

Roller compaction: Roller compaction is a dry process involving compaction of materials into ribbons that are then milled to generate a granulation. This granulation is then lubricated and compressed on a tablet machine. This process can be used with moisture-sensitive active pharmaceutical ingredients and is readily adaptable to continuous processing. Use of Avicel PH grades in roller compaction includes improvement of compaction in the ribbon phase, enhancement of flow of the granules, and preserving content uniformity of the final granulation.[6]

BINDER

Binders hold the ingredients in a tablet together to ensure that tablets and granules can be formed with the required mechanical strength, and give volume to low active dose tablets. The appearance, elegance, ease of compression and the overall quality of the tablets are directly related to the presence of the appropriate concentration of binders in a tablet blend be it for direct compression or for wet granulation procedures. MCC, due to its hydrophilic water wicking actions, forms a very useful binder in tablet compression.

MCC as a dry binder: Due to cost concerns, MCC cannot always be used as sole filler in tablet making. For example, in making placebos/dummy tablets for coating, one may use much cheaper filler in large concentrations. Spray dried lactose has the poorest compressibility among all directly compressible fillers, however, it is cheap and is normally used for making placebos for coating. A blend with 200 mg of spray dried lactose with appropriate lubricants may not be able to compress unless a correct amount of dry binder is incorporated inside the blend. A 2–5% incorporation of Avicel in the blend will serve the purpose. Similar actions must be taken when making actual tablets with drug. However, it will also function as a disintegrant when compressed dry. A number of Avicel formulations, such as type PH-113, can act as a dry binder.[8,10] The newer technology for manufacturing capsule dosage forms has created another area for the application of MCC. As a binder, MCC is especially useful in formulations that are compressed before insertion into the hard gelatin capsule.

MCC as a wet binder: MCC may be used as a secondary binder in wet granulations and can be used to granulate both soluble and insoluble powders. The granulations compress quickly and produce tablets that generally do not harden with age. The fast wicking action of MCC promotes rapid and even wetting of the powder mix. This is particularly useful in high moisture granulations as it binds the excess moisture keeping the granulation dry and free flowing.[11]

DISINTEGRANT

Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract and release the active ingredients for absorption. They break a tablet into smaller fragments increasing the surface area of the dosage form and the rate of drug absorption. Disintegrants are either water uptake facilitators or tablet rupture promoters. MCC is widely used as a disintegrant in dry compressions and wet granulation procedures. It enhances drug dissolution by speeding tablet disintegration, provides the highest level of disintegration force at low use levels, and utilizes dual disintegration mechanisms of wicking and swelling for more rapid disintegration.

Avicel has a fast wicking rate of water and a small elastic deformation. Both these properties facilitate its disintegration effects. However, Avicel has a tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This occurs when the moisture content in Avicel is above 3%, which produces static charges during mixing and compression. This can be overcome by drying the Avicel to remove moisture. Wet granulated Avicel dried and compressed loses some of its disintegration properties. Unlike starch, it cannot be wet granulated without losing some of its disintegration properties. Normally, Avicel and starch are used in combination to facilitate effective and rapid disintegration of tablets. Avicel has been used as a disintegrant in orally disintegrating tablets also acting as a dissolution enhancer. US6350470 explains the use of Avicel as a disintegrating agent or an effervescent penetration enhancer in effervescent drug delivery system for oral administration. When compressed dry, Avicel functions as disintegrant in a concentration of 5–20%.[12]

LUBRICANT

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall.
Lubricants are generally hydrophobic, which can affect tablet hardness, and this effect is particularly critical in the case of direct compression formulations. Lubricants in granulation decrease disintegration time and increase dissolution times if effective mixing is done. Granules will be coated with the lubricant and the binding of the granules within themselves during compression will be less, which will decrease the disintegration time and may increase the dissolution time.

Avicel has an extremely low coefficient of friction, both static and dynamic, so that it has no lubricant requirement itself. However, when more than 20% of the drug and other excipients are added, lubrication is necessary.

**GLIDANT**

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. Normally, silica-based glidants like silicon dioxide, hydrated sodium silicoaluminate, and silica hydrogel, etc. are used in tablet compression as flow promoters. MCC is available as Proslov, which is high functionality silicified MCC. This excipient imparts superior flow, compaction, and dispersion to a formulation. When used in direct compression, Prosolv SMCC® (JRS Pharma, Patterson, NY) can replace granulations while significantly reducing excipient numbers and levels. Prosolv SMCC formulations produce distinctive, uniform, cost effective tablets. It is available in three grades: Prosolv SMCC 50, SMCC 90, and SMCC HD 90, which differ in average particle size and bulk density. Prosolv SMCC offers enhanced mixing characteristics, enhanced flow, need of less excipients, and shorter disintegration time. Due to improved compactibility and dust free handling in production, it facilitates less loss in production.

In a more recent study, silicified MCC and MCC were found to be good plug formers in hard gelatin capsule shells when tested in a compaction simulator at tamping forces and piston speeds similar to those found in some filling machines. The materials were tested neat using a prelubricated die. Several grades of silicified MCC and a control grade of MCC (typical particle size of 90 μm) produced plugs having a higher maximum breaking force than anhydrous lactose and Starch 1500 under similar compression conditions.

**Application in topical preparations**

MCC, known for its non irritating, inert, and non toxic properties, has been used in many topical preparations as a diluent and lubricant in oil and water ointments and other topical preparations. Topical formulations enable the local delivery of a drug to a specific site of action without systemic exposure and may be creams, gels, or sprays. Formulations that include Avicel® RC-591 have improved skin feel, greater emulsion stability, and stability over a wide range of temperatures and unique thixotropy, which yields suspensions that stay where they are sprayed and do not run or drip.

**Stabilizer in topical and oral preparations**

Adeyeye, et al. examined the viscoelastic properties of topical creams containing various concentrations of MCC and sodium carboxymethyl cellulose (Avicel® CL-611) as a stabilizer. Avicel CL-611 was used at 4 different levels (1%, 2%, 4%, and 6% dispersion) to prepare topical creams, and hydrocortisone acetate was used as a model drug. Avicel has an established use as a stabilizer in suspensions. The recommended grades Avicel RC591, Avicel CL-611, and Viscarin GP-109 and GP-209 maintain suspension uniformity and prevent settling, impart a thixotropic viscosity profile, and increase formulation stability across a wide range of pH.

**Organoleptic enhancement**

MCC is known to provide an excellent mouth feel when used in orally dispersible tablets. Binders such as a number of insoluble filler-binders including MCC have additional advantageous properties that, despite their insolubility, make them nonetheless more desirable than other similar binders. Avicel PH113 can act as a dry binder. However, when placed in an aqueous environment, such as in a patient’s mouth, the binder can actually aid in the disintegration of the tablet. In addition, MCC imparts an almost creamy mouth feel that helps offset the negative impact of its insolubility. The use of such binders therefore helps reduce the overall amount of disintegrant that needs be used.

Chewable tablets as a dosage form are growing in popularity. Palatable chewable tablets offer convenience for customers, broaden the applicability of formulations to pediatric and geriatric markets, and increase patient compliance. In this application, the use of Avicel® CE-15 (mixture of co-processed MCC and Guar gum) can provide smoother, creamier mouthfeel, less tooth-packing, and all this without sacrificing flow or compaction. US 6982093 explains the use of MCC in a chewable tablet to ensure a tablet of proper chewable consistency and to facilitate tablet dissolution.
Anti-reflux

MCC has been effectively used in formulations for the treatment of gastro-esophageal reflux.[22,23] Carbopol and MCC are mixed together in a high-speed mixer granulator. The sodium hydroxide is dissolved in 50 mg of water and the resulting solution is added slowly to the above powder mix while blending. The resulting granules are dried in a fluid bed dryer and the dried granules are subsequently passed through a 1000 µm screen. The screened dried granules, crosscarmellose sodium, and magnesium stearate are blended together and pressed into tablets.

On administration, the tablets disintegrate in the stomach contents to release mucoadhesive granules. The granules slowly release the capsaicin into the stomach contents and, when reflux occurs, the capsaicin is refluxed with the stomach contents to cover the esophagus.

Sustained release applications

Lately, MCC is being widely used in formulating sustained release dosage forms for multiparticulate and matrix tablet drug delivery. Hydrophilic polymers may be included in tablets in order to form a viscous, gelling layer that retards water penetration and acts as a barrier to drug release. Drug release is accomplished by diffusion through and erosion of this barrier. Zero-order release profiles can be achieved by selection of appropriate polymers and other fillers/binders in addition to Avicel.

Avicel is an excipient of choice in multiparticulate delivery of pellets prepared by extrusion spheronization. Extrusion spheronization offers an attractive alternative to traditional drug-layering on pellets. This highly specialized process results in unique spherical, drug-loaded pellets. The formulator can achieve higher drug loading with this approach over that possible with layering. Avicel® PH-101 or PH-102 is highly recommended for this application because they produce reduced spheroid friability, prevents overwetting, and lessens the process sensitivity and improved sphericity of pellets.[34–32]

Chronotherapeutic drug delivery (delayed release applications)

There are conditions in which the drug is neither required to be released immediately after ingestion nor in a sustained release manner. The drug may be required to release after a well-defined lag time as in the case of chronotherapeutic delivery of actives against disease states that follow a time-dependent pattern of symptom manifestation. There may also be conditions in which the drug is required to be released locally in specific regions of the gastrointestinal (GI) tract such as the colon. Avicel finds its potential applications in such delivery systems. US 6531152 B1[33] explains the use of Avicel in an immediate release GI delivery system after a well-defined lag phase. Avicel is used in a core tablet as a swellable disintegrant and forms a part of the coating solution applied over the core tablet as a pore or channel former. The system comprises a drug in combination with a swellable core material such as Avicel. This core is then surrounded by a water insoluble coating material in which particulate water insoluble but hydrophilic material (Avicel) is embedded. Upon entering the GI tract, the hydrophilic particulate matter takes up

<table>
<thead>
<tr>
<th>Purpose/Functionality</th>
<th>Grades</th>
<th>Nominal Particle size</th>
<th>Moisture content %</th>
<th>Bulk density g/cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet granulation, extrusion spheronization of pellets, standard and most widely used grade</td>
<td>Avicel PH-101</td>
<td>50</td>
<td>3-5</td>
<td>0.26-0.31</td>
</tr>
<tr>
<td>Direct compression, Immediate release, Sustained release, Extended release, Delayed release</td>
<td>Avicel PH-102</td>
<td>100</td>
<td>3-5</td>
<td>0.28-0.33</td>
</tr>
<tr>
<td>Better flow than 101</td>
<td>Avicel HFE*-102</td>
<td>100</td>
<td>NMT 5</td>
<td>0.28-0.33</td>
</tr>
<tr>
<td>Superior compactibility</td>
<td>Avicel PH-105</td>
<td>20</td>
<td>NMT 5</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td>Big particle size and better flow than 102</td>
<td>Avicel PH-102 SCG</td>
<td>150</td>
<td>3-5</td>
<td>0.28-0.34</td>
</tr>
<tr>
<td>Use: direct compression filler</td>
<td>Avicel PH-200</td>
<td>180</td>
<td>2-5</td>
<td>0.29-0.36</td>
</tr>
<tr>
<td>Same particle size but higher density and flow than 101</td>
<td>Avicel PH-301</td>
<td>50</td>
<td>3-5</td>
<td>0.34-0.45</td>
</tr>
<tr>
<td>Same particle size but higher density and flow than 102</td>
<td>Avicel PH-302</td>
<td>100</td>
<td>3-5</td>
<td>0.35-0.46</td>
</tr>
<tr>
<td>Uses: wet granulation, direct compression</td>
<td>Low moisture</td>
<td>Avicel PH-103</td>
<td>50</td>
<td>NMT 3</td>
</tr>
<tr>
<td>Uses: dry binder, direct compression filler, organoleptic enhancement, superior mouthfeel</td>
<td>Avicel PH-113</td>
<td>50</td>
<td>NMT 2</td>
<td>0.27-0.34</td>
</tr>
<tr>
<td></td>
<td>Avicel PH-112</td>
<td>100</td>
<td>NMT 1.5</td>
<td>0.28-0.34</td>
</tr>
<tr>
<td>Superior mouthfeel, chewable tablets</td>
<td>Avicel PH-200 LM*</td>
<td>180</td>
<td>NMT 1.5</td>
<td>0.30-0.38</td>
</tr>
<tr>
<td>Stabilizer for liquids and semi-solids</td>
<td>Avicel RC*-591</td>
<td>50</td>
<td>3-5</td>
<td>0.28-0.33</td>
</tr>
<tr>
<td>Stabilizer in oral liquids</td>
<td>Avicel CL-611</td>
<td>50</td>
<td>NMT 3</td>
<td>0.34-0.42</td>
</tr>
</tbody>
</table>

*HFE: Co-spray dried MCC mannitol excipient (offers improved flow, compaction, disintegration, and less sensitivity to lubricants)
RC**: MCC and Sodium CMC
liquid, thus forming channels interconnecting the drug containing core with the outside of the delivery device. Through these channels, the liquid enters the core, which then swells due to the swelling of the disintegrant to the point at which the coating is broken. When the integrity of the coating is destroyed, the core then disintegrates immediately releasing all or most of the drug at a specific site after a well-defined lag.

**Avicel product range**

Table 1 shows the range of Avicel grades available in the market with their important physical properties and purposes.

**CONCLUSIONS**

Since its introduction, MCC has completely altered the pharmaceutical research state of affairs creating entirely new levels of manufacturing efficiencies. The state of the art Avicel grades available today are designed to boost productivity and can meet any formulation challenge. Its wide range of utility and its ability to perform multiple functions have made it an excipient whose popularity can only increase with the coming times. With the pharmaceutical scientists continuing to face formulation challenges, and the intellectual property laws becoming more stringent, more improved grades can be expected in the coming future that will directly impact the products’ quality and performance attribute.

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