Chapter

Microcrystalline Cellulose as Pharmaceutical Excipient

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Abstract

Microcrystalline cellulose (MCC) is a pure partially depolymerized cellulose synthesized from α-cellulose precursor (type Iβ), obtained as a pulp from fibrous plant material, with mineral acids using hydrochloric acid to reduce the degree of polymerization. The MCC can be synthesized by different processes such as reactive extrusion, enzyme mediated, steam explosion, and acid hydrolysis. It is commonly manufactured by spray-drying the neutralized aqueous slurry of hydrolyzed cellulose. The MCC is a valuable additive in pharmaceutical, food, cosmetic, and other industries. MMC obtained from different sources will differ considerably in chemical composition, structural organization, and physicochemical properties (crystallinity, moisture content, surface area and porous structure, molecular weight, etc.). The high demand of microcrystalline cellulose used in pharmaceutical industries has led to the utilization of locally and naturally occurring materials in the production of microcrystalline cellulose. Many studies on the physicochemical properties of locally produced MCC derived from natural sources have been extensively evaluated in the development of a new natural source for MCC as a substitution of wood, the most abundant one.

Keywords: microcrystalline cellulose, excipient, MCC, filler, Avicel

1. Introduction

Cellulose, a fibrous carbohydrate found in all plants, is the most abundant natural polymer with biomass production of 50 billion tons per year [1]. Cellulose is a linear polymer of glucose. Based on solubility in alkaline, cellulose is divided into three groups which are alpha, beta, and gamma celluloses. Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose having the formula $(C_6H_{10}O_5)_n$. It is prepared by treating alpha cellulose with mineral acids (type Ib). This polysaccharide polymer consists of a linear chain of several hundred to over ten thousand β(1 → 4) linked D-glucose units, consisting of linear chains of *β*-1,4-D anhydroglucopyranosyl units. Raw material used for MMC preparation is a pulp from a fibrous plant such as conifer wood. Cotton is also a possible cellulose source for MCC [2, 3]. Pharmaceutical grade MCC, which needs a high-quality pulp, used wood as the most common source. From such wooden source, cellulose chains are packed in layers and held together by strong hydrogen bonds from lignin, a cross-linking polymer. For that purpose, both softwoods (evergreen conifer) and hardwoods (deciduous broadleaf) can be used [4]. These woods differ not only in chemical composition including cellulose proportions, hemicelluloses, and lignin

but also in structural organization, i.e., regions which are relatively more crystalline or amorphous. The amorphous regions are more prone to hydrolysis by acid resulting in shorter and more crystalline fragments.

Non-woody lignocellulosic materials have also been developed as source of MCC such as cotton linters [5], cotton stalks [6], cotton rags [5], cotton fabric waste [7], cotton wool [8], soybean husk [9], corn cob [10], water hyacinth [11], coconut shells [12], oil palm biomass residue [13, 14], oil palm fronds [15], rice husk [6, 16], sugar cane bagasse [6, 16–20], jute [21, 22], ramie [23], fibers and straw of flax [24], wheat straw [25], sorghum stalks [26], sisal fibers [27] and mangosteen [28], alfa grass fibers [29, 30], soybean hulls [31], orange mesocarp [32], Indian bamboo [33], roselle fiber [34], and alfa fiber [35]. Seed flosses from milkweed pods (*Calotropis procera*), shrubs, and kapok (*Ceiba pentandra*) trees are also known as cellulosic resources. Due to its high purity of alpha cellulose, most seed flosses must be treated to remove impurities including lignin, pectin, and wax [36].

Wooden sources contain cellulose chains which are packed as layers held by cross-linking hydrogen bonds [37]. Chemically it consists of polymeric matrix of lignin, hemicelluloses, and pectin [38]. Different woods considerably possessed different chemical composition of cellulose (including allocations of cellulose, hemicelluloses, and lignin in cell wall) and structural organization as well. Relatively different crystallinity in particular regions is observed as more amorphous according to softwoods (evergreen conifer) and hardwoods which are termed as deciduous broadleaf [4, 37]. The amorphous regions of cellulose provide a more susceptible property for depolymerization by acid hydrolysis. At optimum acid concentration, the process gave shorter and more crystalline fragments such as the MCC [2, 37].

2. Synthesis of MCC

The MCC can be synthesized by different processes including extrusion and enzyme-mediated process [25]. Other studies reported that it can also be synthesized by steam explosion and acid hydrolysis process [5, 6]. The acid hydrolysis process is more preferable due to shorter duration than others. It also offered the possibility to be applied as a continuous process rather than a batch-type process. Limited quantity of consumed acid is also the advantage of the process, while, despite the lower unit cost from less chemicals used, this process offered more fine particles of the MCC as the final product [5]. Fibrous plant pulp is hydrolyzed by mineral acid under heat and pressure. In the presence of water and acid, hydrolysis process breaks cellulose polymers into smaller chain polymers or microcrystals. Other celluloses, to which soluble components of cellulose such as beta and gamma celluloses, hemicelluloses, and lignin are dissolved with acid and water, are separated out during washing process by water which continued by filtration. The obtained pure alpha cellulose has then been neutralized and given the slurry final product [3]. This suspension is dried to obtain the insoluble white, odorless, tasteless powder, which has later been characterized as MCC [39]. MCC is hygroscopic in nature, and insoluble in water, but swells when in contact with water.

Another synthesis procedure of the MCC reported by Ohwoavworhua et al. [40] can be concluded as follows: the α-cellulose was hydrolyzed with hydrochloric acid at a boiling temperature of 105° for 15 min. The neutralized slurry obtained from the hydrolysis process was washed, and the fraction passing through 710 μm sieve was stored at room temperature in a desiccator. MCC is commonly dried from the slurry by spray-drying method. By varying spray-drying conditions, the degree of agglomeration and moisture content can be manipulated. In order to obtain smaller particle sizes (below 50 μm), further milling MCC can be performed [1].

Other drying techniques may be used, which may require additional screening steps postdrying in order to control particle size distribution [41, 42]. Higher bulk density grades are also available by using specific cellulose pulps (raw material), and median particle sizes below 50 mm can be obtained by further milling MCC [1].

Several studies have compared microcrystalline cellulose with various sources, including different manufacturers and different sites [4, 43–47]. MCC produced by various manufacturers or in various manufacturing sites may have different properties due to the kinds of pulp used as raw materials and their respective manufacturing conditions [2, 4]. A number of studies have confirmed that the moisture content of MCC influences compaction properties, tensile strength, and viscoelastic properties [48].

Type	Conc.	Hydrolysis condition		MCC-Y (%)	Duration (minute)	References
		L/C (vol./wt)	Temperature (°C)			
HCl	2 N	10:1	105	15	n.a	[5]
HCl	2 N	10:1	45	15	n.a	[6]
HCl	2.5 N	20:1	85	90	80	[5]
HCl	2.5 N	62.5:1	105	15	19	[6]
HCl	2 N	10:1	n.a	45–60	n.a	[7]

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.

MCC Type	Particle size (micron)	Utilization
PH 101	50	It is most widely used for direct compression tableting, for wet granulation, for spheronization, and in capsule filling processes
PH 102	100	It is used as the PH-101, but its larger particle size improves the 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 is the most compressible of the PH products owing the smallest particle size. Well known as excipient for direct compression for granular or crystalline materials. When mixed with PH-101 or PH-102, specific flow and compression characteristics will be obtained. It has applications in roller compaction
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 is denser providing more flowability and tablet weight uniformity. Useful for making smaller tablets and in capsule filling excipient

Table 2.
Types of the commercial microcrystalline cellulose [1, 51].

It was generally recognized that batch-to-batch variability from a sole manufacturing site was less important than differences observed between multiple sources. Only a few studies have tried to correlate the manufacturing conditions of microcrystalline cellulose with its physicochemical properties and its performance in tableting applications [2, 49, 50]. The effect of some parameters on hydrolysis process on yield value of production is shown in **Tables 1** and **2**.

3. Physicochemical properties of MCC

3.1 Moisture content

A number of studies have confirmed that the moisture content of MCC influences compaction properties, tensile strength, and *viscoelastic* properties [48, 52, 53]. Moisture within the pores of MCC may act as an internal lubricant, reduce frictional forces, and facilitate slippage and plastic flow within the individual microcrystals [54, 55]. The lubricating properties of water may also reduce tablet density variation by providing a better transmission of the compression force through the compact and by decreasing the adhesion of the tablet to the die wall [55, 56]. Compressibility of MCC depends on moisture content, which means that when MCC having different moisture content is compressed with the same pressure, it may not result in the same compact porosity. It is very well known that compaction pressure required to produce certain porosity (or solid fraction) decreases with increasing moisture content. Sun reported that below 3% water content, the compaction properties of MCC were insensitive to variation of moisture [53]. However up to an optimum level, an increase of moisture will increase the tablet strength of most excipients. This can be explained by the fact that molecular binding in water vapor layers reduces interparticular surface distances, hence increasing intermolecular attraction forces [56].

The storage conditions of the MCC compacts also play an important role, as an increase in relative humidity will negatively impact tablet strength [47]. However this softening is often reversible when tablets are removed from the humid environment [1]. Fundamental forces affecting powder flow are cohesion and friction [55]. Frictional forces and electrostatic charges between particles during the compression process will decrease as moisture content increases. Moisture may also play a role in increasing cohesion forces inside particles due to the creation of liquid or even solid bridges. In the case of MCC as excipient, significant changes in flowability were observed when increasing moisture contents were applied which resulted in changes in powder cohesiveness. This phenomenon was described by the increase in compressibility index and the shear cell [48].

3.2 Particle size

Particle size has a very little effect on the tabletability of neat MCC, i.e., not lubricated nor blended with other excipients or active pharmaceutical ingredients (APIs) [57–60]. MCC particle size and moisture content are often considered as the most important CMAs for tableting performance [61]. Considering that the brittle-ductile transition diameter (Dcrit) of MCC is 1949 mm, standard MCC grades, having particle sizes below Dcrit, should all deform plastically when compression pressure exceeds yield pressure. Coarser grades of MCC, characterized by a smaller envelope surface area, have been reported to be more lubricant sensitive than finer MCC [52, 58, 62, 63]. In complete formulations finer MCCs would therefore promote tablet (compact) strength [64, 65]. Reducing the particle size of MCC

will increase cohesiveness and hence as a consequence surely affect its flowability. Kushner et al. reported that different particle sizes of excipient may impact tablet characteristics including hardness, friability, disintegration, and content uniformity [66]. Improved flowability will be obtained when coarser MCCs are employed as well as reduction in tablet weight variation [67]. Hlinak et al. suggested that particle size may also impact wetting properties, dissolution of the API, and stability of drug products [68].

Albers et al. evaluated the tableting properties of three batches from five different brands MCC type 101 [43]. Batches using single manufacturer source produced more similar tablet characteristic than those using samples from various sources. Statistically significant differences were also observed within single brands of MCC. From a different batch of MCC studied, the greatest differences in powder properties were observed in the median particle size and specific surface area. Despite the lower median particle size of Avicel PH-101 (FMC), this MCC was described as easy flowing powder compared to other brands as illustrated by its low compressibility index and high values of shear cell flow functions (FFc) which exceed 4.

Williams et al. used tableting indices to investigate the compaction properties of MCC types 101 and 102 (median particle size of about 50 and 100 mm, respectively), each type being represented by two batches from five different sources [47]. The lubricant sensitivity of MCC expressed as its compressibility decreased when this excipient was mixed with other materials such as magnesium stearate. Another factor affecting lubricant sensitivity of MCC is the particle size. A higher particle size of MCC, Avicel PH-200 (180 microns), is more sensitive to lubricant than Avicel PH-101 (50 microns). At the same concentration, the lubricant covers more efficiently a larger particle size of MCC (PH-200) than that of the smaller particle size of MCC (PH-101) due to a larger particle surface area of smaller particles of MCC [51].

Compactability of the MCC particles is affected by the porosity. Avicel PH-101, Avicel PH-102, and Avicel PH-200 as marketed products of MCC owing almost the same density showed the same compressibility despite their mean particle size which varies from 50 to 180 microns. Avicel PH-301 (50 microns) and Avicel PH-302 (90 microns) which physically are more dense revealed less compressible or compactable properties [51].

3.3 Particle morphology

Obae et al. suggested that MCC morphology, described by the length of particles (L) and their width (D), was one of the most important factors influencing tabletability [69]. Rod-shaped particles which are fibrous and having higher L/D ratios resulted in higher tablet strengths than round-shaped particles. Other physicochemical properties of MCC including moisture content, bulk density, and specific surface area did not correlate well with tensile strength of obtained tablet. Obae et al. illustrated the reduction of bulk density and flowability and the increase of specific surface area when the L/D ratio increased. This may be due to the property of the particles which is more fibrous. MCC morphology was found to be affecting the drug dissolution which may due to porosity [70].

3.4 Crystallinity

Modifying the hydrolysis conditions, including temperature, time, and acid concentration, also has a very little impact on the degree of crystallinity, i.e., the regularity of the arrangement of the cellulose polymer chains [2, 50]. This

observation indicates that crystallinity cannot be controlled at the hydrolysis stage. Crystallinity appears to be more dependent on pulp source rather than on processing conditions [4], which is consistent with the method of MCC manufacture where the acid preferentially attacks the (pulp dependent) amorphous regions.

The total amount of sorbed water in MCC is proportional to the fraction of amorphous material [48, 54, 55]. Therefore MCC powders with a lower degree of crystallinity may contain more water than their counterparts with a higher degree. If low-crystallinity MCC preferentially binds more water, moisture-sensitive APIs may exhibit lower rates of degradation [71]. Despite the controversial impact of crystallinity, it may influence the adsorption of water on cellulose microfibrils, which may in turn influence flowability, tabletability, and stability of the drug product.

3.5 Bulk density

Mostly, direct compression excipients are spray-dried; therefore porous structure was produced as a result. This property is characterized by a relatively low bulk density. Increase in porosity (lower density) facilitates higher compressibility, i.e., the densification of a powder bed due to the application of a stress [56]. The improved compressibility of plastically deforming materials, such as MCC, might then result in improved tabletability as a result of the increased bonding surface area [72]. The higher roughness of low density MCC particles may also contribute to particle interlocking [73]. Low bulk density MCC will provide higher dilution potential and hence better counteract the poor tableting properties of APIs. Granulation or drying as preprocesses of tablet formulation will densify MCC hence less tabletable than the original porous MCC [74, 75]. It can therefore be generalized that a decrease in bulk density improves tabletability; however, it will often hinder flowability [62].

3.6 Degree of polymerization

The degree of polymerization (DP) expresses the number of glucose units ($C_6H_{10}O_5$) in the cellulose chain. It decreases exponentially as a function of hydrolysis conditions, including temperature, acid concentration, and time of reaction. The rate of hydrolysis slows down to a certain value which is stated as level-off degree of polymerization (LODP). The LODP value is specific for a particular pulp, and it is usually between the range of 200 and 300 [44, 61], e.g., 180–210 range for hardwood pulps and 210–250 for softwood pulps. Theoretically, to obtain a certain degree of polymerization which is higher than the LODP value, hydrolysis process could be terminated at any time. However, due to the exponential decay of DP, this termination is neither a robust nor a reproducible approach. The degree of polymerization is used as an identity test, as pharmacopoeial MCC is defined by a DP below 350 glucose units, compared to DPs in the order of 10,000 units for the original native cellulose [1].

The correlation between the degree of polymerization (DP) of MCC and its tabletability has not been explored yet. Therefore, it is merely an identity test to distinguish the tabletability of MCC (DP < 350) compared with powdered cellulose (DP > 440). Dybowski showed that the origin of the raw materials and the production method of MCC more decisively influence the physical characteristics than DP. DP value is a criterion used to guide the manufacturer about hydrolysis of MCC, whereas for the user it is a characteristic to distinguish between properties of MCC and powdered cellulose.

Wood pulps with high bulk density grades which can be characterized by lower level-off DP should not be directly compared with standard grades. This parameter reflects the lack of distinction between the degree of polymerization (DP) and level-off degree of polymerization (LODP). LODP is typical of a particular raw material, with a common value between the range of 200 and 300 [44]. Cellulose having LODP value at this range usually difficult for further hydrolysis. In contrast, cellulose materials with DP values higher than the level-off degree of polymerization plateau are more difficult to control due to their greater sensitivity to hydrolysis. Owing LODP above 200–300, the MCC remains to be more fibrous, which would result in a lower bulk density, with improved tabletability, but would hinder powder flow [49, 50]. Below the LODP MCC is less fibrous, denser, and less tabletable. Tabletability is not related to a particular DP value; as an example powdered cellulose has a higher DP than MCC but is not as tabletable [1].

3.7 Effect of lignin

Landín et al. compared four brands of MCC [45]. Different woods used as raw materials, i.e., hardwood versus softwood, suggested differences in lignin and hemicelluloses composition. The non-cellulose component has also significantly different manufacturing process intensities which resulted in variable suggestive composition and potentially varying qualities of product. Landín et al. found that lignin content increased the dissolution rate of prednisone [46]. Lignin being hydrophobic may alter cellulose–cellulose and/or cellulose–API interactions and hence drug release rate.

Thoorens et al. [37] studied that differences in packing and flow properties which are shown by scanning electron micrographs from Avicel PH-101 and Avicel PH-102 were attributed to differences in moisture content, particle shape, and particle size distribution. Tabletability which also varied among the MCC samples were attributed to the differences in moisture content and the internal structure of the particles. These are mostly caused by different processing conditions which are specific to each manufacturer. However, the impacts of crystallinity and particle morphology are negligible. Significant differences in lubricant sensitivity, compressibility, and tablet disintegration were also noted between MCCs due to various manufacturing processes by different manufacturers. Variability between lots from the same manufacturer was found to give a smaller effect on properties of MCC product. A current study from Doelker concluded that even if all of various MCCs comply with compendial specifications, large differences still exist among them [44].

4. MCC as pharmaceutical excipients

According to the International Pharmaceutical Excipient Council (IPEC), excipients are the process aids or any substances other than the active pharmaceutical ingredient that are included in pharmaceutical dosage forms. The functionalities of excipient are to impart weight, consistency, and volume which allow accuracy of dose, improve solubility, and in the end increase stability. It can also be proposed to enhance bioavailability, modifying drug release and used in product quick identification, increase patient acceptability, and facilitate dosage form design.

Excipients classified as:

1. Primary excipients: diluents (filler), binders (adhesives), disintegrants, lubricants, antiadhesives, glidants

2. Secondary excipients: coloring agents, flavors, sweeteners, coating agents, plasticizers wetting agents, buffers, and adsorbents

Diluents are incorporated into tablet or capsule dosage forms to increase dosage form volume or weight and can also be referred as fillers. Direct compression binders are functional even at low use levels and offer superior tabletability [1]. Some diluents, such as microcrystalline cellulose, can also be considered as dry binders since they improve the compactibility or tabletability of the compression mix.

Microcrystalline cellulose, according to many publications, is an excipient of outstanding merit and remains the most widely used direct compression excipient serving as a strong dry binder, tablet disintegrant, an absorbent, filler or diluent, a lubricant, and anti-adherent.

MCC is generally considered as the diluent having the best binding properties and is recognized as one of the preferred DC binders [44, 76]. It is used as a binder/diluent in oral tablet and capsule formulations including both wet granulation and direct compression processes. It also has some lubricant and disintegrant properties which is useful in direct tableting. Small amounts of MCCs are able to efficiently bind other materials, especially poorly tabletable active pharmaceutical ingredients. MCC exhibits a high dilution potential, whereas the broad particle size range provides optimum packing density and coverage of other materials [44, 54].

MCC has been the most favorite diluent among others due to its low bulk density. Excipient having 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 [77].

MCC is commercially available in different particle sizes, density, and moisture grades that have different properties and applications. The most widely pronounced grades are Avicel PH 101 and Avicel PH 102 (FMC Corporation, Princeton, NJ, USA). PH stands for the pharmaceutical grade of MCC. Avicel PH 101 is the original grade of MCC, while PH 102 is available as a partially agglomerated product with a larger particle size distribution and slightly better fluidity. Both grades show no significant difference in the compressibility [78].

4.1 MCC as directly compressible filler

MCC has been very well known as the most compressible of all direct compression fillers which has the highest dilution potential and capacity. It is defined as the amount of active ingredient that a diluent can successfully carry in the direct compression method. This property can be explained by the basis of the physicochemical nature of MCC particles, which are held together by hydrogen bonds. 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 [78].

Direct compression (DC) is the tableting process of a blend of ingredients without a preliminary granulation or agglomeration process. Despite involving only few process steps, product design in DC can be challenging because of the numerous competing objectives [79]. Direct compression requires increased performance, quality, and consistency from the starting ingredients including excipients [44, 56, 80, 81]. The use of poorly controlled or inadequately specified raw materials may lead to several challenges in DC, such as poor flowability and inconsistent tablet weight, unsatisfactory tablet strength, lack of content uniformity or segregation, and dissolution failure [56, 82, 83]. Among several requirements, the compression mix has to flow to ensure a consistent tablet weight; it has to compress and compact into robust tablets. Overall, as a 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.

Lately, MCC can be considered as the most widely used diluent in the direct compression and wet granulated tablet making procedures. MCC type 102, having a median particle size of about 100 mm (D50 value measured by laser diffraction), presents acceptable flow properties required for successful high-speed tableting [2, 84]. 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 [43, 44, 59, 82]. 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 [78]. The larger particle size grades generally provide better flow properties, while low-moisture grades are used for moisture-sensitive materials. Higher-density grades have improved flowability. Flowability may be improved by selecting coarser grades of MCC with a larger number of aggregates, such as MCC type 200 with a median particle size approximating 200 mm [58, 85].

The difference between these common excipients is less pronounced on a volumetric basis [86], which determines die fill. Another approach may be to combine MCC with other free flowing excipients or glidants [59, 62, 87]. Gamble et al. observed that the particle size distributions of coarser grades of MCC do not scale up proportionally [58]. MCC types 101, 102, and 200 all have primary particles of about 50 mm but differ in the number of larger aggregated particles. These aggregates, accounting for a large volume/mass fraction but a low number fraction, enable improved flow.

During compression, MCC plastically deforms and therefore maximizes the area of interparticle bonding [88]. Mechanical interlocking of irregularly shaped and elongated MCC particles has also been suggested to enhance tabletability [44, 60, 75]. The plasticity of MCC is the main reason of its exceptional binding properties. However, compared to brittle excipients, MCC is more lubricant sensitive. For a constant number of revolutions, tabletability may also decrease with increasing blender sizes and decreasing loadings in the blender [89]. The viscoelastic behavior of MCC also explains its strain rate sensitivity (SRS), which refers to the greater elastic effects at higher tableting speeds where there is insufficient compaction time for plastic deformation [90]. The strain rate sensitivity of viscoelastic excipients has to be taken into account by the formulation scientists in order to design robust formulations.

4.2 MCC as wet granulation filler

MCC is one of the types of filler which is water insoluble having swelling tendencies and excellent water imbibing or wicking action. Other filler examples with the same property are calcium pectinate and sodium alginate. This property makes MCC as also an excipient of choice for wet granulation. Both Avicel PH 101 and Avicel PH 102 can be used advantageously as fillers in wet granulation in a concentration of 5.15%. When used as filler in wet granulation method, the wicking action of MCC promotes rapid wetting of the powder mix. Another advantage offfered by using MCC as wet granulation filler is the 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 will be much easier due to less clogging of the screen; hence it will produce a more uniform granules. Drying process also will be more homogeneous, and the case of hardening can be reduced. Case hardening is a phenomenon

which is observed in incompletely dried granules. This case happened when the granules are dried at a high temperature, from which the inside part of the granules remains wet, while the surface seems dried. The granules are often hard and resist disintegration. When coming to compaction process, the compression forces will break the granules and deform plastically to form soft tablets due to the moisture coming out of the incompletely dried granules. The use of Avicel PH 101 or Avicel PH 302 as filler in wet granulation promotes rapid wetting as a result of the wicking action of MCC. They reduce sensitivity of the wet mass to overwetting and increase the drying process speed. Since there is fewer excess of granulating fluid, screen blockages and case hardenings can be reduced. Homogeneous and uniform granule when MCC is used as wet granulation filler will reduce dye migration. When MCC is employed, faster disintegration from granules and tablets will be obtained.

4.2.1 Benefits of MCC in wet granulation

Basically, using MCC in wet granulation included wetting MCC with water followed by drying and compression. The process resulted in lower hardness tablets than that with dry compression. The wet granulation reduces the density of agglomerated particles thereby decreasing their internal surface area. In contrast, it can also cause adhesion between particle agglomerates, reducing external surface area resulting in less particle interlocking and hydrogen bonding. In general, using Avicel PH-101 or Avicel PH-102 in wet granulation formulations with concentration between 5 and 20% offers the following benefits [51]:

1. Rapid adsorption of water by MCC and distribution through the mixture

2. Decrease of sensitivity to water content, wet screening, and localized overwetting due to the large surface area of MCC, hence high adsorptive capacity

3. Increased drying efficiency

4. Decreased color mottling

5. Better drug content uniformity

6. Higher tablet hardness at the same compression force with less friability

4.3 Filler in dry granulation

Roller compaction is a dry process involving compaction of materials that are then milled to generate a granulation. This granulation is then lubricated and compressed on a tablet machine. This process can be used for moisture-sensitive active pharmaceutical ingredients. The use of Avicel PH grades in roller compaction includes improvement of compaction in the ribbon phase, enhancement of flow of the granules, and preserving of the content uniformity of the Þ nal granulation.

4.4 MCC as binder

MCC is a self-disintegrating binder [91] with low lubricant requirement with regard to its dry binding properties due to the extreme low coefficient of friction and its very low residual die wall pressure [56, 62, 92]. However these properties do not replace the need for true disintegrants and lubricants as an addition when MCC is used in a tablet formulation. In fact combination of MCC and superdisintegrants

may be complementary to promote fast disintegration [93, 94]. Other advantages of MCC include broad compatibility with various APIs, physiological inertness, ease of handling, and ease of supply for manufacturer [54].

Study on the use of MCC with spray-dried lactose as the poorest compressibility among all directly compressible fillers showed that a blend of 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. Incorporation of 2.5% of Avicel to the formulation proved that MCC has served the purpose. A number of Avicel such as PH-113 can act as a dry binder [95]. However, it will also function as a disintegrant when dry compression is employed.

4.4.1 MCC as a wet binder

MCC can also be used as a secondary binder in wet granulation tablet preparation either to granulate both soluble and insoluble APIs. This formulation will produce less hard tablets than that without MCC. The fast wicking action of MCC promotes rapid wetting of the powder mix. This is particularly useful in high moisture granulations as it binds the excess moisture and keeps the granules dry and free flowing.

4.5 MCC as disintegrant

Disintegrants expand and dissolve once it is in contact with water causing the tablet to break apart in the GI tract and release the active ingredients for absorption. It will break a tablet into smaller fragments therefore increasing the surface area of the active drug in the dosage form; hence it will also increase the rate of drug absorption. The mechanism of disintegrants in the tablet disintegration could be as either water uptake facilitators or tablet rupture promoters. MCC has been widely used as a disintegrant in dry compressions and wet granulation method for tablet manufacturing. It enhances drug dissolution by increasing the rate of tablet disintegration. Basically a disintegrant should provide the highest level of disintegration force at low use levels and utilizes dual disintegration mechanisms either in wicking or swelling for faster tablet disintegration.

The Avicel derivate showed the nature in a fast wicking rate of water with small elastic deformation. These properties provide the ability for tablet disintegration. However, Avicel has a tendency to develop static charges with increased moisture content. Sometimes it even can cause striation or separation in the granules. This occurs when the moisture content in Avicel is above 3%, in which the static charges during mixing and compression become more pronounced. The problem can be overcome by drying the Avicel prior the formulation process to reduce the moisture to lower level. Wet granulated Avicel will lose some of its disintegration properties when performing drying and compression during formulation [4]. In contrast with starch, it cannot be wet granulated without losing some of its disintegration properties. Normally, to overcome this problem, Avicel and starch are used in combination in order to facilitate effective and rapid disintegration of tablets.

MCC has a very high intraparticle porosity with approximately 90–95% of the surface area being internal [44]. Therefore the surface area is not directly influenced by the nominal particle size [58]. High porosity of MCC promotes swelling and disintegration of formulated tablets, which is attributed to either by the penetration of water into the hydrophilic tablet matrix by means of capillary action of the pores or even by a disruption of the hydrogen bonds. By increasing compaction pressure, water penetration into the tablets will decrease; therefore disintegration time will increase [54, 85].

In intramolecular view, water is only sorbed in the amorphous regions of MCC, which are more hydrophilic than the crystalline regions [3, 54]. Therefore the total amount of sorbed water is proportional to the fraction of amorphous material in the MCC crystallinity and is independent of the surface area [48]. The crystallinity of MCC determined by X-ray diffraction and infrared measurement was found to be in the range of 60–80% [53].

Recently, Avicel has been used as a disintegrant in orally disintegrating tablets. Besides being a disintegrant, it also acts as a dissolution enhancer. US Patent No 6350470 explains the use of Avicel as a disintegrating agent in effervescent drug delivery system for oral administration. In this system, by performing dry granulation, Avicel acts as disintegrant in a concentration of 5.20% [96]. Avicel acts as an effervescent penetration enhancer.

4.6 MCC as lubricant

Lubricants ensure that tablet formation and ejection can occur with low friction between the solid and die wall.

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.

4.7 MCC as glidant

In tablet formulation, glidant is used to promote powder flow by reducing interparticle friction and cohesion. Glidants can be 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, silica hydrogel, etc. are used in tablet compression to promote good flow property. Proslov as a marketed product of coprocess excipient containing MCC is available which imparts superior flow, good compactibility, and dispersion to tablet formulation [97].

When used as excipient in direct compression, Prosolv SMCC® (JRS Pharma, Patterson, NY) can replace granulation step and significantly reduce excipient numbers and levels. Prosolv SMCC® formulations produce distinctive, uniform, and cost-effective tablets. It is available in three grades: Prosolv SMCC 50, Prosolv SMCC 90, and Prosolv SMCC HD 90. The products differ in average of particle size and bulk density [98]. They offer many benefits including enhanced mixing characteristics, enhanced flow properties, lower unit cost of production due to less excipients needed, and shorter disintegration time. Due to improvement in powder compactibility and dust-free handling during production, Prosolv facilitates less loss in production hence a higher manufacturing efficiency.

In a more recent study, it is reported that silicified MCC and MCC were found to be good plug formers in hard gelatin capsule shells. The study was conducted in a compaction simulator at tamping forces and piston speeds similar to those found in some filling machines. Several grades of silicified MCC and a particular grade of MCC having particle size of 90 μm produced plugs with a higher maximum breaking force than anhydrous lactose and Starch 1500 under similar compression conditions [99].

4.8 MCC as a spheronizing agent

MCC is an excipient of choice in a multiparticulate delivery of pellets prepared by extrusion spheronization. The extrusion-spheronization process aims to produce drugs into sphere-shaped tablets. Extrusion-spheronization process offers an

alternative to traditional drug layering on pellets. This highly specialized process results in unique spherical, drug-loaded spherical pellets. Higher drug loading can be employed with this approach over that which looks impossible with conventional drug layering. The product, initially called as extrudates, is plastic without rigidity, which tends to agglomerate into very large spherical balls. The formulation mixture which will be manufactured by extrusion method must fulfill the requirements:

1. Cohesive and deformable in order to have good flow through the die without sticking and able to retain its shape after extrusion process

2. Plastic, so that it can proceed rolling process into spheres in the spheronizer but possesses non-cohesive property so that the final sphere form can remain discrete

MCC, especially Avicel PH-101, can act as an excellent extrusion-spheronization aid excipient that absorbs the water added to the formulation more as a molecular sponge. This ability alters the rheological properties of the wet mass, therefore enhancing the tensile strength of the wet mass during spheronization process through autoadhesion.

Avicel® PH-101 or Avicel PH-102 is highly recommended to be used for this method because it can reduce spheroid friability, prevent overwetting of spheres, and improve sphericity of pellets. Process sensitivity during the whole manufacture can be lessened to the lower level.

4.9 Sustained release applications

Recently, MCC has been widely used in the formulation of multiparticulate and matrix tablet dosage forms for sustained release drug delivery system. In general, hydrophilic polymers in matrix tablet formulation are included to form a viscous, gelling layer which can retard water penetration and acts as a barrier to drug release. Drug release is accomplished by diffusion through the gel layer and at the same time through erosion of this layer. Some studies proved that zero-order release profiles can be achieved by selection of appropriate polymers in addition of Avicel as fillers/binders.

5. Conclusions

Microcrystalline cellulose is a pure partially depolymerized cellulose synthesized from α-cellulose precursor with hydrolysis by mineral acids, usually in forms of a pulp from a fibrous plant. In the presence of water and acid, hydrolysis process breaks cellulose polymers into smaller chain polymers or microcrystals. Other celluloses, to which more soluble, such as beta and gamma celluloses, hemicelluloses and lignin are dissolved with acid and water, are separated out during washing. MCC is commonly dried from the slurry by spray-drying method. By varying spray-drying conditions, the degree of agglomeration and moisture content can be manipulated, in order to obtain particular particle sizes.

Mostly, a raw material for MMC is a cellulose pulp from fibrous plant such as conifer wood. Another source is from cotton either its linters, stalks, rags, fabric waste, or wool. Another study reported a potential source for MCC such as soybean, corn cob, water hyacinth, coconut shells, oil palm biomass residue, oil palm fronds, rice husk, sugar cane bagasse, jute, ramie, fibers and straw of flax, wheat straw, sorghum stalks, sisal fibers, mangosteen, alfa grass fibers, soybean

hulls, orange mesocarp, Indian bamboo, roselle fiber, and alfa fiber. Seed flosses from milkweed pods, shrubs, and kapok (*Ceiba pentandra*) trees are also known as sources of cellulose.

A different manufacture will produce variability in properties of MCC due to the kinds of pulp used as raw materials and applied process parameters. This can be characterized from the physicochemical properties of product including moisture content, particle size, particle morphology, crystallinity, bulk density, and degree of polymerization.

Microcrystalline cellulose, according to many publications, is an excipient most widely used for direct compression. Besides, it also serves as a strong dry binder, tablet disintegrant, absorbent, filler or diluent, a lubricant, and anti-adherent.

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References

[1] Carlin B. Direct compression and the role of filler-binders. In: Augsburger LL, Augsburger LL, Hoag SW, Hoag SW, editors. Pharmaceutical Dosage Forms: Tablets. 3rd edition. Vol. 2. Informa; 2008. pp. 173-216

[2] Shlieout G, Arnold K, Muller G. Powder and mechanical properties of microcrystalline cellulose with different degrees of polymerization. AAPS PharmSciTech. 2002;**3**:E11

[3] Suzuki T, Nakagami H. Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets. European Journal of Pharmaceutics and Biopharmaceutics. 1999;**47**:225-230

[4] Landín M, Martínez-Pacheco R, Gómez-Amoza JL, Souto C, Concheiro A, Rowe RC. Effect of batch variation and source of pulp on the properties of microcrystalline cellulose. International Journal of Pharmaceutics. 1993;**91**:133-141

[5] Chauhan YP, Sapkal RS, Sapkal VS, Zamre GS. Microcrystalline cellulose from cotton rags (waste from garment and hosiery industries). International Journal of Chemical Sciences. 2009;**7**(2):681-688

[6] El-Sakhawy M, Hassan ML. Physical and mechanical properties of microcrystalline cellulose prepared from agricultural residues. Carbohydrate Polymers. 2007;**67**:1-10

[7] Chuayjuljit S, Su-uthai S, Charuchinda S. Poly(vinyl chloride) film filled with microcrystalline cellulose prepared from cotton fabric waste: Properties and biodegradability study. Waste Management & Research. 2010;**28**(2):109-117

[8] Rashid M, Gafur MA, Sharafat MK, Minami H, Miah MAJ, Ahmad H. Biocompatible microcrystalline cellulose particles from cotton wool and magnetization via a simple in situ co-precipitation method. Carbohydrate Polymers. 2017;**170**:72-79

[9] Uesu NY, Pineda EA, Hechenleitner AA. Microcrystalline cellulose from soybean husk: Effects of solvent treatments on its properties as acetylsalicylic acid carrier. International Journal of Pharmaceutics. 2000;**206**:85-96

[10] Suvachittanont S, Ratanapan P. Optimization of micro crystalline cellulose production from corn cob for pharmaceutical industry investment. Journal of Chemistry and Chemical Engineering. 2013;**7**:1136-1141

[11] Gaonkar SM, Kulkarni PR. Improved method for the preparation of microcrystalline cellulose from water hyacinth. Textile Dyer and Printer. 1987;**20**(26):19-22

[12] Gaonkar SM, Kulkarni PR. Microcrystalline cellulose from coconut shells. Acta Polymer. 1989;**40**:292-293

[13] Fahma F, Iwamoto S, Hori N, Iwata T, Takemura A. Isolation, preparation, and characterization of nanofibers from oil palm empty-fruit-bunch (OPEFB). Cellulose. 2010;**17**(5):977-985

[14] Mohamad Haafiz MK, Eichhorn SJ, Hassan A, Jawaid M. Isolation and characterization of microcrystalline cellulose from oil palm biomass residue. Carbohydrate Polymers. 2013;**93**(2):628-634

[15] Owolabia A, Haafiza M, Hossain M, Hussin H, Fazita N. Influence of alkaline hydrogen peroxide pre-hydrolysis on the isolation of microcrystalline cellulose from oil palm fronds. International Journal of Biological Macromolecules. 2017;**95**:1228-1234

[16] Ilindra A, Dhake JD. Microcrystalline cellulose from bagasse and rice straw. Indian Journal of Chemical Technology. 2008;**15**(5):497-499

[17] Paralikar KM, Bhatawdekar SP. Microcrystalline cellulose from bagasse pulp. Biological Wastes. 1988;**24**:75-77

[18] Padmadisastra Y, Gonda I. Preliminary studies of the development of a direct compression cellulose excipient from bagasse. Journal of Pharmaceutical Sciences. 1989;**78**(6):508-521

[19] Shah DA, Shah YD, Trivedi BM. Production of microcrystalline cellulose from sugar cane bagasse on pilot plant and its evaluation as pharmaceutical adjunct. Research and Industry. 1993;**38**(3):133-137

[20] Tang L-G, Hon DN-S, Pan S-H, Zhu Y-U, Wang Z, Wang Z-Z. Evaluation of microcrystalline cellulose. I. Changes in ultrastructural characteristics during preliminary acid hydrolysis. Journal of Applied Polymer Science. 1996;**59**:483-488

[21] Abdullah ABM. Production of jute microcrystalline cellulose. Journal of Bangladesh Academy of Science. 1991;**15**(2):85-87

[22] Jahan MS, Saeed A, He Z, Ni Y. Jute as raw material for the preparation of microcrystalline cellulose. Cellulose. 2011;**18**(2):451-459

[23] Kuga S, Brown RM. Lattice imaging of ramie cellulose. Polymer Communications Guildford. 1987;**28**(11):311-314

[24] Bochek AM, Shevchuk IL, Lavrentev VN. Fabrication of microcrystalline and powdered cellulose from short flax fiber and flax straw. Russian Journal of Applied Chemistry. 2003;**76**(10):1679-1682

[25] Monschein M, Reisinger C, Nidetzky B. Enzymatic hydrolysis of microcrystalline cellulose and pretreated wheat straw: A detailed comparison using convenient kinetic analysis. Bioresource Technology. 2013;**128**:679-687

[26] Ohwoavworhua FO, Adelakun TA. Non-wood fibre production of microcrystalline cellulose from *Sorghum caudatum*: Characterisation and tableting properties. Indian Journal of Pharmaceutical Science. 2010;**72**(3):295-301

[27] Bhimte NA, Tayade PT. Evaluation of microcrystalline cellulose prepared from sisal fibers as a tablet excipient: A technical note. Association of Pharmaceutical Scientists (AAPS). Pharmaceutical Science and Technology. 2007;**8**(1):E56-E62

[28] Winuprasith T, Suphantharika M. Microfibrillated cellulose from mangosteen (*Garcinia mangostana* L.) rind: Preparation, characterization, and evaluation as an emulsion stabilizer. Food Hydrocolloids. 2013;**32**(2):383-394

[29] Trache D, Donnot A, Khimeche K, Benelmir R, Brosse N. Physico-chemical properties and thermal stability of microcrystalline cellulose isolated from alfa fibres. Carbohydrate Polymers. 2014;**104**:223-230

[30] Trache D, Khimeche K, Mezroua A, Benziane M. Physicochemical properties of microcrystalline nitrocellulose from alfa grass fibers and its thermal stability. Journal of Thermal Analysis and Calorimetry. 2016;**124**(3):1485-1496

[31] Merci A, Urbano A, Grossmann MVE, Tischer CA, Mali S. Properties of microcrystalline cellulose extracted from soybean hulls by reactive

extrusion. Food Research International. 2015;**SI**(73):38-43

[32] Ejikeme PM. Investigation of the physicochemical properties of microcrystalline cellulose from agricultural wastes I: Orange mesocarp. Cellulose. 2008;**15**(1):141-147

[33] Ngozi UO, Chizoba NA, Ifeanyichukwu OS. Physico-chemical properties of microcrystalline cellulose derived from Indian Bamboo (*Bambusa vulgaris*). International Journal of Pharmaceutical Sciences Review and Research. 2014;**29**(2):5-9. Article No. 02

[34] Kiana LK, Jawaida M, Ariffina H, Alothmanb OY. Isolation and characterization of microcrystalline cellulose from roselle fibers. International Journal of Biological Macromolecules. 2017;**103**(2017):931-940

[35] Trachea D, Donnotb A, Khimechea K, Benelmirb R, Brosse N. Physico-chemical properties and thermal stability of microcrystalline cellulose isolated from Alfa fibres. Carbohydrate Polymers. 2014;**104**:223-230

[36] Hindi SSZ. Calotropis procera: The miracle shrub in the Arabian Peninsula. International Journal of Science and Engineering Investigations (IJSEI). 2013;**2**(16):48-57

[37] Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment: A review. International Journal of Pharmaceutics. 2014;**473**(1-2):64-72

[38] Hindi SSZ, Abohassan RA. Cellulosic microfibril and its embedding matrix within plant cell wall. International Journal of Innovative Research in Science, Engineering and Technology. 2016;**5**(3):2727-2734

[39] Guy A. Cellulose, microcrystalline. In: Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of Pharmaceutical Excipients. Vol. 6. UK: Pharmaceutical Press; 2009. pp. 129-133, American Pharmacists Association (USA). ISBN 978 0 85369 792 3 (UK), ISBN 978 1 58212 135 2 (USA)

[40] Ohwoavworhua FO, Kunle OO, Ofoefule SI. Extraction and characterization of microcrystalline cellulose derived from *Luffa cylindrica* plant. African Journal of Pharmaceutical Research and Development. 2004;**1**:1-6

[41] Reier GE. Problem Solver. Avicel1 PH Microcrystalline Cellulose, NF, Ph Eur. JP, BP. 2000. Available from: http://www.fmcbiopolymer.com/Portals/bio/content/Docs/PS-Section% 2011.pdf

[42] Christiansen OB, Sardo MS. Find the optimum flash dryer to remove surface moisture. CEP magazine. 2001;54-58. Available from: http://www.barr-rosin.com/library_pdfs/find_optimum_flash_dryer_remove_moisture.pdf

[43] Albers J, Knop K, Kleinebudde P. Brand-to-brand and batch-to-batch uniformity of microcrystalline cellulose in direct tableting with a pneumo-hydraulic tablet press. La Pharmacie Industrielle. 2006;**68**:1420-1428

[44] Doelker E. Comparative compaction properties of various microcrystalline cellulose types and generic products. Drug Development and Industrial Pharmacy. 1993;**19**:2399-2471

[45] Landín M, Martínez-Pacheco R, Gómez-Amoza JL, Souto C, Concheiro A, Rowe RC. Influence of microcrystalline cellulose source and batch variation on the tabletting behaviour and stability of prednisone formulations. International Journal of Pharmaceutics. 26 April 1993;**91**(2-3):143-149

[46] Landín M, Martínez-Pacheco R, Gómez-Amoza JL, Souto C, Concheiro A, Rowe RC. Influence of Microcrystalline Cellulose Source and Batch Variation on the Tabletting. 1993

[47] Williams RO, Sriwongjanya M, Barron MK. Compaction properties of microcrystalline cellulose using tableting indices. Drug Development and Industrial Pharmacy. 1997;**23**:695-704

[48] Amidon GE, Houghton ME. The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. Pharmaceutical Research. 1995;**12**:923-929

[49] Wu J-S, Ho H-O, Sheu M-T. A statistical design to evaluate the influence of manufacturing factors and material properties on the mechanical performances of microcrystalline cellulose. Powder Technology. 2001;**118**:219-228

[50] Wu J-S, Ho H-O, Sheu M-T. A statistical design to evaluate the influence of manufacturing factors on the material properties and functionalities of microcrystalline cellulose. European Journal of Pharmaceutical Sciences. 2001;**12**:417-425

[51] Reier GE. Fun facts about Avicel® microcrystalline cellulose also known as cellulose gel. 2013. Available from: http://www.fmcbiopolymer.com/Food/Home/News/FiftyYearsofAvicel.aspx

[52] Doelker E, Mordier D, Iten H, Humbert-Droz P. Comparative tableting properties of sixteen microcrystalline celluloses. Drug Development and Industrial Pharmacy. 1987;**13**:1847-1875

[53] Sun CC. Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose. International Journal of Pharmaceutics. 2008;**346**:93-101

[54] Bolhuis GK, Chowhan ZT. Materials for direct compaction. In: Alderborn G, Alderborn G, Nyström C, Nyström C, editors. Pharmaceutical Powder Compaction Technology. New York: Marcel Dekker, Inc.; 1996. pp. 419-500

[55] Nokhodchi A. An overview of the effect of moisture on compaction and compression. Pharmaceutical Technology. 2005;**46-66**

[56] Patel S, Kaushal AM, Bansal AK. Compression physics in the formulation development of tablets. Critical Reviews in Therapeutic Drug Carrier Systems. 2006;**23**:1-65

[57] Almaya A, Aburub A. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. AAPS PharmSciTech. 2008;**9**:414-418

[58] Gamble JF, Chiu WS, Tobyn M. Investigation into the impact of sub-populations of agglomerates on the particle size distribution and flow properties of conventional microcrystalline cellulose grades. Pharmaceutical Development and Technology. 2011;**16**:542-548

[59] Jivraj M, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. Pharmaceutical Science & Technology Today. 2000;**3**:58-63

[60] Pesonen T, Paronen P. The effect of particle and powder properties on the mechanical properties of directly compressed cellulose tablets. Drug Development and Industrial Pharmacy. 1990;**16**:31-54

[61] Thoorens G, Krier F, Rozet E, Carlin B, Evrard B. Understanding the

impact of microcrystalline cellulose physicochemical properties on tabletability. International Journal of Pharmaceutics. 2015;**490**:47-54

[62] Hwang R-C, Peck GR. A systematic evaluation of the compression and tablet characteristics of various types of microcrystalline cellulose. Pharmaceutical Technology. June 2001:112-132

[63] Whiteman M, Yarwood RJ. Variations in the properties of microcrystalline cellulose from different sources. Powder Technology. 1988;**54**:71-74

[64] Herting MG, Kleinebudde P. Roll compaction/dry granulation: Effect of raw material particle size on granule and tablet properties. International Journal of Pharmaceutics. 2007;**338**:110-118

[65] Kushner J, Langdon BA, Hiller JI, Carlson GT. Examining the impact of excipient material property variation on drug product quality attributes: A quality-by-design study for a roller compacted, immediate release tablet. Journal of Pharmaceutical Sciences. 2011;**100**:2222-2239

[66] Kushner J. Utilizing quantitative certificate of analysis data to assess the amount of excipient lot-to-lot variability sampled during drug product development. Pharmaceutical Development and Technology. 2013;**18**:333-342

[67] Hasegawa M. Direct compression: Microcrystalline cellulose grade 12 versus classic grade 102. Pharmaceutical Technology. 2002;**26**:50-60. Available from: http://www.pharmtech.com/pharmtech/data/articlestandard//pharmtech/192002/18599/article.pdf

[68] Hlinak AJ, Kuriyan K, Morris KR, Reklaitis GV, Basu PK. Understanding critical material properties for solid dosage form design. Journal of Pharmaceutical Innovation. 2006;**1**:12-17

[69] Obae K, Iijima H, Imada K. Morphological effect of microcrystalline cellulose particles on tablet tensile strength. International Journal of Pharmaceutics. 1999;**182**:155-164

[70] Friedman R. Pharmaceutical quality systems: US perspective. Pharmaceutical Quality System (ICH Q10) Conference. 2011. Available from: http://www.fda.gov/downloads/drugs/ developmentapprovalprocess/manufacturing/ucm288108.pdf

[71] Vehovec T, Gartner A, Planinsek O, Obreza A. Influence of different types of commercially available microcrystalline cellulose on degradation of perindopril erbumine and enalapril maleate in binary mixtures. Acta Pharmaceutica. 2012;**62**:515-528

[72] Abdel-Hamid S, Alshihabi F, Betz G. Investigating the effect of particle size and shape on high speed tableting through radial die-wall pressure monitoring. International Journal of Pharmaceutics. 2011;**413**:29-35

[73] Liao Z, Zhang N, Zhao G, Zhang J, Liang X, Zhong S, et al. Multivariate analysis approach for correlations between material properties and tablet tensile strength of microcrystalline cellulose. Pharmazie. 2012;**67**:774-780

[74] Pönni R, Vuorinen T, Kontturi E. Proposed nano-scale coalescence of cellulose in chemical pulp fibers during technical treatments. BioResources. 2012;7:6077-6108

[75] Westermarck S, Juppo AM, Kervinen L, Yliruusi J. Microcrystalline cellulose and its microstructure in pharmaceutical processing. European Journal of Pharmaceutics and Biopharmaceutics. 1999;**48**:199-206

[76] Bolhuis GK, Armstrong NA. Excipients for direct compaction—An

update. Pharmaceutical Development and Technology. 2006;**11**:111-124

[77] Sheth BB, Bandelin FJ, Shangraw RF. Compressed tablets. In: Lachman L, Liberman HA, Schwartz JB, editors. Pharmaceutical Dosage Forms: Tablets. Vol. 2. New York, Basel, HongKong: Marcel Dekker Inc.; 1990. p. 109

[78] Schwartz JB, Lachman L. Compressed tablets by wet granulation. In: Bandelin JF, editor. Pharmaceutical Dosage Forms: Tablets. Vol. 1. New York, Basel, HongKong: Marcel Dekker Inc; 1990. p. 133

[79] Peck GE, Anderson NR, Banker GS. Principles of improved tablet production system design. In: Liebermann HA, Lachman L, Schwartz JB, editors. Pharmaceutical Dosage Forms: Tablets. Lea & Febiger; 1990. pp. 1-76

[80] Kása P, Bajdik J, Zsigmond Z, Pintye-Hódi K. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chemical Engineering and Processing—Process Intensification. 2009;**48**:859-863

[81] Tho I, Bauer-Brandl A. Quality by design (QbD) approaches for the compression step of tableting. Expert Opinion on Drug Delivery. 2011;**8**:1631-1644

[82] Hentzschel CM, Sakmann A, Leopold CS. Comparison of traditional and novel tableting excipients: Physical and compaction properties. Pharmaceutical Development and Technology. 2012;**17**:649-653

[83] Ilic I, Govedarica B, Sibanc R, Dreu R, Srcic S. Deformation properties of pharmaceutical excipients determined using an in-die and out-die method. International Journal of Pharmaceutics. 2013;**446**:6-15

[84] Shi L, Chattoraj S, Sun CC. Reproducibility of flow properties of microcrystalline cellulose—Avicel PH102. Powder Technology. 2011;**212**:253-257

[85] Lahdenpää E, Niskanen M, Yliruusi J. Crushing strength, disintegration time and weight variation of tablets compressed from three Avicelä PH grades and their mixtures. European Journal of Pharmaceutics and Biopharmaceutics. 1997;**43**:315-322

[86] Wallace JW, Capozzi JT, Shangraw RF. Performance of pharmaceutical filler/binders as related to methods of powder characterization. Pharmaceutical Technology. 1983;**7**:94-104

[87] Patel NK, Upadhyay AH, Bergum JS, Reier GE. An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station tablet press. International Journal of Pharmaceutics. 1994;**110**:203-210

[88] Rubinstein MH. Tablets. In: Aulton ME, Aulton ME, editors. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone; 1988

[89] Kushner J, Moore F. Scale-up model describing the impact of lubrication on tablet tensile strength. International Journal of Pharmaceutics. 2010;**399**:19-30

[90] Roberts RJ, Rowe RC. The effect of punch velocity on the compaction of a variety of materials. The Journal of Pharmacy and Pharmacology. 1985;**37**:377-384

[91] Ferrari F, Bertoni M, Bonferoni MC, Rossi S, Caramella C, Nyström C. Investigation on bonding and disintegration properties of pharmaceutical materials. International Journal of Pharmaceutics. 1996;**136**:71-79

[92] Saigal N, Baboota S, Ahuja A, Ali J. Microcrystalline cellulose as a versatile excipient in drug research. Journal of Young Pharmacists. 2009;**1**:6-12

[93] Bala R, Khanna S, Pawar PK. Formulation and optimization of fast dissolving intraoral drug delivery system for clobazam using response surface methodology. Journal of Advanced Pharmaceutical Technology & Research. 2013;**4**:151-159

[94] Mostafa HF, Ibrahim MA, Sakr A. Development and optimization of dextromethorphan hydrobromide oral disintegrating tablets: Effect of formulation and process variables. Pharmaceutical Development and Technology. 2013;**18**:454-463

[95] Saha S, Sahiwala AF. Multifunctional coprocessed excipients for improved tabletting performance. Expert Opinion on Drug Delivery. 2009;**6**:197-208

[96] Indiran PS, Robinson JR, Eichman JD, Khankari RK, Hontz J, Gupte SV. Effervescent drug delivery system for oral administration. US 6350470. 2002

[97] Rios M. Debating Excipient Functionality. Special Report. International Pharmaceutical Excipients Council. 2006. Available from: http://ipecamericas.org/newsletters/PT9-30-06e.pdf [Accessed: Mar 19, 2009]

[98] Ausburger LL. Hard Shell Capsules. FMC Biopolymer. 2008. Available from: http://www.fmcbiopolymer.com/Portals/bio/content/Docs/Pharmaceuticals/Problem%20Solver/8_hardshellcapsules.pdf [Accessed: Mar 25, 2009]

[99] Guo M, Muller FX, Augsburger LL. Evaluation of the plug formation process of silicified microcrystalline cellulose. International Journal of Pharmaceutics. 2002;**233**:99-109