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Review

Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review

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ABSTRACT

The ICH quality vision introduced the concept of quality by design (QbD), which requires a greater understanding of the raw material attributes, of process parameters, of their variability and their interactions. Microcrystalline cellulose (MCC) is one of the most important tableting excipients thanks to its outstanding dry binding properties, enabling the manufacture of tablets by direct compression (DC). DC remains the most economical technique to produce large batches of tablets, however its efficacy is directly impacted by the raw material attributes. Therefore excipients' variability and their impact on drug product performance need to be thoroughly understood. To help with this process, this review article gathers prior knowledge on MCC, focuses on its use in DC and lists some of its potential critical material attributes (CMAs).

Contents

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1. Introduction

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use has set a new quality paradigm as described in its guidelines Q8(R2), Q9, and Q10. The new paradigm promotes science and risk-based approaches to product development, dossier submission, review, inspection and post-approval change management. Furthermore, manufacturers are now encouraged to effect continuous improvement and technical innovation throughout the product life cycle.

The ICH quality vision impacts not only drug manufacturers but others in the pharmaceutical supply chain. Excipients, and therefore excipients suppliers, play an important and sometimes critical role with regard to drug product quality (Kushner, 2013). It is now paramount to identify, understand and control excipient variability, so that it can be compensated or controlled to deliver consistent product quality (ICH, 2005, 2009). Excipient performance is rarely fully understood (Moreton, 2009c; Wang et al., 2013) and at times underestimated (Carlin, 2012; Friedman, 2011). This is true even for one of the most popular tablet diluents used in the most straightforward process to produce oral solid dosage forms, namely microcrystalline cellulose (MCC) in direct compression (DC).

Direct compression (DC) is the tableting 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 (Peck et al., 1990). Among several requirements, the compression mix has to flow to ensure a consistent tablet weight; it has to compress and compact into robust tablets; and the resulting tablets have to remain stable over time to maintain safety and efficacy. DC is directly impacted by material properties since these are not altered by preceding process steps. Therefore, direct compression requires increased performance, quality and consistency from the starting ingredients including excipients (Carlin, 2008; Kása et al., 2009; Patel et al., 2006; Tho and Bauer-Brandl, 2011). 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 (Friedman, 2011; Hentzschel et al., 2012; Ilic et al., 2013; McCormick, 2005; Patel et al., 2006).

Diluents are incorporated into tablet or capsule dosage forms to increase dosage form volume or weight, and as such they can also be referred to as fillers (USP37-NF32, 2014a). Some diluents, such as microcrystalline cellulose (MCC), can also be considered as dry binders since they improve the compactibility or tabletability of the compression mix. True DC binders are functional even at low use levels and offer superior tabletability (Carlin, 2008). Most DC grade excipients also offer superior flow compared to grades used in granulation techniques.

The scale of manufacture of excipients is very different from that typically encountered in pharmaceutical product manufacture. Indeed in continuous production, a 'batch' is usually a time period or slice (days) from a larger production campaign (weeks) (Carlin, 2012), but even days or weeks of production can still amount to many tons. Considering these large batch sizes and the intrinsic variability of continuous processes, intra-batch (container-to-container) variability is inevitable (Hoag, 2011; Moreton, 2006). For this reason, traceability of individual containers to the nearest relevant in-process results is essential. Additional excipient variability can be caused by (1) the seasonal quality variation of raw materials having natural origins and (2) the sourcing from multiple suppliers or from multiple sites, each of them using different processes (with or without processing aids), which may create issues due to performance disparities (Sheehan, 2012; Sheehan and Amidon, 2011).

The purpose of this review article is (1) to thoroughly describe MCC and its behavior in direct compression, (2) to highlight the need for a greater understanding of excipient variability and excipient performance, and (3) to gather prior knowledge relating to some possible critical material attributes (CMAs) of MCC when used in direct compression.

2. Microcrystalline cellulose, a direct compression binder

Microcrystalline cellulose (MCC) was discovered in 1955 by Battista and Smith and was first commercialized under the brand name Avicel® (FMC, 2013). In 1964 FMC Corporation introduced Avicel® PH to the pharmaceutical industry as an ingredient for direct compression tableting (Albers et al., 2006). MCC was first registered in the supplement to the National Formulary, twelfth edition, in 1966 (Suzuki and Nakagami, 1999). More than 50 years later, MCC is manufactured globally by more than 10 suppliers.

MCC is a purified, partially depolymerized cellulose prepared by treating alpha cellulose (type I_β), obtained as a pulp from fibrous plant material, with mineral acids. Cellulose is the most abundant natural polymer on earth with an annual biomass production of 50 billion tons (Carlin, 2008). Cellulose consists of linear chains of β-1,4-D anhydroglucopyranosyl units.

The most common source of pharmaceutical MCC is wood, in which cellulose chains are packed in layers held together by a cross-linking polymer (lignin) and strong hydrogen bonds. Cotton has also been mentioned as a possible cellulose source for MCC (Shlieout et al., 2002; Suzuki and Nakagami, 1999). Both softwoods (evergreen conifer) and hardwoods (deciduous broadleaf) can be used (Landín et al., 1993a). These woods differ considerably in chemical composition (proportions of cellulose, hemicelluloses and lignin) and structural organization, i.e., regions which are relatively more crystalline or amorphous. The amorphous regions are more prone to hydrolysis so partial depolymerization by acid hydrolysis results in shorter and more crystalline fragments, i.e., microcrystalline cellulose.

Degree of polymerization (DP), i.e., the number of glucose units $(C_6H_{10}O_5)_n$ in the cellulose chain, exponentially decreases as a function of hydrolysis conditions, which include temperature, acid concentration and time. The rate of hydrolysis slows to a certain level-off degree of polymerization (LODP). The LODP is a characteristic of a particular pulp and is typically found in the 200–300 range (Doelker, 1993), e.g., 180–210 range for hardwood pulps and 210–250 for softwood pulps. In theory, hydrolysis could be terminated at any time to obtain a degree of polymerization higher than the LODP. However this is neither a robust nor a reproducible approach considering the exponential decay of DP. The reduction of degree of polymerization with hydrolysis time is shown in Fig. 1 (courtesy of FMC Health and Nutrition). 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 (Carlin, 2008; Dybowski, 1997).

MCC is commonly manufactured by spray drying the neutralized aqueous slurry resulting from the hydrolysis of cellulose. Most commercial grades are formed by varying and controlling the spray drying conditions in order to manipulate the degree of agglomeration (particle size distribution) and moisture content (loss on drying). Other drying techniques may be used, which may require additional screening steps post drying in order to control particle size distribution. Higher bulk density grades are also available by using specific cellulose pulps (raw material), and median particle sizes below 50 μm can be obtained by further milling MCC (Carlin, 2008).

MCC is generally considered as the diluent having the best binding properties and is recognized as one of the preferred DC binders (Bolhuis and Armstrong, 2006; Carlin, 2008). In addition

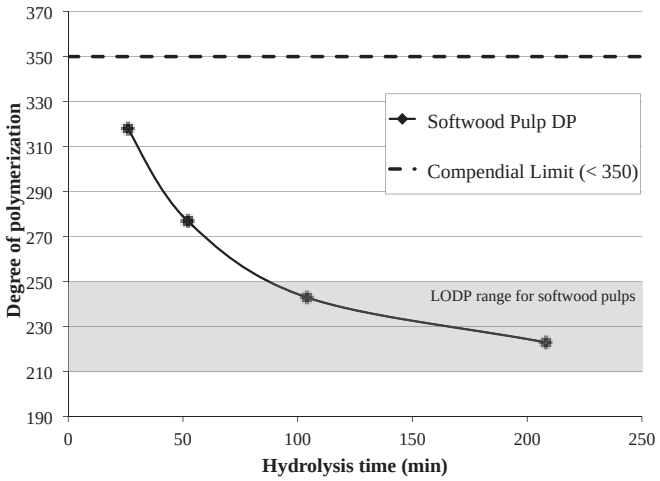

Fig. 1. LODP of softwood pulps.

to its dry binding properties, and in comparison to brittle excipients, MCC is self-disintegrating (Ferrari et al., 1996) with low lubricant requirement due to its extremely low coefficient of friction and its very low residual die wall pressure (Hwang and Peck, 2001; Patel et al., 2006; Saigal et al., 2009). However these properties do not replace the need for true disintegrants and lubricants when MCC is used in a formulation. In fact MCC and superdisintegrants may be complementary to promote fast disintegration (Bala et al., 2013; Mostafa et al., 2013). MCC offers other advantages including broad compatibility with APIs, physiological inertness, ease of handling, and security of supply (Bolhuis and Chowhan, 1996).

During compression MCC plastically deforms and therefore maximizes the area of interparticle bonding (Rubinstein, 1988). Porous, often spray-dried, agglomerates deform on a macroscale; then due to the presence of slip planes, MCC dislocates on a microscale (Carlin, 2008; Haware et al., 2009). This proximity of hydrogen groups on adjacent cellulose molecules enables the formation of numerous hydrogen bonds, which account almost exclusively for the strength and cohesiveness of compacts, even under low compression forces (Bolhuis and Chowhan, 1996; Carlin, 2008; Saigal et al., 2009). Mechanical interlocking of irregularly shaped and elongated MCC particles has also been suggested to enhance tabletability (Doelker, 1993; Nyström et al., 1993; Pesonen and Paronen, 1990; Westermarck et al., 1999).

The plasticity of MCC is the main reason of its exceptional binding properties. However, compared to brittle excipients, MCC is more lubricant sensitive. Lubricated MCC particles will deform under pressure and will not fracture to create new and clean (lubricant-free) surfaces (Hoag et al., 2008; Wang et al., 2010; Zuurman et al., 1999). The presence of high levels of hydrophobic lubricants, such as magnesium stearate, the use of long blend times and high blend speeds would then result in softer tablets (Bolhuis and Chowhan, 1996). For a constant number of revolutions, tabletability may also decrease with increasing blender sizes and decreasing loadings in the blender (Kushner and Moore, 2010). Furthermore the transit of the lubricated blend via the hopper and the feed frame of tablet presses may result in additional coverage of lubricant over the MCC particles (Narang et al., 2010; Otsuka et al., 2004). The addition of brittle excipients and/or colloidal silicon dioxide to blends containing MCC can successfully prevent lubricants to occupy the MCC surfaces, and would in turn minimize the negative influence of these lubricants on tablet strength (de Lourdes Garzón and Villafuerte, 2002; van Veen et al., 2005).

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 (Roberts and Rowe, 1985). In other words, the tabletability of MCC always decreases when scaled up from slow development tablet presses to high speed production rotary machines. The Strain Rate Sensitivity of viscoelastic excipients has to be taken into account by the formulation scientists in order to design robust formulations. The MCC content should not be minimized based on low speed trials alone. Sufficient overage should be included to compensate for increased elastic effects at higher speeds. Despite the lower tabletability of brittle excipients, which fragment in a time-independent manner, these excipients have been widely combined with plastically deforming binders to minimize the overall Strain Rate Sensitivity of formulations and to facilitate scale-up.

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 active pharmaceutical ingredients. MCC exhibits a high dilution potential, whereas the broad particle size range provides optimum packing density and coverage of other materials (Bolhuis and Chowhan, 1996; Carlin, 2008).

MCC type 102, having a median particle size of about 100 μm (D_{50} value measured by laser diffraction), presents acceptable flow properties required for successful high speed tableting (Shi et al., 2011; Shlieout et al., 2002). 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 (Albers et al., 2006; Doelker, 1993; Hentzschel et al., 2012; Jivraj et al., 2000). The difference between these common excipients is less pronounced on a volumetric basis (Wallace et al., 1983), which determines die fill. Flowability may of course be further 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 μm (Gamble et al., 2011; Lahdenpää et al., 1997). Another approach may be to combine MCC with other free flowing excipients or glidants (Hwang and Peck, 2001; Jivraj et al., 2000; Patel et al., 1994). Gamble et al. observed that the particle size distributions of coarser grades of MCC do not scale up proportionally (Gamble et al., 2011). MCC types 101, 102 and 200 all have primary particles of about 50 μm 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. Scanning electron micrographs of Avicel® PH-101 and Avicel® PH-102 are shown in Fig. 2 (Gamble et al., 2011).

MCC has a very high intraparticle porosity with approximately 90–95% of the surface area being internal (Doelker, 1993). Therefore surface area is not directly influenced by the nominal particle size (Gamble et al., 2011). This high porosity promotes swelling and disintegration of MCC tablets, which is attributed to the penetration of water into the hydrophilic tablet matrix by means of capillary action of the pores and by a subsequent disruption of the hydrogen bonds. Increasing compaction pressure decreases water penetration into the tablets and increases disintegration time (Bolhuis and Chowhan, 1996; Lahdenpää et al., 1997). Similarly MCC densified via an extrusion process tends to disintegrate very slowly without the presence of a superdisintegrant or of a pore former (Chamsai and Sriamornsak, 2013).

MCC is a stable though hygroscopic material, which can be attributed to the presence of abundant hydroxyl groups on cellulose chains and to the relatively large surface to volume ratio of microfibrils due to their small size (Guy, 2009; Sun, 2008). When exposed to 25 °C and 50% relative humidity, its equilibrium moisture content is approximately 5%. The sorption mechanism involves water molecules tightly bound to accessible hydroxyl groups of the anhydroglucose units, followed by a second less

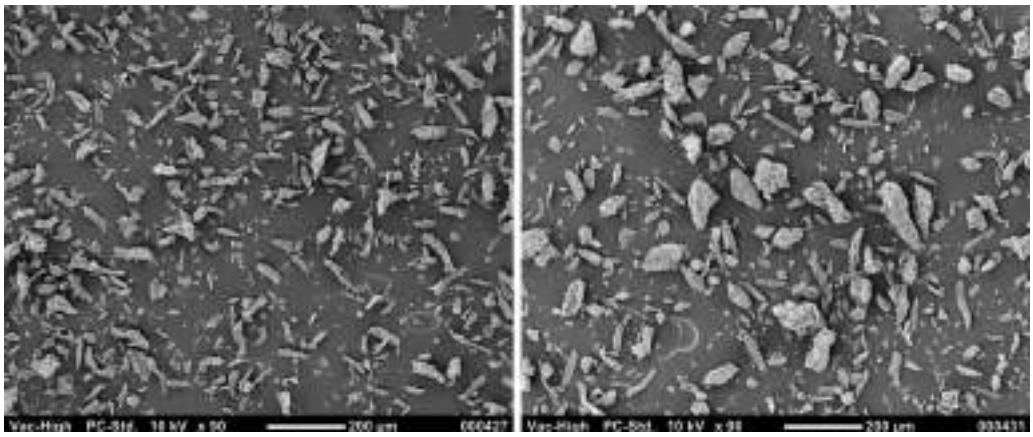

Fig. 2. Scanning electron micrographs of Avicel® PH-101 (left) and Avicel® PH-102 (right).

tightly bound layer, with further additional layers of water. Water is only sorbed in the amorphous regions of MCC, which are more hydrophilic than the crystalline regions (Bolhuis and Chowhan, 1996; Suzuki and Nakagami, 1999). Therefore it is proposed that the total amount of sorbed water is proportional to the fraction of amorphous material and is independent of the surface area (Amidon and Houghton, 1995). The crystallinity of MCC determined by X-ray diffraction and infrared measurement is about 60–80% (Bolhuis and Chowhan, 1996; Sun 2008).

The presence of free hydroxyl groups on the surface of MCC tablets (or pellets) also provide excellent binding sites for cellulosic films, which are common coating polymers (Felton and McGinity, 1999; Khan et al., 2001). This results in improved film adhesion and strength. However the inability of lubricated MCC to create clean and uncontaminated surfaces during compression may negatively impact film adhesion (Rowe, 1977; Wang et al., 2010).

MCC may contain low levels of non-saccharide organic residues. These originate from lignin, a cross-linked biopolymer, which is hydrophobic and aromatic in nature (Crowley and Martini, 2001). As a result of the pulp delignification process, it is possible that lignin breakdown products may be present in MCC. These will be derivatives of the three main monolignols that compose lignin: coniferyl alcohol, sinapyl alcohol and paracoumaryl alcohol. Some other minor components may include cellulose type II, hemicelluloses, sugar residues resulting from the hydrolysis, peroxides from the pulping process, and trace ammonia used to neutralize the acid from the hydrolysis step (Moreton, 2009c; Wasylaschuk et al., 2007). The reducing sugars and the reactive glucose end group on each cellulose chain may also exhibit keto-enol tautomerism via an aldehyde intermediate. Too aggressive a method of aldehyde determination, e.g., long exposure to acids and high temperature, may generate false positives by stripping end glucose groups from the cellulose chain, giving a higher apparent aldehyde content (Wu et al., 2011). Formaldehyde is not used in MCC manufacture; however at a ppm level of scrutiny, all cellulosic excipients will exhibit trace aldehyde reactions.

In addition to various minor components, 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 (Landín et al., 1993a; Shlieout et al., 2002). These different properties or attributes may affect the tabletability of MCC. Several studies confirmed that despite some batch-to-batch variation, the major performance differences were observed between multiple manufacturers (Albers et al., 2006; Doelker, 1993; Doelker et al., 1987; Landín et al., 1993a,b,c; Williams et al., 1997).

Albers et al. evaluated the tableting properties of three batches from five different brands MCC type 101 (Albers et al., 2006). As expected the batches from a single manufacturer were more similar than the samples from various sources; however, statistically significant differences were also observed within single brands of MCC. 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) compared to other brands, this MCC was described as easy flowing as illustrated by a low compressibility index and shear cell flow functions (FFc) values exceeding 4. Particle shape or morphology was not assessed in this study, but one could imagine particle morphology to be influenced partly by the drying conditions and would most probably vary between each manufacturer. No correlation could be found between particle size, specific surface area and tablet strength. However spray dried MCC provided acceptably low tablet friability. It was concluded that the MCC brands cannot be directly substituted by other brands based on the physico-mechanical properties examined.

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 μm, respectively), each type being represented by two batches from 5 different sources (Williams et al., 1997). Spray dried MCCs presented most similarities and negligible batch-to-batch differences, whereas MCCs from other sources, and most certainly processed in a different manner, were less consistent. The importance of completely characterizing and evaluating each MCC product prior to use in a tablet formulation was highlighted. It was also suggested that differences in the compaction properties of various MCCs may impact tablet formulation robustness, and may require the formulation to be further optimized to cope with this variability.

Landín et al. compared four brands of MCC (Landín et al., 1993b). Compositional differences in lignin and hemicelluloses suggested that different woods were used as raw materials, i.e., hardwood versus softwood. These non-cellulose components were also suggestive of manufacturing processes of significantly different intensities, which resulted in variable composition and potentially varying qualities. In a subsequent study, Landin et al. found that lignin content increased the dissolution rate of prednisone (Landín et al., 1993c). Lignin being hydrophobic may alter cellulose–cellulose and/or cellulose–API interactions and hence drug release rate.

Doelker et al. conducted one of the most complete studies by comparing sixteen MCCs from seven manufacturers (Doelker et al., 1987). Differences in packing and in flow properties were

attributed to differences in moisture content, particle shape and particle size distribution. Tabletability also varied among the MCC samples and was attributed partly to differences in moisture content and in the internal structure of the particles caused by processing conditions specific to each manufacturer. The impact of crystallinity and particle morphology was however deemed negligible. Significant differences in lubricant sensitivity, in compressibility and in tablet disintegration were also noted between MCCs from various manufacturers. In contrast, variability between lots from the same manufacturer was smaller. In another paper Doelker concluded that large differences exist among various MCCs, even if all of them comply with compendial specifications (Doelker, 1993). Therefore substitution of one product for another must be validated.

3. Understanding excipient variability and performance

In light of the quality by design (QbD) initiative, detailed understanding of the impact of raw material variability on the performance and manufacturability of new drug products is now a significant concern (Kushner, 2013; Kushner et al., 2011). The potential impact of APIs and of their variability is undeniable. However excipients form also an important and maybe critical part of any pharmaceutical formulation (Moreton, 2010). Unfortunately the principles that govern how excipient properties influence the critical quality attributes (CQAs) of a drug product are rarely understood. The interactions of excipient attributes with other raw materials and with manufacturing processes render the situation even more complex (Wang et al., 2013). The creation of excipient databases, such as the PharmaHUB, and review articles may help closing this gap by providing prior knowledge to formulation scientists.

An excipient is included in a drug product to impart functionality. Excipient functionality can be defined as a desirable property that aids and/or improves the manufacture, quality, or performance of the drug product (IPEC, 2008). Functionality is a broad, qualitative, and descriptive term for the general purpose or role an excipient serves in a formulation (Sheehan, 2011; USP37-NF32, 2014a). Excipient performance refers to the outcome in the finished product, which is not only determined by the intrinsic properties of an excipient but also depends on formulation and processing effects that influence an excipient's ability to perform its intended functional purpose (Carlin and Moreton, 2010; Sheehan, 2011).

MCC, as any pharmaceutical excipient, needs to meet its compendial specifications, i.e., a minimum set of specifications for identity, quality, and purity (Moreton, 2009a; Sheehan, 2012). However, since these tests do not consider the application nor the purpose of the excipient, Pharmacopoeial attributes might not be the critical material attributes (CMAs) (Albers et al., 2006; Carlin, 2012; Carlin and Moreton, 2010; Pifferi et al., 1999; Whiteman and Yarwood, 1988). Considering it may be difficult for excipient suppliers to provide an ideal set of samples to the pharmaceutical manufacturers to adequately investigate the impact of excipient material properties on drug product performance (Kushner et al., 2014; Moreton, 2009b), some excipient variability may nonetheless be captured by the compendial attributes listed on the certificate of analysis (CoA) (Kushner, 2013; Moreton, 2009c). However it is important to realize that, for high volume continuously produced excipients, CoA values may understate the true variability as they may be averages of in-process data or derived from composite samples, i.e., blends of in-process samples.

Since the relevance of excipient attributes may differ in each formulation and manufacturing process (Díaz Ramírez and Robles, 2010; Sheehan and Amidon, 2011), the users are responsible to identify the critical material attributes of the excipient for their particular application, and if necessary to set the appropriate specifications (Carlin et al., 2007; Moreton, 2009a; Tho and Bauer-Brandl, 2011). To ensure consistent excipient performance in a particular application, one should fully understand the physico-chemical properties, the composition, the method of manufacture, and the supplier process capability for each excipient (Carlin et al., 2007; Moreton, 2009a). Only then can the appropriate Control Strategies be established to guarantee that the drug product critical quality attributes (CQAs) are maintained throughout the product life cycle (Sheehan, 2012). In order to achieve this level of understanding, early discussion with excipient suppliers is advisable (IPEC, 2008).

According to the European Pharmacopoeia (Ph.Eur. 8.0, 2014) potential CMAs, called functionality-related characteristics (FRCs), of MCC used as binder, diluent or disintegrant may include particle size distribution and flowability. The non-mandatory USP information chapter on excipient performance lists additional physical properties relevant to tablet diluents, and therefore to MCC, and includes: (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 (USP37-NF32, 2014a). This list is not exhaustive. Additional methods, together with a set of verified physical models that link physical properties to processing behavior and final product performance, could provide scientists with comprehensive databases of properties for commonly used excipients (Hlinak et al., 2006). Although the compaction properties of tablet diluents are considered as relevant, and guidelines can be found to assess tablet strength (Podczeck, 2012; USP37-NF32, 2014b), no recommendations are currently made as to how to prepare powder samples or blends and how to compress them, which makes comparisons with literature values difficult (Edge et al., 2000). Standardized compaction tests could be useful to evaluate dry binders, such as MCC, and to ensure excipient suppliers and users speak the same language while assessing excipient performance.

4. Potential critical material attributes of microcrystalline cellulose

The interdependence of material properties and their potential impact on product attributes and processing behavior has been summarized by Hlinak et al., as shown in Table 1 (Hlinak et al., 2006).

For example, powder flow is influenced by particle size and shape, bulk density, surface area and several other material properties. Identifying and understanding which property is truly critical is not an easy task, especially when these properties are often interdependent. It can be expected that particle size, surface area and bulk density are correlated. The use of multivariate analysis, such as principal component analysis and multiple regression, is preferred to correlate excipients attributes with their performance (Gabrielsson et al., 2002; Haware et al., 2009; Huang et al., 2009; Klevan et al., 2010; Kothari et al., 2002; Kushner, 2013; Moore, 2013; Tho and Bauer-Brandl, 2012).

In order to gather prior knowledge, the following sections summarize studies on MCC and highlight some of its potential critical material attributes.

4.1. Moisture content

A number of studies have confirmed that the moisture content of MCC influences compaction properties, tensile strength, and viscoelastic properties (Amidon and Houghton, 1995; Doelker,

Table 1
Potential impact of material properties on quality attributes and processing behavior (list is not exhaustive).

Property	Impact						
	Flow	Blending	Wetting	Drying	Mechanical	Dissolution	Stability
Particle size distribution	X	X	X	X	X	X	X
Particle shape distribution	X						
True density				X	X		
Bulk density – poured and tapped	X		X		X		
Pore size distribution			X	X		X	
Surface area	X	X	X	X	X	X	X
Surface energy	X	X	X				
Flow	X						
Cohesiveness	X	X					
Internal friction	X				X		
Wall friction	X				X		
Amorphous content			X				X
Elastic modulus					X		
Tabletability					X		
Brittleness					X		
Static charge	X	X					
Hygroscopicity	X			X			X

1993; Sun 2008). 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 (Bolhuis and Chowhan, 1996; Hoag et al., 2008; Nokhodchi, 2005). 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 (Nokhodchi, 2005; Patel et al., 2006). Because compressibility of MCC depends on moisture content, MCC powders compressed to the same pressure may not result in the same compact porosity. Indeed the compaction pressure required to produce a compact at a certain porosity (or solid fraction) decreases with increasing moisture content.

Sun observed that the compaction properties of MCC were largely insensitive to moisture variation below 3% water (Sun, 2008). However an increase of moisture, up to an optimum level, will typically increase the tablet strength of most excipients. This may be due to the fact that bound water vapor layers reduce interparticular surface distances and increase intermolecular attraction forces (Patel et al., 2006). Moisture in a material may also exert Van der Waals' forces. Above 3% water, which corresponds to monolayer coverage, bonding strength decreases due to the disruption of the hydrogen bonds which cross-link the hydroxyl groups on the cellulose chains (Doelker, 1993). It can also be said that the presence of free water reduces intermolecular attractive forces and allows separation of the particles. However, thanks to the plasticizing effect of water and its positive effect on bonding surface area, tabletability remains constant or increases for moisture contents between about 3 and 5%. It has been suggested by Sun, Amidon and Houghton that the mechanical properties of MCC significantly change for moisture contents exceeding 5–6%. Above this level, the decrease in bonding strength outplays the increase in bonding area and results in a decrease in tabletability. A transition from the glassy state to the rubbery state has also been proposed (Amidon and Houghton, 1995; Sun, 2008).

The storage conditions of the MCC compacts also play an important role, as an increase in relative humidity will negatively impact tablet strength (Williams et al., 1997). However this softening is often reversible when tablets are removed from the humid environment (Carlin, 2008; Gohel, 2005).

The two fundamental forces that can affect powder flow are cohesion and friction (Nokhodchi, 2005). As moisture content increases, frictional forces and electrostatic charges between particles may be reduced. Moisture may also increase cohesion due to the creation of liquid or even solid bridges between particles. In the case of MCC, significant changes in flowability were observed as powder cohesiveness, described by the compressibility index and the shear cell, increased with increasing moisture contents (Amidon and Houghton, 1995).

These observations support an upper moisture content specification of 5%, as it is the case with some MCC grades. However most microcrystalline cellulose suppliers align their specifications to the USP monograph (NF32), which states an upper loss on drying limit of 7%.

4.2. Particle size

Particle size has very little effect on the tabletability of neat MCC, i.e., not lubricated nor blended with other excipients or active pharmaceutical ingredients (APIs) (Almaya and Aburub, 2008; Gamble et al., 2011; Jivraj et al., 2000; Pesonen and Paronen, 1990). Considering that the brittle-ductile transition diameter (D_{crit}) of MCC is 1949 μm, standard MCC grades, having particle sizes below D_{crit}, should all deform plastically when compression pressure exceeds yield pressure (Narayan and Hancock, 2005). Coarser grades of MCC, characterized by a smaller envelope surface area, have been reported to be more lubricant sensitive than finer MCC (Doelker et al., 1987; Gamble et al., 2011; Hwang and Peck, 2001; Whiteman and Yarwood, 1988).

In complete formulations finer MCCs would therefore promote tablet (compact) strength (Herting and Kleinebudde, 2007; Kushner et al., 2011). However reducing the particle size of MCC will certainly affect its flowability, as a consequence of its increased cohesiveness.

Kushner et al. confirmed that variability in excipient particle size may impact not only tablet hardness, friability and disintegration, but also content uniformity (Kushner, 2013). Using coarser MCCs may improve flowability and reduce tablet weight variation (Hasegawa, 2002); however, due to the increased risk of segregation, content uniformity will not always be better. Blends of various MCC types, having different particle size distributions, may be considered to design robust formulations having the optimum compromise between powder flow and tabletability (Lahdenpää et al., 1997).

In addition to the above, Hlinak et al. suggested that particle size may also impact wetting properties, dissolution of the API and stability of drug products (Hlinak et al., 2006). As such particle size may be considered as one of the most important material attributes.

4.3. 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 (Obae et al., 1999). Rod-shaped (fibrous) particles with higher L/D ratios resulted in higher tablet strengths when compared to round-shaped particles. Other physico-chemical properties of MCC did not correlate well with tablet tensile strength. These properties included moisture content, bulk density, and specific surface area. Even though not discussed, Obae et al. also indirectly illustrated the reduction of bulk density and flowability and the increase of specific surface area as the L/D ratio increased, i.e., as particles were more fibrous. In some cases MCC morphology may also impact drug dissolution (Friedman, 2011).

4.4. Bulk density

Many direct compression grade excipients are spray-dried and are therefore characterized by a porous structure and a relatively low bulk density. This increased porosity (lower density) facilitates compressibility, i.e., the densification of a powder bed due to the application of a stress (Patel et al., 2006). The improved compressibility of plastically deforming materials, such as MCC, might then result in improved tabletablity as a result of the increased bonding surface area (Abdel-Hamid et al., 2011). The higher roughness of low density MCC particles may also contribute to particle interlocking (Liao et al., 2012). Low bulk density MCC will have a higher dilution potential and may better counteract the poor tableting properties of APIs. MCC densified by pre-processes such as granulation or drying is typically less tabletable than the original more porous MCC (Pönni et al., 2012; Westermarck et al., 1999). It can therefore be generalized that a decrease in bulk density improves tabletability; however, it will often hinder flowability (Hwang and Peck, 2001; Sonnergaard, 2006).

4.5. Specific surface area

The specific surface area and particle surface rugosity of microcrystalline cellulose may positively impact its tabletability, potentially due to the numerous hydrogen bonds between the large bonding surface areas of adjacent particles and to the mechanical interlocking of irregular particles (Nyström et al., 1993; Pesonen and Paronen, 1990; Wu et al., 2001). However in the case of direct compression binders, tabletability has to be balanced with flowability. High specific surface area and rugosity may improve cohesion but it can be expected to negatively impact powder flow.

4.6. Degree of polymerization

There is no obvious correlation between the degree of polymerization (DP) of MCC and its tabletability. It is merely an identity test to distinguish MCC ($DP < 350$) from powdered cellulose ($DP > 440$). Dybowski showed that the origin of the raw materials and the production method more decisively influence the characteristics of MCC than DP (Dybowski, 1997). For the manufacturer, DP is only a criterion used to help guide the hydrolysis of MCC, whereas for the user DP is a manner to distinct between MCC and powdered cellulose.

Schlieout et al. claimed a correlation between DP and tablet hardness based on two out of only three data points (Shlieout et al., 2002). There was no difference between MCC with DPs of 244 and 299 but both were more tabletable than MCC with a DP of 190. Liao et al. studied 16 MCC samples, including the high density grades “301” and “302”, and concluded that DP positively impacts tabletability (Liao et al., 2012). High bulk density grades are obtained from special wood pulps characterized by lower level-off DP, and should not be directly compared with standard grades.

This reflects the lack of distinction between degree of polymerization (DP) and level-off degree of polymerization (LODP). LODP is typical of a particular raw material, commonly in the range 200–300 (Doelker, 1993), after which it is difficult to further hydrolyze the MCC. DP values higher than the level-off degree of polymerization plateau are more difficult to control due to their greater sensitivity to hydrolysis conditions.

Above the LODP MCC retains more of the fibrous cellulose characteristics, which would result in a lower bulk density, may improve tabletability but would hinder powder flow (Wu et al., 2001). 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 (Carlin, 2008). Within a single MCC grade, and in order to meet DP and bulk density specifications, MCC manufacturers need to tightly control the hydrolysis conditions to avoid producing out of specification (OOS) material.

4.7. Crystallinity

The wide range of reported values of degree of crystallinity for microcrystalline cellulose (60–80%) could be explained by the different methods used to determine this parameter, including X-ray diffraction and infrared spectroscopy, but also by the method of data manipulation and analysis (Landín et al., 1993a; Rowe et al., 1994).

When a single method is selected, it has been reported that crystallinity does not vary much between various MCCs (Pesonen and Paronen, 1990; Suzuki and Nakagami, 1999; Williams et al., 1997). This was confirmed by similar sorption characteristics when exposed to elevated humidity levels. Indeed considering that the amorphous region is more hydrophilic, lower degrees of crystallinity should result in higher equilibrium moisture contents.

Modifying the hydrolysis conditions, including temperature, time and acid concentration, also have very little impact on the degree of crystallinity, i.e., the regularity of the arrangement of the cellulose polymer chains (Shlieout et al., 2002; Wu et al., 2001). 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 (Landín et al., 1993a), which is consistent with the method of MCC manufacture where the acid preferentially attacks the (pulp dependent) amorphous regions.

The impact of crystallinity on tabletability is far from obvious (Gohel, 2005). Suzuki and Nakagami were able to reduce crystallinity, from about 65% down to 12% (as measured by X-ray diffraction), by pulverizing MCC using a vibrational rod mill (Suzuki and Nakagami, 1999). Only then was it possible to observe a reduction of tabletability. Reducing crystallinity to about 37% reduced the dissolution rate of acetaminophen tablets, however dissolution rates were increased compared to a standard MCC when crystallinity became less than 26%.

The total amount of sorbed water in MCC is proportional to the fraction of amorphous material (Amidon and Houghton, 1995; Bolhuis and Chowhan, 1996; Nokhodchi, 2005). 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 (Vehovec et al., 2012).

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 (Pifferi et al., 1999).

5. Conclusions

Thanks to its ability to economically produce large batches of tablets, DC remains one of the preferred techniques to produce oral solid dosage forms. However DC is directly impacted by the raw material attributes since these are not altered by preceding process steps. MCC is widely recognized as one of the best tablet diluents. Considering the scale of manufacture, MCC presents some inevitable variability, which can be amplified by sourcing from multiple sites or from multiple suppliers.

The deformation mechanism and the physico-chemical properties of MCC dictate its performance. The plasticity of MCC together with its relatively low bulk density, high surface area and high hygroscopicity explains its unique binding properties. When compared to brittle excipients, MCC is more lubricant sensitive, strain rate sensitive and cohesive.

QbD is driving the pharmaceutical industry to better understand the impact of raw material variability on the performance and manufacturability of new drug products. Considering the number of excipients in formulations, the number of physico-chemical parameters that may be studied, the difficulty of obtaining or producing representative samples, and the interactions with APIs and manufacturing processes, identifying excipients' CMAs is not an easy task.

There is evidence that moisture content, particle size, particle shape, bulk density and surface area do influence the tableting properties of MCC, i.e., tabletability and flowability. However since a criticality can only be confirmed in a specific formulation and a given application, drug manufacturers and excipients suppliers need to work together in order to promote excipients and processes understanding.

References

Abdel-Hamid, S., Alshihabi, F., Betz, G., 2011. Investigating the effect of particle size and shape on high speed tableting through radial die-wall pressure monitoring. Int. J. Pharm. 413, 29–35.

Albers, J., Knop, K., Kleinebudde, P., 2006. Brand-to-brand and batch-to-batch uniformity of microcrystalline cellulose in direct tableting with a pneumo-hydraulic tablet press. Pharm. Ind. 68, 1420–1428.

Almaya, A., Aburub, A., 2008. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. AAPS PharmSciTech 9, 414–418.

Amidon, G.E., Houghton, M.E., 1995. The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. Pharm. Res. 12, 923–929.

Bala, R., Khanna, S., Pawar, P.K., 2013. Formulation and optimization of fast dissolving intraoral drug delivery system for clobazam using response surface methodology. J. Adv. Pharm. Technol. Res. 4, 151–159.

Bolhuis, G.K., Armstrong, N.A., 2006. Excipients for direct compaction—an update. Pharm. Dev. Technol. 11, 111–124.

Bolhuis, G.K., Chowhan, Z.T., 1996. Materials for direct compaction. In: Alderborn, G., Alderborn, G., Nyström, C., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology. Marcel Dekker, Inc., pp. 419–500.

Carlin, B., 2008. Direct compression and the role of filler-binders. In: Augsburger, L.L., Augsburger, L.L., Hoag, S.W., Hoag, S.W. (Eds.), Pharmaceutical Dosage Forms: Tablets. Informa, pp. 173–216.

Carlin, B., 2012. Quality risk management of compliant excipients. J. Excipients Food Chem. 3, 143–153.

Carlin, B., Carter, D., Griffiths, M., Larner, G., Moore, K., Rothman, B., Schoneker, D., Sheehan, C., Uppoor, R., Walsh, P., Wiens, R., 2007. Joint position paper on pharmaceutical excipient testing and control strategies. Pharm. Technol. http://www.pharmtech.com/pharmtech/Article/Joint-Position-Paper-on-Pharmaceutical-Excipient-T/ArticleStandard/Article/detail/452937.

Carlin, B., Moreton, R.C., 2010. Flexible approaches to accommodate excipient variability using the principles of QbD. Pharm. Technol. s36–s39. http://www.pharmtech.com/pharmtech/Standards+%26+Regulation/Flexible-Approaches-to-Accommodate-Excipient-Varia/ArticleStandard/Article/detail/668160.

Chamsai, B., Sriamornsak, P., 2013. Novel disintegrating microcrystalline cellulose pellets with improved drug dissolution performance. Powder Tech. 233, 278–285.

Crowley, P.J., Martini, L.G., 2001. Drug-excipient interactions. Pharm.Technol. Eur. 13, 26–34.

de Lourdes Garzón, M., Villafuerte, L., 2002. Compactibility of mixtures of calcium carbonate and microcrystalline cellulose. Int. J. Pharm. 231, 33–41.

Díaz Ramírez, C.C., Robles, L.V., 2010. Surrogate functionality of celluloses as tablet excipients. Drug Dev. Ind. Pharm. 36, 1422–1435.

Doelker, E., 1993. Comparative compaction properties of various microcrystalline cellulose types and generic products. Drug Dev. Ind. Pharm. 19, 2399–2471.

Doelker, E., Mordier, D., Iten, H., Humbert-Droz, P., 1987. Comparative tableting properties of sixteen microcrystalline celluloses. Drug Dev. Ind. Pharm. 13, 1847–1875.

Dybowski, U., 1997. Does polymerisation degree matter? Manuf. Chem. Aer. N. 19–21.

Edge, S., Steele, D.F., Chen, A., Tobyn, M.J., Staniforth, J.N., 2000. The mechanical properties of compacts of microcrystalline cellulose and silicified microcrystalline cellulose. Int. J. Pharm. 200, 67–72.

Felton, L.A., McGinity, J.W., 1999. Adhesion of polymeric films to pharmaceutical solids. Eur. J. Pharm. Biopharm. 47, 3–14.

Ferrari, F., Bertoni, M., Bonferoni, M.C., Rossi, S., Caramella, C., Nyström, C., 1996. Investigation on bonding and disintegration properties of pharmaceutical materials. Int. J. Pharm. 136, 71–79.

FMC, 2013. Fun facts about Avicel® microcrystalline cellulose also known as cellulose gel. http://www.fmcbiopolymer.com/Food/Home/News/FiftyYearsofAvicel.aspx (accessed 17.09.13).

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

Gabrielsson, J., Lindberg, N.-O., Lundstedt, T., 2002. Multivariate methods in pharmaceutical applications. J. Chemom. 16, 141–160.

Gamble, J.F., Chiu, W.S., Tobyn, M., 2011. Investigation into the impact of sub-populations of agglomerates on the particle size distribution and flow properties of conventional microcrystalline cellulose grades. Pharm. Dev. Technol. 16, 542–548.

Gohel, M.C., 2005. A review of co-processed directly compressible excipients. J. Pharm. Pharm. Sci. 8, 76–93.

Guy, A., 2009. Cellulose, microcrystalline, In: Rowe, R.C., Rowe, R.C., Sheskey, P.J., Sheskey, P.J., Quinn, M.E., Quinn, M.E. (Eds.), Handbook of Pharmaceutical Excipients. 6 Pharmaceutical Press (UK), American Pharmacists Association (USA), pp. 129–133 ISBN 978 0 85369 792 3 (UK), ISBN 978 1 58212 135 2 (USA).

Hasegawa, M., 2002. Direct compression: microcrystalline cellulose grade 12 versus classic grade 102. Pharm. Technol. 26, 50–60. http://www.pharmtech.com/pharmtech/data/articlestandard//pharmtech/192002/18599/article.pdf.

Haware, R.V., Tho, I., Bauer-Brandl, A., 2009. Application of multivariate methods to compression behavior evaluation of directly compressible materials. Eur. J. Pharm. Biopharm. 72, 148–155.

Hentzschel, C.M., Sakmann, A., Leopold, C.S., 2012. Comparison of traditional and novel tableting excipients: physical and compaction properties. Pharm. Dev. Technol. 17, 649–653.

Herting, M.G., Kleinebudde, P., 2007. Roll compaction/dry granulation: effect of raw material particle size on granule and tablet properties. Int. J. Pharm. 338, 110–118.

Hlinak, A.J., Kuriyan, K., Morris, K.R., Reklaitis, G.V., Basu, P.K., 2006. Understanding critical material properties for solid dosage form design. J. Pharm. Innov. 1, 12–17.

Hoag, S.W., 2011. Excipient Variability and Functionality Testing. ExcipientFest, Baltimore, Maryland. http://ipecamericas.org/sites/default/files/ctools/ef11May11BaltimoreLunchSpeakerPMSteveHoagUMD.pdf.

Hoag, S.W., Dave, V.S., Moolchandani, V., 2008. Compression and compaction. In: Augsburger, L.L., Augsburger, L.L., Hoag, S.W., Hoag, S.W. (Eds.), Pharmaceutical Dosage Forms: Tablets. Informa, pp. 555–630.

Huang, J., Kaul, G., Cai, C., Chatlapalli, R., Hernandez-Abad, P., Ghosh, K., Nagi, A., 2009. Quality by design case study: an integrated multivariate approach to drug product and process development. Int. J. Pharm. 382, 23–32.

Hwang, R.-C., Peck, G.R., 2001. A systematic evaluation of the compression and tablet characteristics of various types of microcrystalline cellulose. Pharm. Technol. 112–132.

ICH, 2005. Quality Risk Management Q9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf.

ICH, 2009. Pharmaceutical Development Q8(R2). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.

Ilic, I., Govedarica, B., Sibanc, R., Dreu, R., Srcic, S., 2013. Deformation properties of pharmaceutical excipients determined using an in-die and out-die method. Int. J. Pharm. 446, 6–15.

IPEC, 2008. Qualification of excipients for pharmaceutical use. 1–56. http://www.ipec-europe.org/UPLOADS/2008_Qualification_of_Excipt_for_Pharma_Use_-_PDF_final(1).pdf.

Jivraj, M., Martini, L.G., Thomson, C.M., 2000. An overview of the different excipients useful for the direct compression of tablets. Pharm. Sci. Technol. Today 3, 58–63.

Kása, P., Bajdik, J., Zsigmond, Z., Pintye-Hódi, K., 2009. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chem. Eng. Process. Process Intensification 48, 859–863.

Khan, H., Fell, J.T., Macleod, G.S., 2001. The influence of additives on the spreading coefficient and adhesion of a film coating formulation to a model tablet surface. Int. J. Pharm. 227, 113–119.

Klevan, I., Nordstrom, J., Tho, I., Alderborn, G., 2010. A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials. Eur. J. Pharm. Biopharm. 75, 425–435.

Kothari, S.H., Kumar, V., Banker, G.S., 2002. Comparative evaluations of powder and mechanical properties of low crystallinity celluloses, microcrystalline celluloses, and powdered celluloses. Int. J. Pharm. 232, 69–80.

Kushner, J., 2013. Utilizing quantitative certificate of analysis data to assess the amount of excipient lot-to-lot variability sampled during drug product development. Pharm. Dev. Technol. 18, 333–342.
Kushner, J., Langdon, B.A., Hicks, I., Song, D., Li, F., Kathiria, L., Kane, A., Ranade, G., Agarwal, K., 2014. A quality-by-design study for an immediate-release tablet platform: examining the relative impact of active pharmaceutical ingredient properties, processing methods, and excipient variability on drug product quality attributes. J. Pharm. Sci. 103, 527–538.
Kushner, J., Langdon, B.A., Hiller, J.I., Carlson, G.T., 2011. 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. J. Pharm. Sci. 100, 2222–2239.
Kushner, J., Moore, F., 2010. Scale-up model describing the impact of lubrication on tablet tensile strength. Int. J. Pharm. 399, 19–30.
Lahdenpää, E., Niskanen, M., Yliruusi, J., 1997. Crushing strength, disintegration time and weight variation of tablets compressed from three Avicelä PH grades and their mixtures. Eur. J. Pharm. Biopharm. 43, 315–322.
Landín, M., Martínez-Pacheco, R., Gómez-Amoza, J.L., Souto, C., Concheiro, A., Rowe, R.C., 1993a. Effect of batch variation and source of pulp on the properties of microcrystalline cellulose. Int. J. Pharm. 91, 133–141.
Landín, M., Martínez-Pacheco, R., Gómez-Amoza, J.L., Souto, C., Concheiro, A., Rowe, R.C., 1993b. Effect of country of origin on the properties of microcrystalline cellulose. Int. J. Pharm. 91, 123–131.
Landín, M., Martínez-Pacheco, R., Gómez-Amoza, J.L., Souto, C., Concheiro, A., Rowe, R.C., 1993c. Influence of microcrystalline cellulose source and batch variation on the tabletting behaviour and stability of prednisone formulations. Int. J. Pharm. 91, 143–149.
Liao, Z., Zhang, N., Zhao, G., Zhang, J., Liang, X., Zhong, S., Wang, G., Chen, X., 2012. Multivariate analysis approach for correlations between material properties and tablet tensile strength of microcrystalline cellulose. Pharmazie 67, 774–780.
McCormick, D., 2005. Evolutions in direct compression. Pharm. Technol. 52–65. http://www.pharmtech.com/pharmtech/data/articlestandard/pharmtech/152005/155374/article.pdf.
Moore, C.M.V., 2013. Multivariate tools for modern pharmaceutical control—FDA perspective. IFPAC Annual Meeting. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM359262.pdf.
Moreton, C., 2006. Functionality and performance of excipients. Pharm. Technol. http://www.pharmtech.com/pharmtech/Excipients/Functionality-and-Performance-of-Excipients/ArticleStandard/Article/detail/378395.
Moreton, C., 2009a. Functionality and performance of excipients in a quality-by-design world, part 1. Am. Pharm. Rev. 12, 1–4.
Moreton, C., 2009b. Functionality and performance of excipients in a quality-by-design world, part 2: excipient variability, QbD and robust formulations. Am. Pharm. Rev. 12, 1–3.
Moreton, C., 2009c. Functionality and performance of excipients in a quality-by-design world, part 4: obtaining information on excipient variability for formulation design space. Am. Pharm. Rev. 12, 28–33.
Moreton, C., 2010. Functionality and performance of excipients in a quality-by-design world, part VIII: excipient specifications. Am. Pharm. Rev. 13, 46–50. http://www.americanpharmaceuticalreview.com/Specialty/Formulation_Development/Featured-Articles/117308-Functionality-and-Performance-of-Excipients-in-Quality-by-Design-World-Part-VIII-Excipient-Specifications/.
Mostafa, H.F., Ibrahim, M.A., Sakr, A., 2013. Development and optimization of dextromethorphan hydrobromide oral disintegrating tablets: effect of formulation and process variables. Pharm. Dev. Technol. 18, 454–463.
Narang, A.S., Rao, V.M., Guo, H., Lu, J., Desai, D.S., 2010. Effect of force feeder on tablet strength during compression. Int. J. Pharm. 401, 7–15.
Narayan, P., Hancock, B.C., 2005. The influence of particle size on the surface roughness of pharmaceutical excipient compacts. Mater. Sci. Eng.: A 407, 226–233.
Nokhodchi, A., 2005. An overview of the effect of moisture on compaction and compression. Pharm. Technol. 46–66.
Nyström, C., Alderborn, G., Duberg, M., Karehill, P.-G., 1993. Bonding surface area and bonding mechanism – two important factors for the understanding of powder compactability. Drug Dev. Ind. Pharm. 19, 2143–2196.
Obae, K., Iijima, H., Imada, K., 1999. Morphological effect of microcrystalline cellulose particles on tablet tensile strength. Int. J. Pharm. 182, 155–164.
Otsuka, M., Yamane, I., Matsuda, Y., 2004. Effects of lubricant mixing on compression properties of various kinds of direct compression excipients and physical properties of the tablets. Adv. Powder Technol. 15, 477–493.
Patel, N.K., Upadhyay, A.H., Bergum, J.S., Reier, G.E., 1994. An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station tablet press. Int. J. Pharm. 110, 203–210.
Patel, S., Kaushal, A.M., Bansal, A.K., 2006. Compression physics in the formulation development of tablets. Crit. Rev. Ther. Drug Carrier Syst. 23, 1–65.
Peck, G.E., Anderson, N.R., Banker, G.S., 1990. Principles of improved tablet production system design. In: Liebermann, H.A., Liebermann, H.A., Lachman, L., Lachman, L., Schwartz, J.B., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Froms: Tablets. Lea & Febiger, pp. 1–76.
Pesonen, T., Paronen, P., 1990. The effect of particle and powder properties on the mechanical properties of directly compressed cellulose tablets. Drug Dev. Ind. Pharm. 16, 31–54.
Ph.Eur. 8.0, 2014. Microcrystalline Cellulose. European Pharmacopoeia, pp. 1824–1828.
Pifferi, G., Santoro, P., Pedrani, M., 1999. Quality and functionality of excipients. Farmaco 54, 1–14.
Podczeck, F., 2012. Methods for the practical determination of the mechanical strength of tablets—from empiricism to science. Int. J. Pharm. 436, 214–232.
Pönni, R., Vuorinen, T., Kontturi, E., 2012. Proposed nano-scale coalescence of cellulose in chemical pulp fibers during technical treatments. BioResources 7, 6077–6108.
Roberts, R.J., Rowe, R.C., 1985. The effect of punch velocity on the compaction of a variety of materials. J. Pharm. Pharmacol. 37, 377–384.
Rowe, R.C., 1977. The adhesion of film coatings to tablet surfaces—the effect of some direct compression excipients and lubricants. J. Pharm. Pharmacol. 29, 723–726.
Rowe, R.C., McKillop, A.G., Bray, D., 1994. The effect of batch and source variation on the crystallinity of microcrystalline cellulose. Int. J. Pharm. 101, 169–172.
Rubinstein, M.H., 1988. Tablets. In: Aulton, M.E., Aulton, M.E. (Eds.), Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, pp. 304–321.
Saigal, N., Baboota, S., Ahuja, A., Ali, J., 2009. Microcrystalline cellulose as a versatile excipient in drug research. J. Young Pharm. 1, 6–12.
Sheehan, C., 2011. USP Excipient Performance Chapter: Excipient QbD as it Relates to Performance and Functionality. ExcipientFest, Baltimore, Maryland. http://ipecamericas.org/sites/default/files/ctools/ef11May11HallA-2CatherineSheehanUSP.pdf.
Sheehan, C., 2012. Understanding the role of excipient functional category & performance-related tests in a quality-by-design framework. Drug Dev. Deliv. 12, http://www.drug-dev.com/Main/Back-Issues/Understanding-the-Role-of-Excipient-Functional-Cat-340.aspx.
Sheehan, C., Amidon, G.E., 2011. Compendial standards and excipient performance in the QbD era: USP excipient performance chapter. Am. Pharm. Rev. 14. http://www.americanpharmaceuticalreview.com/Featured-Articles/37322-Compendial-Standards-and-Excipient-Performance-in-the-QbD-Era-USP-Excipient-Performance-Chapter-1059/.
Shi, L., Chattoraj, S., Sun, C.C., 2011. Reproducibility of flow properties of microcrystalline cellulose—Avicel PH102. Powder Tech. 212, 253–257.
Shlieout, G., Arnold, K., Muller, G., 2002. Powder and mechanical properties of microcrystalline cellulose with different degrees of polymerization. AAPS PharmSciTech 3, E11.
Sonnergaard, J.M., 2006. Quantification of the compactibility of pharmaceutical powders. Eur. J. Pharm. Biopharm. 63, 270–277.
Sun, C.C., 2008. Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose. Int. J. Pharm. 346, 93–101.
Suzuki, T., Nakagami, H., 1999. Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets. Eur. J. Pharm. Biopharm. 47, 225–230.
Tho, I., Bauer-Brandl, A., 2011. Quality by design (QbD) approaches for the compression step of tableting. Expert Opin. Drug Deliv. 8, 1631–1644.
Tho, I., Bauer-Brandl, A., 2012. Chemometrics (PCA) in pharmaceutics: tablet development, manufacturing and quality assurance. In: Sanguansat, P., Sanguansat, P. (Eds.), Principal Component Analysis – Multidisciplinary Applications. InTech.
USP37-NF32, 2014a. Excipient Performance. U.S. Pharmacopeia, pp. 752–769.
USP37-NF32, 2014b. Tablet Breaking Force. U.S. Pharmacopeia, pp. 1146–1148.
van Veen, B., Bolhuis, G.K., Wu, Y.S., Zuurman, K., Frijlink, H.W., 2005. Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose. Eur. J. Pharm. Biopharm. 59, 133–138.
Vehovec, T., Gartner, A., Planinsek, O., Obreza, A., 2012. Influence of different types of commercially available microcrystalline cellulose on degradation of perindopril erbumine and enalapril maleate in binary mixtures. Acta Pharm. 62, 515–528.
Wallace, J.W., Capozzi, J.T., Shangraw, R.F., 1983. Performance of pharmaceutical filler/binders as related to methods of powder characterization. Pharm. Technol. 7, 94–104.
Wang, J., Wen, H., Desai, D., 2010. Lubrication in tablet formulations. Eur. J. Pharm. Biopharm. 75, 1–15.
Wang, T., Alston, K.M., Wassgren, C.R., Mockus, L., Catlin, A.C., Fernando, S.R., Fernando, S., Basu, P.K., Hoag, S.W., 2013. The creation of an excipient properties database to support quality by design (QbD) formulation development. Am. Pharm. Rev. http://www.americanpharmaceuticalreview.com/Featured-Articles/140508-The-Creation-of-an-Excipient-Properties-Database-to-Support-Quality-by-Design-QbD-Formulation-Development/.
Wasylaschuk, W.R., Harmon, P.A., Wagner, G., Harman, A.B., Templeton, A.C., Xu, H., Reed, R.A., 2007. Evaluation of hydroperoxides in common pharmaceutical excipients. J. Pharm. Sci. 96, 106–116.
Westermarck, S., Juppo, A.M., Kervinen, L., Yliruusi, J., 1999. Microcrystalline cellulose and its microstructure in pharmaceutical processing. Eur. J. Pharm. Biopharm. 48, 199–206.
Whiteman, M., Yarwood, R.J., 1988. Variations in the properties of microcrystalline cellulose from different sources. Powder Tech. 54, 71–74.
Williams, R.O., Sriwongjanya, M., Barron, M.K., 1997. Compaction properties of microcrystalline cellulose using tableting indices. Drug Dev. Ind. Pharm. 23, 695–704.
Wu, J.-S., Ho, H.-O., Sheu, M.-T., 2001. A statistical design to evaluate the influence of manufacturing factors on the material properties and functionalities of microcrystalline cellulose. Eur. J. Pharm. Sci. 12, 417–425.
Wu, Y., Levons, J., Narang, A., Raghavan, K., Rao, V., 2011. Reactive impurities in excipients: profiling, identification and mitigation of drug-excipient incompatibility. AAPS PharmSciTech 12, 1248–1263.
Zuurman, K., Van der Voort Maarschalk, K., Bolhuis, G.K., 1999. Effect of magnesium stearate on bonding and porosity expansion of tablets produced from materials with different consolidation properties. Int. J. Pharm. 179, 107–115.