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Fine grade engineered microcrystalline cellulose excipients for direct compaction: Assessing suitability of different dry coating processes

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ABSTRACT

Recent work showed that contrary to conventional wisdom, fine surface engineered excipients outperform their larger counterparts in blends of highly loaded blends of cohesive drug powders in terms of their packing, flowability and tablet tensile strength. Here, two continuous devices, fluid-energy mill (FEM) and conical mill (Comil), are compared with LabRAM, a batch device used in previous work, for nano-silica dry coating of microcrystalline cellulose (MCC) excipients, 20 and 30 μm. Coated MCCs from all three devices had higher bulk densities and flow function coefficients (FFCs) compared with Avicel PH-102. Silica coating quality was best with LabRAM, but also good with FEM and Comil, although Comil was less effective for the finer MCC. However, the better coating quality of LabRAM had a downside of having poorer compaction properties. The most surprising outcome was that multi-component blends of 17 wt% coated MCC with 60 wt % Ibuprofen 50 had higher bulk density, higher or similar flowability, higher tablet tensile strength, and comparable Ibuprofen dissolution from tablets, compared to those with Prosolv 50, a silicified excipient. The FEM dry coated MCC blends, having only 0.17 wt% silica, performed the best, having desirable bulk density, FFC, and tensile strength that could facilitate high-speed direct compression tableting. In summary, considering that achieving best coating quality need not be the primary objective, FEM may be the best option for producing desired sized dry coated fine excipients.

1. Introduction

Direct compression is the preferred method for tablet formulation due to its obvious advantages such as shorter processing time involving fewer unit operations (Carlin, 2008; Garg et al., 2015), better applicability to moisture and heat sensitive active pharmaceutical ingredients (APIs) (Jivraj et al., 2000), and time and cost effective processing (Li et al., 2017). Unfortunately, many fine and cohesive APIs are unsuitable for direct compression at medium or high drug loading due to the lack of flowability and/or compactibility (Li et al., 2018; Chen et al., 2019b). Specialized or high functional excipients that serve more than single purpose are needed for such challenging APIs to fulfill the critical but competing requirements such as good flowability and compactibility at high drug loadings (Jivraj et al., 2000; Rojas et al., 2012; Chen et al., 2019a). The required excipient functionality is further pushed by the use of finer APIs, e.g. to enhance the bioavailability (Noyes and Whitney, 1897). Further, it is preferred that the particle sizes of APIs and excipients are similar in order to avoid segregation and achieve good content uniformity, which may necessitate use of finer excipients (Jivraj et al., 2000; Rojas et al., 2012; Chen et al., 2018a). Unfortunately, the fine sized APIs and excipients tend to be very cohesive, resulting in handling and feeding problems (Castellanos, 2005; Jallo et al., 2012). Consequently, it is desirable to develop fine grade excipients that have very good flow, packing density and compactibility, for use in direct compression of the challenging APIs.

There has been continued efforts on co-processing of existing excipients to develop novel excipients with improved functionality (Block et al., 2009; Saha and Shahiwala, 2009). Commercially available excipients such as Prosolv (JRS), Ludipress (BASF), and Avicel CE-15 (FMC) are produced through co-processing via spray drying technique, having a high environmental footprint and require milling and drying (Carlin, 2008; Luo et al., 2008; Capece et al., 2015). The need for multiple processing steps may lead to relatively low yield due to the loss of product (20%-70%) (Ståhl et al., 2002; Maury et al., 2005). Moreover, the concentration of silica used in such excipients is as high as 2.0 wt %.

Previous studies from the author's group have shown that dry

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particle coating (Pfeffer et al., 2001; Yang et al., 2005), an environmentally benign process, may be used to develop fine grade high functional excipients for direct compression (Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2019b). A major shortcoming with dry coated excipients is that although the presence of nano-silica on the surface leads to improved flow and bulk density (Yang et al., 2005; Chen et al., 2008; Jallo et al., 2012), it may reduce the compaction strength due to the lower surface energy (Etzler et al., 2011; Sun, 2011). In (Chen et al., 2018b), a high-intensity vibrational mixer called the LabRAM was used to coat nano-silica (Aerosil 200) onto Avicel PH-105. The coated Avicel PH-105 at low silica concentrations, e.g., 0.5 wt % to 0.7 wt %, demonstrated excellent overall performance, i.e., bulk density, flowability, and tablet strength, in comparison to commercially available high functional excipients, including all grades of Prosolv. Although dry coated Avicel PH-105 had reduced compaction strength for placebo tablets, it outperformed commercially available silicified excipients. Unfortunately, the paper did not examine the blends of cohesive APIs. In (Chen et al., 2018a), a continuous process was used to simultaneously mill and coat larger MCC down to low sizes (25-40 μm) with two different grades of silica using a fluid energy mill (FEM). It was shown that the coated MCCs had very good flowability, high bulk density and compaction properties as compared to commercially available excipients. Unfortunately, the paper did not examine how the novel excipients would fare in blends of cohesive APIs. In (Chen et al., 2019b), the LabRAM coated Avicel PH-105 was used in binary blends of three fine cohesive APIs at 10, 30 and 60 wt % drug loadings. It was shown that the fine dry coated excipient outperformed all other available excipients for these API blends. Most surprisingly, these tablets had higher tensile strength as compared to uncoated Avicel PH-105. The overall conclusion was that contrary to conventional wisdom, finer engineered excipients perform better with respect to all three critical properties in blends of cohesive APIs at higher drug loadings. Even within the Prosolv family of silicified MCCs, the best overall performer was the finest grade, Prosolv 50 (Chen et al., 2019b).

Two important questions remain unanswered; can dry coated excipients be produced using commercially relevant continuous devices and, how those excipients would fare in standard blends that also include disintegrants, lubricants, etc. at high cohesive API loading. Towards that goal, in addition to the LabRAM and FEM, a conical mill (Chattoraj et al., 2011; Huang et al., 2018), also called the Comil is used. In a Comil, its high shear may promote silica coating in conjunction with either multiple passes or pre-blending with silica (Chattoraj et al., 2011; Huang et al., 2015). Thus, three different coating methods, LabRAM, FEM, and Comil, are investigated where the highest normal and shear forces are expected to be from the FEM device, whereas longer mean residence processing time is in the LabRAM.

First, the as received Avicel PH-105 was dry coated using the LabRAM and a Comil. The FEM-based milling and coating was not relevant for Avicel PH-105. Next, in order to examine all three devices in a head-to-head comparison, the same sized dry coated excipients were prepared: (1) The milled Avicel PH-102 (~30 μm) was dry coated with 1.0 wt% hydrophilic silica (A200) via LabRAM; (2) Pre-blended Avicel PH-102 with 1.0 wt% A200 was milled and coated down to ~30 μm via FEM; (3) The milled Avicel PH-102 (~ 30 μm) was coated with 1.0 wt% A200 via Comil. The schematic for these processes is in Fig. 1. Bulk density, flowability, and compaction of the excipients produced using these three different methods were assessed. Multi-component blends of the excipients with a model BCS II drug (Ibuprofen) at 60 wt% drug loading were prepared and blend bulk density, flowability, compaction, as well as tablet disintegration and dissolution were evaluated.

2. Materials and methods

2.1. Materials

Microcrystalline Cellulose Avicel PH-105 and PH-102 (donated by FMC Biopolymer) were used as starting materials to prepare the fine grade of high functional excipients. Prosolv 50 (donated by JRS Pharma, NY, USA) was used as a model high functional excipient for comparison. Aerosil 200 (nano-sized hydrophilic fumed silica) was provided by Evonik Corporation (Piscataway, NJ, USA) and used as guest particle for all three processes due to its fine size and lower surface energy as compared to other grades of fumed silica (Chen et al., 2018b). Ibuprofen 50, used as a model BCS II drug, was purchased from BASF Corporation (South Bishop, Texas 78343). Pharmatose 450 (donated by DFE Pharma, USA) was the additional filler excipient for the tablet formulation. Kollidon-CL was used as a tablet disintegrant, was obtained from BASF (Crospovidone, BASF, USA), and magnesium stearate severed as lubricant (Mallinckrodt Inc., USA). The silica concentration was kept as 1.0 wt % for all three dry coating methods.

2.2. Preparing milled-uncoated MCC and milled-coated MCC via FEM

Avicel PH-102 was fed into FEM through a volumetric feeder (Schenck Process GmbH, WI, USA) with a feed rate of 2.0 g/min. The feeding pressure of 40 psi and grinding pressure of 35 psi were used for preparing the milled powders. These conditions were selected to achieve the particle size after milling as well as milling and coating at around 30 μm. The milled Avicel PH-102, termed as milled-uncoated MCC30, was used as starting material for LabRAM and Comil dry coating. In order to prepare the milled-coated MCC, Avicel PH-102 and silica particles were pre-mixed with a mass ratio of 99:1 in V-blender (Blend Master, PA, USA) to avoid the handling problems of the nano-sized silica. The pre-mixed mixture was then fed into FEM for simultaneous milling and coating using the same operation conditions as described above to obtain the milled-coated MCC, hereafter called FEM-MC-MCC30.

2.3. Preparing dry coated MCC via LabRAM

The Avicel PH-105 and MCC30 were the starting materials for LabRAM coating. Two batches of dry coated excipients were prepared via LabRAM (Resodyn, USA): (1) A total of 50 g of Avicel PH-105 and silica powders were placed in a 300 mL plastic jar with a mass ratio of 99:1 to produce the dry coated Avicel PH-105, hereafter called RAM-DC-A105; (2) A total of 50 g of the milled-uncoated MCC and silica powders were placed in a 300 mL plastic jar with a mass ratio of 99:1 to produce the milled-coated Avicel PH-102, hereafter called RAM-MC-MCC30. The LabRAM vibrates in a vertical direction at a frequency set to 60 Hz. Its intensity was set at 70G acceleration with 5 min of the mixing time based on previous work (Chen et al., 2018b).

2.4. Preparing dry coated MCC via Comil

Due to the handling and feeding problems of nano-sized silica, the excipients and silica powders (mass ratio of 99:1) were pre-mixed in a V-blender for 30 minutes at 25 rpm. In some cases, the pre-blending in a V-blender also used an intensifier bar. The pre-blended material was fed into the Comil using a screw feeder (M0D106M AccuRate, Schenck Process GmbH, Whitewater, WI, USA), better representing the conditions in continuous manufacturing. Once the powders flowed through the screen, it was collected at the bottom of the milling chamber. A round impeller, at a rotational speed of approximately 1300 rpm, a screen with 457 micron round holes, and the inlet powder flow of 10 grams per minute were used as the operating conditions (Huang et al., 2015). Two batches of dry coated MCC were prepared: (1) 200 grams pre-blended Avicel PH-105 with 1wt% A200 pass through the Comil to obtain the dry coated Avicel PH-105, hereafter called COM-DC-A105; (2) 200 grams pre-blended milled-uncoated MCC with 1wt% A200 pass through the Comil to obtain the milled-coated Avicel PH-102, hereafter called COM-DC-MCC30. All the processed powders via three different methods were stored in tightly sealed plastic bags at room temperature

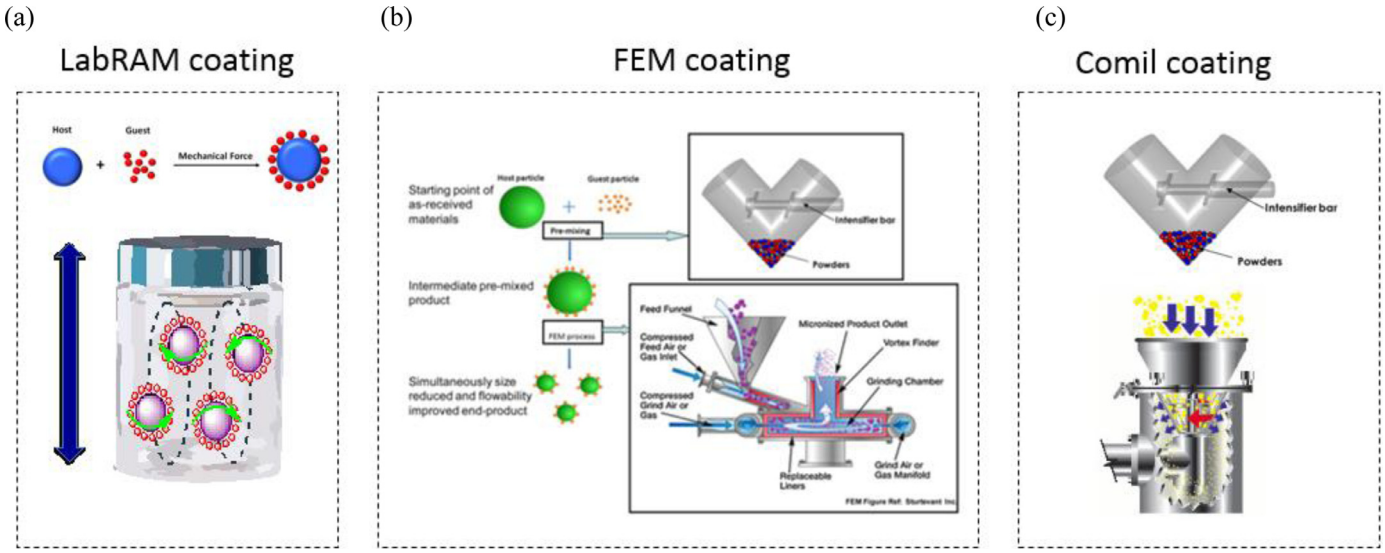


Fig. 1. Process schematic for (a) LabRAM coating, (b) FEM coating, and (c) Comil coating.

(25°C), and 24% relative humidity.

2.5. Scanning Electronic Microscope

A small amount of each sample was slowly deposited onto a double-sided carbon tape with one side mounted on a sample holder. Loose and excess powder was removed by compressed air. Samples were sputter-coated (Q150T 16017, Quorum Technologies Ltd, Laughton, East Sussex, England) with carbon to enhance the conductivity. A Field Emission Scanning Electron Microscope (FESEM) (LEO 1530170, Carl Zeiss SMT Inc., Germany) was used to qualitatively assess the particle morphology as well as coating efficiency of dry coated powders from different dry coating processes.

2.6. Helos/Rodos particle size analyzer

The volume-based particle sizes d_{10}, d_{50}, d_{90} and of processed powders were measured in a Sympatec Helos/Rodos laser diffraction particle size analyzer (Sympatec Inc., NJ). The Fraunhofer theory was used to calculate the particle size distribution and has been described in detail elsewhere (Jallo et al., 2012). From a set of initial tests using Rodos employing dispersion pressures of 0.1, 0.5, 1.0, 1.5, 2.0 bar, the final testing was at 1.0 bar, in line with the previous work (Chen et al., 2018b). This dispersion pressure was not high enough to cause any unwanted attrition while it assured that the size measured was that of the primary particles and not their agglomerate sizes. Each measurement was done in triplicate.

2.7. Powder characterization using FT4 powder tester

The Freeman FT4 powder tester (Freeman Technologies Ltd., Worcestershire, UK) was utilized to obtain the flow function coefficient (FFC), defined as the ratio of major principle stress to the unconfined yield stress, and the bulk density. The latter was measured through a standard FT4 testing procedure that first conditions the powder to yield very repeatable results. The FFC values of powders were attained from shear tests performed under the consolidation pressure of 3 kPa. Detailed procedures for both bulk density and shear tests may be found elsewhere (Freeman, 2007; Huang et al., 2015). A classification of powder flow behavior based on FFC values, similar to that of Jenike, has been defined by Schulze: FFC < 1 - not flowing, 1 < FFC < 2 - very cohesive, 2 < FFC < 4 - cohesive, 4 < FFC < 10 - easy flowing, and FCC > 10 - free-flowing (Jenike, 1964; Schulze, 2008).

2.8. Tablet performance

Tablets were produced under four compression forces (4.9, 9.8, 14.7, and 19.6 kN) via Carver platen press (Carver, Inc., USA), each case with a 500 mg powder sample, using a stainless die of 0.5-inch inner diameter with flat-faced round punch. The die and the punch were cleaned by alcohol wipes before each compression. Tablets were placed vertical on the texture analyzer model TA-XT Plus where probe moved at 10 mm/s till the tablet breaks. The maximum breaking force was recorded. The tensile strength, σ was calculated using Eq. (1), F is the breaking force, D_t is the tablet diameter, and t is the thickness of the tablet measured by Vernier caliper;

$$\sigma = \frac{2F}{\pi \mathrm{Dtt}} \tag{1}$$

2.9. Disintegration and dissolution studies

The disintegration testing for the tablets was performed using a USP disintegration test apparatus (DT2, Sotax, Aesch, Switzerland), in 800 mL of PBS buffer (pH = 7.2) with 0.04 g/mL sodium dodecyl sulfate (SDS) at 37 ± 0.5°C. Each formulation was repeated five times. Dissolution testing for the tablets was carried out through the Distek 2100C dissolution tester (North Brunswick, NJ, USA) using the USP II paddle method. PBS (pH = 7.2) with 0.04 g/mL SDS was used for the dissolution media and the temperature was set at 37 ± 0.5°C, and the rotating speed of the paddle was 50 RPM. 5 mL samples were withdrawn at time intervals of 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes respectively. All samples were filtered through a 0.45 μm filter to separate out drug that was not dissolved in the sample at the time of collection. The filtered samples were diluted 5 times and then assessed using the UV spectrophotometer (Thermo Scientific Inc., USA) at a wavelength of 213 nm. All the experiments were performed in triplicate and average values are reported.

3. Results and discussion

The results discussed in this section first include the comparison between the LabRAM and Comil for the finest sized excipient, Avicel PH-105 (~20 μm), followed by the comparison between all three devices for the milled and coated Avicel PH-102 or MCC30, which in all cases is at ~ 30 μm size.

Table 1
Particle size distributions of dry processed engineered excipients presented as D10, D50, and D90.

	d10(μm)	d50(μm)	d90(μm)
Avicel PH-105	7.3	19.8	40.2
RAM-DC-A105	7.5	20.2	42.7
COM-DC-A105	7.4	20.1	41.3
Avicel PH-102	36.4	116.7	235.4
MCC30	9.8	30.8	70.3
RAM- DC-MCC30	9.6	30.5	71.5
FEM- MC-MCC30	9.7	31.1	70.8
COM- DC-MCC30	9.5	30.3	69.8

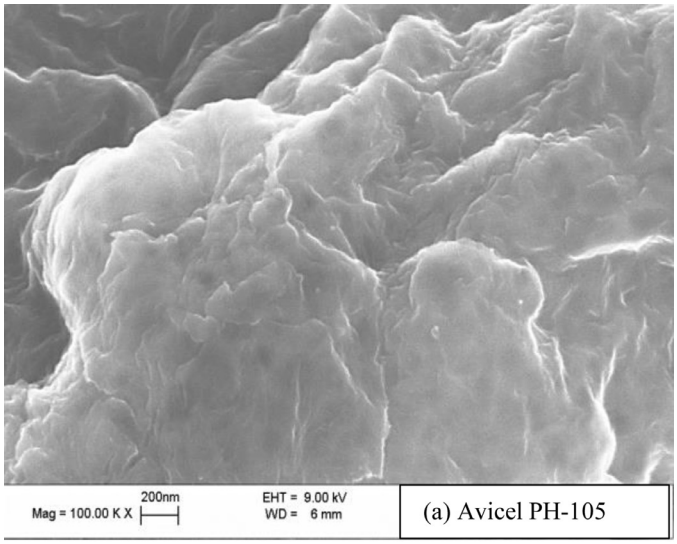
3.1. Particle size distribution of dry coated powders

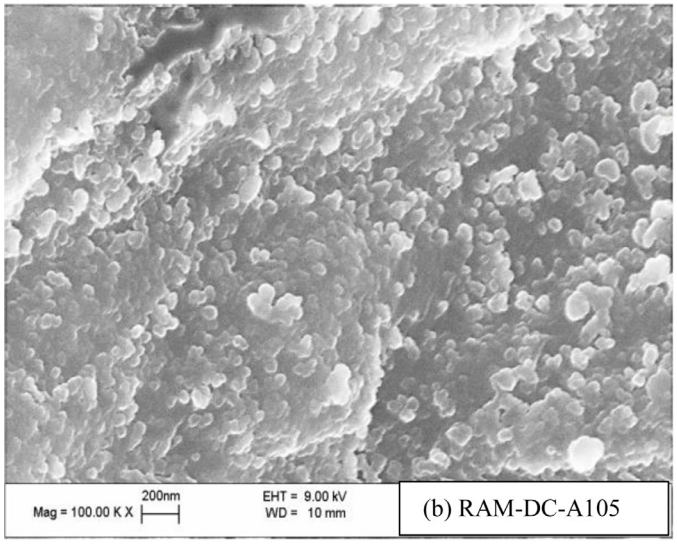
The particle size distributions (d10, d50, d90) of the materials are reported in Table 1, which shows that as-received Avicel PH-102 was effectively milled using the FEM to obtain the starting material MCC30 at 30 μm size for the LabRAM and Comil dry coating. For the fine grade of microcrystalline cellulose (Avicel PH-105), there is little size reduction or enlargement after coating with 1.0 wt% A200 for both LabRAM and Comil processes. As discussed in previous work (Chen et al., 2018b), LabRAM coating with silica particles does not affect the particle size distribution for Avicel PH-105 since there is little or no attrition during the dry coating process. For Comil, previous studies reported that it can reduce the particle size due to attrition (Deng et al., 2015; Huang et al., 2015). However, the particle size of COM-DC-A105 is comparable to Avicel PH-105 as shown in Table 1. The possible reasons include short residence time, low impeller speeds and ductile nature of the material. It should be noted that the pre-blend of Avicel PH-105 and silica posed feeding and Comil processing problems. This was likely due to the existence of unattached or attached agglomerated silica particles. This problem was mitigated when the pre-blending was done using an intensifier bar during the pre-mixing process. Fortunately, the pre-blend of milled Avicel PH-102 of 30 μm size with silica did not pose such issues. This is likely due to the coarser size of MCC which seems to form better pre-blend with silica without the use of an intensifier bar. A similar effect was also observed for larger, as received Avicel PH-102 (~120 μm), where the larger excipients may have helped in breaking down of large silica agglomerates (Zhou et al., 2012). After dry coating, no significant change in particle size for milled-uncoated Avicel PH-102 was found for both LabRAM and Comil processes as shown in Table 1.

3.2. Morphology of coated particles

SEM images for as-received Avicel PH-105, LabRAM coated Avicel PH-105 with 1.0 wt% A200, and Comil coated Avicel PH-105 with 1.0 wt% A200 are shown in Fig. 2. As-received Avicel PH-105 has a fine size and very rough surface as depicted in Fig. 2 (a). For the LabRAM dry coating, the nano-sized silica particles are evenly distributed on the surface of Avicel PH-105, leading to nano-scale surface roughness as shown in Fig. 2(b). However, for the Comil dry coating, the silica particles are not well distributed on the surface of Avicel PH-105 as seen in Fig. 2(c), including some uncoated areas highlighted in red circles. It is evident that the coating quality is much better for LabRAM dry coating than that of Comil even when the silica concentration is kept the same (1.0 wt%).

Fig. 3 shows the SEM images of FEM-MC-MCC30 (a), RAM-DC-MCC30 (b), and COM-DC-MCC30 (c), all coated with 1.0 wt% A200. Even for these coarser MCC powders, LabRAM shows a better coating quality as the silica particles are evenly distributed on the surface of MCC30 (Fig. 3(b)), whereas the coating of silica particles using both the FEM and Comil is mostly similar but not as good as with LabRAM (Fig. 3(a and c)). In the next few sections, how such coating quality differences may influence the key bulk properties is examined.





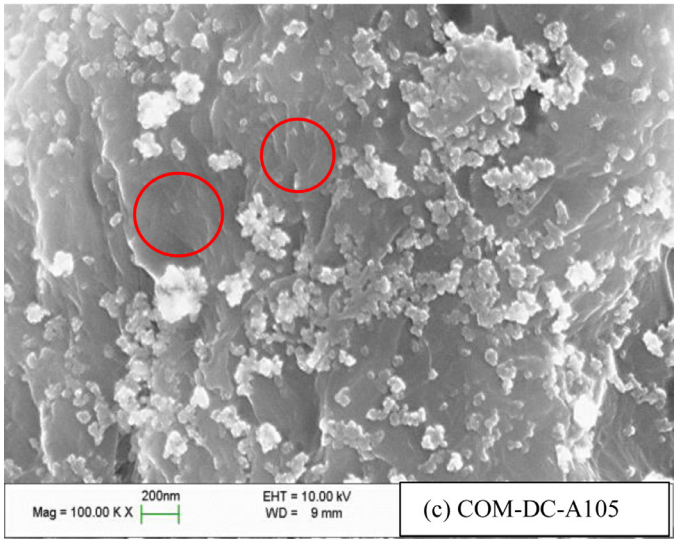


Fig. 2. SEM images of as-received Avicel PH-105 (a), RAM dry coated Avicel PH-105 with 1.0 wt% A200 (b), and Comil dry coated Avicel PH-105 with 1.0 wt% A200 (c).

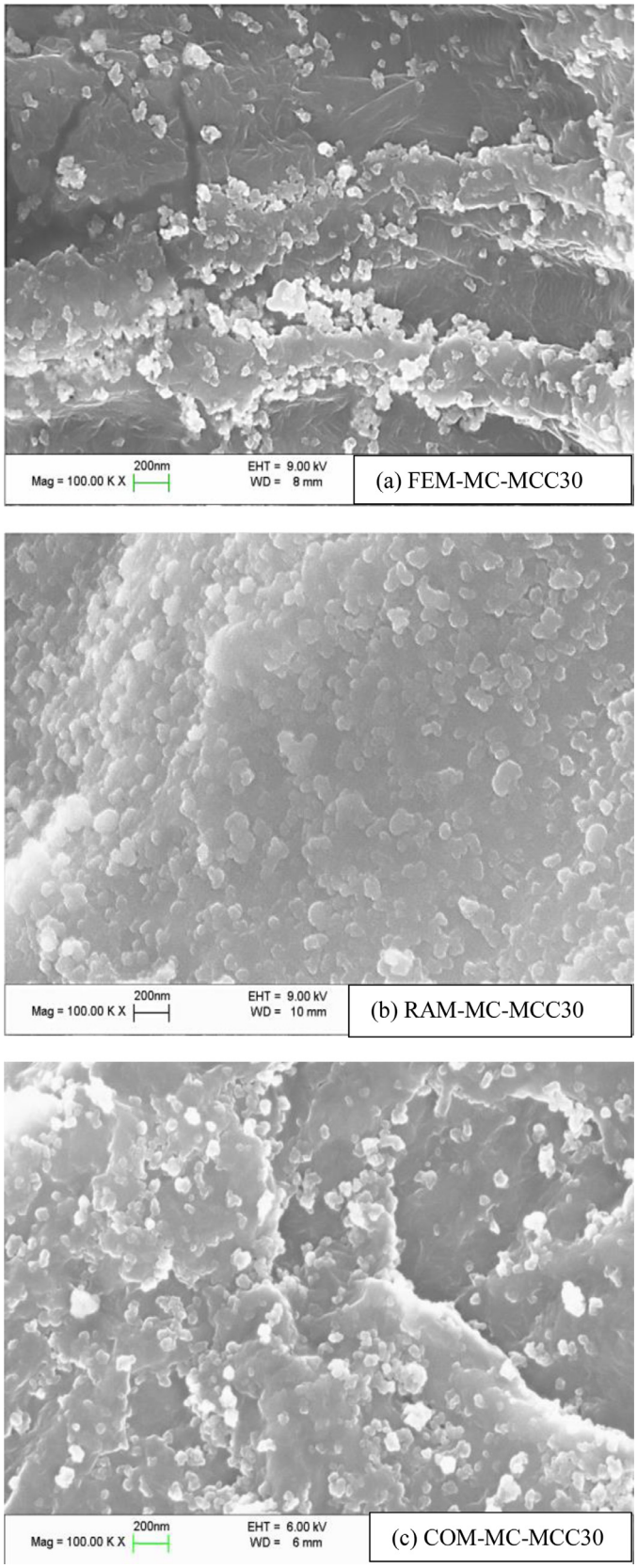


Fig. 3. SEM images of FEM-MC-MCC30 (a), RAM-DC-MCC30 (b), and COM-DC-MCC30 (c) all coated with 1.0 wt % silica A200.

3.3. Comparison of bulk density and flowability of excipients using different coating methods

Bulk Density: This is a key property that greatly impacts processability in terms of the ease of handling, processing, and feeding. As may be seen, the bulk density of Avicel PH-105 was significantly improved after LabRAM coating. The coating using Comil when the intensifier bar was used for pre-blending is also very good but not as good as that from LabRAM coating. However, the enhancement in the bulk density after Comil coating without the intensifier bar during pre-blending is not that good. The results in the dark gray bars are for FEM-MC-MCC30, RAM-DC-MCC30, COM-DC-MCC30, all being coarser sized (~30 μm) excipients dry coated with 1.0 wt % A200 using three different coating devices. All three dry coating processes exhibited drastic improvements in the bulk density. An important observation is that the Comil coating for milled Avicel PH-102 without intensifier bar demonstrated a significant improvement in bulk density, unlike what was the case for the Avicel PH-105 which is finer. However, as may be anticipated from the coating quality seen in the SEM images (Fig. 3), the enhancement in the bulk density after dry coating with Comil is lower than that of LabRAM and FEM coating. In Fig. 4, the black reference line is the bulk density of as received Avicel PH-102 and the red reference line is the bulk density of Prosolv 50. All dry coated excipients of finer size (coated Avicel PH-102) and coarser size (dry coated MCC30) have significantly higher bulk density values as compared to that of Prosolv 50, which is a larger, silicified excipient. This is a remarkable result considering finer sizes and use of lesser silica concentrations. All dry coated excipients also have slightly higher bulk density values as compared with as received Avicel PH-102, which means they reach the minimum bar for high-speed direct compression tableting potential (Sun, 2010).

Flowability: Fig. 5 presents the flow function coefficient (FFC), a standardized method to quantify powder flowability (Schulze, 2008), another critical property that impacts pharmaceutical operations including tableting. As shown in the light gray bars, the FFC of as-received Avicel PH-105 is very low hence it is a very cohesive powder according to the classification by Schulze (Schulze, 2008). However, the Comil coated Avicel PH-105 without intensifier bar leads to definite improvement in FFC, yet it is borderline cohesive behavior. That may explain its poor performance during processing in the Comil, where the agglomerates blocked the screen. However, when Avicel PH-105 was pre-blended with A200 using the intensifier bar, the FFC after Comil processing exhibited drastic increase to almost free-flowing regime. These results indicate that for finer powders, especially for irregularly shaped materials like Avicel PH-105, the use of Comil for dry coating requires much better pre-blending. In contrast, after dry coating in the LabRAM, the FFC is well over 10 to a free-flowing regime. It is noted that a larger scatter in the FFC values is expected for free-flowing powders and in general, FFC values over about 12-14 may not indicate significant differences. Such drastic improvements are expected when dry coating quality is very good as per cohesion reduction models (Yang et al., 2005; Chen et al., 2008). For the milled Avicel PH-102 of coarser size ~ 30 μm, all three dry coating methods including Comil that did not require pre-bending using an intensifier bar, reached free-flowing regime with FFC values of over 12, with the highest value being that for the LabRAM as expected. Two horizontal reference lines in Fig. 5 are for the FFC of as received Avicel PH-102 and Prosolv 50, the latter being a much higher value, which is its major positive feature. All dry coated excipients of finer size (coated Avicel PH-105) and coarser size (dry coated MCC30) have significantly higher FFC values as compared with as received Avicel PH-102, which means they reach the minimum bar for high-speed direct compression tableting potential (Sun, 2010). Further, they are also comparable to the FFC of Prosolv 50, which is a larger, silicified excipient. Since FFC is well above 10, high FFC values of these dry coated excipients is a remarkable result considering their finer sizes and use of lesser silica concentrations.

Overall, important conclusions may be made based on the bulk

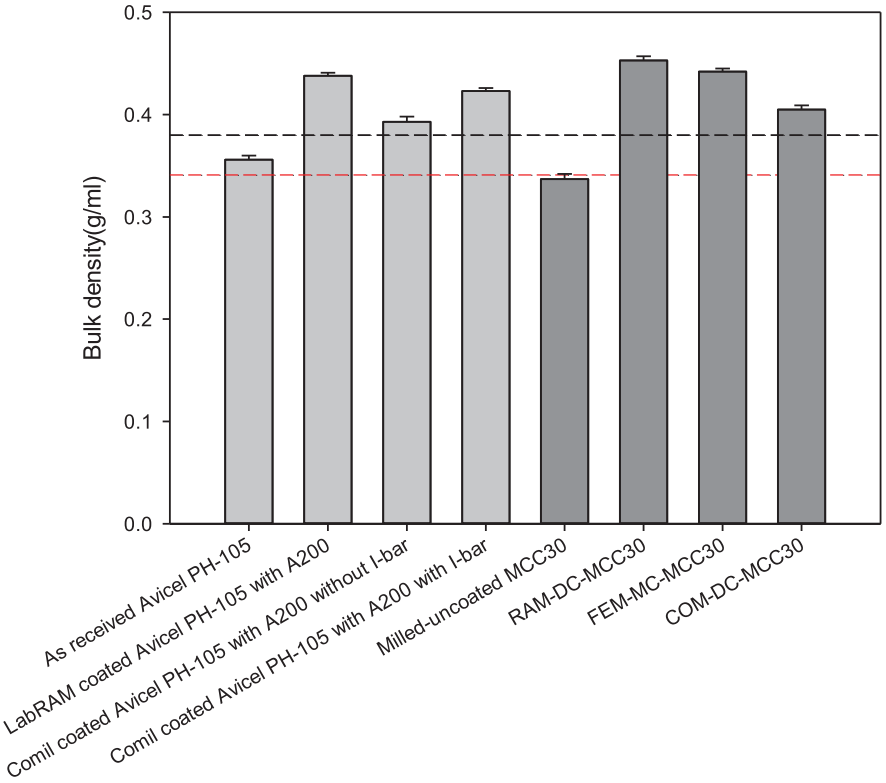


Fig. 4. Bulk density of as-received Avicel PH-105, LabRAM coated Avicel PH-105 with 1.0 wt% A200, comil coated Avciel PH-105 with 1.0 wt% A200 without intensifier bar, comil coated Avciel PH-105 with 1.0 wt% A200 with intensifier bar, milled-uncoated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, and COM-DC-MCC30. The black reference line is the bulk density of as received Avicel PH-102 and the red reference line is the bulk density of Prosolv 50.

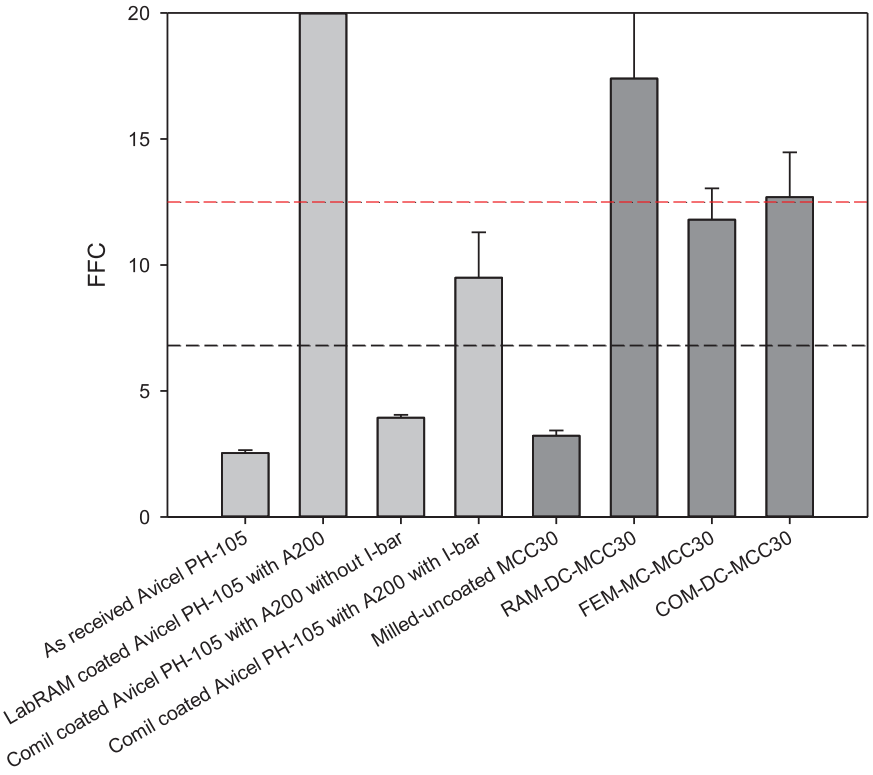


Fig. 5. Flowability (FFC) of as-received Avicel PH-105, LabRAM coated Avicel PH-105 with 1.0 wt% A200, comil coated Avciel PH-105 with 1.0 wt% A200 without intensifier bar, comil coated Avciel PH-105 with 1.0 wt% A200 with intensifier bar, milled-uncoated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, COM-DC-MCC30. The black reference line is the flowability of as received Avicel PH-102 and the red reference line is the flowability of Prosolv 50.

density, flowability and SEM imaging results. First, very fine excipients are difficult to dry coat using a Comil without requiring intense pre-blending or several comilling cycles (Chattoraj et al., 2011), which is not practical being a specialized extra step. Second, for the coarser sized, yet fine MCC-based excipient sized at about 30 μm, all three dry coating methods work well and achieve dramatic flow and bulk density enhancements, which all qualitatively match the coating quality seen in Figs. 2 and 3. Third, it is remarkable that after good quality dry coating, fine MCC powders in small sizes of 20 and 30 μm flow and pack better than much larger Avicel PH-102 having d50 of about 120 μm, and also pack better than Prosolv 50 while achieving similar free-flowing level. Last, based on the overall performance and its versatility in producing desirable sized coated MCC excipients (Chen et al., 2018a), the FEM device may be the best industrially relevant, continuous method

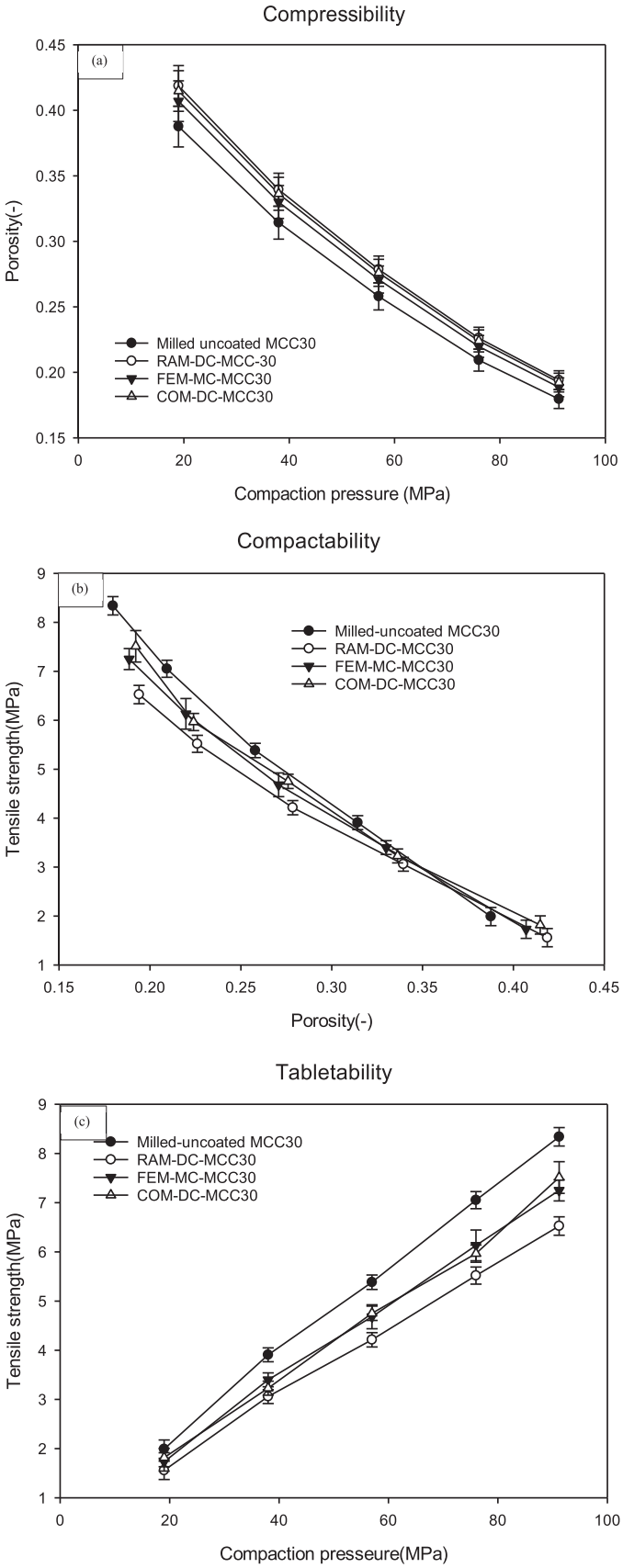


Fig. 6. (a) Compressibility, (b) compactability, and (c) tabletability of milled-uncoated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, COM-DC-MCC30.

Table 2
Formulation for IBU-50 tablets prepared using MCC30, FEM-MC-MCC30, RAM-DC-MCC30, COM-DC-MCC30, or Prosolv 50.

Ingredients	Percentage (%)
IBU-50	60
MCC-based Excipients*	17
Lactose 450	17
Crospovidone	5
MgSt	1

MCC-based Excipients*: Milled-uncoated MCC30, FEM-MC-MCC30, RAM-DC-MCC30, COM-DC-MCC30, and Prosolv 50

because it can provide product in size that is not normally available. It is noted that none of the devices were individually optimized in terms of their operating conditions. However, it is likely that for producing finer dry coated excipients that are not easily available or manufactured at a desired size, LabRAM or Comil would also require a milling step. In those cases, simultaneous milling and coating using the FEM device would be a better option. In the next two sections, any adverse impact of the silica coating is evaluated on the compaction properties for placebo and high API loaded blends made with Ibuprofen 50, which is relatively fine and cohesive.

3.4. Compaction profiles of different dry processed excipients

Compressibility, Compactibility, and Tabletability are commonly used to study the powder compaction properties (Tye et al., 2005). Compressibility, which is compaction pressure vs tablet porosity, and compactibility, which is porosity vs tensile strength, are two vital indicators that give a good indication regarding the bonding area and bonding strength as discussed in the BABS model (Sun, 2011). Whereas tabletability, which is compaction pressure vs tensile strength, is used for evaluating the manufacturability of pharmaceutical blends during the tableting process (Capece et al., 2017).

The profiles of compressibility, compactibility, and tabletability of fine ~30 μm MCC, i.e., FEM-MC-MCC30, RAM-DC-MCC30, COM-DC-MCC30, are presented in Fig. 6. As the compaction pressure increases, the powders tend to be better packed and ultimately deform, leading to a lower porosity. Since the particle sizes of all the dry processed materials are about the same, the bonding area is expected to be similar with each other (Sun, 2011). Compressibility profiles, Fig. 6(a), indicate that the MCC30 has lower porosity at the same compaction pressure compared to other products, implying higher bonding area, hence higher tablet strength at the same compaction pressure. Three different dry coated materials exhibited similar compressibility profiles with minor differences. Such differences are also seen in the compactibility profiles, a measure of the ability of a material to form the compacts of sufficient tensile strength under densification, in Fig. 6(b). At lower porosities, the differences are pronounced and the uncoated MCC30 exhibits the highest tensile strength while RAM-DC-MCC30 has the lowest tensile strength, and the other two coated MCCs, FEM-MC-MCC30, and COM-DC-MCC30, have values in between. These results are in line with the expected impact of silica in reducing the tablet strength, and better coating quality leads to higher adverse impact on the tablet strength. These trends are in line with the coating quality observed in the SEM images in Fig. 3 (a–c) where LabRAM shows the best coating quality, and FEM and Comil demonstrated poorer coating quality. These trends continue for the tabletability profiles in Fig. 6(c), where naturally the tensile strength increases with the increasing compaction pressure, but there is a very clear trend in the tensile strength values as was expected from the results of Fig. 6(b). Overall, considering the dramatic improvements in the flowability and bulk density of these fine ~30 μm MCC-based excipients that well exceed those of Avicel PH 102 and to a large extent Prosolv 50, slight drop in the tablet strength due to the presence of silica is not a major negative. That is especially true because even the reduced tensile strength is

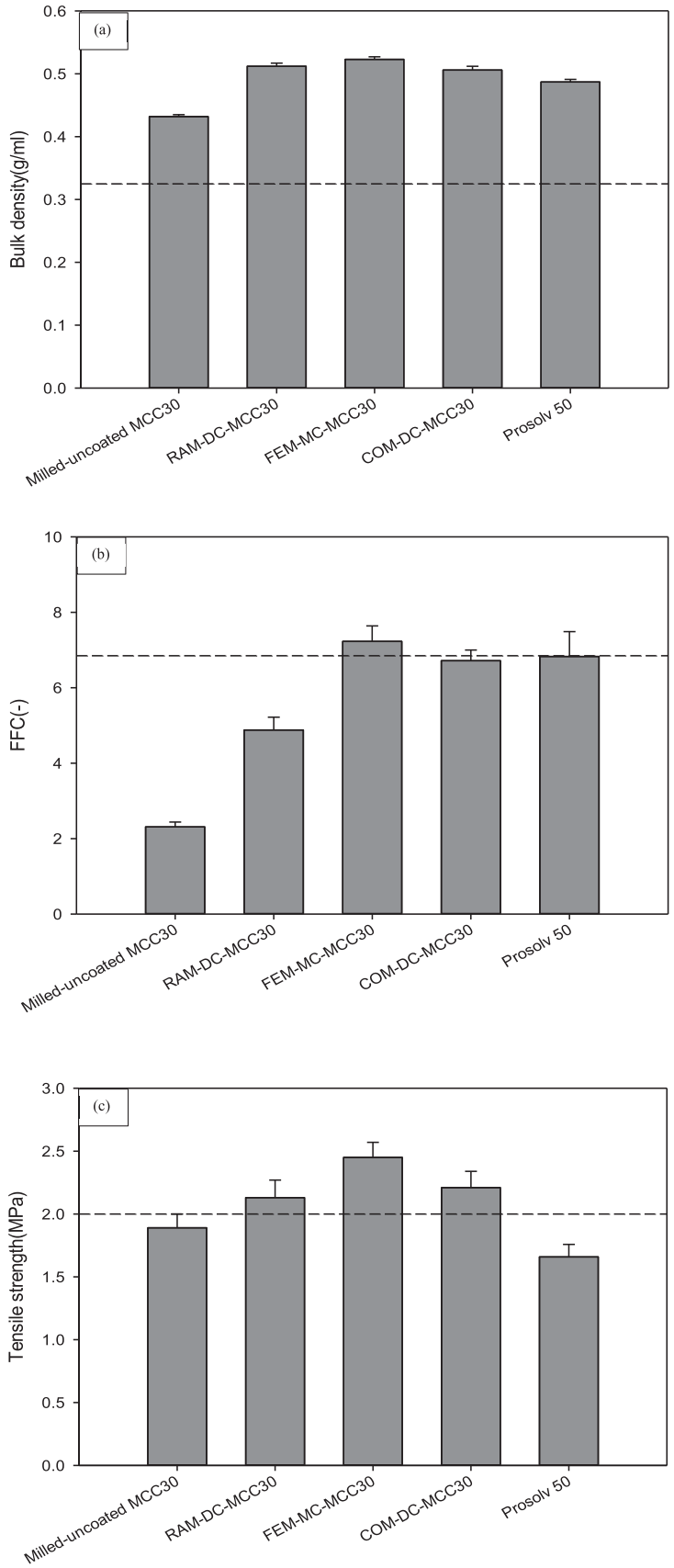


Fig. 7. (a) Bulk density, (b) flowability, and (c) Tabletability of Ibuprofen blends prepared from milled-uncoated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, COM-DC-MCC30, and Prosolv 50. For (a) and (b), the horizontal reference lines represent bulk density and FFC of as received Avicel PH-102, whereas for (c) the horizontal line is a desired value of tablet tensile strength of 2 MPa (or higher).

Table 3
Disintegration time of IBU tablets prepared from milled-uncoated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, COM-DC-MCC30, and Prosolv 50 at 60% IBU 50 loading.

Materials	Disintegration time (s)
IBU tablets with milled-uncoated MCC30	28.3
IBU tablets with RAM-DC-MCC30	28.0
IBU tablets with FEM-MC-MCC30	27.9
IBU tablets with COM-DC-MCC30	28.1
IBU tablets with Prosolv 50	22

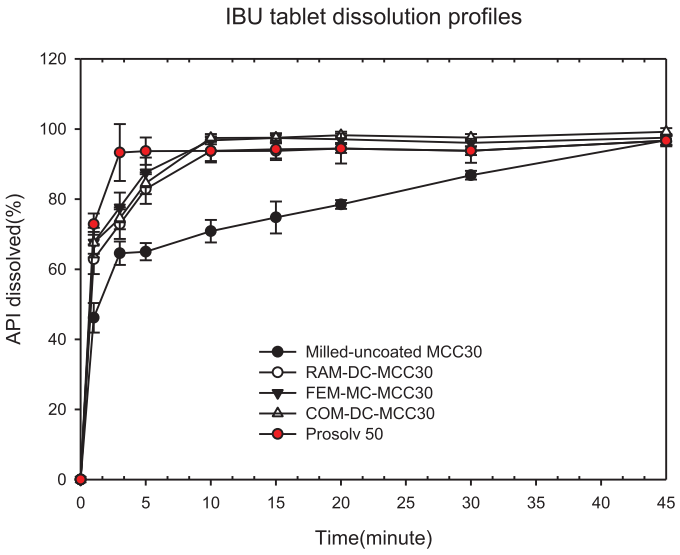


Fig. 8. Dissolution profiles of Ibuprofen tablets prepared from milled-unocated MCC30, RAM-DC-MCC30, FEM-MC-MCC30, COM-DC-MCC30, and Prosolv 50 at 60% IBU 50 loading.

significantly higher than what would be expected from coarser excipients such as Avicel PH 102 (6.8MPa) or Prosolv 50 (7.7MPa) (Chen et al., 2018b). Next, IBU blends at high drug loading are examined for further emphasizing this point, since previous work suggests that finer excipients perform better for cohesive API blends (Chen et al., 2019b).

3.5. Effect of dry processed excipients on IBU blends and tablet properties at 60% drug loading

The dry coated 30 μm sized excipients prepared via three different processes were evaluated for the blend processability and dissolution performance of a model BCS II drug (Ibuprofen) at 60 wt% drug loadings, see Table 2 for the blend formulation. Previous work (Chen et al., 2019b) demonstrated that amongst commercially available silicified MCCs, Prosolv 50 had the best overall performance. Therefore, the blends with Prosolv 50 were also considered. Fig. 7 presents the bulk density, flowability, and tablet strength of Ibuprofen blends prepared from the uncoated and three different dry coated MCCs as well as Prosolv 50 as a control. The bulk density, Fig. 7(a), for all formulations with three different dry coated MCCs was very good, also slightly higher than the blend with Prosolv 50, and well above the reference line for the bulk density of Avicel PH-102. The flowability, Fig. 7(b), of all three dry coated excipients blends was higher than uncoated MCC30 blends, demonstrating the positive impact of dry coating. However, the LabRAM dry coated MCC blend flowability was the lowest amongst three and the FEM-DC-MCC30 blend flowability is the highest, while COM-DC-MCC30 blends and Prosolv 50 blends are about the same yet above the Avicel PH-102 reference line. The possible reason is that propensity for the silica to migrate from the MCC powders surfaces to IBU and other excipient powder surfaces is higher for the FEM and Comil formulations than for LabRAM formulations. It also indicates that achieving the best silica coating may not be the most desirable objective for preparing engineered excipients. Since flowability is a critical parameter for tableting, these results indicate that the fine FEM dry coated excipient has an excellent potential for promoting high-speed tableting at high drug loadings. The next set of results, Fig. 7(c), are for the tablet tensile strength at 114 MPa compaction pressure, and they are most surprising because even when dry coating led to reduced tablet strength for the placebo tablets (see Fig. 6(c)), here dry coating led to improved tablet strength for all three dry coated excipient blends with cohesive IBU 50. This finding is in agreement with previous work, where the tablet strength of IBU increased after silica coating of the entire blend, including the IBU and MCC (Zhou et al., 2013). In contrast, Prosolv 50 had the lowest tablet strength, which is also below the desirable level of 2 MPa. This once again establishes that finer dry coated excipients perform very well when formulated with fine cohesive APIs at high drug loadings (Chen et al., 2019b). It is noted that since the formulation includes cohesive API at 60 % drug loading and fine excipients, including very poorly flowing and compacting Lactose 450, the overall results for the bulk density, flowability and tablet strength are remarkable when only 17 wt % of dry coated fine ~30 μm MCC is used.

Last, the disintegration and dissolution behavior for the tablets from all the formulations from Table 2 are presented. Disintegration time, presented in Table 3, for the Prosolv 50 formulation is the fastest. However, all other formulations have similarly fast, under 30 sec disintegration time, which indicates that the presence of silica for the dry coated excipients does not have any adverse effect. Surprisingly, the dissolution profiles showed in Fig. 8 demonstrated that all three dry processed excipients have a faster and more complete dissolution behavior compared to the tablets prepared with uncoated MCC30. One potential reason is that during the mixing process for preparing the blends, the dry coated excipients and the silica present on their surfaces may promote deagglomeration of the relatively cohesive ibuprofen, leading to enhanced available surface area during dissolution (Kunnath et al., 2018). Another possible reason is that the hydrophilic silica, A200, helps increase the wettability of the blend (Kumar et al., 2014). Therefore, the combined effects of the API deagglomeration and enhanced wettability may have contributed to slightly faster and more complete dissolution.

4. Conclusions

Silica dry coating of fine microcrystalline cellulose (MCC) using three dry coating methods resulted in varying performance of their blends and tablets. For 30 μm sized MCCs, after dry coating with all three methods lead to higher bulk densities and flow function coefficients (FFCs) compared with much larger as received Avicel PH-102. However, the better coating quality of LabRAM had a downside of having poorer compaction properties as compared with the FEM and Comil coated MCCs. The most interestingly, multi-component blends of coated MCCs with 60 wt % Ibuprofen 50, had higher bulk density, higher or similar flowability, and higher tablet tensile strength compared to blends with Prosolv 50. Amongst the blends made with dry coated MCC using LabRAM, FEM and Comil, the FEM produced MCC blends performed the best, reaching very high, desirable levels of bulk density, flowability, and tensile strength that could facilitate high-speed direct compression tableting. These outcomes corroborate the previous results that demonstrated that finer silica coated MCC-based excipients work better in high drug loaded blends of finer cohesive APIs even when the MCC was only 17 wt % (Chen et al., 2019b). A major conclusion is that best coating quality need not be the primary objective when producing fine surface modified excipients, and therefore, it may be better to use the industrially relevant continuous FEM device, which also has the ability to produce different sized coated excipient powders.

CRediT authorship contribution statement

Liang Chen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - review & editing. **Zizhou He:** Investigation. **Kuriakose Kunnath:** Investigation. **Kai Zheng:** Investigation. **Sangah Kim:** Investigation. **Rajesh N. Davé:** Conceptualization, Formal analysis, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or relationships that could have appeared to influence the work reported in this paper.

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