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Moisture sorption and desorption of different commercially available microcrystalline cellulose grades as a function of relative humidity

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ABSTRACT

Microcrystalline cellulose (MCC) is extensively used in pharmaceutical formulations due to its exceptional functionality as a diluent, dry binder, disintegrant, and absorbent. Despite being marketed in numerous grades that vary in particle size, source, extraction techniques, and co-processing methods, its basic chemical structure remains consistent across grades, with differences primarily in physical properties. This study investigates moisture sorption and desorption behavior and its effects on solid-state properties of thirteen different MCC grades, including eleven regular and two co-processed varieties, as moisture content significantly influences compaction, tensile strength, and viscoelastic properties. Dynamic vapor sorption analysis was conducted at 25 °C by systematically increasing relative humidity (RH) from 10% to 90% RH in one case and from 10% to 80% RH in another, and then decreasing the RH to 0%. All MCC grades, except one co-processed MCC, exhibited identical moisture sorption-desorption profiles, adsorbing 9.5-10.3% moisture at 80% RH and 12.4-13.5% at 90% RH. Prosolv® 730, a co-processed MCC with silicon dioxide and copovidone, was the only exception showing lower moisture uptake of ~11% and ~8 % at 90 and 80% RH, respectively. Powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) confirmed the semi-crystalline nature of all grades, with increased crystallinity observed at 90% RH, except for Prosolv® 730, which had only minimal change in crystallinity at 90% RH. BET Type II moisture sorption-desorption isotherms were observed with all MCC grades. There were hysteresis loops in the sorption-desorption profiles, where the difference between moisture contents of desorption and sorption profiles was larger when the materials were exposed to the maximum 90% RH versus those exposed to 80% RH, which indicates that moisture is more tightly bound when it is exposed to a higher RH. Despite the reported differences in moisture contents of different marketed MCC grades, this investigation demonstrates that they equilibrate to similar moisture contents when exposed to identical RH conditions. Therefore, protection from humidity would be required to maintain any difference in moisture content among different MCC grades during product processing, stability testing, and storage.

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KEY WORDS: Microcrystalline cellulose, MCC, co-processed excipients, moisture sorption-desorption, hysteresis loop, thermal analysis, crystallinity, differential scanning calorimetry, powder X-ray diffraction, silicified microcrystalline cellulose

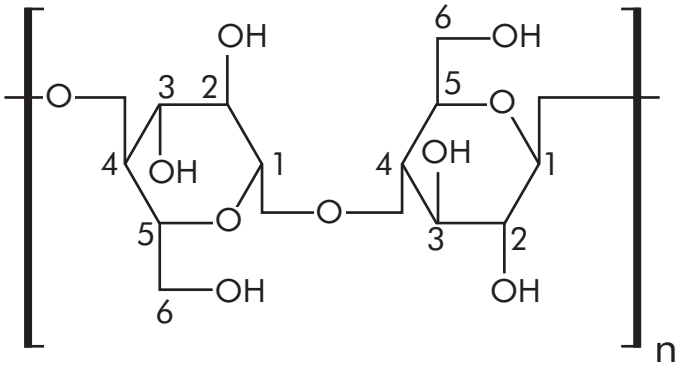
INTRODUCTION

Excipients are critically important to the development of drug products, as active pharmaceutical ingredients (API) are rarely taken by or administered to patients alone. Rather, excipients ranging from less than 5% w/w to as high as 99% w/w are used in developing drug products to make the size of individual units convenient for administering to patients, increase accuracy in dosing, improve drug absorption, improve therapeutic effects by modifying drug release rates, improve manufacturability of products, and so forth (1,2). However, despite the importance of excipients to the development of drug products, not as much attention is given in the pharmaceutical field to the physicochemical properties and variability of excipients as is given to different APIs. To fill this gap, we have undertaken systematic investigations of the physicochemical properties of different classes of pharmaceutical excipients as part of our teaching and research program (3–9)

Microcrystalline cellulose (MCC) is one of the most versatile and widely used pharmaceutical excipients, serving multiple functions, including as a diluent, dry binder, disintegrant, and absorbent in solid oral dosage forms. Its widespread application can be attributed to its excellent compressibility, superior binding properties, and good flow characteristics. Additionally, it has versatile functionality in various dosage forms as a spheronizing aid for pellet formation and a matrix former for sustained drug release formulations (10). However, like many cellulose-based materials (8), MCC exhibits hygroscopic behavior, making its moisture sorption characteristics a critical quality attribute that demands a thorough understanding for optimal pharmaceutical applications (11).

The interaction of MCC with atmospheric moisture is complex and dynamic, significantly influencing its functionality in pharmaceutical formulations. Moisture affects several critical quality attributes of MCC, including flowability, compressibility, and mechanical strength of the resultant tablets (11). Studies have shown that changes in relative humidity (RH) can alter the mechanical properties of MCC-based tablets, with higher moisture generally leading to decreased tablet tensile strength and increased tablet capping tendency. Moisture impacts MCC's functional properties through several mechanisms. In particular, moisture can disrupt hydrogen bonding between cellulose chains at a molecular level, affecting the material's mechanical properties (12). In one recent study, Koumbogle et al. (13) demonstrated that moisture sorption may negatively impact the tableting of MCC as moisture evaporation from the powder bed and accumulation at the punch-tablet interfaces can induce capillary condensation of water between the tablet and the punch during the dwell time, leading to sticking. Based on these considerations, it is essential that the moisture content of the MCC used be controlled for optimal processing and performance of dosage forms.

Figure 1. Chemical structure of microcrystalline cellulose. The repeating unit of two anhydroglucose moieties with the 1,4β-glycosidic bond between them is shown, where 'n' represents the number of units in a chain. The complete chain has two -OH groups at the two ends.



The chemical structure of MCC is shown in Figure 1. It is generally produced by the acid hydrolysis of cellulose from natural sources, primarily wood and cotton, whereby the chain length of cellulose reduces to a molecular weight in the range of 30,000 to 50,000 (14,15). The hydrolyzed materials are obtained as aqueous slurries, which are then neutralized, washed, and dried. Spray drying is currently the preferred method for drying MCC. Different commercial grades of MCC are produced by controlling their particle size distribution, bulk density, specific surface area, and moisture content during drying, while their fundamental chemical structure remains consistent.

The issue of the moisture content of MCC remains contentious. It is generally recognized that moisture sorption by MCC occurs by hydrogen bonding of water with the hydroxyl groups of MCC. Therefore, different MCC grades should exhibit comparable moisture sorption-desorption patterns, as the interactions between MCC and water are primarily governed by the cellulose chemical structure rather than physical characteristics (14). However, there are different reports in the literature, especially from the manufacturers of MCC, that the commercially available MCC of different grades and sources may differ in their moisture contents. It has been suggested that MCC grades with lower moisture contents should be used for moisture-sensitive drugs. However, no explanation for how moisture contents for different MCC grades vary despite having similar chemical structures, and whether the difference could be retained during the processing and storage of drug products, has been reported in the literature. Therefore, understanding similarities and differences in moisture sorption and desorption patterns across various MCC grades is crucial for optimal excipient selection and process design in pharmaceutical manufacturing.

For determining any possible differences in equilibrium moisture contents of different MCC grades, we have conducted a comparative investigation of moisture sorption and desorption as a function of humidity by 13 commercially available grades, where 11 are regular MCC, and two are co-processed MCC. While there are several studies on moisture sorption and desorption by individual MCCs, comparing multiple grades under identical conditions is scarce. Such a comparison is essential for understanding whether the chemical similarity of different MCC grades translates to similar moisture sorption behaviors despite their physical differences.

MATERIALS

Table 1 lists 13 MCC grades used in the present investigation, along with the names of their manufacturers and some relevant physicochemical properties collected from the literature. Eleven of them are regular MCCs with differing physical properties, and two are co-processed MCCs containing colloidal silicon dioxide only or a combination of colloidal silicon dioxide and copovidone. Microcrystalline cellulose containing silicon dioxide is also commonly known as silicified microcrystalline cellulose or SMCC. There are certain differences in particle sizes of MCC grades in Table 1; however, their bulk densities are around 0.3 and do not differ significantly. According to the manufacturers' brochures, the moisture contents of different grades could differ. All materials were supplied as gifts by their manufacturers.

METHODS

Moisture sorption analysis

Moisture sorption and desorption studies were conducted using a dynamic vapor sorption analyzer (VTI SA, TA Instruments, Wilmington, DE, USA) by applying experimental parameters developed previously in our laboratory (9). Briefly, the accurately weighed amount of approximately 25 mg of sample was first dried at 40 °C and ~0% RH for 1h using the dry nitrogen flow. Following drying, the relative humidity (RH) of the sample chamber was increased to the range of 10 to 90% RH at 10% RH intervals at 25 °C to assess moisture sorption by the sample. Subsequently, desorption studies were conducted by decreasing humidity from 90% to 10% RH at 10% RH intervals to determine the loss of moisture by the materials. This study defined equilibrium with the exposed RH as a percentage weight change below 0.004% within 5 minutes. Each equilibration period was allowed a maximum of 24 h (1440 min) to reach this threshold. If the weight change remained below 0.004% in 5 minutes, the RH progressed to the next step. Otherwise, the sample remained at the given RH for up to 24 h before transitioning to the next RH level.

In addition to moisture sorption and desorption between the RH range of 10 to 90%, they were also studied, in separate experiments, between 10 and 80% RH to determine what effects, if any, the exposure to different high humidity conditions might have on the desorption profile and thus the hysteresis loops produced by the different grades of MCC.

Solid-state characterization of MCC samples

Solid state properties of several MCC grades before and after exposure to high humidity were characterized by differential scanning calorimetry and powder X-ray diffraction. To incorporate predetermined amounts of moisture into the MCC samples, we used the moisture sorption analyzer according to a method previously developed by Patel and Serajuddin (9). An accurately weighed sample (~15 mg) was taken in a flat-bottom aluminum pan for moisture sorption analysis. The sample

Table 1: Microcrystalline cellulose (MCC) used for moisture sorption-desorption analysis*

Trade name with grades	Manufacturer	Average particle size (μm)	Moisture content (%)	Bulk Density (g/cm^3)	Comments
Avicel® PH 200	IFF (International Flavors & Fragrances) Pharma Solutions, New York, USA**	180	2-5	0.29-0.36	Superior flowability; optimized for direct compression
Avicel® PH 101	Same as above	50	3-5	0.26-0.31	Excellent binding properties
Avicel® PH 102	Same as above	100	3-5	0.28-0.33	Enhanced flow; preferred for direct compression
Avicel® PH 103	Same as above	50	NMT 3.0***	0.26-0.31	Low moisture grade for moisture-sensitive APIs
Avicel® PH 105	Same as above	20	NMT 5.0	0.20-0.30	High surface area; wet granulation applications
Avicel® PH 112	Same as above	100	NMT 1.5	0.28-0.34	Ultra-low moisture, for moisture sensitive formulations
Avicel® PH 113	Same as above	50	NMT 2.0	0.27-0.34	Lower moisture variant of PH 101
Vivapur® 101 (VIVA 101)	JRS Pharma LP, Patterson, NJ, USA	65	Max 7.0	0.26-0.31	High compactibility
Vivapur® 102 (VIVA 102)	Same as above	130	Max 7.0	0.28-0.33	Improved flow
Emcocel® 50M (EMO 50M)	Same as above	65	Max 6.0	0.25-0.37	High compactibility
Emcocel® 90M (EMO 90M)	Same as above	130	Max 6.0	0.25-0.37	Enhanced flow
Prosolv® SMCC 90 (PS_SMCC)	Same as above	125	Max 6.0	0.25-0.37	Co-processed or silicified MCC, hence SMCC, with 2% colloidal silicon dioxide. Used in formulation for a balance of flow and compaction.
Prosolv® 730 (PS_730)	Same as above	50	Not reported	Not reported	Co-processed MCC with colloidal silicon dioxide and copovidone. The exact composition is proprietary. Developed to solve challenges presented by oily active ingredients and poorly water-soluble, lipophilic substances.

*All specifications are based on manufacturers' technical documentation. **IFF announced the sale of its Pharma Solutions business to Roquette Frères S.A., France, in March 2025. ***NMT = Not More Than.

was then dried inside the moisture sorption analyzer at 50 °C for 15 minutes by purging with dry nitrogen, followed by purging with nitrogen for another 60 minutes when the samples had cooled down to 25 °C and equilibrated. The dried sample was then exposed to 25 °C/90% RH inside the VTI moisture sorption analyzer until the pre-determined weight gain due to moisture sorption was achieved. For DSC analysis, the sample was immediately transferred to a DSC pan and hermetically sealed to prevent moisture loss. For PXRD analysis, the sample pan was quickly transferred to the PXRD sample holder, and analysis was conducted immediately to minimize any potential moisture loss during the measurement. The rapid sample transfer and immediate analysis ensured that the moisture content remained representative of the equilibrated state.

Differential scanning calorimetry (DSC)

DSC analysis of the sealed sample was conducted using a Q200 DSC analyzer (TA Instruments, DE, USA). Approximately ~5-10 mg of the sample was weighed accurately on a Tzero aluminum DSC pan and hermetically sealed to perform modulated DSC. For the analysis of 'as is' materials received from their manufacturers, a pinhole was made in the lid to allow evaporation of any volatile matter produced. The ramp rate of 10 °C was used. However, as mentioned above, no pinhole was used when it was necessary to control the moisture content within the sealed pan precisely. As previously reported (9), in such a case, moisture may partially escape from the sample matrix during heating and become trapped in the headspace of the sealed pan rather than being completely lost. The resulting DSC thermograms were examined for endothermic events that might appear differently in moisture-treated MCC samples compared to the 'as is' samples (as received from the manufacturer). This analysis allowed the identification of any thermal transitions associated with added moisture content in the humidity-exposed MCC samples.

Powder X-ray diffraction (PXRD)

Powder X-ray diffractograms of MCC were obtained using a Shimadzu XRD-6000 diffractometer (Shimadzu, Kyoto, Japan) equipped with a Ni-filter and monochromatic Cu-Kα radiation source. The diffractometer was operated at a current of 30 mA with a copper anode tube at a generator voltage of 40 kV. Samples were scanned from 5° to 45° 2θ at a rate of 2° per minute, as explained by Patel et al. (7). Following equilibration at 90% RH, the sample was immediately transferred to the PXRD sample holder to preserve the moisture-equilibrated state and prevent unintended moisture loss. The PXRD patterns generated were analyzed for the MCC samples exposed to 90% RH moisture to identify any characteristic peaks compared to the 'as is' MCC samples.

RESULTS AND DISCUSSION

Moisture sorption and desorption by different MCC grades between 0 and 90% RH

Figure 2 shows the moisture sorption and desorption isotherms of various microcrystalline cellulose (MCC) grades at 25 °C**,** where weight gains and losses are plotted as a function of relative humidity between 0 and 90% RH. All grades, except for one, exhibit remarkably similar moisture sorption and desorption profiles, with moisture content reaching approximately 12.4-13.5% w/w at 90% RH. A notable exception is Prosolv® 730, which shows a lower moisture uptake, peaking at 10.9% w/w at 90% RH. A hysteresis loop is observed between the sorption and desorption curves for all MCC grades, and is particularly pronounced at RH levels above 60%. The sorption isotherms (Figure 2A) reveal a gradual increase in moisture uptake up to about 50% RH, followed by a steeper increase at higher RH levels. The desorption curves (Figure 2B) show a similar trend across all MCC grades, with a more gradual release of moisture compared to the sorption process, demonstrating a hysteresis loop (Figure 2C). The moisture sorption or desorption profiles of different grades of MCC are similar, except for Prosolv® 730, as the plots overlap and cannot be distinguished from each other. For this reason, individual moisture contents of different samples at different RH are tabulated in Table 2, which also demonstrates no significant differences in moisture contents of various grades of MCC, except for Prosolv® 730, during moisture sorption and desorption.

According to Brunauer et al. (16), there are six main types of isotherms for the adsorption of gases or vapors by solids (Types I to VI), each reflecting different adsorbent-adsorbate interactions and pore structures. The sorption-desorption isotherms in Figure 2 demonstrate a Type II isotherm pattern for all MCC

Figure 2. Moisture sorption and desorption profiles of different grades of microcrystalline cellulose (MCC) between 10 and 90% relative humidity (RH): (A) samples were dried at 0% RH and then weight gains were recorded by raising RH gradually up to 90% RH at 10% intervals, (B) samples equilibrated at 90% RH were subjected to a gradual decrease in humidity at 10% intervals down to 0% RH and weight loss was recorded, and (C) moisture sorption and desorption isotherms of various MCC grades between 0 and 90% RH range are overlaid to determine the hysteresis loop.

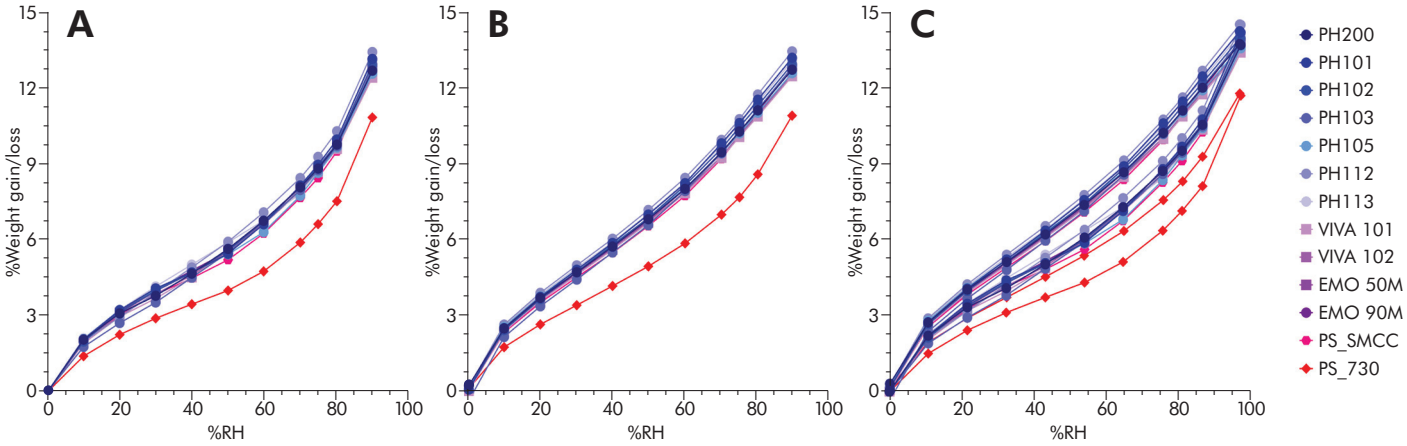


Table 2: Moisture contents from moisture sorption-desorption isotherms of various MCC grades between 0 and 90% RH

% RH	Avicel PH 200	Avicel PH 101	Avicel PH 102	Avicel PH 103	Avicel PH 105	Avicel PH 112	Avicel PH 113	Vivapur 101	Vivapur 102	Emcocel 50M	Emcocel 90M	Prosolv® SMCC 90	Prosolv® 730
Moisture Sorption													
0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10.0	2.1	2.1	2.0	1.8	2.1	2.0	2.1	1.9	1.9	2.0	2.0	1.9	1.4
20.0	3.1	3.2	3.1	2.7	3.2	3.0	3.2	3.0	3.1	3.1	3.2	3.0	2.3
30.0	3.8	4.1	4.0	3.5	4.1	4.0	4.2	3.7	3.9	4.0	4.0	3.9	2.9
40.0	4.7	4.7	4.7	4.5	4.7	5.0	5.0	4.5	4.6	4.7	4.8	4.5	3.5
50.0	5.7	5.5	5.6	5.5	5.4	6.0	5.9	5.5	5.6	5.5	5.6	5.2	4.0
60.0	6.8	6.6	6.7	6.6	6.3	7.1	6.8	6.6	6.7	6.7	6.6	6.3	4.8
70.0	8.1	8.2	8.1	8.0	7.8	8.5	7.8	7.9	8.0	8.0	8.0	7.7	5.9
75.0	8.8	9.0	8.9	8.8	8.7	9.3	8.8	8.7	8.7	8.8	8.8	8.5	6.6
80.0	9.8	10.0	9.8	9.7	9.7	10.3	9.8	9.6	9.7	9.7	9.7	9.5	7.5
90.0	12.7	13.2	13.0	12.8	12.6	13.5	13.1	12.4	12.6	12.7	12.8	12.9	10.9
Moisture Desorption													
80.2	11.2	11.6	11.3	11.2	11.1	11.8	11.5	10.9	11.0	11.2	11.1	11.1	8.6
75.1	10.3	10.6	10.5	10.3	10.2	10.8	10.7	10.1	10.2	10.3	10.3	10.1	7.7
70.1	9.5	9.8	9.6	9.5	9.4	10.0	9.8	9.3	9.3	9.5	9.5	9.2	7.0
60.0	8.1	8.3	8.2	8.0	8.1	8.5	8.3	7.9	7.9	8.0	8.0	7.8	5.9
49.9	6.9	7.0	6.9	6.6	6.9	7.2	7.1	6.7	6.7	6.8	6.8	6.6	5.0
40.0	5.8	5.9	5.8	5.5	5.9	6.1	5.9	5.7	5.7	5.7	5.7	5.5	4.2
30.1	4.8	4.9	4.8	4.5	4.9	5.0	4.9	4.6	4.7	4.7	4.7	4.6	3.5
20.0	3.8	3.8	3.7	3.4	3.8	3.9	3.9	3.6	3.6	3.6	3.7	3.6	2.7
10.0	2.5	2.6	2.5	2.2	2.6	2.7	2.6	2.4	2.4	2.4	2.5	2.4	1.8
0.2	0.3	0.1	0.1	-0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2

grades, indicating multilayer adsorption followed by capillary condensation at higher RH levels. The similarity in sorption-desorption behavior across various MCC grades (excluding Prosolv® 730) suggests that the fundamental moisture interaction mechanisms remain consistent despite differences in physical properties. This consistency can be attributed to the similar chemical structure of cellulose across different MCC grades (14). It has been reported that moisture sorption by MCC could also be influenced by its crystallinity (17) since the higher crystallinity would lead to lower moisture sorption. The similar moisture sorption-desorption profiles of 12 of the 13 MCC grades used in the present investigation indicate that their crystallinity is also similar.

Two co-processed MCCs, Prosolv® SMCC 90 and Prosolv® 730, have been used in the present investigation. Between them, Prosolv® SMCC 90 is a co-processed or silicified MCC with 2% colloidal silicon dioxide (CSD). Based on an extensive study comparing physicochemical properties of Prosolv® SMCC 90 with those of standard MCC, Tobyn et al. (18) determined that the two materials are chemically and physically very similar. Accordingly, the moisture sorption and desorption of Prosolv® SMCC 90 in the present investigation were identical to the regular MCC grades.

Interestingly, compared to Prosolv® SMCC 90 (PS_SMCC) or any regular grade of MCC, the moisture sorption by Prosolv® 730 in the present investigation is significantly lower (Figure 2). As will be shown later, the PXRD patterns of Prosolv® 730 also appear similar to or slightly less intense than those of the other grades of MCC, indicating that it would be similarly or marginally less crystalline. Thus, it was expected that Prosolv® 730 would have similar or higher moisture uptake based on its crystallinity. The apparent discrepancy between the observed lower and the expected higher moisture uptake by Prosolv® 730 could be related to its composition and method of preparation, which are proprietary information and not reported in the literature. Its manufacturer only reported that it contains CSD and copovidone, and it was developed to address challenges presented by oily active ingredients and poorly water-soluble, lipophilic substances. Without further information about the relative amounts of CSD and copovidone added and the preparation method indicating how these materials were deposited on MCC, the mechanism for its lower moisture sorption compared to Prosolv® SMCC 90 or any other MCC grades may not be ascertained. It could be due to the difference in moisture sorption between MCC and the added materials like CSD and copovidone, or it is possible that the addition of copovidone blocked pores within MCC, as it was reported previously that PVP could prevent liquid adsorption into the microstructure of a porous material (19).

The hysteresis loop observed between sorption and desorption curves implies that MCC undergoes structural changes or forms strong hydrogen bonds with water molecules during the moisture sorption process. This phenomenon, known as moisture sorption hysteresis, is common in cellulosic materials and has been reported in previous studies with MCC (17, 20, 21). The hysteresis suggests that the equilibrium moisture content at any given RH depends on whether the equilibrium is approached by adsorption or desorption, a critical consideration for pharmaceutical processing and storage. The gradual increase in moisture uptake up to about 60% RH, followed by a steeper increase at higher RH levels, can be attributed to initial monolayer and multilayer adsorption at lower RH, transitioning to capillary condensation in the MCC's porous structure at higher RH (22). Zografi and Kortny (23) postulated that moisture sorption by MCC ensues by its penetration into the amorphous portions of the cellulose structure and interaction with individual anhydroglucose units, and at higher humidity, it likely exists in at least 3 states: tightly bound to anhydroglucose unit, less tightly bound, and bulk water. This behavior is consistent with the Brunauer-Emmett-Teller (BET) adsorption theory (24).

Moisture sorption and desorption by various grades of MCC between 0 and 80% RH

Figure 3 presents the moisture sorption-desorption behavior of various MCC grades at 25 °C with a maximum RH of 80%, designed to investigate whether limiting the maximum humidity exposure would affect the hysteresis phenomenon observed earlier at 90% RH in Figure 2. Individual data are tabulated in Table 3 as the isotherms overlap in Figure 3 and cannot be distinguished. The sorption-desorption isotherms in Figure 3 maintain the characteristic Type II isotherm pattern, consistent with the behavior observed in Figure 2. A comparison of the moisture sorption profiles in Figure 3A with those in Figure 2A shows that, as expected, there

Figure 3. Moisture sorption and desorption profiles of different grades of microcrystalline cellulose (MCC) between 10 and 80% relative humidity (RH): (A) samples were dried at 0% RH and then weight gains were recorded by raising RH gradually up to 80% RH at 10% intervals, (B) samples equilibrated at 80% RH were subjected to a gradual decrease in humidity at 10% intervals down to 0% RH and weight loss was recorded, and (C) moisture sorption and desorption and isotherms of various MCC grades between 0 and 80% RH levels are overlaid to determine the hysteresis loop.

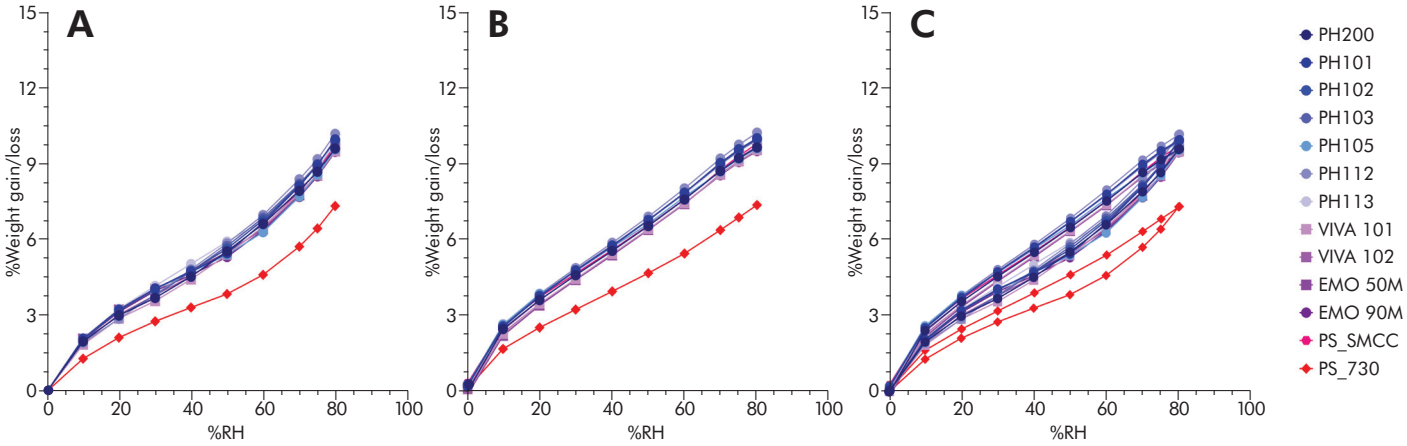


Table 3: Moisture contents from sorption-desorption isotherms of various MCC grades to 80% RH level

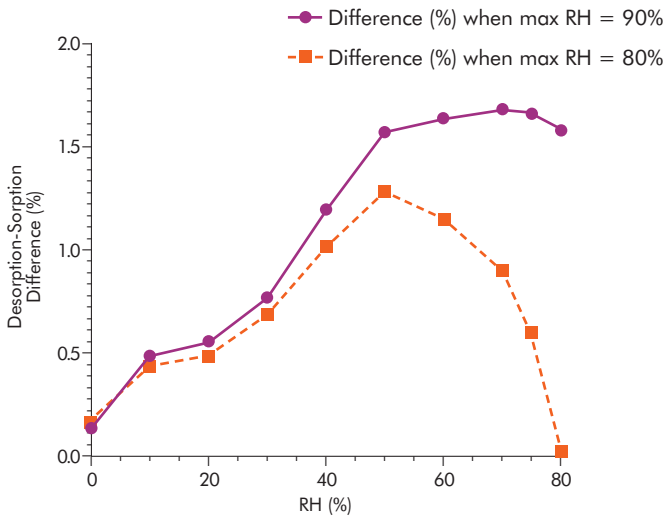
% RH	Avicel PH 200	Avicel PH 101	Avicel PH 102	Avicel PH 103	Avicel PH 105	Avicel PH 112	Avicel PH 113	Vivapur 101	Vivapur 102	Emcocel 50M	Emcocel 90M	Prosolv® SMCC 90	Prosolv® 730
Moisture Sorption													
0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10.0	2.0	2.1	2.0	2.0	2.1	1.9	2.1	1.8	1.9	2.1	2.0	2.1	1.3
20.0	3.0	3.2	3.2	3.0	3.2	2.9	3.3	2.9	3.0	3.2	3.1	3.2	2.1
30.0	3.7	4.1	4.0	3.8	4.0	3.8	4.2	3.6	3.8	4.1	4.1	4.0	2.8
40.0	4.5	4.7	4.8	4.7	4.7	4.8	5.0	4.4	4.6	4.8	4.6	4.7	3.3
49.9	5.5	5.5	5.6	5.8	5.4	5.9	5.9	5.4	5.5	5.5	5.3	5.4	3.9
59.9	6.6	6.7	6.8	6.9	6.3	7.0	6.8	6.5	6.6	6.4	6.4	6.5	4.6
70.0	7.9	8.1	8.2	8.2	7.7	8.4	7.9	7.8	8.0	7.8	7.7	7.9	5.7
75.0	8.7	9.0	9.0	9.0	8.6	9.2	8.8	8.6	8.7	8.6	8.5	8.8	6.5
79.9	9.6	10.0	10.0	9.9	9.6	10.2	9.9	9.5	9.6	9.5	9.5	9.7	7.3
Moisture Desorption													
80.2	9.6	10.0	10.0	9.9	9.6	10.2	9.9	9.5	9.7	9.5	9.5	9.8	7.4
75.1	9.2	9.6	9.5	9.5	9.2	9.7	9.5	9.1	9.2	9.1	9.1	9.3	6.9
70.0	8.7	9.0	9.0	9.0	8.7	9.2	8.9	8.6	8.7	8.6	8.5	8.7	6.4
60.1	7.6	7.8	7.8	7.8	7.7	8.0	7.8	7.4	7.6	7.4	7.4	7.6	5.4
50.1	6.5	6.7	6.8	6.7	6.6	6.9	6.8	6.4	6.5	6.4	6.4	6.5	4.6
40.2	5.5	5.7	5.7	5.7	5.7	5.9	5.8	5.4	5.5	5.4	5.4	5.6	3.9
30.1	4.6	4.8	4.8	4.7	4.7	4.8	4.8	4.4	4.6	4.4	4.4	4.6	3.2
20.1	3.6	3.7	3.7	3.7	3.8	3.8	3.8	3.4	3.6	3.4	3.4	3.7	2.5
10.0	2.4	2.5	2.5	2.5	2.6	2.6	2.6	2.2	2.4	2.2	2.3	2.6	1.6
0.2	-0.1	0.2	0.2	0.2	0.2	0.2	0.2	-0.1	0.0	-0.2	-0.1	0.3	0.1

is no significant difference between them. In both cases, the maximum moisture content reached at 80% RH was 9.5-10.3% w/w for all MCC grades, except for Prosolv® 730, which continued to show distinctly lower moisture uptake, reaching 7.5% w/w at 80% RH. The primary difference between the exposure to 80% RH vs. 90% RH is in the hysteresis loops produced between moisture sorption and desorption. Although the hysteresis loop persisted between sorption and desorption curves (Figure 3C) when the materials were exposed up to a maximum of 80% RH, its magnitude was notably reduced compared to the 90% RH study (Figure 2C). This observation aligns with research by Mirranyan et al. (17), which demonstrated that higher relative humidity exposure leads to stronger water cellulose interactions and more pronounced hysteresis effects due to increased moisture retention in the cellulose structure.

To further clarify the effect of high humidity exposure on the moisture sorption by MCC, the differences between moisture contents of one representative MCC grade, Avicel PH101, between desorption and sorption processes for samples exposed to maximum 90% and 80% RH conditions are plotted in Figure 4. These results show that there could be about a 1.5-1.7% difference in moisture contents of MCC if the sample is pre-exposed to 90% RH compared to the pre-exposure to 80% RH, where the difference is about 1-1.2%. It is possible that more moisture is adsorbed into the deeper pores of MCC after exposure to higher RH, which does not easily desorb when the RH is lowered.

The persistence of hysteresis, even after exposure to a maximum of 80% RH, suggests that significant structural modifications or strong water-cellulose interactions occur below this humidity threshold. The reduced but still present hysteresis loop indicates that while limiting maximum RH exposure can minimize moisture-related structural changes, it cannot eliminate them. This finding aligns with observations by Sun (11) who reported that water-cellulose interactions begin at relatively low humidity levels and become progressively stronger as RH increases. The sorption patterns demonstrate that the fundamental moisture interaction mechanisms remain consistent across different MCC grades at both 80% and 90% RH, supporting the hypothesis that these interactions are primarily governed by the common chemical structure of cellulose rather than physical variations between grades (25). This understanding is particularly relevant for pharmaceutical processing, as it suggests that moisture-related quality control measures may be similar across different MCC grades, except for the co-processed material like Prosolv® 730 discussed earlier.

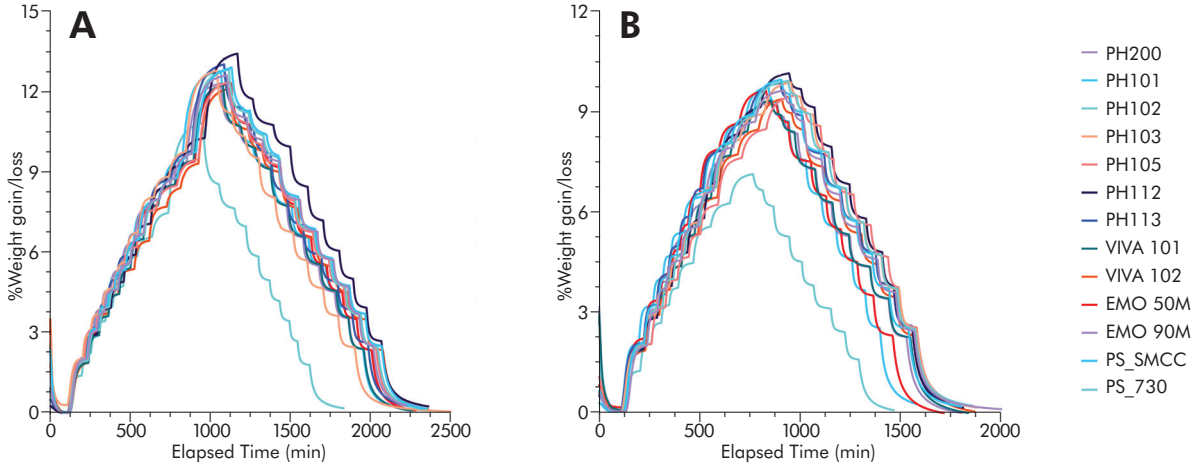
Figure. 4: Comparison of hysteresis magnitude (desorption-sorption difference) for Avicel PH101 when exposed to maximum relative humidity (RH) of 90% versus 80%. The data show reduced hysteresis when maximum RH exposure is limited to 80%, with the greatest differences observed between 50-70% RH.



Moisture Sorption-Desorption Kinetics of Different MCC Grades

The time-dependent moisture sorption-desorption kinetics of various MCC grades at 25 °C are given in Figure 5, where RH was changed at 10% steps in both sorption and desorption profiles. The data reveal similarities in the sorption-desorption kinetics among all MCC grades, except for Prosolv® 730, prepared by co-processing MCC with CSD and copovidone. The moisture uptake follows a stepwise pattern corresponding to incremental increases in RH from 10% to 90% (Figure 5A) and 80% (Figure 5B), followed by desorption to 0% RH. For most MCC grades, the sorption phase (ascending portion) shows rapid initial moisture uptake at each RH step, followed by a slow uptake to equilibrium. The maximum weight gains reached were approximately 12.4-13.5% for 90% RH exposure (Figure 5A) and 9.5-10.3% for 80% RH exposure (Figure 5B). The time required to reach equilibrium varied with RH level, generally requiring a longer time for equilibration at each step at higher

Figure 5: Graphical representation of moisture sorption-desorption times of all grades of MCC at 25 °C under experimental conditions of <0.004% weight change in 5 min and maximum equilibration time of 1440 min at each RH condition, where A gives moisture sorption times to 90% RH, and B gives moisture sorption times to 80% RH.



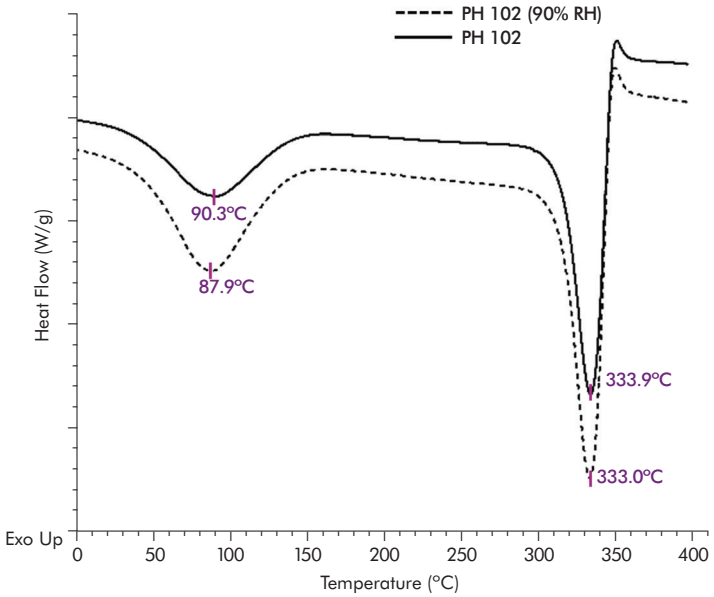
RH (>60%). The desorption phase exhibited slower kinetics than sorption, particularly in the RH range of 90 to 60% for Figure 5A and 80 to 60% for Figure 5B. This slower desorption rate suggests stronger binding of water molecules to MCC at higher humidity levels, likely due to the formation of multiple water layers and capillary condensation within the cellulose structure. Prosolv® 730 demonstrated notably different kinetics, reaching equilibrium more rapidly at each RH step and showing lower maximum moisture uptake of 10.9% w/w at 90% RH and 7.3% w/w at 80% RH. The mechanism for this difference has not been delineated. As mentioned earlier, it could be possible that copovidone might have blocked some of the pores of MCC, resulting in less capillary condensation of moisture.

The similarity in sorption-desorption kinetics among different MCC grades suggests that the rate-limiting step in moisture uptake and desorption is primarily governed by the fundamental cellulose structure rather than particle size, surface area, and related physicochemical characteristics.

Thermal Analysis of MCC

Any possible effects of moisture on crystallinity and thermal properties of different MCC grades were investigated by differential scanning calorimetry (DSC). First, the DSC scans of one MCC grade, Avicel PH102, were recorded from 0 °C to 400 °C using the material 'as is' (as received from the manufacturer) and after exposure to 90% RH to determine the general effects of temperature. The results are shown in Figure 6, where the materials "as received" and after exposure to 90% RH show dehydration endotherms with peaks around 88-90 °C. The endothermic peak was, however, smaller in the 'as is' sample than that exposed to 90% RH. Additionally, both samples had endothermic peaks at around 333-334 °C, followed by exotherms, which have been attributed in the literature to the decompo-

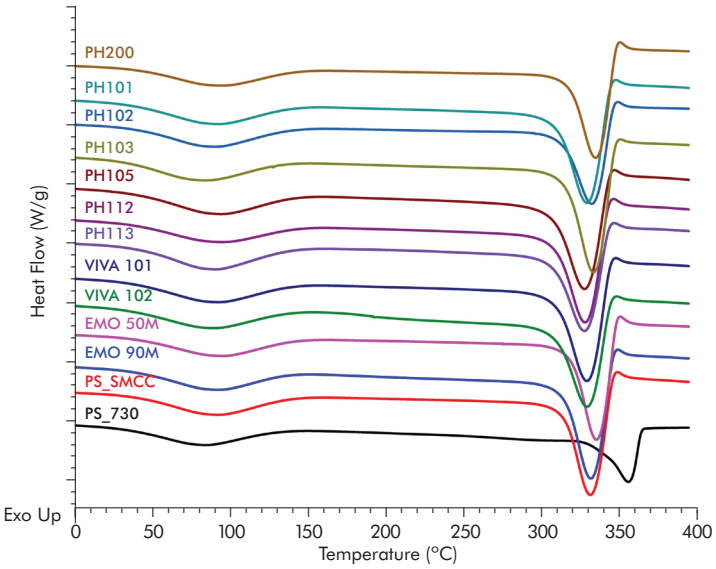
Figure 6: DSC scans of Avicel PH102 'as is' sample and after exposure to 90% RH.



sition of MCC due to its pyrolysis into levoglucosan and then charring (26). It requires high energy to be degraded, forming an endotherm, because of its high degree of molecular ordering.

To compare the thermal behavior of different MCC grades, the DSC scans were recorded from 0 °C to 400 °C (Figure 7). All MCC grades, except Prosolv® 730 (PS_730), exhibited similar DSC scans characterized by two distinct endothermic events, as shown in Figure 6. The first endothermic events were observed at approximately 80 to 90 °C, which, as mentioned earlier, corresponded to the dehydration process of sorbed and bound water molecules from the MCC structure. The second endothermic event, occurring at approximately 330 to 340 °C, could be attributed to the thermal decomposition of the cellulose structure. Prosolv® 730, a co-processed grade containing silicon dioxide and copovidone, showed a slightly lower dehydration temperature at 75 to 85 °C and a slightly higher decomposition temperature at 365 °C. Prosolv® SMCC 90, a silicified MCC co-processed with colloidal silicon dioxide only, did not show any deviation in thermal properties. The reason for the difference in thermal properties of Prosolv® 730 and other MCC grades has not been elucidated because of the proprietary nature of Prosolv® 730's composition and method of manufacture. The consistency in dehydration and decomposition temperatures across different MCC grades (excluding Prosolv® 730) suggests that the basic chemical structure and thermal properties remain largely unchanged despite particle size, moisture content, and morphology variations. There is also no significant effect of moisture sorption on the thermal properties of MCC grades. Although the DSC scans indicate that MCC is chemically stable at high temperatures, dehydration in the 50 to 100 °C range is particularly relevant for its pharmaceutical applications since any moisture release could impact product quality and stability during processing and storage.

Figure 7: DSC scans of 'as is' samples of all MCC grades from 0 °C to 400 °C.



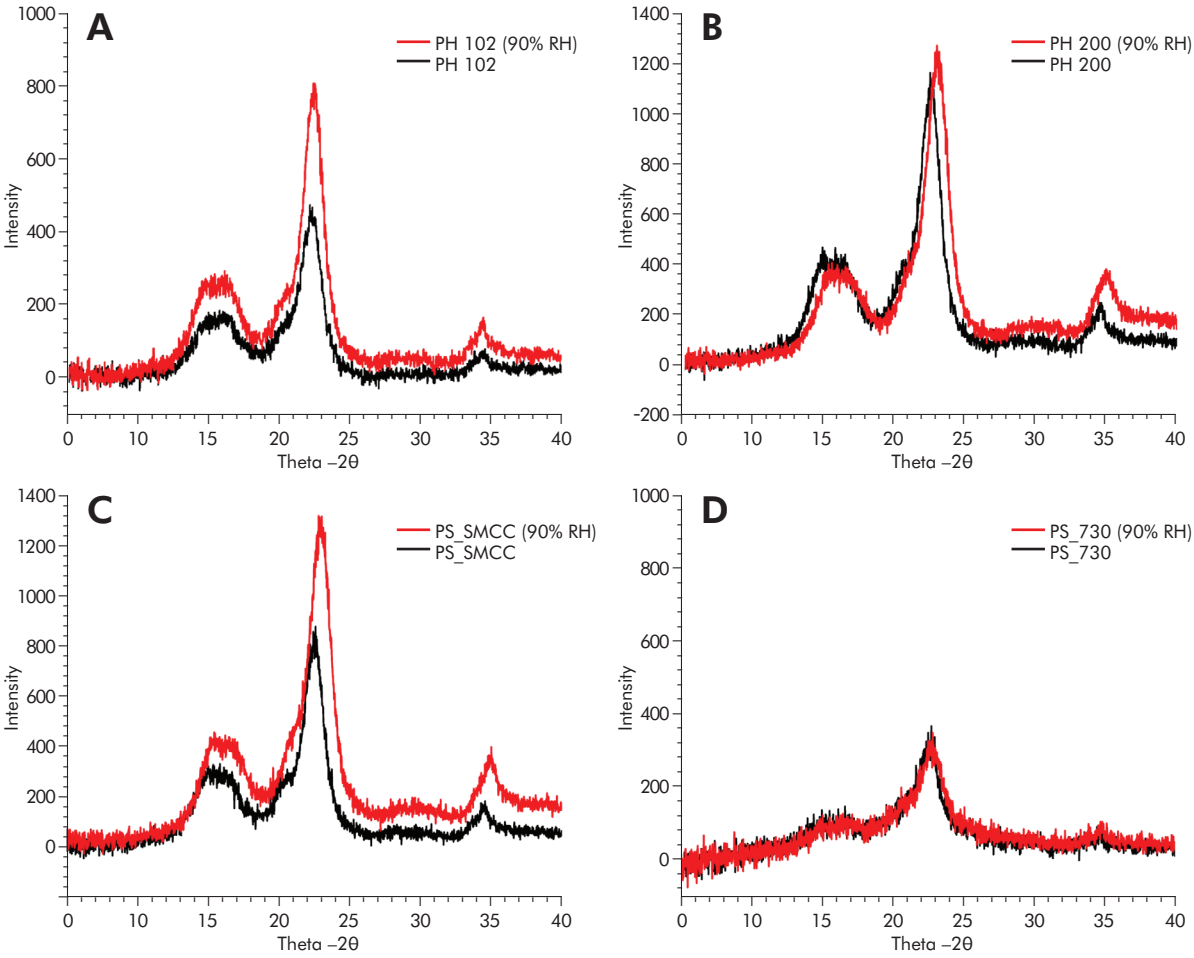
Analysis of the Effect of Moisture on Crystallinity by Powder X-ray Diffraction (PXRD)

The powder X-ray diffraction patterns of several MCC grades 'as is' and exposed to 90% relative humidity (RH) are presented in Figure 8. All diffractograms show characteristic peaks in the 10-35° 2θ range, with a primary diffraction peak at approximately 22°. PH 200 exhibits higher initial peak intensities than PH 102 in the 'as is' sample. Under 90% RH conditions, PH 102 shows a notable increase in peak intensity, particularly at 22°, while the diffraction pattern of PH 200 remains relatively unchanged. Prosolv® SMCC 90, despite containing 2% colloidal silicon dioxide and having an intermediate particle size, demonstrates behavior like PH 102. In contrast, Prosolv® 730 (Figure 8D), which contains colloidal silicon dioxide and copovidone, shows practically no intensity changes after humidity exposure, suggesting that copovidone may prevent the moisture-mediated structural reorganization observed in other grades.

The powder X-ray diffraction patterns of various MCC grades are compared in Figure 9. The diffraction patterns reveal a broad, amorphous hump in the 14-19° 2θ range, followed by a distinct crystalline peak at approximately 21-24°. All regular MCC grades exhibited similar PXRD patterns, suggesting comparable crystalline structures despite their different particle sizes and manufacturing processes. Like moisture sorption-desorption profiles and DSC scans, the co-processed Prosolv® 730 showed slightly different diffraction patterns than other grades. This variation might be attributed to copovidone, which may influence the overall crystalline structure of the material.

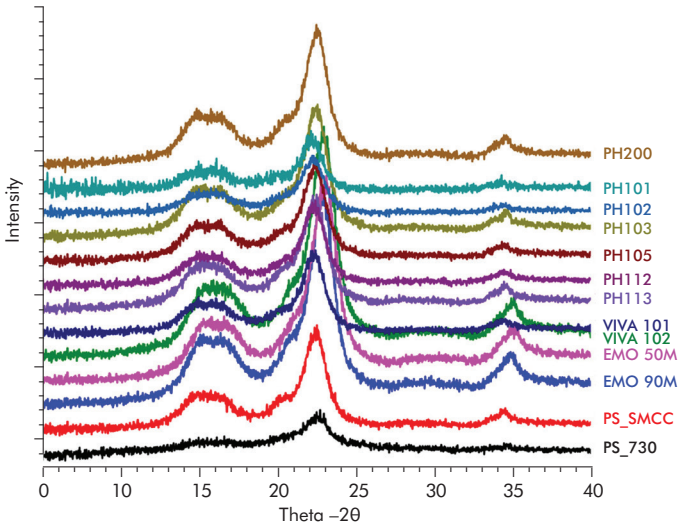
The presence of both crystalline and amorphous regions in the diffraction patterns suggests a semi-crys-

Figure 8: Powder X-ray diffraction (PXRD) patterns of various microcrystalline cellulose (MCC) 'as is' samples (black lines) and after exposure to 90% relative humidity (RH) (red lines). **A)** PH 102, **B)** PH 200, **C)** PS_SMCC (Prosolv® SMCC 90) (MCC with colloidal silicon dioxide), and **D)** PS_730 (Prosolv® 730; MCC with silicon dioxide and copovidone).



talline nature of the MCC grades, which is essential for their performance in pharmaceutical applications. This semi-crystalline character contributes to the material's ability to undergo plastic deformation during compression while maintaining structural integrity, making it an effective excipient in tablet formulation.

Figure 9: Powder X-ray diffraction patterns of 'as is' samples of microcrystalline cellulose.



SUMMARY AND CONCLUSION

A comprehensive investigation of the moisture sorption-desorption behavior of eleven regular, non-co-processed, MCC grades and two co-processed MCC grades was conducted. Despite their diverse physical properties (particle size distribution: 20-180 μm; bulk density: 0.20-0.37 g/cm³), all regular MCC grades exhibited remarkably similar moisture sorption-desorption behavior due to their identical chemical structure. All regular MCC grades displayed characteristic Type II moisture sorption isotherms with comparable moisture uptake (12.7-13.2 % w/w at 90% RH), similar thermal transitions in DSC scans (endotherms at 88-90 °C for dehydration and 333-334 °C for decomposition), and similar PXRD patterns for their semi-crystalline nature. Between the two co-processed MCC grades, Prosolv® SMCC 90, which contains 2% colloidal silicon dioxide, also showed moisture sorption-desorption behavior and thermal properties similar to the regular MCC grades. The other co-processed MCC, Prosolv® 730, containing colloidal silicon dioxide and copovidone, showed reduced moisture uptake (10.9% w/w at 90% RH vs. ~13% w/w for regular MCC and Prosolv® SMCC 90), which could be related to its composition and processing. The moisture sorption and desorption of MCC grades were studied at 10% RH steps, and at each step, the initial weight gain or weight loss was sharp, indicating rapid moisture sorption or desorption with the change in humidity. Additionally, the moisture sorption-desorption profiles showed hysteresis loops, indicating that all the moisture adsorbed during the increase in RH may not be desorbed readily when the RH is decreased. The hysteresis loop also depends on how high humidity the MCC is exposed to; the higher the RH, the bigger the hysteresis loop, suggesting moisture retention within MCC pores or moisture-related structural modifications.

Moisture sorption-desorption of the MCC grades in the RH ranges of 0 to 90 °C and 0 to 80 °C was studied to comprehensively understand the effect of moisture on the performance of different MCC grades. We believe the findings will provide valuable insights for pharmaceutical scientists in selecting and processing MCC grades, particularly for moisture-sensitive drugs where precise humidity control is critical. The relative humidity in different locations of a pharmaceutical manufacturing plant may vary widely, and even in a cGMP manufacturing facility, the RH may usually range from 30 to 60% RH (27). Moreover, drug products are exposed to 25 °C/60% RH, 35 °C/65% RH, and 40 °C/75% RH during their stability testing for registration in different countries (28). The effects of such variation in RH on the moisture sorption and performance of solid dosage forms containing MCC should be carefully evaluated. When a drug substance is susceptible to hydrolytic degradation, the moisture content of the drug product is especially important. Different low-moisture grades of MCC are available to keep the moisture content of drug products low, as shown in Table 1. Since it has been observed in the present investigation that such low-moisture grades of MCC can rapidly reabsorb moisture when exposed to relatively higher humidity conditions, care must be taken to protect any moisture-sensitive drug products from exposure to high humidity during manufacturing and after packaging. Preferably, a dry place should be used, which, according to the US Pharmacopeia (USP<659>11), is a place that does not exceed 40% average relative humidity at 20 °C.

ACKNOWLEDGEMENTS

The authors became interested in the present research after reading a post by Philippe Tschopp from Glatt Pharmaceutical Services on LinkedIn on December 19, 2022, where, under the title "Excipients & Drug Delivery — What else?", he asked a survey question: "Which type of microcrystalline cellulose has the lowest moisture content?". From the responses to the survey, there appeared to be no consensus on the moisture contents of different MCC grades. The authors thank Mr. Tschopp for this and other important posts on pharmaceutical excipients. The authors also gratefully acknowledge JRS Pharma (Patterson, NY) and IFF Pharma Solutions (New York, NY) for generously providing MCC samples used in this study.

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