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INVESTIGATING THE EFFECT OF MCC CONTENT IN THE FORMULATION ON PRODUCT ATTRIBUTES IN CONTINUOUS POWDER TO TABLET MANUFACTURING LINE

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Abstract

Continuous manufacturing (CM) offers improved efficiency and control in pharmaceutical production, but the influence of formulation on the stability performance across the unit operations remains a critical challenge. This study aims to establish a link between process outcomes with final product quality by investigating the effect of microcrystalline cellulose (MCC) content on the process performance and tablet properties in a continuous powder to tablet line (Consigma-25). Powder blends containing three ratios of lactose and MCC were processed under fixed operating conditions through twin-screw wet granulation, fluidized bed drying, conical milling, lubricant blending, and tableting. Inline Process Analytical Technologies (PAT), including built soft sensor, a near-infrared (NIR) moisture probe and a real-time granule size measurement probe, were employed to monitor in-process material behaviour. Produced tablets were collected over time and examine the properties. X-ray imaging technique was employed to evaluate tablet internal structure. Under fixed process settings, powder blend with reduced MCC content shows increased powder caking within the granulator, lower moisture content after drying, and higher bulk density of the milled granules. This led to higher tablet weight and higher actual tablet compression force, contributing to the formation of internal cracks in the tablet cross section area. In contrast, tablets with a higher MCC content showed more pronounced flashing problem, even though at relatively low actual compression force, the tablets showed extended edges during compression. In general, tablet tensile strength increases with higher MCC content; however, the actual compression force remains a critical factor influencing the extent of strength development. These observations emphasize the importance to consider both formulation and process settings when targeting optimal tablet performance in continuous manufacturing.

Keywords

Continuous wet granulation; Process analytical technology; Tableting

1. Introduction

The United States Food and Drug Administration (FDA) has advocated for the implementation of continuous manufacturing (CM) in pharmaceutical production due to its ability to improve product quality and reliability while simultaneously minimizing costs and waste (Fisher et al., 2022). In recent years, several studies have focused on the ConsiGma-25 continuous wet granulation line because it integrates multiple unit operations—including loss-in-weight powder feeding, twin-screw wet granulation, fluidized bed drying, milling, blending, and tableting—into one system. Some works focused on the long period operation by running one formulation to evaluate the system stability, looking on the process outcomes from each unit operation, such as twin screw torque, drying cell temperature, additionally using offline methods to monitor the granule moisture content and size distribution as well as the tablet hardness measurement by collecting samples with time (Vercruysse et al., 2015, 2013).

Oral solid dosage forms, particularly tablets, are the most common method of pharmaceutical drug delivery due to their stability and precise dosing (Zhao et al., 2022). Lactose and microcrystalline cellulose (MCC) are common excipients in the tablet manufacturing using wet-granulation method (Rowe et al., 2006). Formulation could become more challenging with higher lactose content due to its greater tendency to form powder caking in twin screw granulation especially more mass accumulation found at the kneading elements (Saleh et al., 2015). This is an undesirable phenomenon that leads to the material loss. Additionally, one research based on roller compaction found the tablet tensile strength does not improve because of the brittleness of lactose even under the high compression force (Rajkumar et al., 2019). On the other hand, formulations with higher MCC content introduce different challenges. As a plastically deforming material, MCC contributes to improve formulation compressibility, however, its high deformability can cause material to flow into the gap between the punches and die under high compression force, resulting in visible flashing or crowning defects that will affect the tablet volume and density (Missaghi et al., 2013; Paul et al., 2017). Although more MCC leads to strong tablet, this benefit is more evident under high compression force. While under low compression force, tablet properties are more strongly influenced by granule strength and porosity, in such case, the loss in compressibility becomes more pronounced in formulations with higher MCC content (Rajkumar et al., 2019).

Traditional quality control methods rely on offline measurements, which often require sample collection and extended testing time. Therefore, real-time quality control was required to be implemented in the continuous process, as recommended by the FDA's Process Analytical Technology (PAT) guidelines (FDA, 2004). Near Infra-Red (NIR) spectroscopy has been reported as an effective method which offers significant advantages over conventional method due to efficiency and non-destructive of estimation moisture content in pharmaceutical industry (Vanhoorne and Vervaet, 2020). This technology has been applied in the six-segmented fluidized bed dryer of the ConsiGma-25 line to develop models for predicting final moisture content (Fonteyne et al., 2014b, 2014a). Other studies have used NIR to monitor granule moisture under varying liquid-to-solid (L/S) ratios, offering insights into segmented dryer operation (Monaco et al., 2021) and linking L/S ratio effects to tablet porosity and tensile strength (Monaco et al., 2023). Particle size is another critical quality attribute (CQA) in pharmaceutical manufacturing, it is essential to monitor the dynamic variations and control the particle size to ensure tablet uniformity. Many studies have demonstrated the effectiveness of Spatial Filtering Velocimetry (SFV) technology in detecting particle size changes during fluidized bed granulation and coating processes (Folttmann et al., 2014; Langner et al., 2020; Nascimento et al., 2021; Roßteuscher-Carl et al., 2014). Although many studies have explored the inline measurement technique in continuous manufacturing to enhance process understanding and control, few have investigated the combined application of multiple probes by integrating two probes, such as Near Infrared (NIR) spectroscopy for monitoring moisture content and SFV technique for real-time particle size analysis, can provide a more comprehensive understanding of the process. In the rotary tablet press, tablet compression force could also serve as PAT method to monitor tablet mass deviation in the production, particularly when a fixed punch-to-punch (tip-to-tip) distance is used, as the tablet compression force is considered as function of both tablet thickness and tablet weight, which means any difference in thickness, weight or both will affect the actual compression force (Manley et al., 2019). However, these inline techniques are unable to offer information about the internal structure of the tablet. To address this limitation, x-ray imaging has been widely used as non-destructive method to assess tablet microstructure. Several studies have generated contour maps to visualize density distribution in tablets or to detect internal cracks, typically using single excipients or binary blends (Mazel et al., 2018; Sinka et al., 2004; Yost et al., 2019). These tablets are typically produced either by direct compression of raw powders or using granules obtained through dry granulation processes. However, few studies have explored the effect of varying MCC content on internal tablet structure using x-ray imaging, particularly using granules produced by continuous wet granulation lines.

This study will contribute toward the effect of formulation on the stability of each unit in continuous manufacturing line utilising advanced analytical techniques for comprehensive understanding. A near-infrared (NIR) probe is employed within a six-segment fluidized bed dryer to monitor the residual moisture content of granules over time, enabling real-time tracking of drying behaviour across formulations with varying MCC concentrations. Simultaneously, an in-line particle size measurement probe is used to assess the size of milled granules. Tablet properties are evaluated using a tablet tester and X-ray imaging to gain detailed insights into internal structure. Data collected from these in-line technologies, along with process outcomes from each unit, are critically analysed to assess their effectiveness and reliability. The findings provide valuable guidance for optimizing the manufacturing process and ensuring consistent product quality.

2. Materials

α-lactose monohydrate (Volac International Ltd., UK, d_{50}=45 μm), Microcrystalline Cellulose (MCC) (Chemicel 101, Chemfield Cellulose Pvt.Ltd., India, d_{50}=41.1 μm) and Low-substituted hydroxypropyl cellulose (L-HPC) (LH-21, Shin-Etsu Chemical Co. Ltd., Japan, d_{50}=44.1 μm) were used as raw materials. The formulations used in this have been listed in Table 1. For each powder blends, 7.5 kg of the powder blend was prepared and mixed in a tumbler mixer (Inversina 20 L) at 20 rpm for 10 minutes prior to being loaded into the feeding hopper. All component ratios were calculated on a weight basis.

Table 1. Formulation variable

Formulation set	Lactose	MCC	L-HPC
1	54%	42%	4%
2	72%	24%	4%
3	90%	6%	4%

3. Equipment and Method

3.1 Consigma-25 continuous line

Experiments were conducted using the ConsiGma-25 continuous manufacturing line (GEA, Collete TM, Wommelgem, Belgium) to evaluate the granulation and drying processes. Consigma-25 integrates the twin screw granulation process, segmented fluidized bed dryer, conical mill, lubricant blender and rotary tablet press and utilises pneumatic conveying system to transport the material from the bottom to the top through pipe. Powder feeding, granulation, drying and milling processes were experimented at constant process parameters (Table 2). Additional inline process analytical technology (PAT) tools, a Near Infra-Red (NIR) moisture content probe (FP710e, NDC Technology, Dayton, Ohio, USA) and inline particle size measurement probe (IPP 70-S/Se, Chemnitz, Germany) were utilised to monitor the granule moisture content in the segmented fluidized bed dryer and granule size distribution after milling respectively.

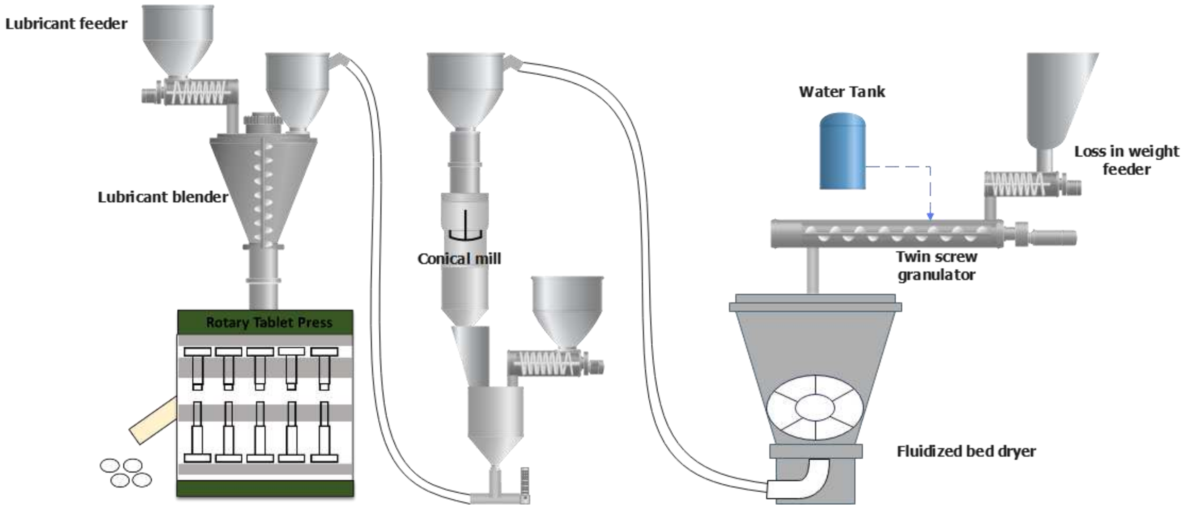


Figure 1. Schematic of Consigma-25 powder to tablet line

Table 2. Constant process parameters

Parameter	Value
Twin screw granulator	
Parameter	**Value**
Powder feed rate	10 kg/h
L/S	0.3
Screw configuration	2 kneading zones (6 elements each at 60° stagger)
Screw speed	400 rpm
Jacket temperature	20 ℃
Fluidized bed dryer	
Parameter	**Value**
Drying temperature	60 ℃
Drying air flow	360 m^3/h
Cell filling time	180 s
Drying time	660 s
Conical mill	
Parameter	**Value**
Mesh size	1575 µm
Milling speed	1200 rpm
Milling time	100 s

3.1.1 Loss in weight powder dosing unit

The K-Tron powder feeder operates on the loss-in-weight feeding principle. To enhance material flowability during the process, it is equipped with a bridge breaker inside the hopper. The feeding screws located beneath the hopper continuously convey the material into the twin-screw granulator.

3.1.2 Continuous twin screw granulator

The pilot scale twin screw granulator is powered by a rear-mounted motor to push and apply shear stress to the raw material. Granules are continuously transported along the barrel until leaving the granulator. The screw configuration mainly consists of conveying elements and two kneading zones. Each kneading zone contains kneading elements staggered at 60°, promoting efficient mixing and distribution of water with the powder.

3.1.3 Segmented fluidized bed dryer

The six cell- segmented fluidized bed dryer introduces the concept of filling time, which refers to the duration of material addition. This parameter determines the quantity of material loaded into each cell which is based on the powder feed rate and the filling time. Figure 2 illustrates the dynamic mass profile in the six-segmented fluidized bed dryer during the continuous process. According to the setting from Table 2, the mass of material in each cell was assumed constant at 500 g. For each cell, Material (500 g per cell) is introduced sequentially at fixed intervals (every 180 seconds), resulting in a linear mass increase. Drying continued following the completion of the filling stage. Beginning at 660 seconds, discharge of material occurs instantaneously at the same interval. As the material was removed in a short period, producing sharp vertical drops in the bed mass. This cycle then continued consistently until the filling process was paused. It is important to note that this representation considers only the accumulation of solids and excludes both the addition of liquid binder during twin-screw granulation and the water loss during fluidized bed drying.

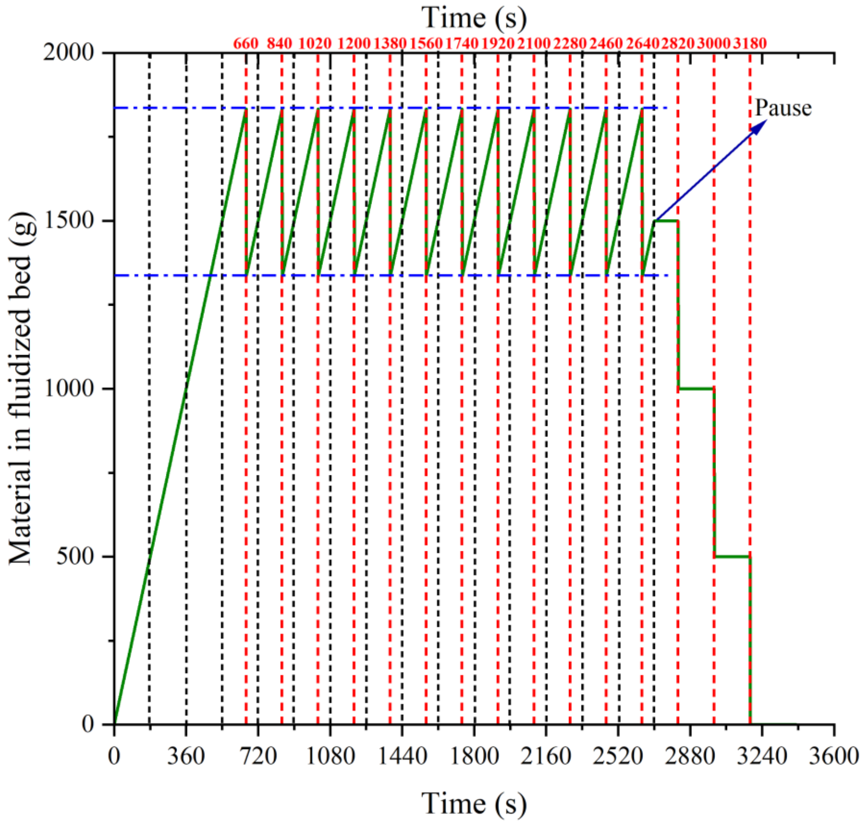


Figure 2. Amount of material inside the segmented fluidized bed. The minor tick at bottom x axis indicates the filling time (180 s in this work), the top x axis represents the discharging time for each cell.

3.1.4 Conical mill

The conical mill locates after the fluidized bed dryer. Dried granules from the segmented fluidized bed are transferred via a pneumatic conveying system to the hopper above the conical mill. During operation, a rotary valve feeds the granules into the mill, where they undergo gentle size reduction to ensure uniform particle size distribution.

3.1.5 Lubricant blender

The lubricant blender is the last operation unit in the continuous manufacturing line before materials entering rotary tablet press. This process adds and blends the lubricant (magnesium stearate) with the milled granules to ensure uniform lubricant distribution.

3.1.6 Rotary tablet press

A rotary tablet press operates by compressing granules into tablets through a rotating turret equipped with multiple sets of punches and dies. As the turret rotates, the powder is filled into the die cavity, then compressed between an upper and a lower punch to form a tablet. Module P rotary tablet press operate by maintaining fixed upper roller position during compression to set the fixed penetration depth of the upper punch. The tablet compression force and the compression height is controlled by the bottom punch penetrate distance via adjusting the position of the lower roller. Module P rotary tablet press also provides unique compensator system which integrates in the upper main compression roller, this design regulating the applied force on the material and prevents the punch overload. If the tableting force exceeds the force set in the compensator during production, the compensator will push upward to lift the roller up. The distance moved by the roller is defined as displacement and measured by a Linear Variable Differential Transformer (LVDT) sensor. In this work, tablet is compressed into bi convex shapes within 12 mm die. The process parameter settings for the tablet press were presented in Table 3 and were consistently applied across all formulations to investigate the effects of formulation on process outcomes and tablet properties.

Table 3. Process parameter setting in rotary tablet press

Rotary tablet press	
Parameter	**Value**
Fill cam	7.58 mm
Lower punch distance at main compression	5.2 mm
Set compression force in the compensator	18 kN
Turret speed	20 rpm
Lubricant amount	1.4%

Tablet tensile strength is a key parameter that reflects the mechanical integrity of a tablet. The tablet band width (W) is determined based on the tablet's thickness and the geometry of its convex surfaces. For bi-convex tablets, tensile strength is calculated using Equation 1, applicable within the range of $0.06 \leqslant W/D \leqslant 0.3$ (Pitt et al., 1988).

$$\sigma_t = \frac{10F}{\pi D^2 \left(2.84\frac{H}{D} - 0.126\frac{H}{H - 2H_{cap}} + 3.15\frac{H - 2H_{cap}}{D} + 0.01\right)} \quad (1)$$

Where σ_t is the tablet tensile strength, F is the tablet breaking force in N, D is the tablet diameter in mm, H is the tablet height in mm, and H_{cap} is the height of the convex cap which is 1.21 mm for the punch used in this work.

3.2 Characterization method

3.2.1 Near Infra-Red probe

The Near Infra-Red probe (FP710e, NDC Technology, Dayton, Ohio, USA) quantifies the moisture by utilizing backscattered or diffusely reflected Near-Infrared (NIR) energy within the product and using total reflected light to estimate the amount of measured material. This probe operates by directing light from a quartz halogen (QH) lamp through a filter wheel containing narrow band pass optical interference filters, which sequentially emits pulses of NIR energy at specific wavelengths absorbed by the water. This light is conveyed to the probe tip and projected as a diverging beam to form 2 separate measurement spots through a sapphire window onto the product. Each spot has 5mm diameter, the total measurement area on the product is 39 mm^2 (Figure 3). To quantify the water content in the granules, calibration is needed for all three formulations by using Loss on Drying (LOD) (M35, Sartorius GA, Germany) as reference. Samples were produced for each formulation by varying six different liquid-to-solid (L/S) ratio from 0 to 0.45. The LOD measurement used 3 g of sample and was run at 80 °C with automatic end point detection. Moisture content measurement were measured five times for each condition to ensure accuracy and repeatability of the results. The probe integration rate was set to the standard value of 1 s with data collected at 1 s interval.

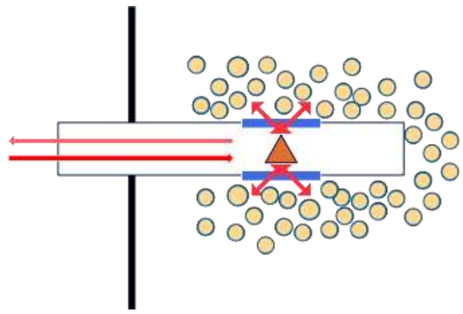


Figure 3. Schematic top view of the FP710e Near-Infrared (NIR) probe tip

3.2.2 Inline particle size measurement probe

IPP 70-S/Se probe applies Spatial Filter Velocimetry (SFV) method to measure the particle size. This technique projects a laser beam onto the granule stream. During the measurement, shadows will be generated and cast onto the optical fibres when particles pass through the laser beam. This inline measurement probe is fitted after milling under a modified hopper to monitor the powder flow. The probe includes a self-cleaning function using compressed air, which was activated every 15 s for a duration of 2 s to prevent the sample accumulation.

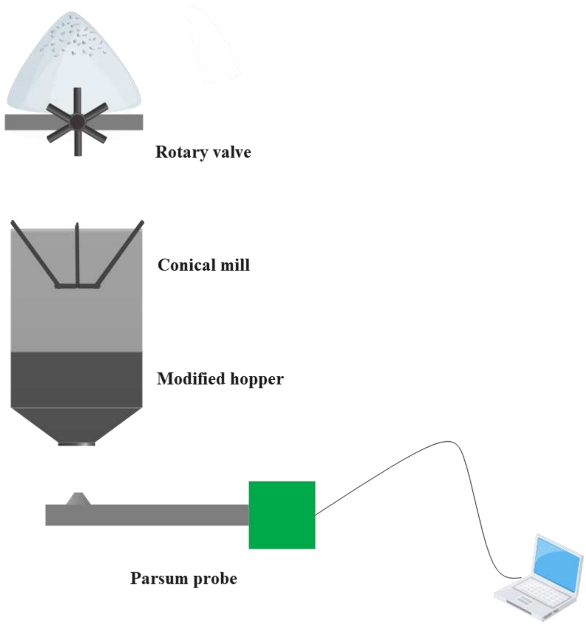


Figure 4. Particle size measured by fibre optical spot scanning

3.2.3 Granule flowability characterisation

A Ring Shear Cell RST–XS.s (Dietmar-Schulze, Germany) was used to classify the flowability of granules collected after milling. A pre-shear normal load of 2000 Pa was applied, followed by shear-to-failure tests performed at normal loads of 400 Pa, 1000 Pa, 1600 Pa, and again at 400 Pa. Each experiment was conducted three times, and the average value was calculated.

3.2.4 X-ray computed microtomography

X-ray computed microtomography (µCT 35, Scanco Medical, Switzerland) was used to obtain 2D images of the vertical cross section area of the tablets. The X-ray source was operated at 70 kVp and a current of 114 µA and 8W. The resolution of the voxel size was set at 2.5 µm. The scanning time for each tablet took 8 hours including the image reconstruction. The obtained images were processed under 8-bit format (0-255 grayscale values) in Matlab to display a block-averaged grayscale intensity distribution map, constructed by averaging grayscale values over areas of 50 × 50 pixels to enhance visualization of grayscale distribution inside the tablet.

4. Result and discussion

4.1. Evaluation of powder dosing unit

The hopper weight during the dosing process exhibited a consistent linear decrease regardless of the percentage of MCC (Microcrystalline Cellulose) in the powder mixture. The agitator inside the hopper improves material flowability, while the screws beneath the hopper convey the material to the twin-screw granulator. The initial powder weight in the hopper was 7.5 kg. As dosing progressed, powder was dispensed until the remaining weight in the hopper dropped below minimum level, triggering a warning alarm and automatically stopping the process.

Figure 5 presents the screw delivery speed of dosing formulations with different percentages of MCC. For all experimental sets, the delivery screw speed operated mainly between 200-300 rpm during the feeding process. At the initial stage, a sudden increase in screw speed was observed. The reason could be that the powder at the bottom of the hopper may be more compacted, requiring a higher screw speed to break through the static powder and start delivering constant material flow. As the powder weight in the hopper decreased during feeding, the screw speed progressively increased. This behaviour indicates the system tried to compensate for the reduced material availability by increasing rotational speed to maintain a consistent powder dosing rate. The powder feed rate in Figure 6 was observed to remain almost constant at approximately 10 kg/h during the stable dosing phase, demonstrating the system's ability to maintain consistent delivery under normal operating conditions. However, the powder feed rate also showed an unsteady state during the initial stage. When the amount of material inside the hopper became limited, the powder feed rate dropped significantly. This drop highlighted the challenge of maintaining consistent feed rate as the available material consumed, highlighting the importance of ensuring sufficient powder levels within the hopper to achieve reliable feeding.

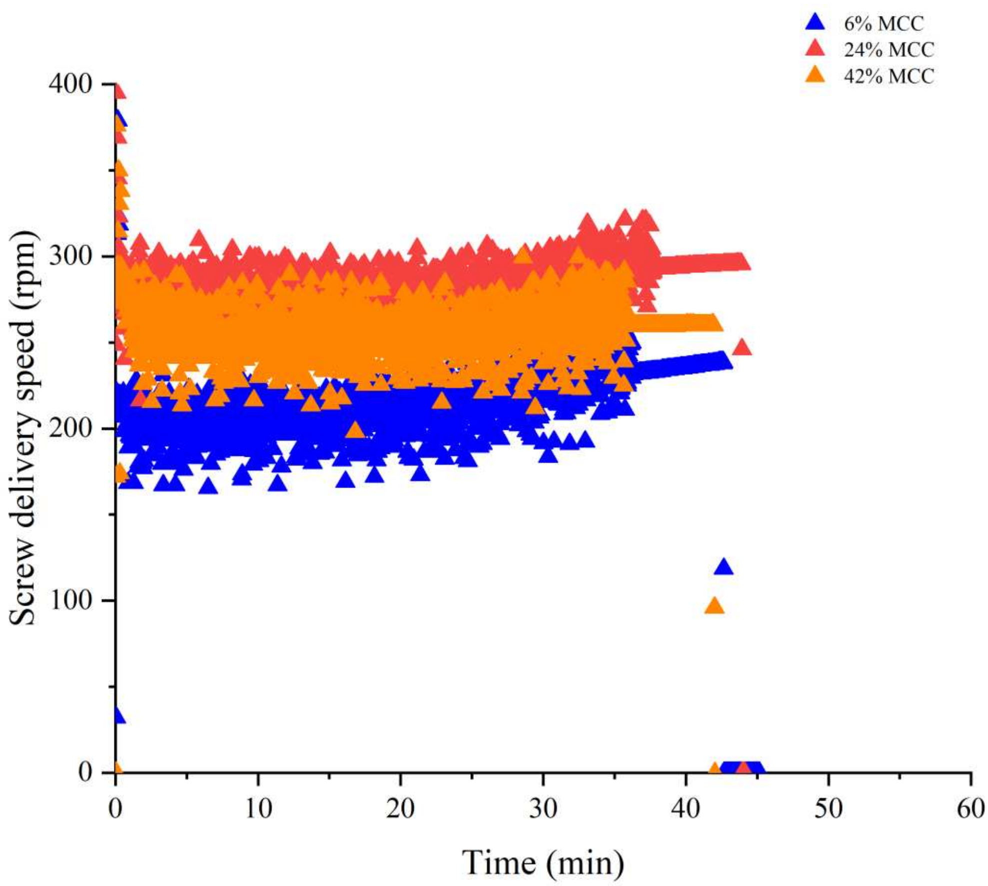


Figure 5. Screw delivery speed of dosing formulation with different percentages of MCC. Time axis refers to dosing operation feeding hopper.

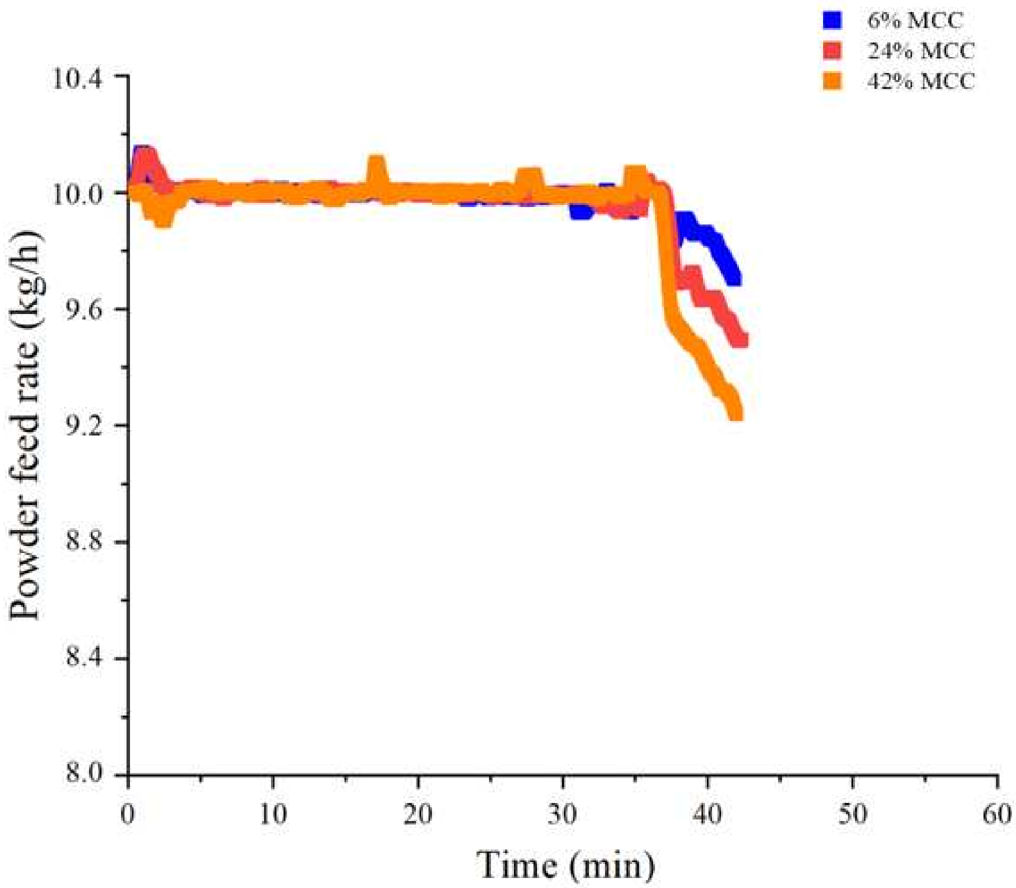


Figure 6. Powder feed rate of formulation with different percentages of MCC. Time axis refers to dosing operation feeding hopper.

4.2. Evaluation of twin screw granulator

In Figure 7, formulations with higher lactose content generally exhibited higher torque and required a longer duration for the torque profile to stabilize. In the initial stage of the twin-screw granulation process, as the screw begins to rotate and the material gradually fills the barrel, the torque gradually increases with the increase in material load. The increased torque observed in high-lactose formulations is attributed to enhanced powder caking during granulation. Lactose, being more sticking, promotes stronger inter-particle interactions upon wetting, leading to increased adhesion, agglomeration, and material build-up within the screw barrel. Figure 8 shows the visible powder caking observed in the twin-screw granulator when processing the formulation containing 90% lactose. Significant powder caking was observed beginning at the liquid addition zone, where localized wetting increased particle cohesion. Consequently, the build-up of caked material around the screw flights restricts powder flow, resulting in high resistance and friction, which directly increases the torque required to maintain screw rotation. In the two kneading zones, mechanical shear and the mixing process promoted by the kneading elements not only facilitated the distribution of water throughout the powder bed, but also contributed to the formation of cohesive flakes. This phenomenon reflects the high stickiness associated with high-lactose formulations, which can compromise granulation consistency and contribute to increased torque variability during operation.

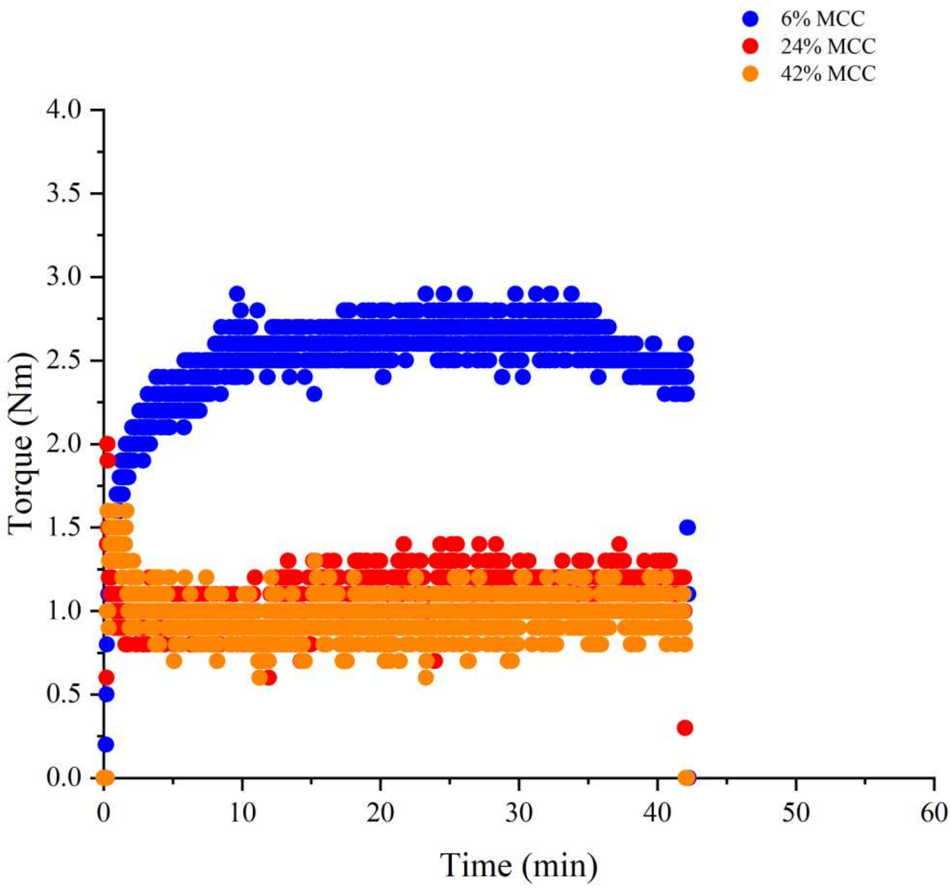


Figure 7. Effect of MCC on torque at 0.3 L/S ratio in twin screw granulator. Time axis refers to granulation period in the twin screw granulator.

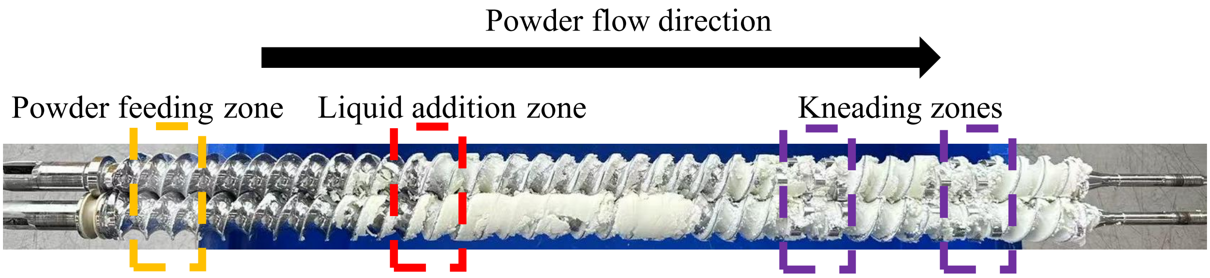


Figure 8. Visible powder caking observed in the twin-screw granulator during continuous granulation of formulation containing 90% lactose at 0.3 L/S

4.3. Evaluation of segmented fluidized bed dryer

NIR probe was installed in one of the fluidized bed dryer cells to monitor the drying behaviour. Figure 9 presents the moisture content of the granules, as measured by the NIR probe during fluidized bed drying. The moisture content of the granules demonstrated a distinct trend throughout the fluidized bed drying process. During the filling phase, wet granules were introduced and drying stage started simultaneously. At this stage, moisture content reading increased steadily as wet granules were continuously introduced into the bed, fluidizing on sides of NIR probe and reaching a maximum toward the end of this stage. This phenomenon was consistent across all formulations, independent of composition. Following the completion of filling, moisture levels began to decline gradually, indicating the evaporation of surface water from the granules. This is more pronounced in formulations with a high lactose content, as the water stays mainly on the surface of the particles, resulting the slope of moisture reduction is steeper compared to formulations with higher MCC content. In contrast, formulations containing more MCC retain higher moisture levels at the drying end point under the same drying conditions. This difference is likely due to the hygroscopic nature of MCC, which not only absorbs more water during granulation but also retains it more effectively.

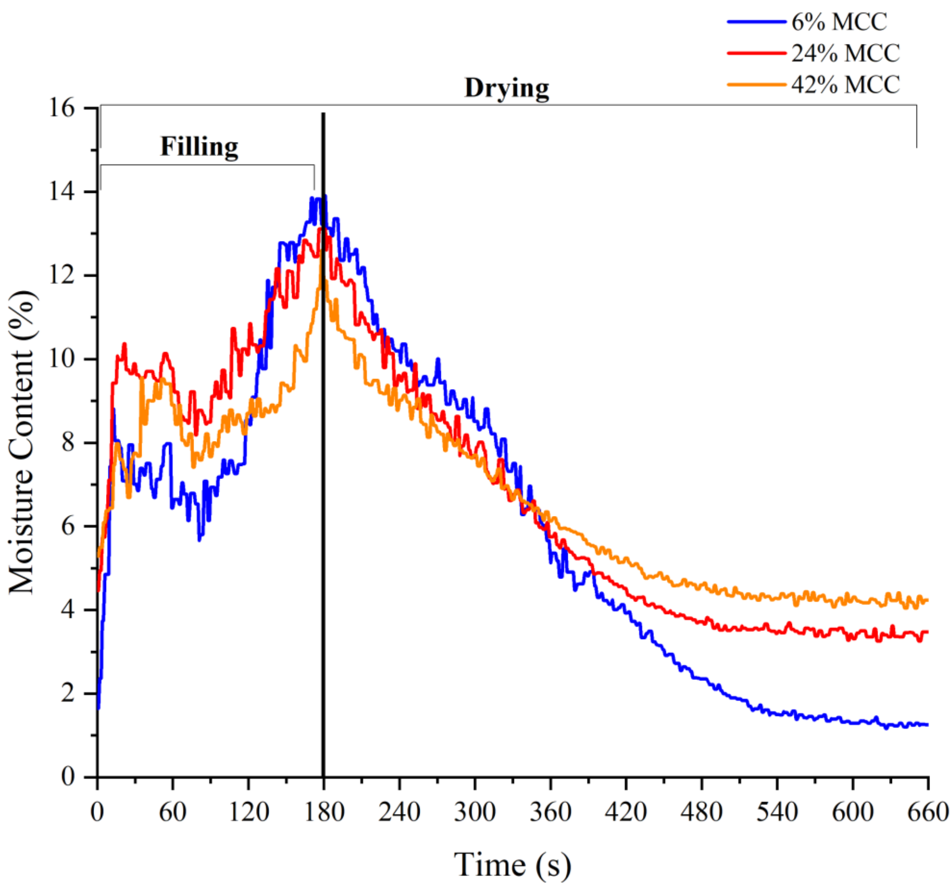


Figure 9. Moisture content profiles at different MCC percentages measured by NIR in one cell. Time axis refers to drying period in one cell only.

This NIR probe also detects the amount of material around the probe by analysing the total amount of reflected light from the products in the measurement zone which is also describe as product presence. As shown in Figure 10, the reflected light trend is close the moisture content profile presented in Figure 9 during the filling stage. This is because wet granules with the same liquid-to-solid (L/S) ratio are being continuously added, and the measurement system is primarily influenced by the accumulation of materials across all formulations. Once the filling stage ends, the amount of reflected light reaches a peak, indicating the maximum amount of material within the probe’s sensing area. After the filling phase ended, it was found that granules produced with less MCC displayed a constant reflected light while granules with more MCC showed a decreasing trend. Material uniformity, granule movement speed during drying may also affect the probe reading. Once drying was complete, amount of reflected decreased as granules were gradually discharged from the cell.

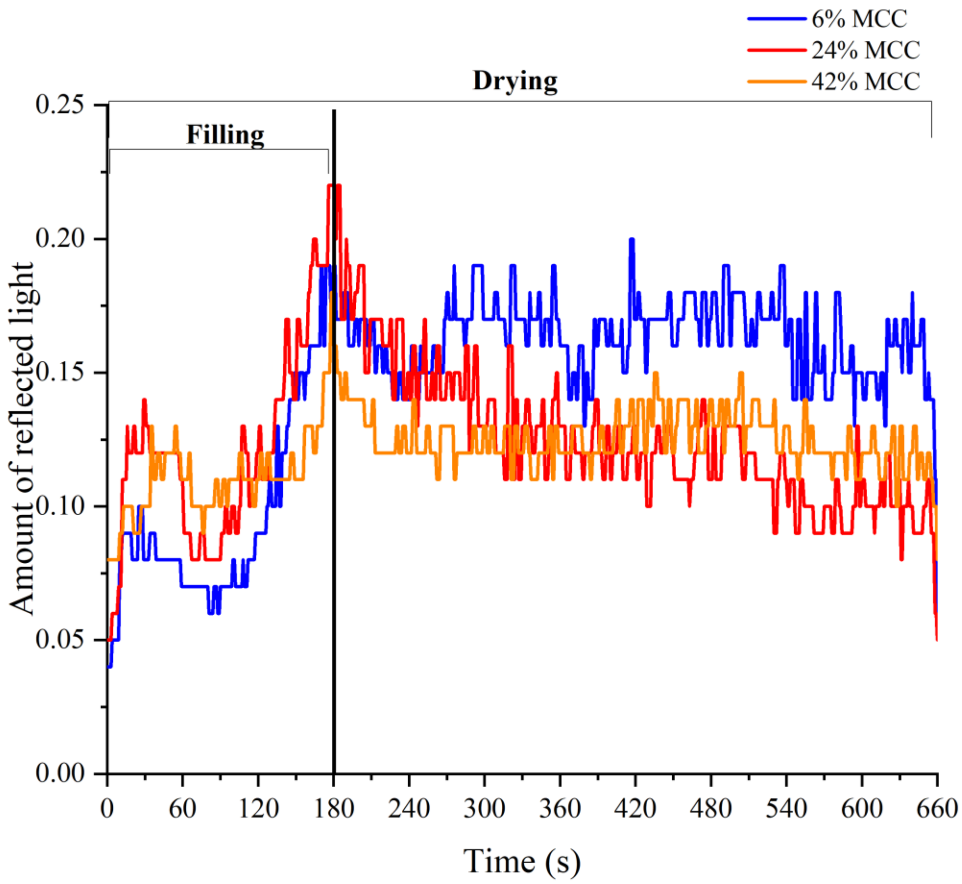


Figure 10. Amount of reflected light collected from NIR probe for different percentage of MCC. Time axis refers to drying period in one cell only.

To further investigate the moisture content across different processes, granules of each formulation were collected after milling and from tablet press and analysed for moisture content using the LOD method. These values were compared with the drying-end moisture content recorded in the fluidized bed dryer in Figure 11. The results indicated that the formulation with less MCC showed minimal differences in moisture content across the three stages (0.99%, 0.83%, and 0.53%). In contrast, the formulation with more MCC showed a more significant decrease in moisture content across the same stages (3.39%, 1.59%, and 0.63%), though the overall moisture levels remained higher than the less MCC formulation. Notably, both formulations demonstrated reduced moisture and smaller differences in the tableting stage, suggesting that the residual moisture would not significantly affect the tablet properties. Although the NIR probe was calibrated using offline LOD method, reading difference were observed between NIR at the FBD and LOD values from milled granules. These deviations can be attributed to the granule movement in the fluidized bed dryer, where high granule velocity reduce the consistency and material density around the NIR probe.

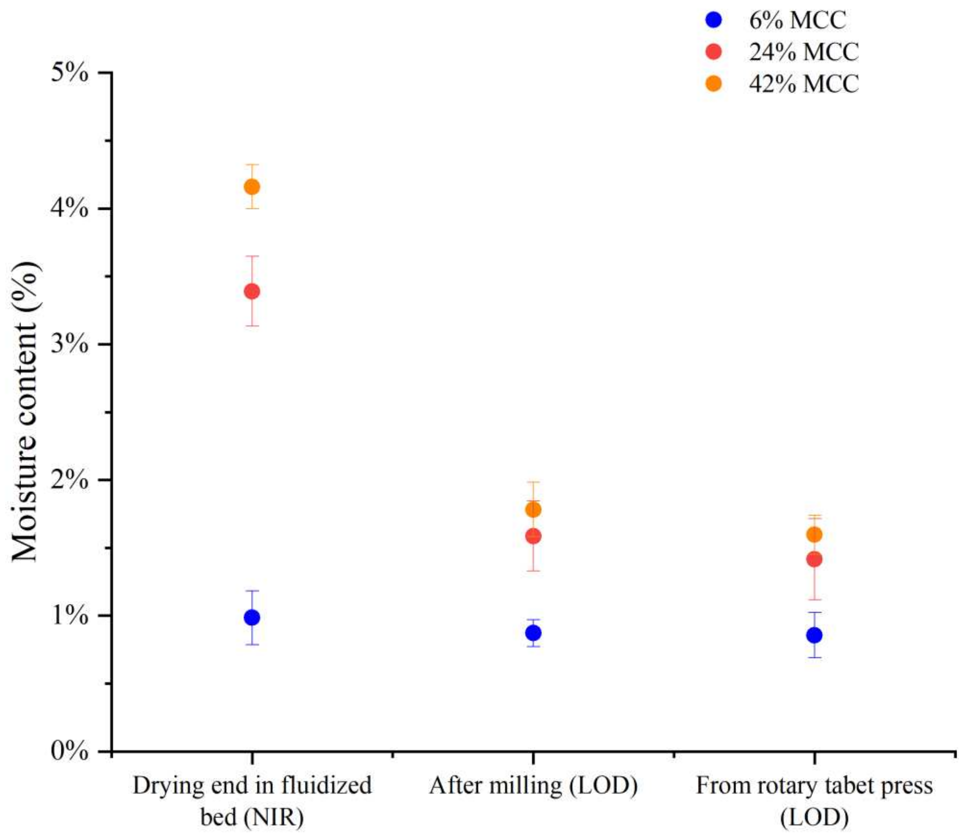


Figure 11. Measured moisture content of granules at three stages: at the end of drying using a calibrated NIR probe, after milling, and from tablets using the Loss on Drying (LOD) method.

4.4. Characterisation of milled granule

The bulk density of the milled granules was carried out in a cylinder using 100 g of sample. The flowability of granules collected after milling was presented in Figure 12. Milled granules produced from three formulations are classified as easy flowing with flow function coefficient (ffc) between 4 and 10. The difference in flowability between 24% and 42% MCC is not significant. As lactose has higher true density than MCC, granules containing higher percentage of lactose shows higher bulk density.

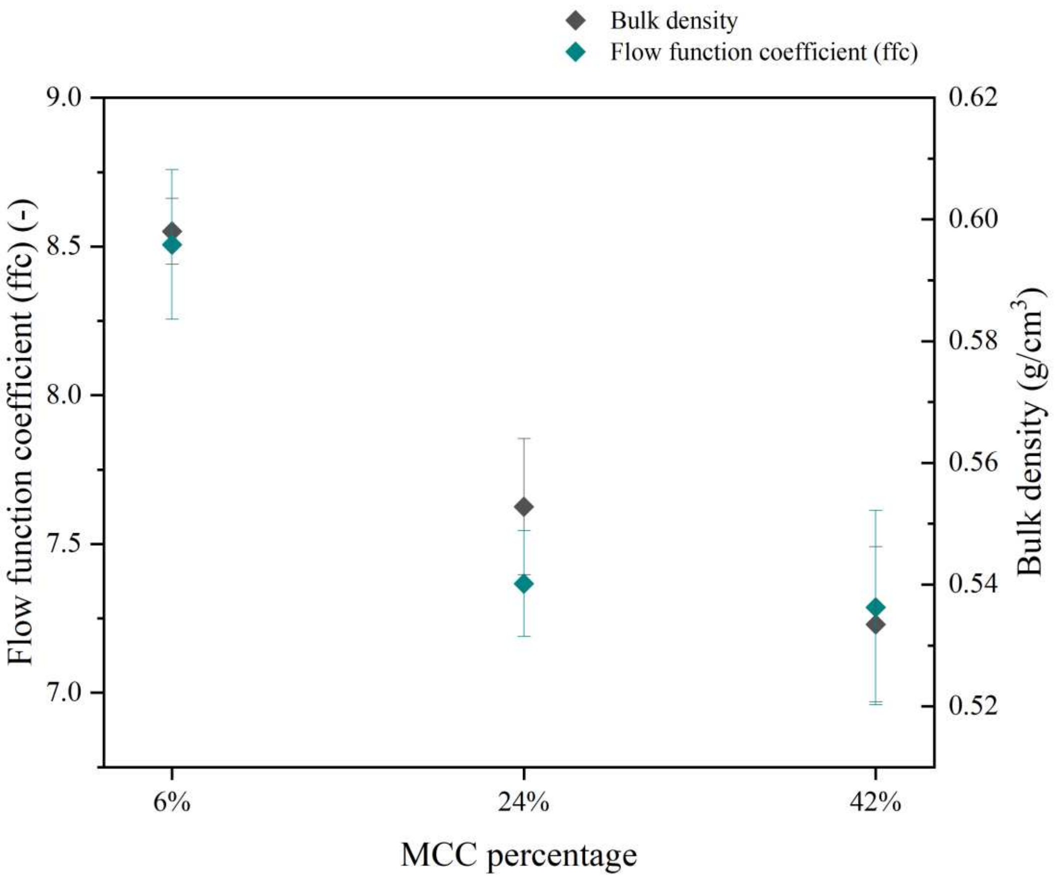


Figure 12. Comparing the flowability and bulk density of the milled granules produced by different formulation

Real-time granule size measurements were obtained using an inline particle size probe installed after the conical mill of three different formulations shown in Figures 13. The probe captured the granules discharged from each individual cell of the segmented fluidized bed dryer. Each measurement cycle began with a rise in D_v50 values from zero, indicating the arrival of granules into the probe. The D_v50 values then increased and stabilized, reflecting the continuous flow of milled granules during each discharge process. Additionally, Figure 13 also illustrates the time gaps between cell discharge in fluidized bed dryer, corresponding to the intervals between granule discharges from the segmented dryer—consistent with Figure 2. This trend also highlights the intermittent nature of material discharge in the continuous process and the capability of the inline probe to capture real-time size variations between dryer segments. Inline particle size measurements taken after the conical mill revealed fluctuations in D_v50

values during continuous process. This variability likely reflects the inherent randomness in how granules pass through the milling mesh during continuous processing. As dried granules from each segment of the fluidized bed dryer are discharged intermittently, their bulk characteristics—such as agglomerate strength and size—may vary slightly, leading to inconsistent breakage during milling. Additionally, the interaction between larger granules and the fixed 1575 μm screen introduces further variability, as coarser particles may occasionally resist fragmentation or pass through intact depending on their orientation and flow dynamics. These fluctuations are consistent with the nature of dry granule movement in continuous processes, where localized differences in cohesion and flow can result in uneven milling performance despite a steady operational setup.

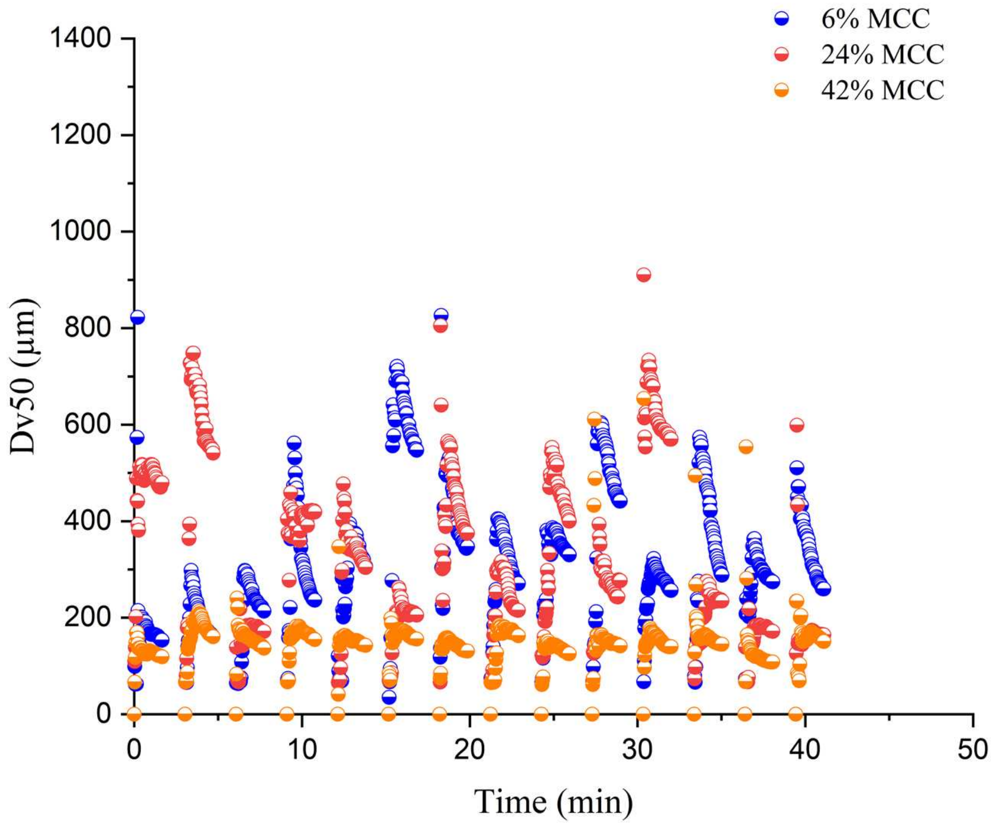


Figure 13. Inline milled granule size measurement of three different formulations after milling. Time axis refers to operation in the conical mill.

4.5. Evaluation of tableting process and characterize tablet quality

The investigation of MCC properties in the tableting process was conducted in a rotary tablet press. Milled granules were blended with 1.4% Magnesium stearate (MgSt) in the lubricant blender before entering the rotary tablet press. Tablets were collected and the properties (weight, thickness, hardness) were measured in tablet tester. The study employed a fixed die depth and fixed punch distance method during the compression stage. Tablets were initially collected at one-minute intervals, with 40 samples measured within the first two minutes. As the process carried on, collection intervals were extended to every two minutes, with 20 samples measured when approaching the process end. Additionally, 40 tablets were measured at the end of production.

At the beginning of the tableting process, the weight and thickness of the tablets increased in the first 8 minute before stabilizing over time in Figure 14. Comparing with the process outcome, the average displacement of the upper punches at main compression stage in Figure 15A also showed an increase in the early stages while the actual compression force was more stable. This could be attributed to the gradual settling of the powder bed in the die and the progressive build-up of uniform compression force as the process stabilized. The correlation between the upper roller displacement and the observed increases in tablet weight and thickness suggests that the mechanical adjustments and material behaviour during the initial phase play a significant role in achieving consistent tablet properties. Although a fixed punch movement distance was used during tableting, the measured main compression force varied across formulations. Specifically, formulations with lower MCC content showed higher upper roller displacement and slightly higher actual compression forces compared to those containing higher MCC percentage (Figure 15B). This can be explained by differences in material compressibility and bulk density. MCC is a porous material, more compressible excipient that undergoes more plastic deformation under compression, resulting in lower resistance to punch movement and more stable force profiles. In contrast, granules with more lactose exhibit high bulk density and are less compressible, making them more resistant to die compaction, which in turn generates higher force readings under fixed punch distance compression method. These findings highlight the critical influence of formulation composition on powder bed compressibility and mechanical response during the compression process.

However, when less material enters the die during the end of the production, tablet weight, thickness, upper roller displacement, and actual compression force all begin to decrease. This indicates that insufficient material fill level in the die not only reduces the mass of the tablet but also affects powder bed resistance and mechanical loading, disrupting the compression consistency.

Importantly, the machine's built-in compensator system designed to protect punches responds to higher actual compression forces than the set value by slightly lifting the upper compression roller to prevent punches overloaded. This mechanism explains the higher upper roller displacement observed in formulations with high lactose percentage and further confirms the presence of higher resistance during the compression. These findings emphasize the importance of understanding both material behaviour and mechanical design when evaluating formulation effects on compression stage in continuous manufacturing process.

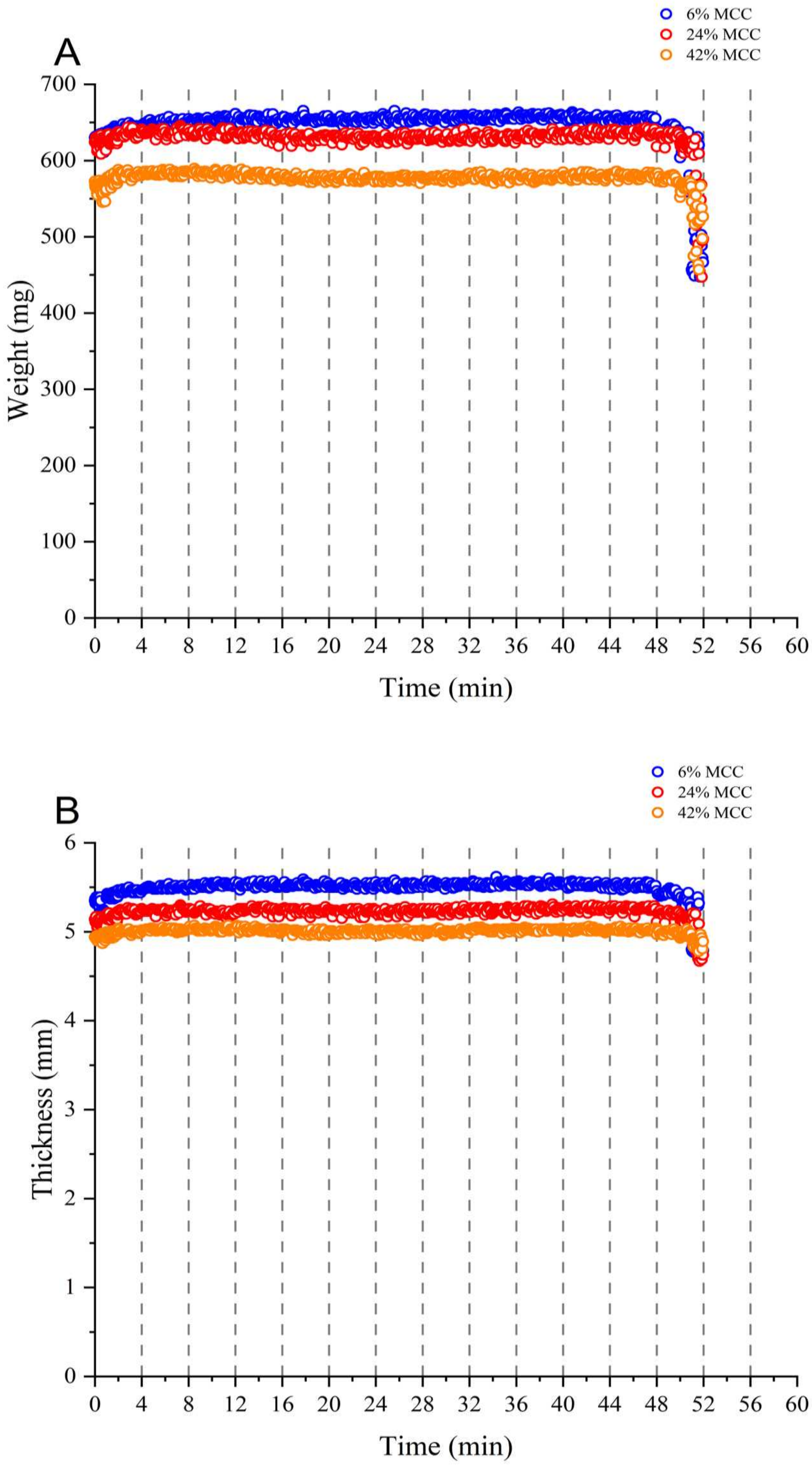


Figure 14. Properties of measured tablets collected during the production: A) tablet weight, B) tablet thickness. To be noticed, tablets located in each time interval only indicated they were collected in this period, not the corresponding specific production time.

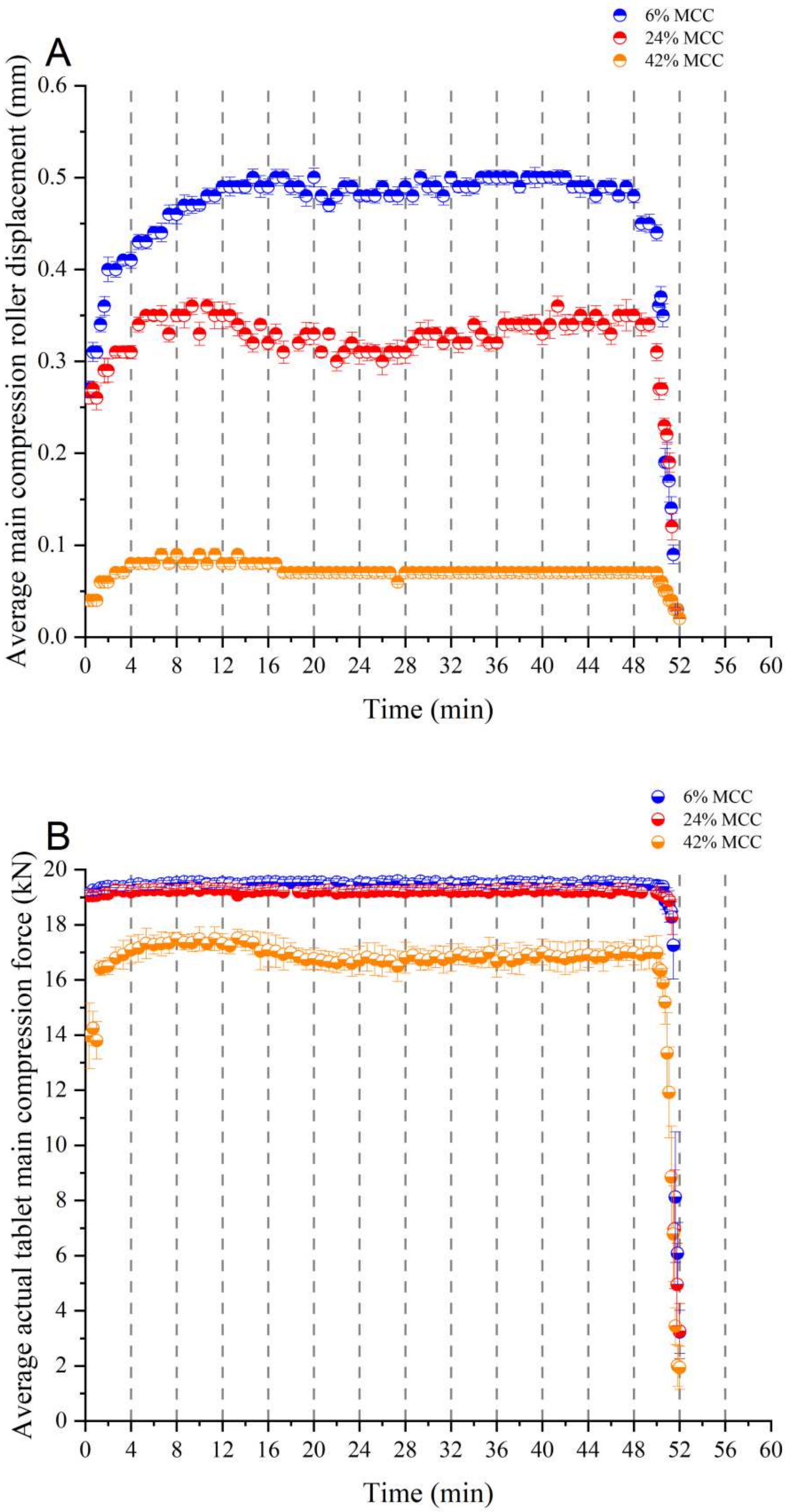


Figure 15. A) Average upper punches displacements at main compression stage when the punch contacted with the material, B) The average value of the measured main compression force

Tablet hardness and tensile strength are influenced by material properties, the actual compaction force, and the quantity of material filled into the die. As illustrated in Figure 16, formulations with higher proportions of MCC consistently yielded tablets with higher hardness and tensile strength compared to those with lower MCC content. This can be attributed to the brittle nature of lactose, which undergoes higher stress during compaction but contributes minimally to tablet strength even under higher actual compression force in Figure 15B.

Increasing the MCC content generally enhances the tensile strength of tablets, this effect becomes less significant at lower compaction force, where tablets show the reduced hardness. With more MCC, actual compression force is reduced if fix compression height method is applied. As a result, the hardness and tensile strength of tablets containing 42% MCC was comparable to those with 24% MCC, as presented in Figure 16. Notably, increasing the MCC content from 6% to 24% enhanced tablet tensile strength, the actual compression force for 6% and 24% MCC formulations were quite close (Figure 14B), under this condition, the resulting differences in tablet hardness and tensile strength were more pronounced. However, tablets containing 42% MCC, despite being compressed under the same tableting settings, showed a reduction in thickness (Figure 14B) and lower actual tableting force (Figure 15B). This can be attributed to the lower bulk density and poor flowability of granules produced with more MCC (Figure 12), which results in less mass being filled into the die. Therefore, despite the higher proportion of plastically deformable material in the tablets, the reduced tablet thickness, which is an important parameter in calculating tensile strength in Equation 1 partially improved mechanical strength. This highlights the importance of formulation composition, particularly the percentage of plastically deformable materials like MCC, in governing the process outcome and final tablet properties. Operating the rotary tablet press with a fixed punch ‘tip-to-tip’ distance enabled direct observation of the influence of formulation variability on the tableting performance. This operating method also offers valuable insight into material sensitivity and highlights the effect of formulation on both equipment mechanical response and the tablet quality.

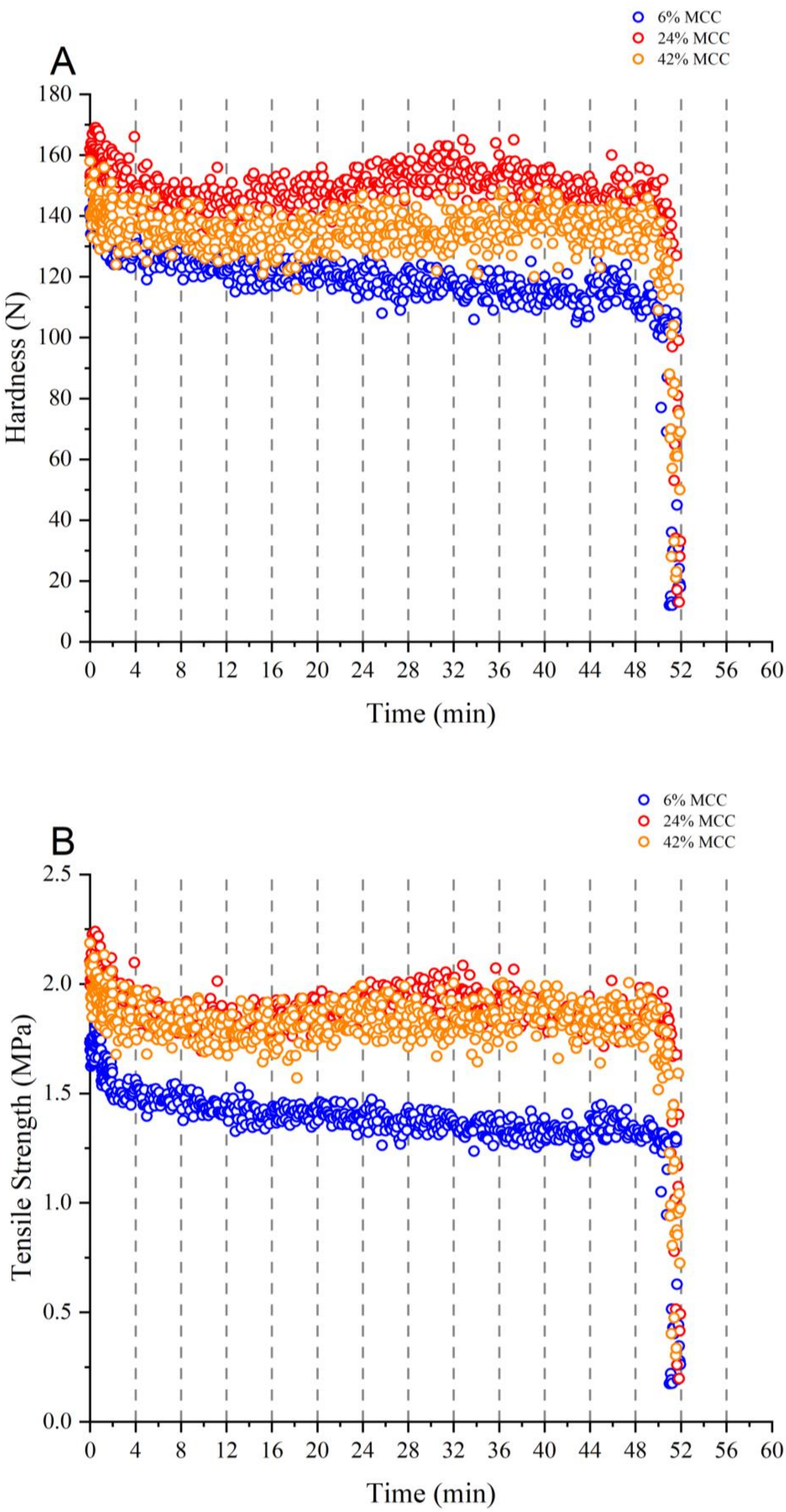


Figure 16. Properties of measured tablets collected during the production: A) tablet hardness, B) tablet tensile strength. To be noticed, tablets located in each time interval only indicated they were collected in this period, not the corresponding specific production time.

4.6. X-ray tomography

X-ray computed microtomography was used to characterise the tablet internal structure. As emitted x-rays traverse through the tablet to the detector, the incident radiation is absorbed depending on and the intensity diminished, and thus the stronger white colour represents a denser component. Figures 17–19 reveal internal features of the tablet cross section area produced with different formulations. All tablets were compressed using a fixed punch tip-to-tip distance, resulting in varying actual compression forces depending on the formulation (Figure 15B). Specifically, the tablet containing 42% MCC experienced the lowest compression force, while the 6% MCC formulation was compressed at the highest force.

In Figure 17, x-ray scanning of tablets formulated with 90% lactose, 6% MCC and 4% L-HPC revealed the presence of a crack line in the centre of the tablet cross-sectional area. Notably, this internal defect did not progress to a full lamination. The enlarged areas highlight the contrast between the tablet edges which appears brighter in colour and less compacted area in the middle with crack which appears darker. Granules with high percentage of lactose promotes brittle fracture behaviour, because of the higher actual compression force applied during tableting process in Figure 14b. In addition, the relatively low amount of MCC may have limited the tablet's plastic deformation. This also suggests that both the compression strategy and the proportion of plastically deforming materials are critical roles in reducing internal tablet defects.

In addition, Figures 17 to 19 also illustrate that increasing the percentage of MCC in the formulation leads to crowning, due to the more deformation material in the granules. X-ray images reveal that these crowned areas occur randomly at different corners of tablet cross section area. The edges of these crowning appear brighter at edge, which indicates these areas undergo higher stress. During the compression, the narrow gap between the punch and die allows trapped air to escape, however, this narrow gap will slightly increase the final tablet diameter beyond the nominal value and highly plastic materials could deform under high compression force, forcing material into this gap between the punch and die wall, resulting in the formation of raised edges. This effect is particularly evident in tablets with higher MCC content (Figure 15B), where crowning becomes more obvious even the tablet is compressed at low actual compression force (Figure 15B).

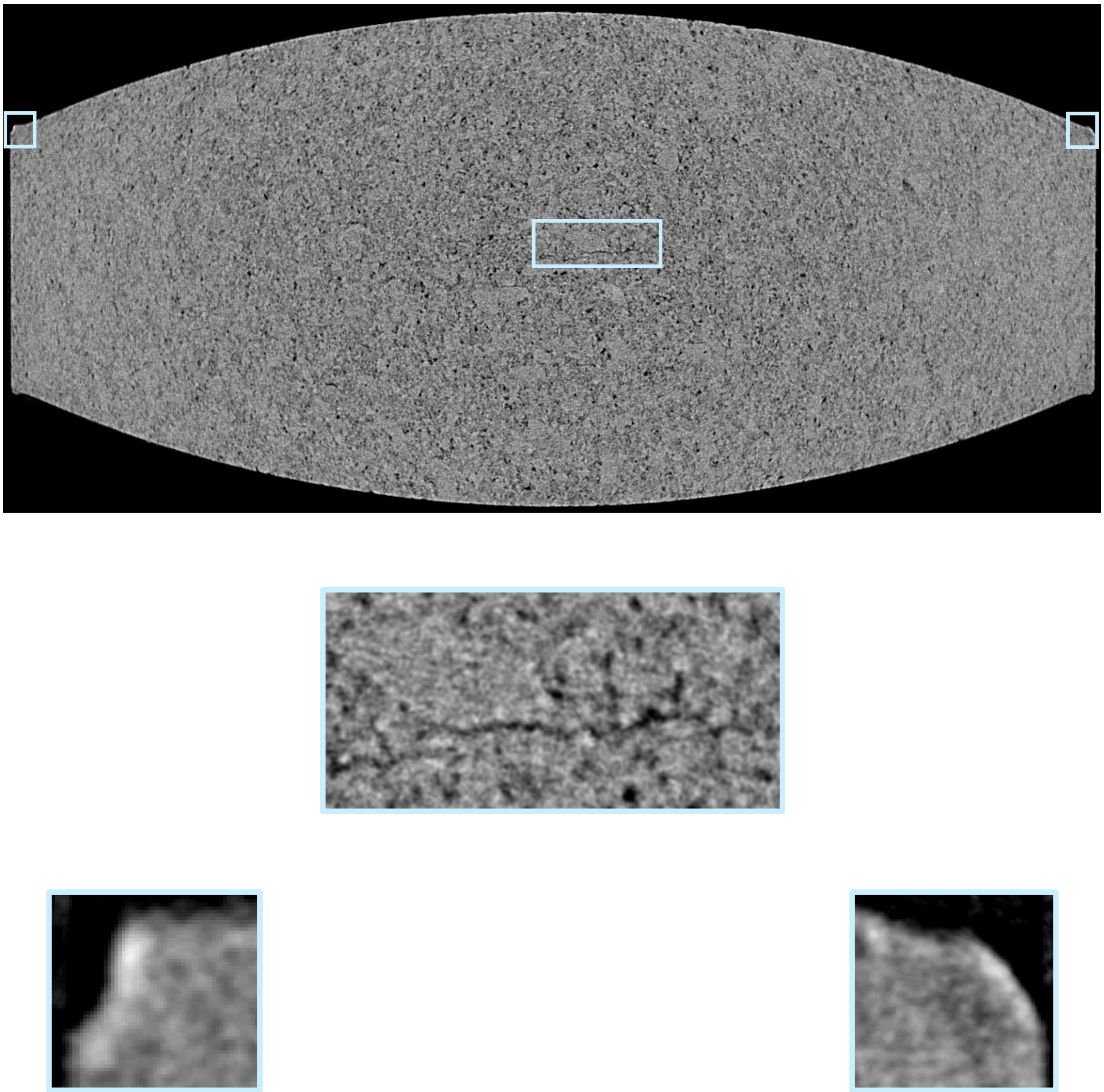


Figure 17. Cross-section of tablet made by 90% lactose, 6% MCC and 4% L-HPC obtained by x-ray microtomography with three regions enlarged to highlight internal structural differences. The tablet side areas appear denser while the central region shows lower density (darker grey) with visible internal cracking.

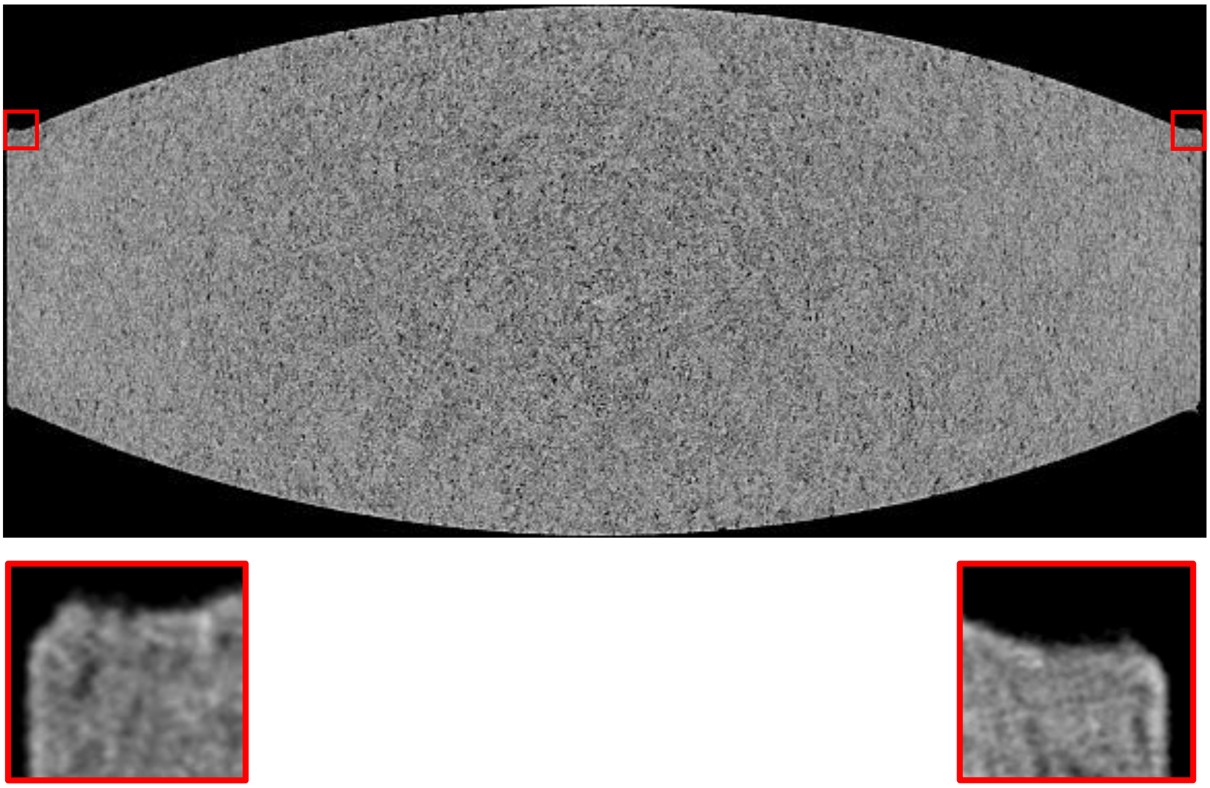


Figure 18. Cross-section of tablet made with 72% lactose, 24% MCC and 4% L-HPC obtained by x-ray microtomography. Enlarged view of highlighted region with the raised edge.

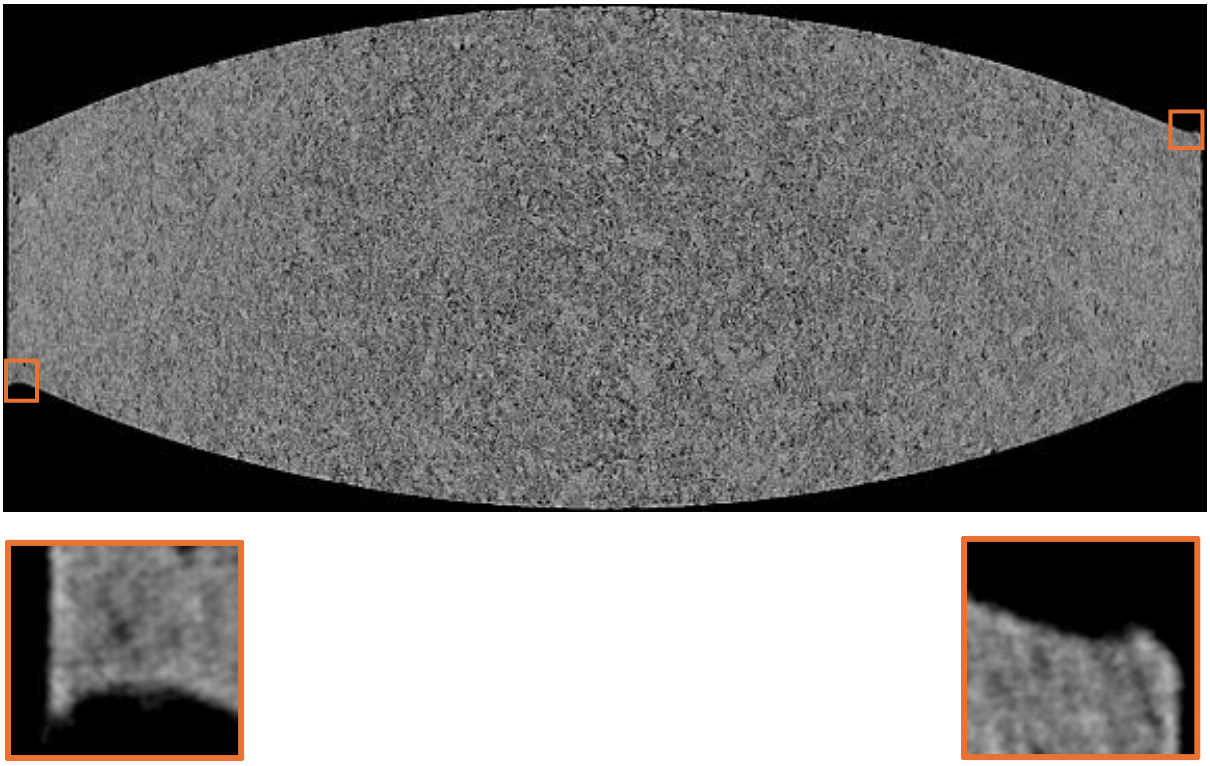
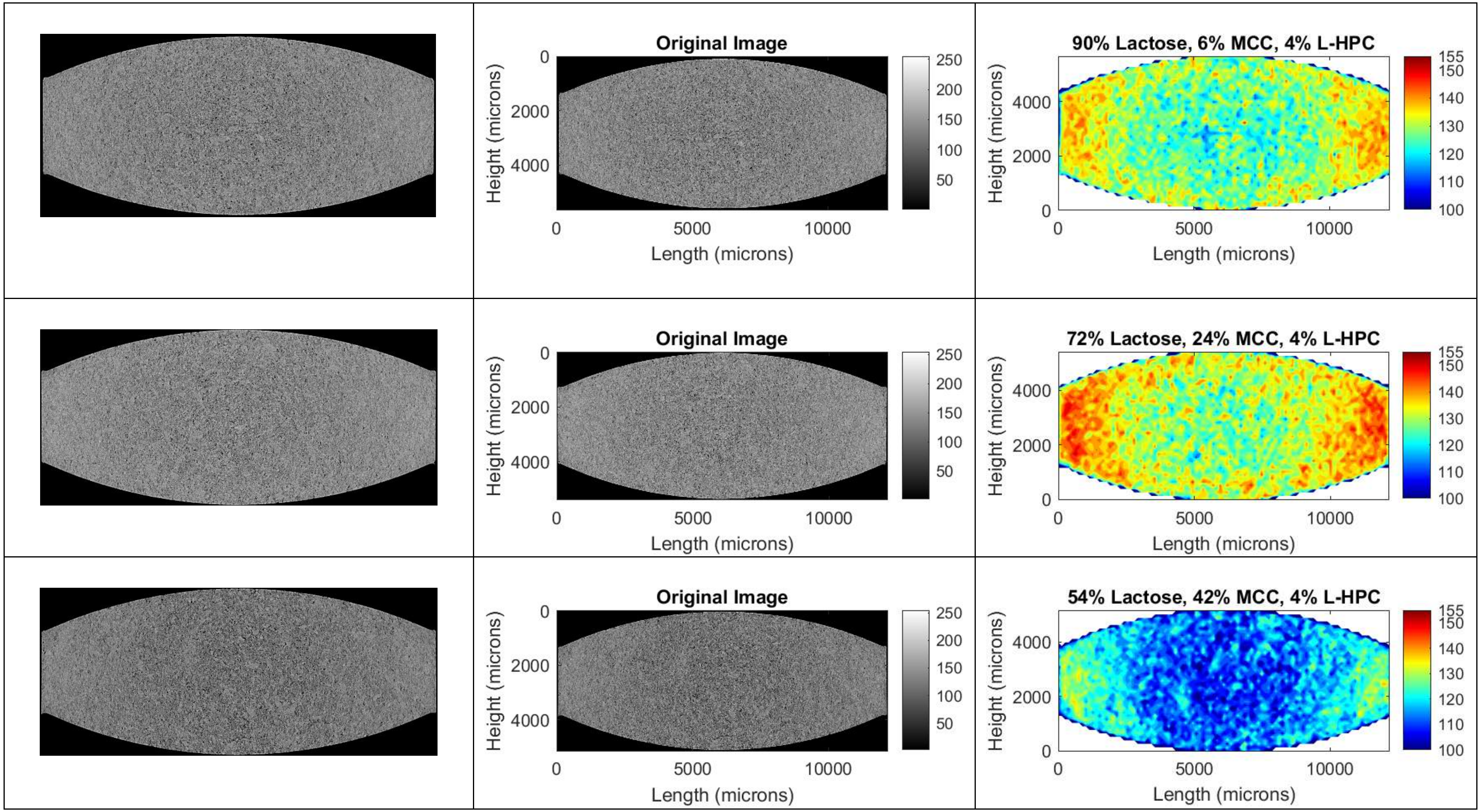


Figure 19. Cross-section of tablet made with 54% lactose, 42% MCC and 4% L-HPC obtained by x-ray microtomography. Enlarged view of highlighted region with the raised edge.

Figure 17 to Figure 19 were processed to convert the 8-bit grayscale images into contour maps (Table 4), which were created by calculating the average grayscale over a 50x50 pixels area from original X-ray image. When comparing tablets compressed at similar actual compression forces (Figure 14B), the formulation containing 24% MCC exhibited a noticeably higher grayscale intensity near the edges than the 6% MCC formulation, which is due to the plastic deformation behaviour of MCC under compression. However, for tablets with 42% MCC, although containing more plastically deformable material, poor granule flowability (Figure 12) and the actual compression force was lower (Figure 14B), resulting in reduced overall density. This also highlighted that both the tablet compression force and material property will significantly influence the internal density (or porosity) of the tablet. This visualization imaging process provides clear insight that the grayscale distribution inside biconvex tablet is not uniform. This is highly influenced by biconvex punch geometry, which affects the compression force on the granules during compression. It can be observed from contour map that for each tablet formulation, the grayscale intensity is higher at the tablet edges, which are in contact with the die wall during compression, and gradually decreases toward the centre. Additionally, the upper and lower curved regions, corresponding to the areas compressed by the punches, also exhibit higher grayscale intensity compared to the tablet central region.

Despite providing highly useful information on the tablet internal structure, this visualization method has limitations when it comes to accurately capturing the tablet's outer edges. In the original grayscale images, the curved regions of the tablet that make contact with the punches appear visibly brighter r due to localized compaction. However, these high-density zones are relatively small areas, and the averaging involved in the mapping process blends them with lower-density regions, reducing the contrast and effectively smoothing out these details.

Table 4. Contour map of tablets made with different percentages of MCC. The first column shows the original images; the second column displays the original image with grayscale value. The colour bar in contour map presents the grayscale value after mapping in the third column.



Conclusion

This study demonstrates that formulation variations have a significant impact on the operation of a continuous manufacturing line under fixed process parameters. The use of process analytical technologies (PAT), including NIR probe for moisture content and inline particle size measurement, provided valuable real-time insights into material behaviour and are capable of revealing differences between formulations. Differences in powder blend properties influence each unit operation outcome, with effects observed on granule bulk density, which affects tablet weight, thickness, and tensile strength. By operating the tablet press at a fixed punch tip-to-tip distance, this study captured the material properties directly influences compression performance and tablet properties, emphasizing the importance of formulation robustness in continuous tableting processes. It is also highlighted that effective handling of different formulations requires thoughtful selection of compression strategy and potential adjustment of process conditions to accommodate differences in material deformation behaviour. X-ray imaging confirmed that tablet density is higher at the edges, likely due to punch design and biconvex shape, while the inclusion of more plastically deformable materials led to increased flashing. These findings highlight the critical role of formulation design and real-time monitoring in ensuring product quality and process consistency in continuous manufacturing.

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