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Original Research Article

Characterization and evaluation of the performance of starch and cellulose as excipients for direct compression technique

Hamad S Alyami[1]*, Samer S Abu-Alrub[2], Mater H Mahnashi[2], Mohammad H Alyami[1], Osaid T Al Meanazel[3]

[1]Department of Pharmaceutics, [2]Department of Pharmaceutical Chemistry, College of Pharmacy, Najran University, Najran, [3]AlKayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, King Saud University, Riyadh, Saudi Arabia

For correspondence: **Email: hsalmukalas@nu.edu.sa*

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Abstract

Purpose: *To investigate the influence of two often-used excipients (starch and microcrystalline cellulose) on the physical properties of powder blends and tablets that contain mannitol as diluent.*
Methods: *Powder and powder mixtures of three commonly used excipients (starch, mannitol and microcrystalline cellulose) were thoroughly examined using the angle of repose for flowability, particle size analyzer to determine the diameter of the particles, scanning electron microscopy (SEM) for morphological assessment, and x-ray diffraction to determine crystalline/amorphous characteristics. Tablets were prepared by direct compression technique and were evaluated for mechanical strength and disintegration behavior as part of quality control test.*
Results: *The results showed that increase in MCC concentration of the mixture leads to significantly enhanced flowability ($p < 0.05$) when compared to starch. The angle of repose for mannitol/MCC powder mixture with 70 % w/w MCC was approximately 29°, indicating good flow properties of the powder mix. Moreover, starch tablets containing MCC exhibited better mechanical strength and longer disintegration time, while, at 1:1 ratio of MCC and mannitol, tablet disintegration was faster (33.0 ± 5.2 s)*
Conclusion: *MCC (at 30 %w/w in the blend) produces optimal flow of the powder blend and superior mechanical strength,*

Keywords: *Tablet disintegration, Flowability, Starch, Hardness, Mechanical strength*

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INTRODUCTION

Oral drug delivery is the preferred route of administration due to the ease of administration, non-invasive, and more likely to improve patients' compliance and adherence to the drug [1]. Tablets are the most used oral dosage form for their stability, ease of manufacturing, and favorable therapeutic results [2]. Functionality and demonstration of excipients have an influence on the performance of the final dosage form, in particular, tablet dosage forms.

Consequently, achieving good flow and content uniformity is essential to attain the required dose per unit. This could be achieved by optimizing the formula thorough the adequate selection of excipients [3,4].

The performance tests or functionality interrelated investigations should be conducted earlier to understand the effect of each excipient on the final dosage form performance and to classify the combined effect of using multiple excipients on the physicochemical property that considered essential to the use of excipients [5].

Subsequently, two different excipients were investigated in the current study for their impacts on the physicochemical properties of mixing powder that includes mannitol. Mannitol is used as a diluent in solid dosage forms, which offers many benefits for the formulation of a solid dosage form such as; appropriate balance for sweetness, enhancing the taste buds sensation, increase the solubility, and rapid dispersibility of tablets dosage forms [6]. However, mannitol has significant issues, which are poor flowability and low compressibility [7].

Starch and microcrystalline cellulose (MCC) are widely used as excipients in pharmaceutical solid dosage forms. The different forms of starch had been extensively studied for tablet dosage forms development. Corn starch can be used in tablets to improve flowability, disintegration, and hardness [8]. Starch deforms by plastic deformation under pressure, which offers the basis for its dual functionality as disintegration and binding ability. However, the only disadvantage reported for starch tablet development is the sensitivity and physical incompatibility upon mixing with lubricants, which harms tablet mechanical properties [9,10].

MCC is a cellulose-derived material from wood pulp; it is considered as a natural polymer. MCC has a high binding ability and used in solid dosage forms for direct compression and wet granulation. Moreover, it has excellent mechanical properties, intrinsic lubricity, as well as high dilution ability. MCC is available in different grades that vary according to the particle size. The most commonly used grade is Avicel PH-102, which has good flowability but lacks good mouth feeling [11]. The current study aims to explore the influence of using dual excipients on the physical properties of powder blending and tablet property that contains mannitol as diluent. Concomitantly, the study also aims to investigate the effect of increasing the concentration of corn starch and MCC on D-mannitol powder behavior.

EXPERIMENTAL

Materials

Corn Starch, D-mannitol, and magnesium stearate were obtained from Sigma-Aldrich Company (New York, USA). Microcrystalline cellulose (MCC) Avicel PH-102 was purchased from Penwest Pharmaceutical Co. (Patterson, New York). Other used materials were purchased from local agents.

Powder blending

Powder blends were prepared by cube mixer for 10 min at 500 rpm. The two critical excipients included in blending were MCC and starch; starch was investigated at different concentrations (5, 10, 30, 50, and 70 %). Furthermore, the prepared blends were mixed with 1%w/w magnesium stearate for 1 min. The formulations are listed in Table 1.

Evaluation of powder flowability

Powder flowability was assessed by using the angle of repose method [12]. 5g from each powder was poured through a funnel into a flat surface.

Table 1: Composition of powder formulation

Formulation NO.	Starch (%,w/w)	MCC (%,w/w)	Mannitol (%,w/w)	Mg.st (%,w/w)	Batch size (g)
F1	5	0	94	1	50
F2	10	0	89	1	50
F3	30	0	69	1	50
F4	50	0	49	1	50
F5	70	0	29	1	50
F6	0	5	94	1	50
F7	0	10	89	1	50
F8	0	30	69	1	50
F9	0	50	49	1	50
F10	0	70	29	1	50

The funnel was placed at 10 cm height from the horizontal surface, and the powders were allowed to free flow until the formation of a symmetrical cone. Both the base (b) and height (h) of the formed cone were measured. Eq. 1 was used to calculate the angle of repose (θ). Values were expressed as mean ± standard deviation (n = 3).

$\theta = \tan^{-1} (h/0.5b)$ …… (1)

Scoring of flowability was as follows; Angle less than 30° indicates excellent flowability, between 31-35° is for good flowability, while angles above 45°is an indication of poor flowable powder [13].

Particle size analysis

Powder particle size was determined using the mastersizer 2000 (Malvern, UK). 500 mg of the powder samples were spread over the feeding tray of the VIBRI that transfer the sample into the dispenser. Plots of particle size distribution were obtained covering the range from 0.5-175 µm. Parameters like the volume mean diameter (VMD), X10, X50 (median, 50% volume percentile), and X90 were also measured. Each sample was tested in triplicate to assure the reproducibility of the results.

Scanning electron microscopy (SEM)

SEM technique was performed to study the morphological structure of particles. Samples were distributed by sprinkling on a double adhesive carbon tape placed over an aluminum stub. Then samples were coated twice with gold in a sputter auto fine coater Jeol JFC-1600 (Jeol Equipment, Tokyo, Japan) at 30mA for 5 minutes and then examined by the SEM before imaging to enable sample conductivity. The sample imaging was performed on a field emission scanning electron microscope.

X-ray powder diffraction (XRD)

X-ray diffraction patterns were recorded on an X-ray diffractometer (D2 Phaser, Bruker AXS GmbH, Germany). The x-ray generator was operated at 30 kV and 10 mA employing Co tube at λ 1.79026 Å as a radiation source using a LYNXEYE detector. The angular range (2θ) varied from 4 to 50° at a scanning rate of 0.02° 2θ s^{-1} and measured at 0.24 seconds/step. Powder samples were loaded onto the sample holder, placed on the stage, and locked into place. Diffractive patterns were generated as counts per step and, after that, analyzed using Eva 18.0.0.0 software (Bruker, AXS) (14). Dry coated samples were processed using dry coating device at 2000 rpm, gas flow at 42 L/min, and various processing times ranging from 20-180 minutes using ibuprofen and theophylline as model APIs.

Tablet characterization

Each powder mix was compacted into 500 mg tablets under a compression force of 3 tones, with a dwell time of 10s before the compression force was released. The tablet press applied for preparing the tablets was a bench-top semi-automatic hydraulic press (Specac Ltd. Slough, UK) equipped with flat-faced dies of 13 mm diameter. Tablets were characterized by hardness, disintegration time, and friability.

Tablet hardness

Erweka TBH 425(Heusenstamm, Germany) was used in evaluating the tablet hardness. Three tablets of each formulation were tested to confirm the robustness of the results. The values reported as mean ± standard deviation.

Tablet friability

Friability was measured using a Roche friabilator from J. Engelsmann AG (Ludwigshafen, Germany). 6 tablets were rotated at 25 rpm for 100 revolutions. Tablets were de-dusted before and after the test, and friability showed as the percentage loss in weight. The % friability was calculated using the following Eq 2.

$\%F = (IW-FW)/IW \times 100$ …… (2)

where (% F) represents the percentage friability, (IW) initial weight, and (FW) final weight.

Tablet disintegration

The disintegration test was utilized using Erweka D-63150 (Heusenstamm, Germany). Each tablet was placed in the disintegration basket (without using a disk), which was subjected to up and down movement by the device at a constant frequency of 30 cycles/min in the disintegration medium. Distilled water (800 mL) maintained at 37°C was used as the disintegration medium, while disintegration time was recorded for one tablet at a time to maintain the accuracy of recording. Time of disintegration was recorded when all the disintegrated fractions of the tablet passed through the mesh located at the base of the disintegration basket.

Statistical analysis

Statistical analysis was carried out using GraphPad Prism software (Version 6.01, CA, USA). As applicable, t-test, one-way analysis of variance (ANOVA), and pair-wise multiple comparisons method (Tukeys test) were used to compare data groups by using mean values and standard deviation (SD). The significant difference was determined using the probability value of 95 % *(p* < 0.05).

RESULTS

Flow property and particle size

The morphology of the particles, as well as their particle size distribution, may also affect the flowability. Mannitol is a powder that has poor flowability (angle of repose 42.46±2.5º); improvement of this property will enhance the quality of the final dosage form pertinent to weight uniformity [14]. Additionally, the irregular shape of powder flow might entrap excess air in tablets during compaction that would result in a tablet capping and lamination [15]. The addition of MCC as a binder that has an excellent flow property (angle of repose 21.23±0.98º) had improved the flow properties of mannitol by reducing the angle of repose from 42.46° to 29.11±0.89°. Results of the flowability for the powder mix for all the formulations are illustrated in **Error! Reference source not found.**. The angle of repose for mannitol /MCC powder mixture with a 70% w/w MCC was around 29° indicating excellent flow properties of the powder mix [16] (USP-29, 2009). Therefore, the addition of MCC resulted in a statistically significant improvement in flowability (t-test, p <0.05). The analysis of particle size is shown in Table 2, which demonstrate the X90 of mannitol, starch and MCC, 18.75±0.31, 22.19±1.39, and 143.21±0.66 µm, respectively. The result for particle size analysis designates a very cohesive fine powder for mannitol and starch, while MCC obtained a free-flowing non- cohesive powder. Worth mentioning, particle shape also contributes to the flow properties (see figure 1).

Morphological features

SEM images of mannitol, starch, MCC, and their mixtures at 5 and 70 % w/w are shown in Figure 1 and Figure 2, respectively. The preliminary screening of the morphology of the three excipients had exhibited that mannitol has a needle-shaped particle, and the majority of particles were within the range of 35 µm. The needle-like shape donates to the reduced flow properties and low compressibility of mannitol. Notably, those mannitol particles are agglomerated, possibly owing to its cohesive property [17,18]. However, Starch particles were small in size and had a typical angular, spherical shape or rounded shape with a smooth surface (Figure 1 c and d). Figure 1 e and f, exposed granular, dense surface of particles which are made of primary and agglomerated structures [19].

Table 2: Flow properties of mannitol, starch, MCC, (F1 - F5, 5 -70% concentrations of starch) and (F6 - F10, 5-70% concentrations of MCC) showing the particle size analysis parameter (X90, angle of repose (°) and the corresponding flow property

Product	X90	Θ (°)	Flow property*
Mannitol	18.75±0.31	42.46±2.5	Passable
Starch	22.19±1.39	40.90±2.2	Passable
MCC	143.21±0.66	21.23±0.98	Excellent
F1	19.45±3.11	41.28±1.64	Passable
F2	24.89±0.83	41.35±1.99	Passable
F3	30.14±0.83	40.70±1.23	Passable
F4	30.25±2.22	40.13±0.34	Fair
F5	32.16±2.76	39.33±3.11	Fair
F6	50.26±3.55	45.24±3.18	Passable
F7	67.74±1.11	41.76±0.84	Passable
F8	90.14±3.55	38.22±1.84	Fair
F9	120.17±4.25	32.47±3.19	Good
F10	136.21±1.21	29.11±0.89	Excellent

*Excellent flow when the angle of repose (θ): 25-30°; Good: 31-35°; Fair: 36-40°; Passable 41-45°; Poor: 46-55° (18)

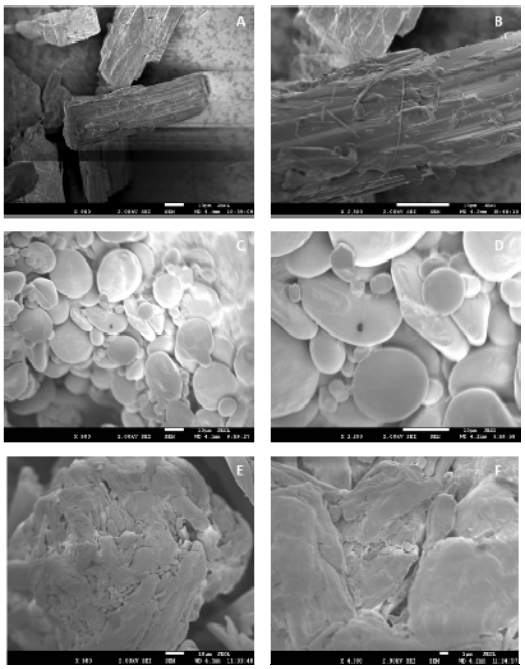

Figure 1: Scanning electron micrographs (x300 and 2500) magnification for (A and B) mannitol, (C and D) starch and (E and F) MCC powders

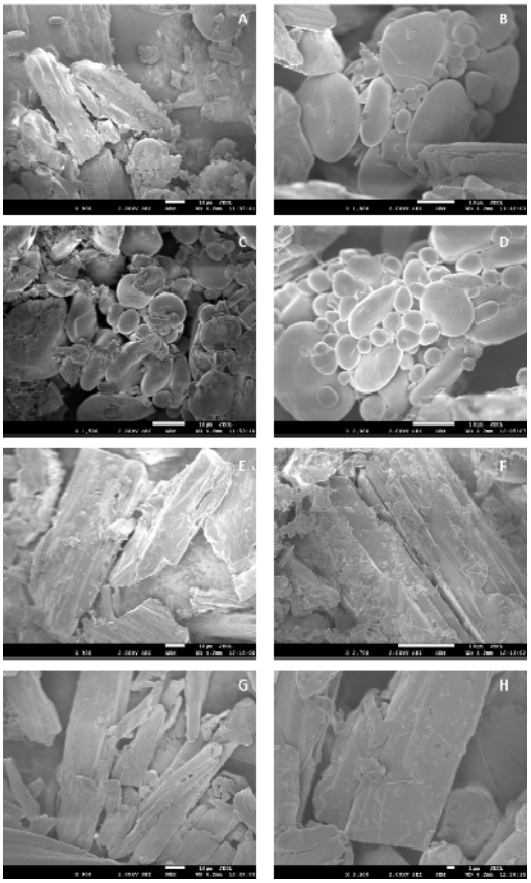

Figure 2: Scanning electron micrograph (x300 and 2500) magnification for (A and B) 5% starch mix, (C and D) 70% starch mix, (E and F) 5 %w/w MCC mix and (G and H) 70% w/w MCC mix

Crystalline properties

Figure 3, Figure 4, Figure 5, Figure and Figure 7 display the x-ray diffraction results, and they that pure mannitol is crystalline and is of the β type. The generation of β polymorph at low temperature leads to fragmentation due to the formation of large droplets on the surface, which in turn causes brittleness to the crystalline surface due to high porosity. On the other hand, starch showed an A-type crystallinity shape in Figure 5. The XRD pattern of MCC pure powder in Figure 5 exhibits a broad, amorphous hump in the 9 - 16º, followed by a crystalline peak at 23º and perhaps another small amorphous peak at 33º. The rate of the amorphous region within MCC is due to MCC spray drying formation, which is known to result in amorphous particles [20]. XRD data showed that 70 % w/w of starch and MCC had caused a reduction in peak intensities due to a reduction in the crystallinity within particles that resulted in further lowering of peak intensity (Figure 6 and Figure 7)

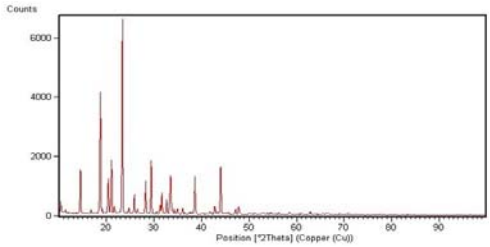

Figure 3: X-ray powder diffraction patterns of mannitol pure powders

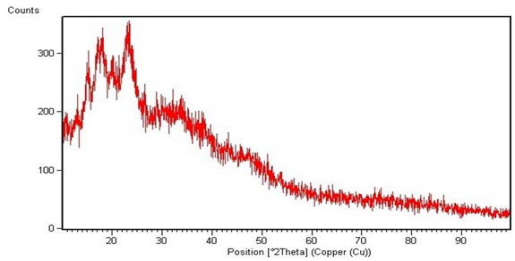

Figure 4: X-ray powder diffraction patterns of starch pure powders

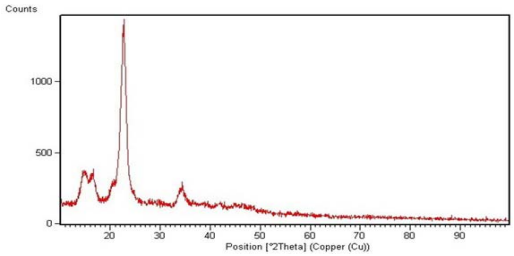

Figure 5: X-ray powder diffraction patterns of MCC pure powders

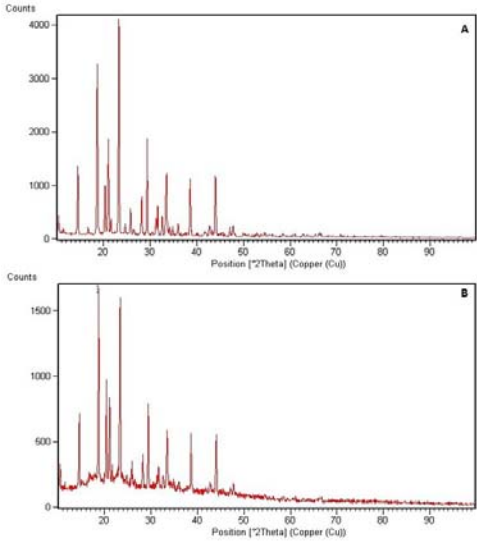

Figure 6: X-ray powder diffraction patterns of (A) 5 % w/w starch interactive mix, (B) 70 % w/w starch interactive mix

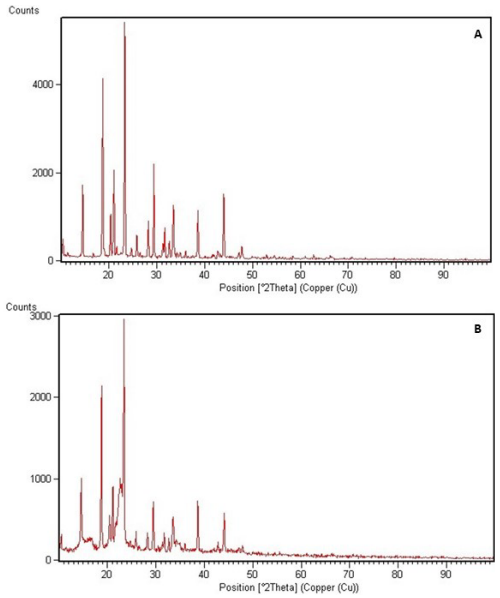

Figure 7: X-ray powder diffraction patterns of (A) 5 % w/w MCC interactive mix and (B) 70 % w/w MCC interactive mix

Mechanical properties of tablets

Powder blends were prepared using the dual excipients and further assessed for compaction to identify the effect of starch and/or MCC on the mechanical and physical properties of mannitol. Moreover, tablet dosage forms are exposed to various mechanical stresses during manufacturing, such as transportation and handling by patients. Thus, a successful tablet formulation must have sufficient mechanical strength. Surprisingly, hardness test results for the ternary mixtures of starch or MCC with mannitol and 1% w/w magnesium stearate tablets indicated a significantly enhanced hardness for all formulas ($p < 0.05$, Figure. 8). As for the hardness test for the different concentrations of mannitol, it had demonstrated fragile tablets due to low mannitol compactability [6]. Furthermore, SEM results (Figure 1 a and b) presents a longitudinally shaped particle of mannitol that could be the reason for the poor hardness of the tablets [7]. Consequently, The high crushing strength for all tablets formulations (> 75 N) could be due to the addition of MCC, which could be explained by the microfibrillar structure of the MCC that had shown a mechanical interlocking, and preventing extensive stress relaxation [21].

Disintegration time

The disintegration time of the tablets was varied according to the type and concentration of excipients. Increasing the concentration of starch (F1 - F5) resulted in a remarkable reduction in disintegration time, suggesting that starch swells upon the contact with water through wicking, which provides the basis of fast disintegration properties. Statistically, all formulations showed significant differences in disintegration time (ANOVA, $p < 0.05$). Regarding the lowest tablet disintegration time, it was observed with F6, which was approximately 29 s (Figure 9). In addition to that, increasing the MCC concentration led to longer disintegration time due to the high cohesive interaction between MCC-MCC particles. However, when the concentration of MCC and mannitol was equivalent, the disintegration was faster (33 ± 5.22 s), indicating a reduction in tablet bonding as a result of the weak interaction between mannitol-MCC [22].

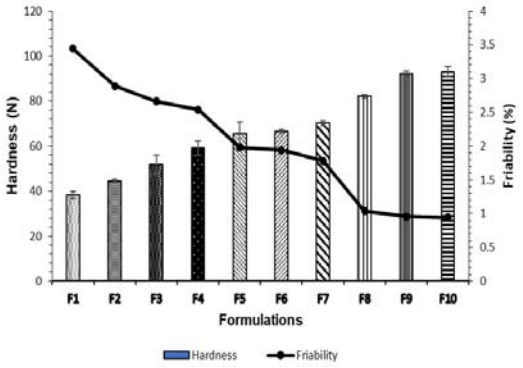

Figure 8: Effect of starch (F1 - F5) and MCC (F6 - F10) concentrations (5-70% w/w) on hardness and friability of binary mixture tablets. Tablets were compressed at 3 tonnes compression force. Results of hardness reported as mean ± SD (n=3)

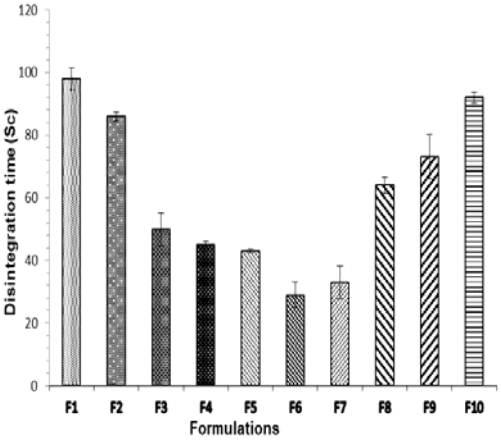

Figure 9: Effect of Strach (F1-F5) and MCC (F6-F10) concentrations (5-70% w/w) on the disintegration time of binary mixture tablets. Tablets were compressed at 3 tonnes compression force. Results reported as mean ± SD (n = 3)

DISCUSSION

When developing a pharmaceutical drug delivery system, it is vital to understand the effect of the excipient on the final dosage form through the evaluation of each subunit influence on the final formulation and other excipients. Starch with D-mannitol or MCC and D-mannitol with respect to all their mixtures were investigated for flowability, particle size distribution, SEM, XRD and FTIR to better understanding of the effect of utilizing starch and MCC on the physical properties of mannitol. A fundamental requirement for excipients in direct compression is good flow properties as it has an impact on uniformity [23]. Characterising flow properties of a powder mixtures was performed through measuring the angle of repose. Particle shape of the excipients showed a great contribution for the flowability of the mixtures, as the spherical shaped particles indicated a free flow powder, in contrast the rod long shaped particles exhibited a significant low flowability ($P < 0.05$) due to the increase in surface/volume ratio. Results of SEM for the interactive mixtures revealed that MCC particles enhanced mannitol dispersibility within the powder bed (Figure 2 g and h). Likewise, the physical mixture showed a large particle of MCC (>140 µm) mixed with mannitol particles. Interestingly, the mixture did not demonstrate an interactive phenomenon as expected; this could be attributed to inadequate shear force found in the system that leads to de-agglomeration and attraction of mannitol particles to the MCC surface. Pharmaceutical material crystallinity has a main influence on the physical, mechanical, and chemical properties. The degree of crystallinity is the ratio of the amount of crystalline constituent compared to the total amount of sample. An increase in crystallinity is allied with an increase in mechanical properties and stability. Furthermore, the increase of crystallinity results in distended dissolution time and delay the release of drug from dosage forms, thus affecting bioavailability. The only results for friability for (F8-F10) batches did achieve the pharmacopeia limit of <1% (Figure 4) upon the increment of MCC concentration that yielded lower friability due to the binding property of MCC. Moreover, improvement in the friability of MCC based tablets is attributed to the high plasticity of MCC and mechanical interlocking ability that overcame the poor binding capability and led to tablets with conventional mechanical properties [24].

CONCLUSION

The findings of the current study show a significant impact of excipient selection on the final dosage form characteristics, specifically, solid dosage forms. The results indicate that the beneficial effect of using MCC and starch in different ratios to alleviate mannitol poor flowability. It is evident that utilizing MCC and starch improves the mechanical and physical properties of mannitol. Further studies on the effect of such excipients on the dissolution and bioavailability of the solid dosage form would also be helpful.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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