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RESEARCH ARTICLE

Magnesium Stearate Fatty Acid Composition, Lubrication Performance and Tablet Properties

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Abstract

Magnesium stearate (MgSt) is a common tablet lubricant. As variations in MgSt properties are known to influence tablet attributes, the impact of MgSt fatty acid composition, particularly the significance of the stearate and palmitate contents, and its effects on tablet properties warrant further investigation. This study investigated the effect of MgSt with different stearate and palmitate contents but comparable physical properties (e.g. particle size, crystallinity, specific surface area and morphology) on lubrication performance and resulting tablet quality attributes, including mechanical strength, disintegratability and drug release. The influence of MgSt concentration and blending duration on the resulting tablet properties was also examined. Tablets produced using the lower stearate content MgSt had slightly higher tensile strength. The effect of MgSt stearate content was more apparent in the disintegration time and drug release, whereby MgSt of lower stearate content resulted in tablets with longer disintegration time and slower drug release. The lower stearate content also resulted in a lower lubrication performance, leading to a lesser reduction in tablet ejection force. As expected, a longer blending time of the tablet formulation blend with MgSt yielded tablets with reduced tensile strength, shorter disintegration time and slower drug release. Tablets with higher MgSt concentration showed a greater reduction in tensile strength, longer disintegration time and faster drug release. The study findings reinforced observations by other researchers and provided a better understanding of the fatty acid composition effects of MgSt on lubrication performance and the resulting tablet properties.

Keywords Ejection force · Lubrication · Palmitate · Stearate · Tablet properties

Introduction

Magnesium stearate (MgSt) is essential in tableting to prevent tablet adherence to surfaces of the die and punches, reduce interface friction and improve granule flowability [1, 2]. Due to its popularity as the lubricant in tablet formulation, MgSt has been widely investigated for its properties and potential impact on formulations. Variations in the MgSt properties have been reported to affect its lubrication performance and the properties of tablets produced [3–7]. Additionally, lubricant blending conditions [8–11] and tablet formulation components [12–14] were reported to influence the tableting process and hence, the resulting tablet properties. Therefore, care should be taken to maintain the MgSt properties and tableting process parameters for each batch of tablets manufactured to minimize inconsistencies in the tablet quality.

MgSt, as a tablet lubricant, primarily consists of magnesium stearate and magnesium palmitate in various proportions and other fatty acids in smaller proportions [15]. It is challenging to produce MgSt of varied stearate and palmitate contents while maintaining similar physical properties [16, 17]. A study attempted to synthesize pure magnesium stearate and pure magnesium palmitate and compare the thermal properties and morphology of the hydrates. The study reported that the pure magnesium stearate and pure magnesium palmitate had comparable thermal properties, except for the trihydrates. The study also observed that pure

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magnesium stearate generally had smaller particle sizes with irregularly shaped layered particles compared to pure magnesium palmitate, which had larger particle sizes with plate-like particles [18]. Wada and Matsubara reported MgSt of varied particle sizes and morphologies for stearate contents ranging from 57 to 77% and palmitate contents ranging from 23 to 41% [19]. The study also reported MgSt of comparable morphology with different particle sizes and stearate/palmitate contents. The fatty acid source, whether from animal or plant sources, has been reported to affect MgSt lubrication performance [20]. However, other studies have shown little to no difference in MgSt's performance between the plant-based and animal-based MgSt [6, 21]. The effect of fatty acid composition on MgSt's performance has been investigated by synthesizing MgSt of different stearate and palmitate contents. However, the fabricated MgSt showed different specific surface areas and crystal structures, potentially confounding the results [16, 22]. Clearly, the influence of the fatty acid composition of MgSt on its lubrication performance and resulting tablet properties has not been conclusively established.

Although much work has been performed on characterizing MgSt and MgSt's effect on powder flow or the tableting process, the effect of the fatty acid composition is difficult to discern from the other properties [23–25]. The fatty acid composition needs to be deconvoluted from the other properties to further provide an understanding of its effect on lubrication performance and the resulting tablet properties. Using MgSt designed to contain different fatty acid compositions, this study aimed to elicit the effect of the primary fatty acids, stearate and palmitate. Herein, two MgSt grades of different stearate and palmitate contents but with comparable physical properties (such as particle size, crystallinity, specific surface area and morphology) were evaluated through their effect on the mechanical strength, ejection force, disintegration and dissolution properties of the tablets produced. The influence of MgSt concentration and blending duration on the resulting tablet properties was also investigated.

Materials and Methods

Materials

Two MgSt grades of different fatty acid compositions – MGS-L (43.5% stearate, 54.9% palmitate, other carbon chains: insignificant, specific surface area: 3.4 m^2/g) and MGS-H (70.4% stearate, 28.8% palmitate, other carbon chains: insignificant, specific surface area: 2.9 m^2/g) were supplied by Faci Asia Pacific Pte. Ltd., Singapore. Other tablet components included microcrystalline cellulose (MCC; PH101, Asahi Kasei, Japan) as the filler, chlorpheniramine maleate (Vetpharm Laboratories Pte. Ltd., Singapore) as the model drug, and sodium starch glycolate (Primojel, DFE Pharma, Germany) as the disintegrant.

Morphological Evaluation

The morphology of MGS-L and MGS-H was evaluated using a scanning electron microscope (SEM; JSM-6010LV, JEOL, Japan). Before the evaluation, the samples were sputter coated with platinum (MSP-2 S, IXRF Systems, USA). The samples were subsequently examined at 5.0 kV acceleration voltage with 1000× magnification.

Particle Size Analysis

Particle size and size distribution of MGS-L and MGS-H were determined using the SEM. The sample preparation was similar to that for the morphological evaluation. Using an in-built software (InTouchScope JSM-6010 v.1.11, JEOL, Japan), the size of at least 1000 randomly selected particles was measured. A cumulative undersize particle size distribution plot was constructed and used to determine the particle size at the 10th (D_{10}), 50th (D_{50}) and 90th (D_{90}) percentiles of the plot. Particle size distribution (span) was calculated using Eq. 1.

$$\text{Span} = \frac{D_{90} - D_{10}}{D_{50}} \quad (1)$$

Thermal Analysis

Differential thermal-thermogravimetric (DTA-TGA) thermograms of MGS-L and MGS-H were acquired using a differential thermal-thermogravimetric analyzer (DTG; DTG-60, Shimadzu, Japan). The samples (3–5 mg) were contained in crimped aluminum pans and then heated at 5 °C/min from 30 to 250 °C. Nitrogen was used as the purge gas at 50 mL/min. The data were processed using the in-built software (TA60, v.2.30, Shimadzu, Japan). TGA thermograms generated using the DTG also provided information on the moisture content by taking the difference in the sample weight before and after heating [26].

X-ray Diffraction

The x-ray diffraction pattern of MGS-L and MGS-H was investigated using an x-ray diffractometer (XRD-6000, Shimadzu, Japan) with Cu Kα radiation operating at 40 kV and 30 mA. The samples were scanned from a diffraction angle range of 5 to 50° with 0.02° step size and at a rate of 2 °/min. An in-built software (XRD-6100/7000, v.7.00, Shimadzu,

Japan) was used to analyze the relative crystallinity of the samples.

Contact Angle Measurement

Contact angle was measured using a sessile liquid drop technique (FTÅ200, First Ten Ångstroms, USA). The compact was prepared by compressing 100 mg of the MgSt sample at 191 MPa using a compaction simulator (Evolution Styl'One, MedelPharm, France) fitted with a 10 mm punch and die set (Natoli Engineering, USA). The upper and lower punches were set to move at 0.001 and 0.002 mm/ms, respectively. The FTÅ32 v2.0 software was used to analyze the captured images of the sessile liquid drops.

Preparation of Powder Blend for Tableting

Powder blends were prepared with different MgSt concentrations (0.5, 1 and 2%, w/w). MCC was used as the filler to make up to the required amount. The remaining components of the powder blend include 2%, w/w sodium starch glycolate and 1.6%, w/w chlorpheniramine. Chlorpheniramine is a water-soluble compound with water solubility of 5.5 g at 37 °C [27]. A weighed amount of microcrystalline cellulose, sodium starch glycolate and chlorpheniramine was mixed in a cube blender at 20 rpm (J. Engelsmann AG, Germany) for 30 min. MgSt was subsequently added, and the powder blend was further mixed for 10, 30 or 60 min. Control tablets without MgSt were also fabricated. The batch size was kept to 1 kg for each blending formulation.

Tablet Preparation

Tablets of 250 mg each were produced from the powder blends using a compaction simulator (Evolution Styl'One, MedelPharm, France). The simulator was equipped with a 10 mm punch and die set (Natoli Engineering, USA) for the compaction. For each compaction, the upper and lower punches moved at 0.06 and 0.08 mm/ms, respectively. A compression pressure of 127 MPa was applied to the powder blends for each compression cycle. Tablet ejection force was captured using the software AnalisMX v2.08.6. The tablet ejection force measures the force required to eject the tablet from the die. For each formulation, 15 tablets were produced for further characterization.

Tablet Characterization

Tablet Porosity

Tablet porosity was calculated according to the following equations.

$$\rho_{app} = \frac{\text{tabletweight}}{\pi \times \text{tabletradius}^2 \times \text{tabletheight}} \quad (2)$$

$$\frac{1}{\rho_{true,mix}} = \sum_{i=1}^{z} \frac{x_i}{\rho_i} \quad (3)$$

$$\text{Tablet porosity} = \left(1 - \frac{\rho_{app}}{\rho_{true,mix}}\right) \quad (4)$$

where x and z refer to the mixture's weight fraction and number of components, respectively. ρ_i is the true density of the individual components in the formulations and is estimated using a helium pycnometer (Pentapycnometer, Quantachrome Instruments, USA).

Tensile Strength

Breaking force and tablet dimensions were measured at least 24 h post compaction using a hardness tester (TBF 1000, Copley Scientific, UK) and a thickness gauge (547–300 S, Mitutoyo, Japan), respectively. Tablet tensile strength (σ) was calculated using Eq. 5.

$$\sigma = \frac{2 \times F}{\pi \times D \times H} \quad (5)$$

where F, D and H represent the tablet breaking force, diameter and thickness, respectively. The tensile strength was determined in triplicates, and the averaged results were reported.

Disintegration

The disintegration test (PTZ AUTO 2 EZ, Pharma Test, Germany) was performed in 37 °C purified water. The disintegration time of at least three randomly chosen tablets was determined, and the averaged results were reported.

Drug Release

Chlorpheniramine release was determined using dissolution apparatus 2 (VK7010, Varian, USA) at 50 rpm paddle rotation. Degassed purified water (900 mL) was used as the dissolution medium and maintained at 37 °C. At predetermined time points, 5 mL aliquots of the dissolution medium were automatically withdrawn (VK8000, Varian, USA). The aliquots were analyzed spectrophotometrically (U-5100, Hitachi, Japan) at 264 nm for chlorpheniramine. Drug release from at least three randomly chosen tablets was evaluated, and the averaged results were reported.

The drug release profile was quantified by mean dissolution time (MDT) (Eq. 6).

$$MDT = \frac{\sum_{i=1}^{n} \bar{t}_{mid} \ \Delta M_i}{\sum_{i=1}^{n} \Delta M_i} \quad (6)$$

where i and n represent the dissolution sample number and dissolution sampling time point, respectively. $\bar{t}_{mid}$ refers to the time at the midpoint between i = 1 and n. ΔMi is the difference in the amount of drug dissolved between i = 1 and n.

Statistical Analysis

Statistical software (Minitab 17.1.0, Minitab Inc., USA) was used to analyze the effect of the full factorial design used in this study. The level of significance was set to $p < 0.05$. The main effect of the investigated variables is defined as the change in response caused by changing the formulation variables, namely, MgSt type and MgSt concentration, and the processing variable – blending duration. The MgSt type was evaluated at two levels – MGS-L and MGS-H. The MgSt concentration was evaluated at three levels – 0.5, 1 and 2%, w/w. The blending duration was assessed at three levels – 10, 30 and 60 min.

Results

Properties of MgSt

The particle size descriptors are presented in Table I. The particle size and size distribution of MGS-L and MGS-H were comparable, with MGS-H being slightly smaller and of a narrower span than MGS-L. The SEM micrographs also showed that both MGS-L and MGS-H comprised finely milled plate-like shape particles (Fig. 1A).

The results from the thermal data analysis are shown in Fig. 1B. Endothermic peaks were observed at about 68 °C and 105 °C. The first endotherm could be attributed to the melting of the fatty acids and the loss of loosely bound moisture [25]. The second endotherm could be due to the loss of tightly bound water with a corresponding weight loss, as observed in their respective TGA curves. The average moisture content of the MgSt samples determined using the TGA method ranged from 2.62 to 2.76%, a slightly lower value than the theoretical moisture content of 3% for MgSt monohydrate [16].

MGS-L and MGS-H had a comparable x-ray diffraction pattern (Fig. 1C), similar to the pattern reported in the literature [16, 28]. Smaller peaks were observed at about 5° and 41°. A broad peak was observed at around 21°. Data from the DTA-TGA and XRD suggested that the MgSt samples could be a mixture of anhydrous and monohydrate forms.

The surface characteristics of MGS-L and MGS-H compacts were evaluated by their contact angle. A contact angle greater than 90° indicates a hydrophobic substrate with poor wettability. Although not statistically different, the contact angle of MGS-H (103.72° ± 3.29°) was slightly larger than that of MGS-L (102.73° ± 2.83°), suggesting that MGS-H had relatively poorer interaction with water.

Tablet Porosity

The porosity values of tablets produced from the lubricated and non-lubricated formulations were comparable (Table II). There was minimal difference in the tablet porosity with respect to the MgSt type, MgSt concentration and blending duration. As MCC is a flowable, highly compressible and fibrous material, the low concentration of MgSt did not contribute to any significant changes in the porosity of the prepared tablets and hence, their micromeritic properties.

Tablet Tensile Strength

Tablets produced from the lubricated formulations had lower tensile strength than those produced from the non-lubricated formulation (Fig. 2A). It was also observed that the extent of tensile strength reduction increased with increasing MgSt concentration and a longer blending duration. Tablets containing MGS-H had marginally lower tensile strength compared to tablets containing MGS-L.

Tablet Ejection Force

Figure 2B shows the ejection force from the different tablet formulations. Tablets produced without any lubrication had the highest ejection force. Generally, tablets produced with MGS-H had lower ejection force than tablets produced with MGS-L. A longer MgSt blending duration

Table I Properties of MgSt Having Different Stearate and Palmitate Contents

MgSt type	Particle size descriptors				Moisture content (%)	Relative crystallinity (%)
	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span		
MGS-H	1.96 ± 0.24	4.60 ± 0.78	10.41 ± 0.70	1.87 ± 0.27	2.62 ± 0.03	26.51 ± 2.25
MGS-L	2.01 ± 0.10	5.20 ± 0.26	12.18 ± 2.49	1.94 ± 0.40	2.76 ± 0.07	28.80 ± 1.69

± represents standard deviation

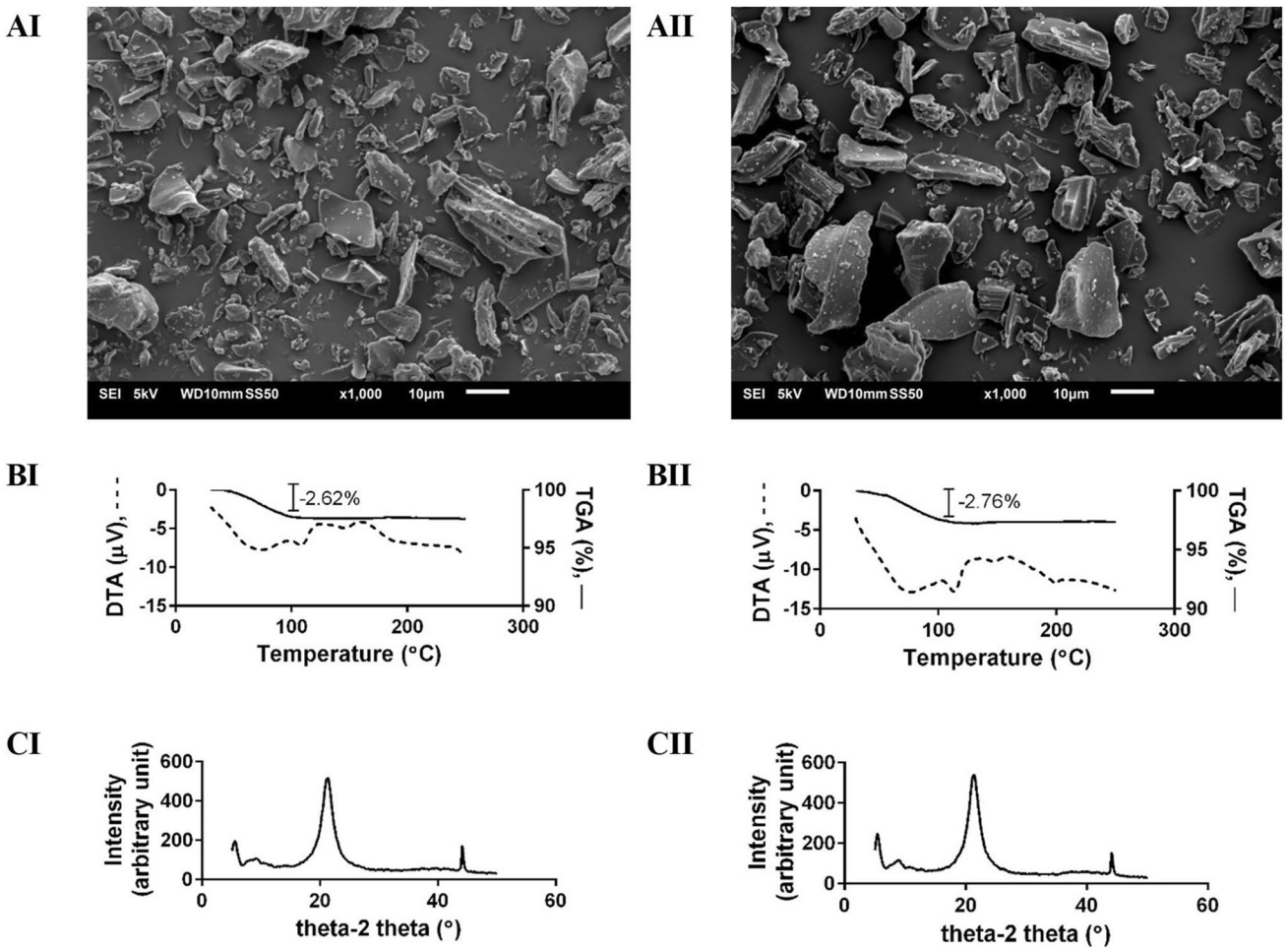

Fig. 1 Properties of (I) MGS-L and (II) MGS-H MgSt. **A** Morphology, **B** thermograms from thermal-thermogravimetric analysis and **C** x-ray diffraction patterns

Table II Tablet Porosity

Blending duration (min)	Porosity of tablets made from lubricated formulations containing different types and concentrations of MgSt					
	MGS-L concentration (%, w/w)			MGS-H concentration (%, w/w)		
	0.5	1	2	0.5	1	2
10	0.15 ± 0.02	0.15 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	0.15 ± 0.00	0.14 ± 0.01
30	0.15 ± 0.01	0.16 ± 0.00	0.14 ± 0.01	0.16 ± 0.01	0.14 ± 0.01	0.15 ± 0.00
60	0.16 ± 0.01	0.16 ± 0.01	0.15 ± 0.00	0.16 ± 0.01	0.15 ± 0.00	0.14 ± 0.01

± represents standard deviation

Porosity of tablets produced from a non-lubricated formulation: 0.15 ± 0.01

also resulted in lower tablet ejection force. However, the effect could be affected by the MgSt type and concentration. Tablets with higher MGS-H concentrations blended for 10 min had a slightly higher ejection force than tablets containing lower MGS-H concentrations. In contrast, a gradual decrease in the tablet ejection force was observed with increasing MGS-L concentration in the formulation. Tablets made with 0.5%, w/w MGS-L had the most prominent reduction in the ejection force with a longer blending duration. At the highest MgSt blending duration (60 min), the effect of MgSt concentration on the ejection force diminished.

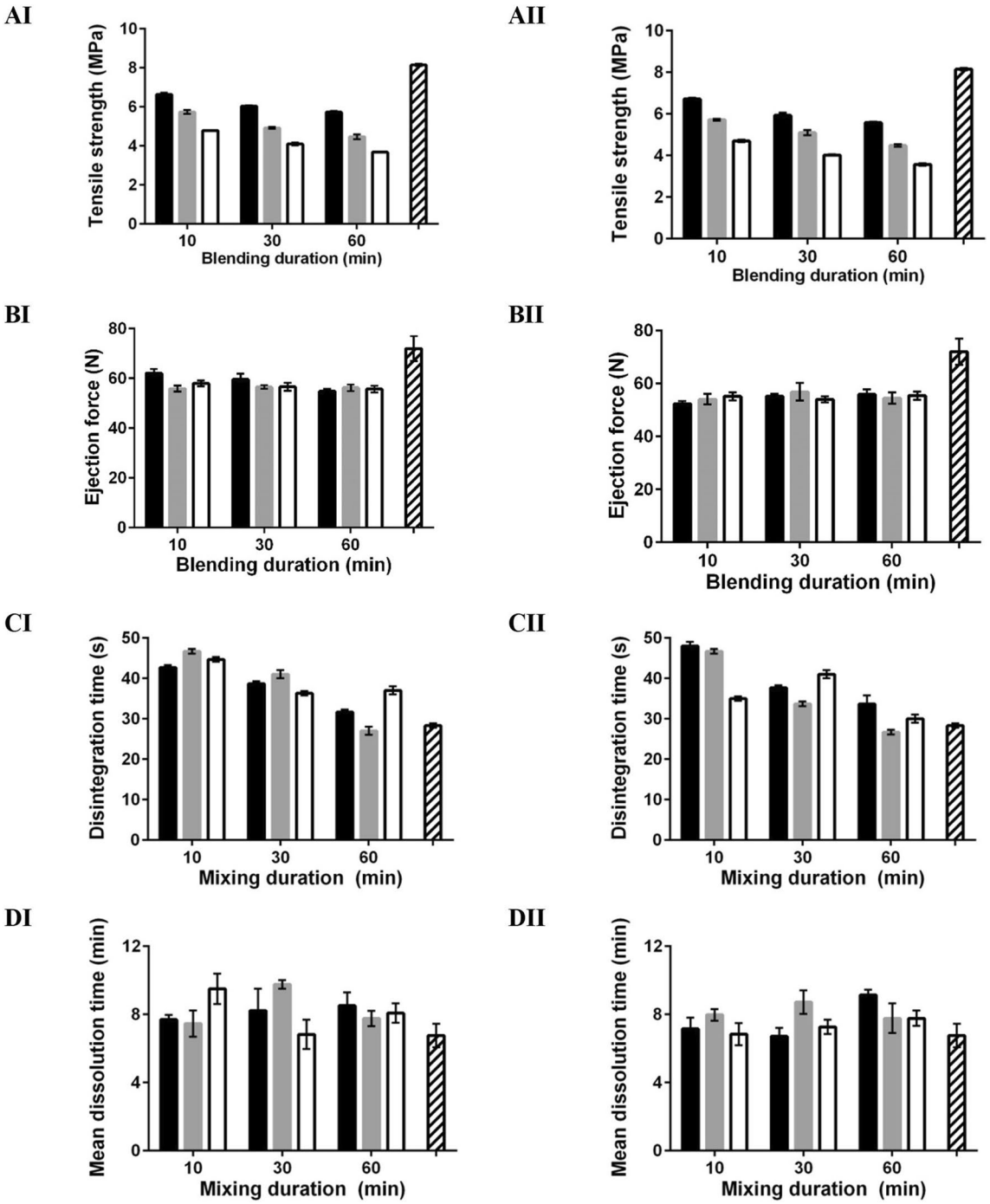

Fig. 2 Tablet properties – **A** tensile strength, **B** ejection force, **C** disintegration time and **D** mean dissolution time of tablets formulated with 0.5% (■), 1% (▒) and 2% (□) of (I) MGS-L and (II) MGS-H compared to tablets not containing MgSt (▨)

Disintegration Time

Figure 2C shows the disintegration time of tablets produced from the different formulations. As expected, tablets containing MgSt had longer disintegration times than those without. Generally, a longer blending duration with MgSt resulted in a shorter disintegration time, while a higher MgSt concentration in the formulations increased the disintegration time. However, the effect of MgSt concentration on the disintegration time could be influenced by blending duration

and MgSt type. For MGS-L, it was observed that a blending duration of 10 min with 0.5%, w/w MgSt produced tablets with a faster disintegration time compared to tablets prepared with 1%, w/w or 2%, w/w MgSt. However, tablets prepared with 2%, w/w MGS-H and had 10 min blending duration resulted in a shorter disintegration time than tablets prepared with 0.5%, w/w or 1%, w/w MGS-H. For 60 min blending duration, tablets prepared with 2%, w/w MGS-L had a longer disintegration time than tablets with lower MGS-L concentrations. In contrast, an opposite trend was observed for MGS-H when mixed with the formulations for 60 min.

Drug Release

The MDT values of tablets produced from the lubricated formulations were higher than those made from the non-lubricated formulation (Fig. 2D). This suggested that MgSt resulted in tablets that had a slower drug release. Overall, tablets produced using formulations containing MGS-H had lower MDT values than similarly produced tablets with MGS-L. It was also observed that prolonged blending duration with MgSt resulted in tablets showing longer MDT values. However, tablets produced from formulations containing 2%, w/w MgSt generally had lower MDT values than tablets containing 0.5%, w/w or 1%, w/w MgSt.

Discussion

Influence of Formulation and Process Variables on Tablet Mechanical Property

Generally, tablets produced from formulations blended with MgSt had a lower tensile strength (Fig. 2A). Tablet strength is affected by the bonding area and bonding strength [29]. The effect of MgSt on tablet tensile strength could be related to the distribution of the MgSt particles on the surface of the other tablet components. The MgSt particles adhering on the surface formed a physical barrier between stronger bonding component particles and replaced the inter-particulate bonding forces with a weaker order of bonding forces [30, 31]. The type of inter-particulate bonding that contributes to tablet strength is very dependent on the consolidation mechanism of the major component in the formulation that percolates the tablet matrix microstructure. MCC, which undergoes plastic deformation when compressed, was the main component for the tablets evaluated in this study. Compared to tablets containing materials that consolidate by brittle fragmentation, tablets containing MCC are reported to be more sensitive to tensile strength reduction by MgSt as no lubricant-free surface is generated during compression [31, 32].

It was observed that tablets produced from formulations containing MGS-L had a higher tensile strength than those containing MGS-H (Fig. 2A), albeit the difference was marginal. The lower tensile strength of tablets containing MGS-H could be attributed to the higher hydrophobicity of MGS-H. Therefore, it could contribute to the reduced inter-particulate bonding strength. From the analysis effects of the investigated variables ($R^2 = 99.6\%$), MgSt blending duration and concentration had a greater influence on tablet tensile strength than the type of MgSt (Fig. 3). A longer blending duration and higher MgSt concentration resulted in greater coverage of the formulation components by MgSt particles, consequently decreasing tablet tensile strength [8, 33, 34]. The presence of significant interaction terms indicates that the other variables can also impact the effect of the investigated variables on the tensile strength. Significant two-way interactions were detected between MgSt type and concentration ($p = 0.007$) and between the blending duration and MgSt concentration ($p = 0.004$). Significant three-way interactions were also observed for MgSt type, MgSt concentration and blending duration ($p = 0.003$) (Table III).

Influence of Formulation and Process Variables on Tablet Ejection Force

Tablet ejection force is critical in a tableting process. A high ejection force could increase the risk of tablet defects such as capping, lamination, or punch sticking [35–37]. Ejection force arises from the residual die wall stress along the radial direction. Force application along the axial direction is needed to overcome the radial restraint and to get a tablet out of the die [38]. Powder or die-wall lubrication could lower tablet ejection force [3, 14]. Therefore, ejection force can be used as an indicator of MgSt's lubrication performance. MgSt's lubrication mechanism could be attributed to the adherence of its polar functional groups to the metal surfaces, forming a boundary between the metal surfaces and the tablet formulation components [39].

The efficiency of MgSt in lowering tablet ejection force could be related to the particle size, whereby the powder form of MgSt could result in a greater reduction of ejection force than MgSt in the granular form [40]. At a comparable particle size, the stearate and palmitate contents affected MgSt's efficiency in lowering ejection force, as evident from Figs. 2B and 4. The higher stearate content of MGS-H could result in MGS-H having a higher hydrophobicity than MGS-L, which helps to lubricate the formulation.

The analysis effects of the investigated variables had an R^2 of 64.8%. The data showed a significant ($p < 0.05$) linear effect of MgSt type, MgSt concentration and blending duration on the ejection force. The data also showed statistically significant two-way interactions ($p < 0.05$) for the MgSt type and blending duration, MgSt type and MgSt concentration,

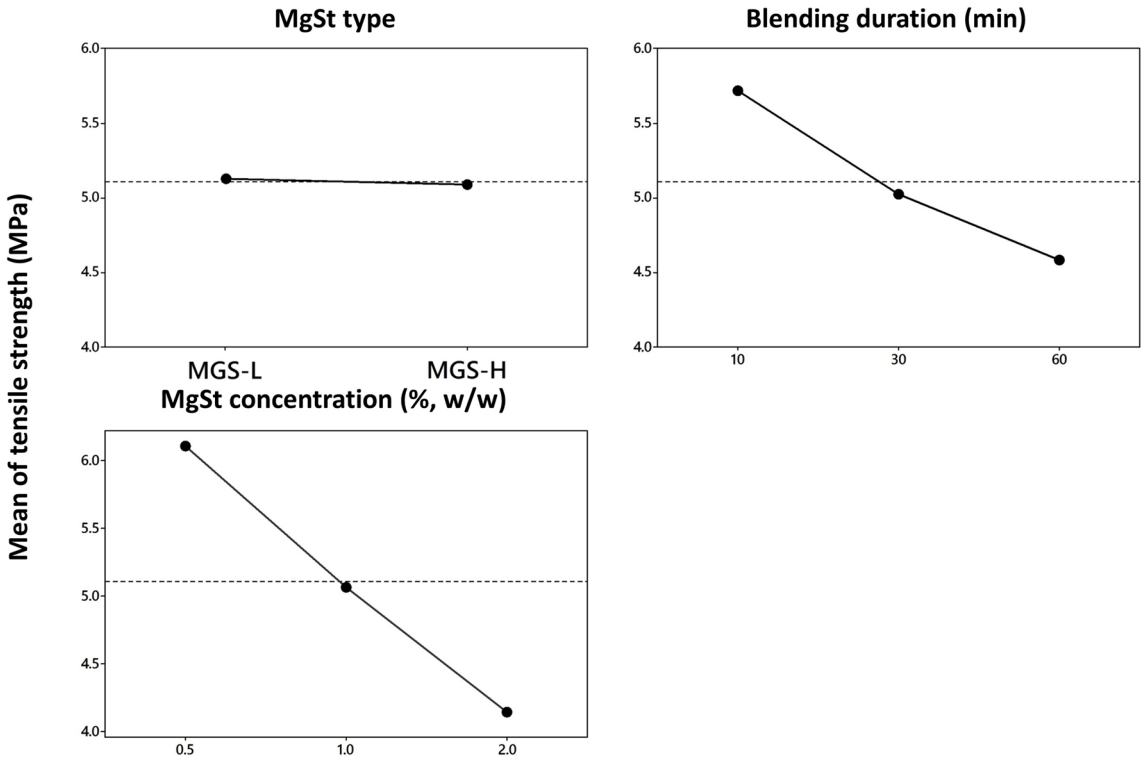

Fig. 3 Plot of the main effects of MgSt type, blending duration and MgSt concentration on tablet tensile strength

and blending duration and MgSt concentration. MgSt type, MgSt concentration and blending duration also had significant three-way interactions ($p < 0.05$) (Table III). The presence of statistically significant interactions suggested that the investigated factors had to be studied concurrently to understand their effects on tablet ejection force. The investigated factors had different extents of influence on tablet ejection force. From the plot of main effects (Fig. 4), the MgSt type had more impact on the ejection force, as evident from the difference in the ejection force between MGS-L and MGS-H. The effect of MgSt concentration on the ejection force diminished at higher MgSt concentrations. A longer blending duration also reduced tablet ejection force.

Influence of Formulation and Process Variables on Tablet Disintegration time

Adding MgSt to tablet formulations prolonged the disintegration times (Fig. 2C) and the effect is attributed to the compactness of the hydrophobic film of MgSt particles over the component particles. Hydrophobicity restricts water penetration into the tablet matrix, hence delaying disintegrant activation by water. The R^2 of the analysis of effect was 98.7%. The analysis also revealed a significant interaction between the investigated factors. MgSt type and concentration had significant two-way interaction ($p < 0.05$) on the tablet disintegration. The blending duration and MgSt concentration showed significant two-way interactions ($p < 0.05$). The analysis also showed significant three-way interactions for MgSt type, concentration and blending duration ($p < 0.05$) (Table III). Compared to the MgSt type, the blending duration and concentration had a greater impact on the disintegration time (Fig. 5). Studies have reported that MgSt increased the hydrophobicity of powder formulations [41, 42]. Additionally, a higher blending intensity could further increase the hydrophobicity [43].

Overall, tablets containing MGS-H disintegrated faster than those with MGS-L. Contrary to the effect of hydrophobicity on delaying tablet disintegration [44], the more hydrophobic nature of MGS-H did not impair the disintegratability of its tablets as compared to tablets containing the less hydrophobic MgSt, MGS-L. It was likely that the slightly lower tensile strength of tablets containing MGS-H had been compensatory as besides accessibility of the matrix to liquid penetration for tablet disintegration, disintegration can also be affected by tablet tensile strength [45, 46]. Tablet disintegration involves the disruption of bonds and therefore, stronger tablets tend towards longer disintegration times.

The disintegration time was shortened when the blending duration was increased from 10 to 60 min. This result contradicts the expected outcome of slower disintegration with prolonged blending duration. A longer blending duration resulted

Table III Coefficients for a Covariate Term

Term	Response variables			
	Tensile strength	Ejection force	Disintegration time	MDT
Constant	5.11	56.05	37.74	7.98
Linear				
MgSt type				
MGS-L	0.02	1.23*	0.70*	0.22*
MGS-H	− 0.02	-1.23	-0.70	-0.22
Blending duration				
10	0.61*	0.21	6.37*	-0.21
30	-0.09*	0.42*	0.32	0.01
60	0.52	-0.63	-6.69	0.19
MgSt concentration				
0.5	1.00*	0.61*	-1.02*	0.00
1	-0.04*	-0.38*	-0.80*	0.26
2	-0.96	-0.23	1.82	-0.26
2-way interactions				
MgSt type × blending duration				
MGS-L × 10	-0.01	1.18*	-0.15	0.22
MGS-L × 30	-0.02	-0.11	-0.09	0.06
MGS-L × 60	0.03	-1.07	0.24	-0.28
MGS-H × 10	0.01	1.18	0.15	-0.22
MGS-H × 30	0.02	0.11	0.09	-0.06
MGS-H × 60	-0.03	1.07	-0.24	0.28
MgSt type × MgSt concentration				
MGS-L × 0.5	0.02	0.96*	0.24	-0.06
MGS-L × 1	-0.05*	-0.68*	0.57*	-0.14
MGS-L × 2	0.03	-0.27	-0.82	0.20
MGS-H × 0.5	-0.02	-0.96	-0.24	0.06
MGS-H × 1	0.05	0.68	-0.57	0.14
MGS-H × 2	-0.03	0.27	0.82	-0.20
Blending duration × MgSt concentration				
10×0.5	-0.04	0.34	-3.76*	-0.35
10×1	0.05*	-0.89*	3.35*	-0.31
10×2	-0.01	0.56	0.41	0.66
30×0.5	-0.03	0.32	1.13*	-0.31
30×1	0.03	0.60*	0.07	0.99*
30×2	0.01	-0.92	-1.20	-0.68
60×0.5	0.07	-0.66	2.63	0.66
60×1	-0.08	0.29	-3.43	-0.68
60×2	0.00	0.36	0.80	0.02
3-way interactions				
MgSt type × blending duration × MgSt concentration				
MGS-L × 10 × 0.5	-0.06*	1.54*	2.54*	-0.12
MGS-L × 10 × 1	0.05	-0.80*	-1.13*	-0.57*
MGS-L × 10 × 2	0.01	-0.74	-1.41	0.69
MGS-L × 30 × 0.5	0.04	0.12	-0.35	0.32
MGS-L × 30 × 1	-0.05*	-0.60*	2.48*	0.38
MGS-L × 30 × 2	0.01	0.48	-2.13	-0.70
MGS-L × 60 × 0.5	0.02	-1.66	-2.19	-0.20
MGS-L × 60 × 1	-0.00	1.40	-1.35	0.19
MGS-L × 60 × 2	-0.02	0.26	3.54	0.02

Table III (continued)

Term	Response variables			
	Tensile strength	Ejection force	Disintegration time	MDT
MGS-H × 10 × 0.5	0.06	-1.54	-2.54	0.12
MGS-H × 10 × 1	-0.05	0.80	1.13	0.57
MGS-H × 10 × 2	-0.01	0.74	1.41	-0.69
MGS-H × 30 × 0.5	-0.04	-0.12	0.35	-0.32
MGS-H × 30 × 1	0.05	0.60	-2.48	-0.38
MGS-H × 30 × 2	-0.01	-0.48	2.13	0.70
MGS-H × 60 × 0.5	-0.02	1.66	2.19	0.20
MGS-H × 60 × 1	0.00	-1.40	1.35	-0.19
MGS-H × 60 × 2	0.02	-0.26	-3.54	-0.02

*indicates statistical significance ($p < 0.05$)

The coefficient for a covariate term represents the change in the mean response associated with a one-unit change in that term while keeping other terms in the model constant

The sign of the coefficient indicates the direction of the relationship between the term and the response variable

The magnitude of the coefficient indicates the degree of its influence on the response variable

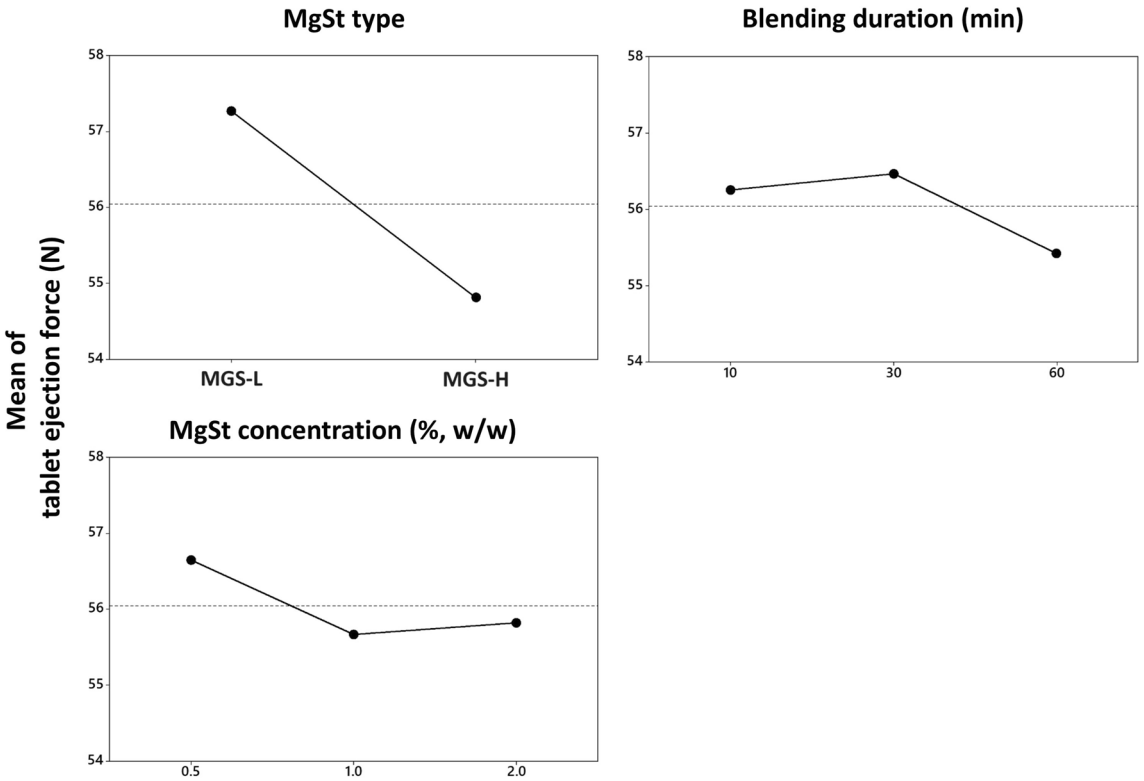

Fig. 4 Plot of the main effects of MgSt type, blending duration and MgSt concentration on tablet ejection force

in better surface coverage by MgSt particles as the clumpish MgSt aggregates further disaggregate with prolonged blending. As a result, the resultant tablets had lower tensile strength because the MgSt particles disrupted the stronger bonds, particularly the MCC-MCC inter-particulate bonding. Hence, with a reasonably good disintegrant system, sodium starch glycolate assisted by MCC, the hydrophobic effects of MgSt in impeding water entry were less effective at prolonging disintegration than the weakened tablet matrix tensile strength caused by MgSt at conferring ease of matrix break-up.

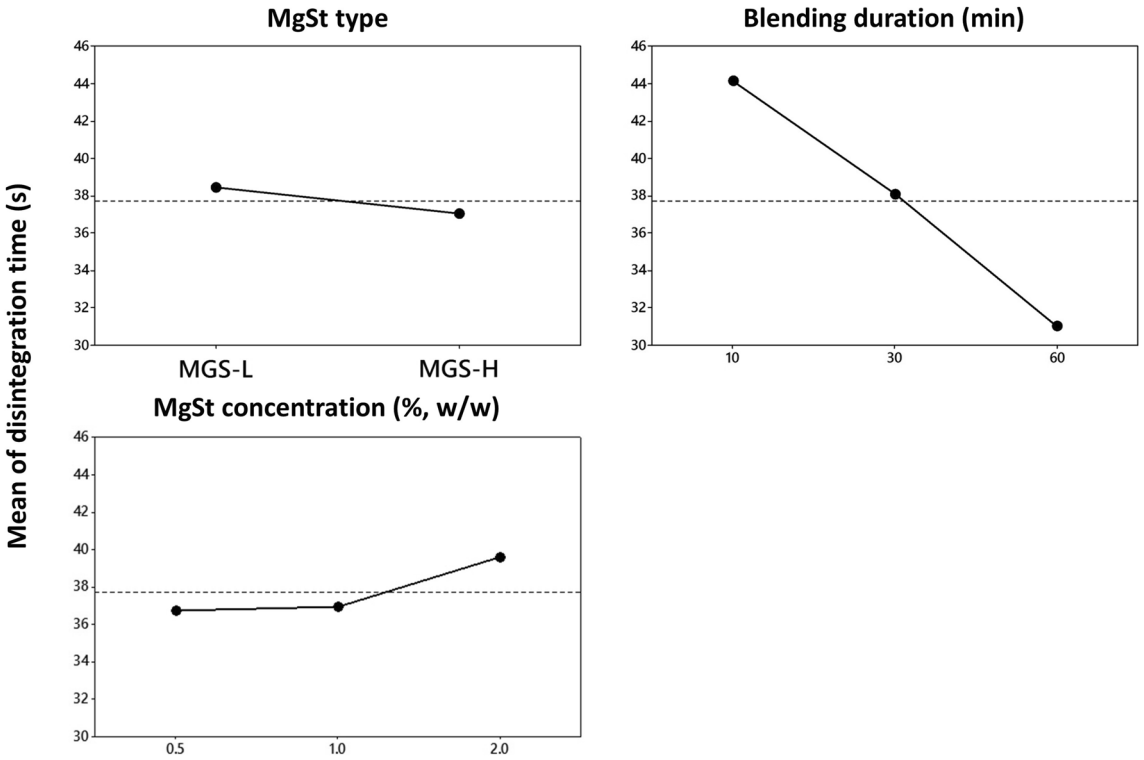

Fig. 5 Plot of the main effects of MgSt type, blending duration and MgSt concentration on tablet disintegration time

Generally, tablets containing higher MgSt concentration had slower disintegration than tablets containing lower MgSt concentration due to increased hydrophobicity. However, this trend was only observed for some blending duration and MgSt type, suggesting that the effect of MgSt on tablet disintegration time could be affected by both the MgSt type and blending duration. It should be noted that the filler type could also influence the effect of MgSt on tablet disintegration. A study reported that a water-soluble filler, e.g. lactose, will be more affected by the presence of hydrophobic components such that the tablet disintegration time is prolonged even at 0.5%, w/w MgSt. In comparison, for tablets that used MCC as the filler, tablets containing higher MgSt concentration had a shorter disintegration time [47].

Influence of Formulation and Process Variables on Drug Release

MgSt retarded tablet dissolution, as evidenced by the longer MDT of tablets produced from the lubricated formulations compared to those from the non-lubricated formulation (Fig. 2D). Figure 6 shows the main effects of the investigated variables on drug release with an R^2 of 68.1%. Significant two-way interactions were detected between the blending duration and MgSt concentration ($p < 0.05$). Significant three-way interactions were also detected for MgSt type, concentration and blending duration ($p = 0.003$) (Table III).

Overall, tablets produced from formulations containing MGS-H had a lower MDT than those of MGS-L. This suggested that the drug was released faster from tablets formulated with MGS-H. This observation aligned with the lower tensile strength and shorter disintegration time of tablets produced from formulations containing MGS-H. The drug release rate could be related to the ease of water penetration into the tablet matrix for tablet disintegration and drug dissolution [48].

While a longer blending duration led to tablets of lower tensile strength and shorter disintegration time, it adversely affected drug release. The prolonged blending duration increased MgSt surface coverage and subsequently, delayed drug release. Abe and Otsuka have confirmed more extensive surface coverage by MgSt as blending duration increased by mapping MgSt on the surface of tablet components [49]. Additionally, flaking of MgSt with prolonged blending resulted in a greater coverage of the other components in the tablet formulation which reduced the effective surface area for drug dissolution [50].

Tablets produced from 1%, w/w MgSt had a slower drug release than those made from 0.5%, w/w MgSt (Fig. 6). However, when MgSt concentration increased to 2%, w/w, a faster drug release was observed, as indicated by the shorter

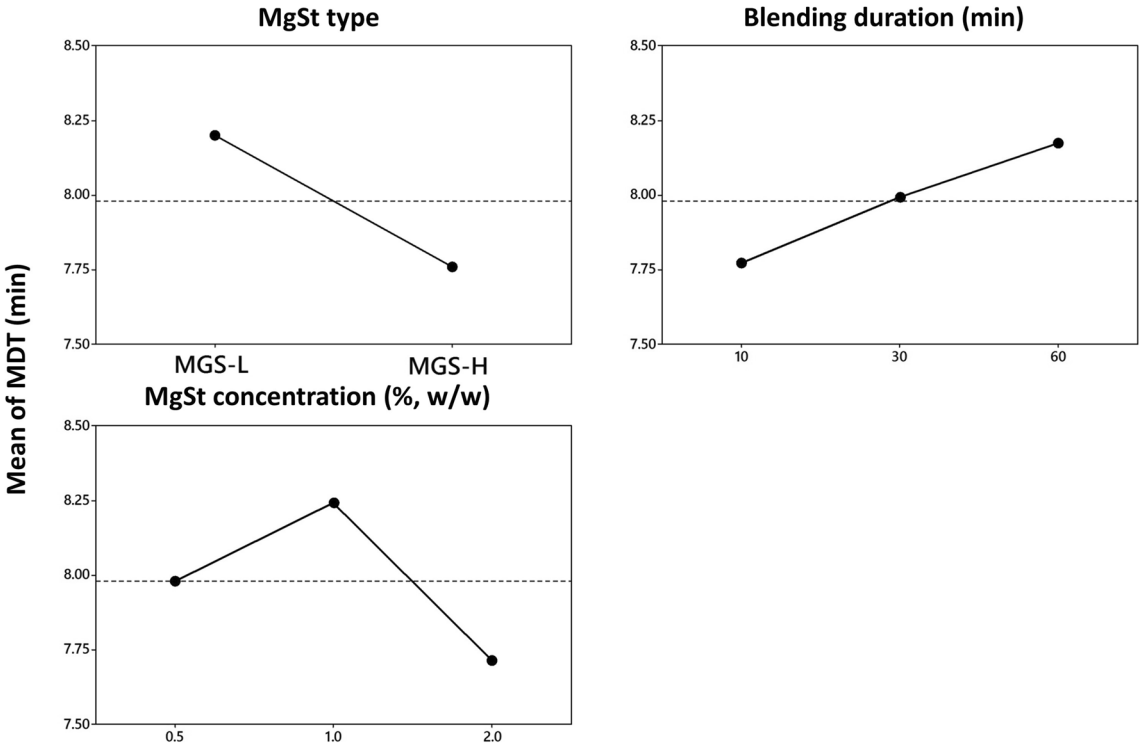

Fig. 6 Plot of the main effects of MgSt type, blending duration and MgSt concentration on tablet mean dissolution time (MDT)

MDT. This observation was in contrast to the adverse effect of MgSt on tablet dissolution that had been commonly reported [49, 51]. Although MgSt reduces the wettability of the tablet, MgSt also interferes with inter-particulate bonding, resulting in tablets of lower tensile strength. Therefore, the tablets could break up more easily, allowing the drug to come into contact with the aqueous medium earlier for drug dissolution and release. Besides the tablet's physical properties, the drug release could be influenced by drug solubility and the hydrophobicity or hydrophilicity of the tablet components [52].

Significance of Magnesium Stearate Fatty Acid Composition on Lubrication Performance and the Resulting Tablet Properties

MgSt consists mainly of stearate and palmitate salts in varied ratios. Marwaha and Rubinstein [22] related the lubricity of MgSt to the stearate and palmitate contents. The study observed that the stearate chain has a higher resistance to dislocation during tableting. This made the powder less compressible, and more energy was needed to produce dislocation compared to the palmitate chain [22]. While both stearate and palmitate confer hydrophobicity to MgSt, variations in the lubricity have been reported only for MgSt grades where the stearate and palmitate contents differed by more than 20% [53]. As demonstrated by Leinonen *et al*., the lubricity of MgSt with a stearate content of 70.5% and a palmitate content of 22.6% was not significantly different from MgSt with a stearate and palmitate content of 20.4% and 73.8%, respectively [54]. Similarly, the MgSt derived from an animal source (66.7% stearate and 28.6% palmitate) had comparable performance as the plant-based MgSt (69.3% stearate and 29.7% palmitate) [20]. Therefore, variations in MgSt lubricity are often related to its physical properties (e.g. particle size, crystallinity, specific surface area and morphology) rather than its chemical properties.

This study attempted to supplement existing studies that compared different MgSt types. Despite numerous studies on MgSt, differences in MgSt's performance are often attributed to differences in the physical properties, and there is a lack of emphasis on the chemical properties. To understand the importance of MgSt chemical properties on its performance, it is important to obtain MgSt of significantly different chemical properties while maintaining similar physical properties to minimize confounding effects from the variation in the physical properties. MGS-L and MGS-H met the pharmacopeial requirements of at least 40.0% stearate and at least 90% for the sum of the stearate and palmitate contents [55]. As MGS-L and MGS-H had comparable physical (particle size, crystallinity, specific surface area and morphology) and thermal properties, differences observed in the resulting tablet properties could be attributed to differences

in the stearate and palmitate contents. Therefore, these two MgSt grades were used to assess the effects of MgSt type and two pertinent formulation/processing variables – MgSt concentration and blending time. With stearate content that differed by more than 20%, differences in the lubrication performance and tablet properties could be observed, albeit some of the response variables were more affected by differences in the MgSt fatty acid composition.

It was observed that the higher stearate content of MGS-H resulted in a slightly more hydrophobic MgSt. The longer carbon chain of stearate could have caused MGS-H, which had higher stearate content, to be more hydrophobic [56, 57]. The present study's findings suggested that the MgSt type had a greater impact on tablet ejection force than MgSt concentration and blending duration. Although MgSt type had equal significance as blending duration and MgSt concentration on the drug release rate, the type of MgSt had less influence on the tablet tensile strength and disintegration time. Instead, the blending duration and MgSt concentration had a greater effect on the tensile strength and disintegration time, as seen from the steeper slope of the main effect line.

Conclusion

This study evaluated MgSt grades with different fatty acid compositions but comparable physical properties. The effect of MgSt concentration and blending duration was also concurrently investigated. It was observed that variations in the fatty acid composition, namely the stearate and palmitate contents, only resulted in marginal differences in tablet tensile strength and disintegration time. However, tablets formulated with MgSt of lower stearate content exhibited a slower drug release than those formulated with MgSt of higher stearate content. Additionally, MgSt of lower stearate content generally had less lubricant efficacy which resulted in less reduction in the tablet ejection force. A prolonged blending duration with MgSt resulted in tablets of reduced tablet tensile strength and shorter disintegration time but with slower drug release. It was also observed that tablets produced with higher concentrations of MgSt had lower tensile strength. The faster drug release of tablets containing higher MgSt concentration could be associated with the lower mechanical strength of the tablets. As MgSt type, blending duration and MgSt concentration interacted with one another, changes in any one of these variables could be consequential to the resulting tablet properties. This study's findings may help better understand the effects of MgSt fatty acid composition on lubrication performance and the resulting properties of tablets.

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Data Availability Data will be made available on request.

Declarations

Conflict of Interest The authors declare that they have no known competing financial or non-financial interests or affiliations with or involvement in any organization that could influence the subject matter or materials discussed in this paper.

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