Regular Article

Effects of Granulated Lactose Characteristics and Lubricant Blending Conditions on Tablet Physical Properties in Direct Powder Compression

Shohei Nakamura, Nanami Ito, Ayumi Sakurada, and Takatoshi Sakamoto*

Department of Pharmaceutical Technology, School of Clinical Pharmacy, College of Pharmaceutical Sciences, Matsuyama University, 4–2 Bunkyo-cho, Matsuyama, Ehime 790–8578, Japan.
Received April 17, 2023; accepted July 6, 2023

Lactose is an excipient used extensively for bulking, diluting, and molding active pharmaceutical ingredients in tablet manufacturing. Particularly, granulated lactose (GL) intended for direct powder compression has distinct properties due to differences in manufacturing methods. It contributes to handling blended powders for tableting and tablet quality. In this study, we aimed to compare the functions of different forms of GL added as excipients during direct powder compression on the tablet properties and the effect of magnesium stearate (Mg-S) used as a lubricant on each type of GL. Different GL types obtained using different manufacturing methods (agitated granulation, GL-AG; spray-dried granulation, GL-SD; fluidized bed granulation, GL-FB) were blended with maize starch, low-substituted hydroxypropyl cellulose, and paracetamol in a V-type blender for 10 min. Mg-S was added at varying amounts (0.1, 1.0, and 2.0%) and blending times (5, 10, and 30 min) for the nine types of blended powders for tableting formulation. The powders were tableted, and the tablets were evaluated for weight and drug loading variations, tensile strength, friability, and disintegration time. When tablets with the same blending conditions were compared, the tensile strength and disintegration time were in the order of GL-FB > GL-SD > GL-AG. For each GL, we analyzed the effects of changes in the added amount of Mg-S and blending time using contour plots, evaluated the effects of blending conditions on tablet properties, and determined the target tablet properties. We investigated the optimization of the lubricant blending conditions to obtain suitable tablets.

Key words direct powder compression, granulated lactose, powder characteristic, tablet property, optimized condition

Introduction

Tablets are the most frequently used dosage forms because they are advantageous for packaging, transportation, and storage, can be prescribed in counting units when dispensing, and are easy for patients to use. Wet granule compression is a commonly used method in tablet manufacturing.[1–3] This method comprises many steps from the raw material to the final product and is labor and time-intensive.[4]

There is a global commitment to carbon neutrality by 2050 following the United Nations Framework Convention on Climate Change. The first goal is to reduce greenhouse gas emissions by 46% from the levels in 2013 by 2030. This carbon-neutral challenge is being promoted globally as it will lead to changes in industrial structure.[5] In tablet manufacturing using the granule compression method, various trial granulations are conducted to establish the granulation conditions in the early stage of development. In addition, in commercial production, it is necessary to uniformly mix the active ingredient and multiple additives immediately before granulation on a production line. However, these requirements can be avoided by using granules consisting only of pure lactose, which likely reduces the considerable time and energy typically required for these processes. Under these circumstances, direct powder compression is more advantageous than wet granule compression in terms of the required work steps, time, and energy consumption. In the future, this tableting method will attract increasing attention from global companies that require decarbonized management.[6,7] Consequently, the development of additives used in direct powder compression and investigation of tableting conditions have increased.[8–14]

Granulated lactose (GL), intended for use in direct powder compression, has significantly different properties depending on the granulation method and is thought to contribute to handling powder formulations and tablet quality. The correct selection of GL is important to satisfy robustness at a high level when manufacturing solid formulations using a high-speed tableting machine.[15–17]

Lubricants are indispensable additives for improving tablet quality and manufacturing productivity.[18] Magnesium stearate (Mg-S) is a commonly used lubricant. However, because it is a highly spreadable hydrophobic compound,[19] it may decrease tablet tensile strength,[20,21] extend the disintegration time,[22] and slow the dissolution rate.[23,24] These factors, in turn, affect the *in vivo* pharmacokinetics of the drug formulation. The quantity of Mg-S added and blending time is important considerations during tablet formulation. However, to date, most Mg-S addition conditions have been based on empirical judgments, and clear indicators regarding the form of excipients and the effects of Mg-S on tablet properties have yet to be determined.

In this study, we compared the functions of different forms of GL added as excipients during direct powder compression on the tablet properties and the effect of Mg-S on each type of GL. Then, the GL species selection and lubricant blending conditions were examined to obtain the tablet properties required as an actual product.

* To whom correspondence should be addressed. e-mail: sakamoto@g.matsuyama-u.ac.jp

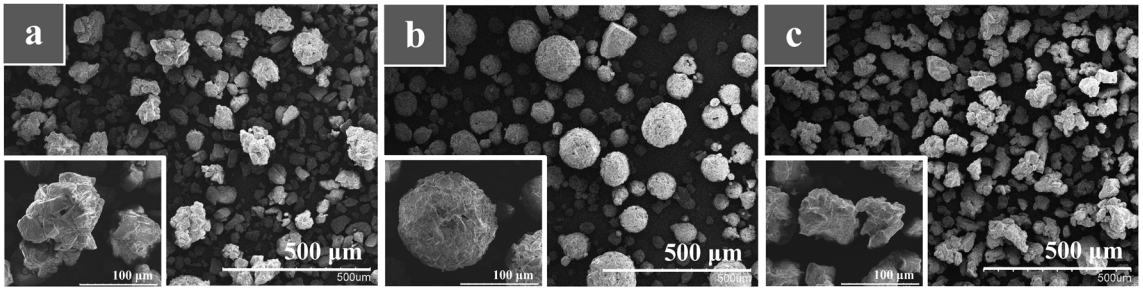

Fig. 1. SEM Image of the Particle Shapes of Pure GL Powder

(a) GL-AG; (b) GL-SD; (c) GL-FB. A magnified image of the particle surface is shown in the lower left-hand corner of the low-magnification image. GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; SEM, scanning electron microscopy.

Table 1. Characteristics of Pure GL Powder

	Mean particle size (μm)	Geometric standard deviation	Tap density (g/mL)	Angle of repose (deg.)	Compressibility (%)	Spatula angle (deg.)	Cohesion (%)	FI
GL-AG	70.16 ± 1.62	1.33 ± 0.04	0.741 ± 0.001	43.0 ± 1.1	20.9 ± 0.2	56.9 ± 3.8	46.2 ± 1.4	55.7 ± 0.6
GL-SD	97.59 ± 4.27	1.31 ± 0.03	0.722 ± 0.003	35.5 ± 0.9	16.3 ± 0.4	44.5 ± 3.5	34.1 ± 2.0	63.0 ± 1.3
GL-FB	84.80 ± 0.94	1.21 ± 0.02	0.666 ± 0.001	37.0 ± 0.6	16.6 ± 0.2	43.7 ± 1.6	19.2 ± 0.9	66.2 ± 0.3

GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; FI, flowability index. * Each value represents the mean ± S.D.

Results and Discussion

Characterization of Pure GL Powder Figure 1 shows the scanning electron microscopy (SEM) images of the three types of pure GL powders. Spray-dried granulation lactose (GL-SD) (Fig. 1b) had a characteristic spherical shape due to the surface tension of droplets during granulation and particle shapes were distinct from those of other GLs. In agitated granulation lactose (GL-AG) (Fig. 1a) and fluidized bed granulation lactose (GL-FB) (Fig. 1c), the individual particles had distorted shapes. The distorted shape in GL-AG was likely due to consolidation *via* the capillary state of wet particles by the shearing force of the agitating blades inside the device during granulation. In contrast, GL-FB had small loosely agglomerated particles, which is potentially because particles adhered *via* pendular or funicular states in the absence of shearing force during granulation. Moreover, magnified observation of the particles revealed that GL-SD had a slightly rough surface when compared with GL-AG and GL-FB. The surface roughness of GL-SD was considered to be due to the formation of small sponge-like pores following moisture evaporation from the surfaces of droplets with GL-SD during granulation drying.

Table 1 lists the characteristics of the pure GL-FB, GL-AG, and GL-SD powders. The three types of GLs had a mean particle size of 70–100 μm and similar sizes. In addition, no significant difference was observed among the three types of geometric standard deviations representing the particle size distribution. The tap densities of each GL powder were in the following order: GL-AG > GL-SD > GL-FB. This observation indicates the presence of voids in the particles, which cannot be evaluated using the SEM images (Fig. 1). Moreover, measurements of the angle of repose, compressibility, spatula angle, and cohesion showed low flowability of GL-AG. This phenomenon was presumed to be due to the distorted shape of the GL-AG. Although GL-SD and GL-FB differed in cohesion, with GL-FB showing a smaller cohesion value than GL-SD, similar results were obtained for other measurements. GL-FB particles have a slightly irregular shape, but the particle surfaces are smoother without pores compared to GL-SD (see Fig. 1). These differences greatly contributed to the flowability, and the FI of the GL powder was calculated in the order of GL-FB > GL-SD > GL-AG, with GL-FB having the highest flowability.

Tablet Properties

Mg-S is an additive frequently used as an essential lubricant during tableting. However, it often negatively affects the manufactured tablet properties. Therefore, the effects of Mg-S on variations in tablet weight and drug loading, tensile strength, friability, and disintegration time were evaluated for tablets containing different forms of GL.

Figure 2 shows the effect of adding Mg-S to the variation in tablet weight and drug loading. Using the GLs, the weight variation was 0.5% coefficient of variation (CV) or less (Fig. 2a). When comparing the GL types, at any added amount of Mg-S, GL-AG had the most significant weight variation, and GL-FB had the least. The FI of each pure GL was GL-FB > GL-SD > GL-AG, and the weight variation corresponded to the flowability of the GL. Furthermore, GL-FB showed the most significant decrease in weight variation with increasing Mg-S added amount. As the GL-FB powder has lower cohesion than the other GLs (Table 1), it is likely difficult to form agglomerates of GL-FB. Therefore, the specific surface area of GL-FB is larger than that of other GLs, suggesting that a greater amount of Mg-S adheres to the GL-FB particle surface. Therefore, these results suggest that the enhancement of the flowability of Mg-S was more pronounced with GL-FB than with other GLs.

In all GLs, the variation in drug loading decreased as the Mg-S added amount increased (Fig. 2b). There was little difference between different GL types under the same conditions, and it was considered that the dispersibility of Paracetamol (AP) improved depending on the amount of Mg-S added to all GLs. The practical angle of internal friction (AIF), which

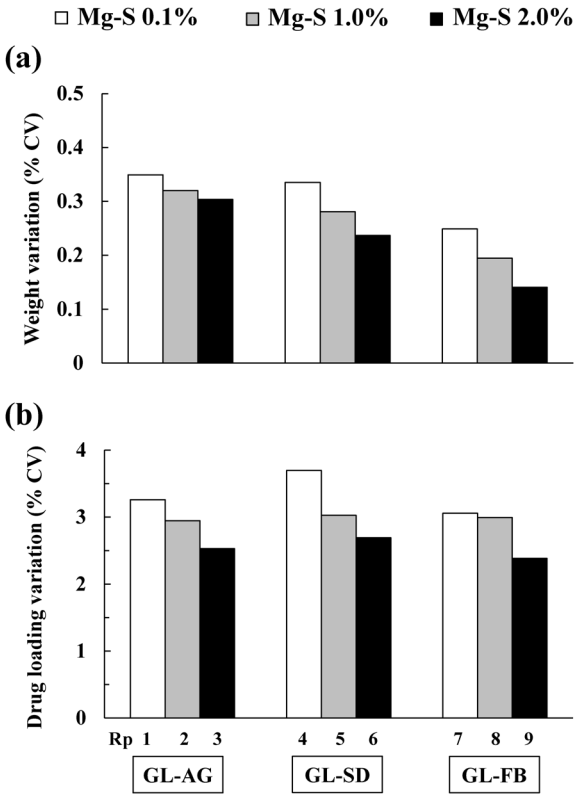

Fig. 2. Effect of the Quantity of Mg-S Added on Properties of Tablets Containing Different Forms of GL

(a) Weight variation; (b) drug loading variation. GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; Mg-S, magnesium stearate; Rp, recipe.

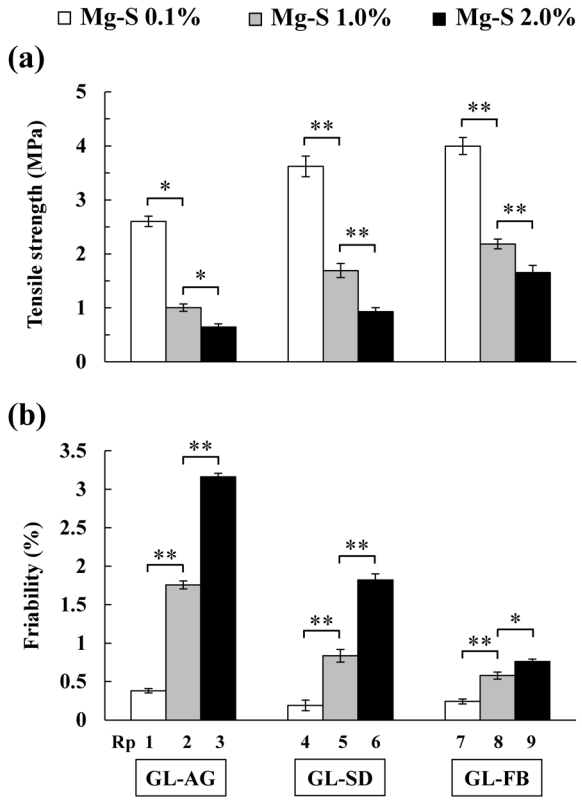

Fig. 3. Effect of the Quantity of Added Mg-S on the Properties of Tablets Containing Different Forms of GL

(a) Tensile strength ($n = 10$); (b) friability ($n = 3$). Data are presented as the mean ± S.D. Differences between tablets prepared using different additives were assessed *via* the Dunnett's test; $^{**}p < 0.001$, $^{**}p < 0.05$. GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; Mg-S, magnesium stearate; Rp, recipe.

expresses the friction of the GL powder under a load, was measured to interpret these phenomena. Previous studies have shown that the dispersion of drugs in blended powders for tableting is affected by the friction between the powder particles.[25,26] The AIF can evaluate the friction generated between powder particles revealed by the shear test; the larger the AIF, the greater the friction, suggesting that the dispersibility of the drug in the blended powder for tableting is good. The AIF of GL-FB (AIF = 6.07 ± 0.49°), which has a bulky and distorted shape, was more significant than that of GL-AG (AIF = 4.59 ± 0.56°) and GL-SD (AIF = 2.76 ± 0.48°). These results indicate that the friction between the AP particles and GL was large, and segregation of AP dispersed in the blended powder for tableting did not occur.

Figure 3 shows the relevance between Mg-S added amount, tablet tensile strength, and friability in each GL. In all GL types, tablet tensile strength decreased as the Mg-S added amount increased (Fig. 3a), which was probably because Mg-S was more attached and spread on the surface of other particles,[27] resulting in decreased adhesion between the particles in the tablet. In addition, the tensile strength of the GL-FB is higher than that of other GLs likely because the inter- and intragranular voids are large and bulky, and the voids in the tablets become smaller owing to plastic deformation during compression. In contrast, because GL-AG is a densely shaped particle with few voids, it is less likely to deform during compression than GL-FB, leading to lower tablet tensile strength.

As shown in Fig. 3b, friability increased with increasing Mg-S added amount for both GL species. The friability of GL-FB, harder than other GLs, was as low as ≤1%, even when 2% Mg-S was added, which was less than that of other GLs.

A compression test was performed on a powder bed composed of each GL pure powder to evaluate the differences in compression properties between the granules used in this study. In general, the compressibility of a powder changes depending on the temporary powder properties, such as particle size, particle surface condition, and particle shape. Kawakita's equation is often used for analysis.[28–30]

$$C = \frac{V_0 - V}{V_0} = \frac{abP}{1 + bP} \quad (1)$$

where P is the vertical load, C is the volume reduction, V_0 is the initial bulk volume, V is the bulk volume under the load, a is the initial porosity, and b is the characteristic constant of the powder. Further, Eq. 1 is rewritten as follows:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \quad (2)$$

Figure 4 shows the results of applying the compression test results for the three types of GL to Eq. 2. Both GLs fit Kawakita's equation, and a linear relevance was established between P and P/C (Coefficient of determination: GL-AG, $R^2 = 0.9962$; GL-SD, $R^2 = 0.9989$; GL-FB, $R^2 = 0.9957$). When evaluating the characteristics of a powder bed, it is explained using a and b in the formula. The values of the constants a and b obtained from the regression line shown in Fig. 4 are

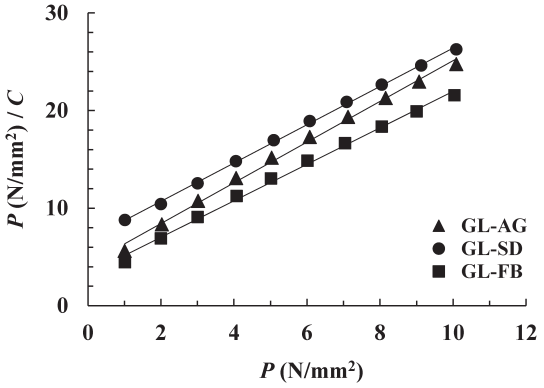

Fig. 4. Relevance between Vertical Load (*P*) and *P*/Compressed Volume (*C*) for Powder Bed Consisting of Pure GL Powder

P, vertical load; *C*, volume reduction; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose.

Table 2. Characteristic Constants *a* and 1/*b* Obtained from Kawakita's Equation

	a	1/*b*
GL-AG	0.479	2.035114
GL-SD	0.510	3.454569
GL-FB	0.535	1.749104

a, initial porosity; *b*, characteristic constants of the powder; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose.

listed in Table 2. Generally, the larger the value of *a*, the more significant the bulk volume change during compression. From the value of *a* for each GL, it was inferred that GL-FB caused the most particle deformation owing to the compression pressure during tableting and formed tablets with high density. Alternatively, the larger the value of 1/*b*, the larger the yield stress and particle strength of the particles and the lower the compactability. The 1/*b* value of each GL was in the order GL-SD > GL-AG > GL-FB, indicating that deformation due to compression of GL-SD is unlikely to occur. These results suggest that bulky GL-FB deformed the most at the time of compression during tableting and formed tablets with high strength. In contrast, GL-AG, which is heavy, did not undergo much deformation of the particles even when compressed, suggesting that tablets with relatively large interparticle voids were obtained. In addition, spherical GL-SD had fewer interparticle points than other GLs, and the tablet strength was considered less than that of GL-FB.[31] When model tablets composed of GL were produced, the tensile strength was 0.68 ± 0.03 MPa for GL-AG, 1.71 ± 0.36 MPa for GL-SD, and 2.20 ± 0.16 MPa for GL-FB.

Figure 5 shows the relevance between the Mg-S added amount and tablet disintegration time for each GL. The order of disintegration time was GL-AG < GL-SD < GL-FB for all Mg-S added amounts. GL-AG disintegrated in approximately 1 min regardless of the Mg-S added amount, but GL-FB and GL-SD had prolonged disintegration time as the quantity of Mg-S increased. This was attributed to the difference in the voids inside the tablets which can be inferred from the value of *a* in Table 2. GL-FB, which has large intragranular voids, was considered to slowly permeate water into the tablet because of particle deformation during compression. In contrast,

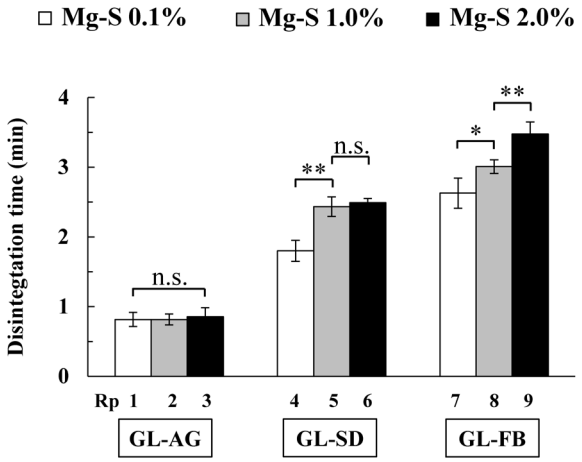

Fig. 5. Effect of Mg-S Added Amount on Tablet Disintegration Time Using Different Forms of GL

Data are presented as the mean ± S.D. ($n = 6$). Differences between tablets prepared using different additives were assessed *via* the Dunnett's test; $^{**}p < 0.001$, $^{**}p < 0.05$, N.S: not significant. GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; Mg-S, magnesium stearate; Rp, recipe.

GL-AG, a heavy particle, tends to be resistant to plastic deformation, and voids inside the tablet persist even after compression.[31] These differences in disintegration properties are due to the voids in the tablets based on the deformation of the particles during compression. It is speculated that the large voids represented by Kawakita's equation formed dense waterways in the tablets.[32,33]

Relevance between the Mg-S Added Amount, Blending Time, and Tablet Properties The international harmonization of product quality is being promoted at the International Conference on Harmonization of Pharmaceutical Regulations in Japan, the United States, and Europe.[34] Subsequently, according to the concept of Quality by Design (QbD), it became necessary to incorporate the quality of formulations into products from the design stage.[35–38] In other words, rather than setting various individual process parameters, it is important in QbD to determine those that directly affect the quality target product profile of the final product. We analyzed the relevance between the Mg-S added amount, blending time, and tablet properties to optimize the initial conditions to obtain tablets with the properties required of an actual product. Figure 6 shows contour plots of the significance between the Mg-S added amount, blending time, and tablet properties. Figures 6a–c shows the tensile strength regions with 1 and 3 MPa boundary values, respectively. The width of the high tensile strength region was in the order of GL-FB > GL-SD > GL-AG, and it was speculated that GL-FB could produce tablets with greater tensile strength under a wide extent of conditions.

Figures 6d–f shows the disintegration time with 1- and 3-min boundary values. In the case of GL-AG, the region showing short disintegration time in the contour plot is broad. Therefore, GL-AG tablets have a wide degree of freedom in the Mg-S added amount and blending time to achieve a short disintegration time.

Figures 6g–i represent regions of drug loading variation with 2, 3, and 4% boundary values. GL-AG had a narrower extent of >3% than other GLs, suggesting that the blending conditions of Mg-S had little effect on drug loading uniformity. GL-FB was as wide as GL-SD, with >3% coverage,

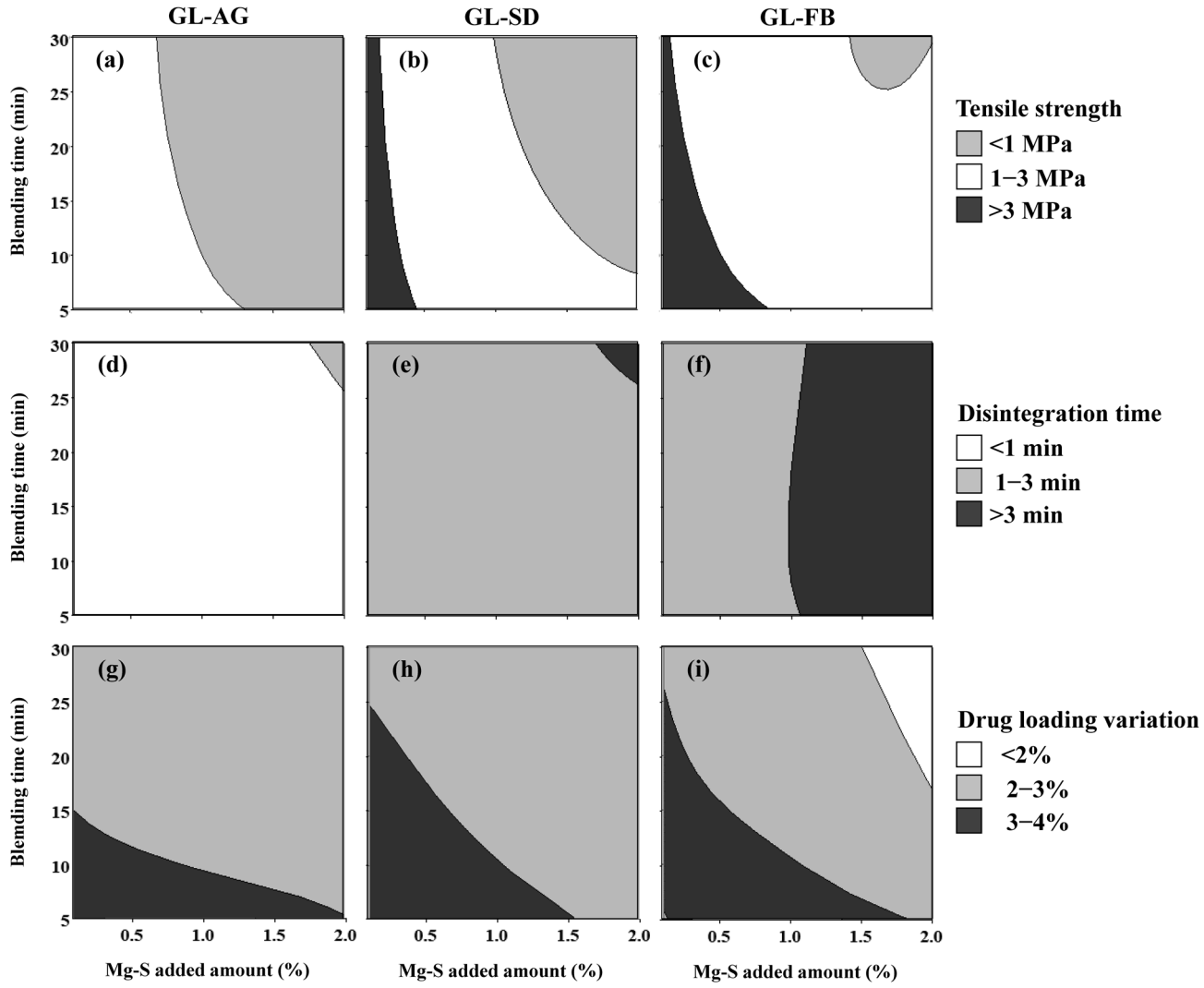

Fig. 6. Contour Plot Showing the Relevance between Mg-S Added Amount, Blending Time, and Properties of the Tablets

GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; Mg-S, magnesium stearate.

but <2% coverage was also present. Therefore, controlling the blending conditions of Mg-S may lead to the highest drug loading uniformity. These findings suggest that the appropriate selection of GL, the major component of the formulation powder, can predetermine the properties of the manufactured tablet. Furthermore, it is possible to predict the optimum blending conditions of Mg-S for GL without an actual investigation.

Optimization of Lubricant Blending Conditions Next, the appropriate blending conditions of Mg-S for each GL were studied to achieve the tablet quality required for an actual product. By superimposing the contour plots of tensile strength, disintegration time, and drug loading variation shown in Fig. 6 for each GL type, the relevance between the obtained tablet properties, Mg-S added amount, and blending time was clarified (Fig. 7). The target quality was based on the values required for the manufacture of tablets as available products, with a tensile strength of 1–3 MPa, disintegration time of ≤3 min, and drug loading variation of ≤3%. In Fig. 7, the white GL regions represent the extent of conditions that achieve the target quality. The wide white region indicates that the Mg-S added amount and blending time can be freely selected over a wide range. GL-AG achieved disintegration of ≤1 min, which is shorter than the target disintegration time under a wide extent of blending conditions, owing to the superior disintegration property of GL. Therefore, it is considered an excipient suitable for direct powder compression for producing tablets that require disintegration, such as orally disintegrating tablets. GL-FB, which is superior in enhancing tablet strength, produced tablets with a tensile strength of 1–3 MPa without limiting the blending conditions of Mg-S. GL-FB was presumed to be a preferable excipient for obtaining the tablet strength required for pan coating. GL-SD is an intermediate product between the other two GL types, with moderate tablet strength and disintegration properties.

Conclusion

This study evaluated the relevance between the type of GL excipient used and the tablet properties in direct powder compression. When GL-FB, prepared by fluidized bed granulation, was used as an excipient, tablets with high tensile strength and low friability were produced. It is believed that the GL-FB has large voids in the particles and is bulky; thus, it tends to be plastically deformed during compression. Using GL-AG

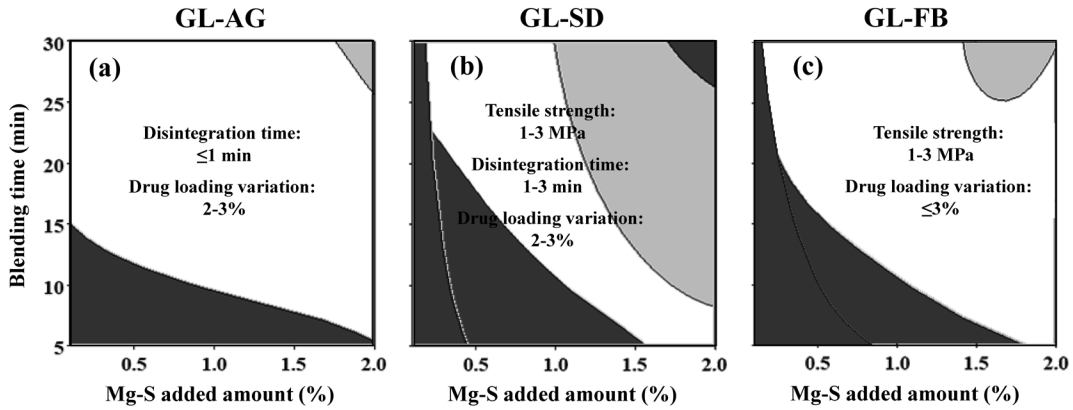

Fig. 7. Relevance between Mg-S Added Amount and Blending Time and the Target Qualities of the Tablets

The target qualities are tensile strength 1–3 MPa, disintegration time ≤3 min, and drug loading variation ≤3%. The white extent represents the Mg-S blending condition that achieves the required tensile strength, disintegration time, and drug loading variation. (a) GL-AG, (b) GL-SD, (c) GL-FB. GL, granulated lactose; GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; Mg-S, magnesium stearate.

prepared *via* agitated granulation, it was possible to produce tablets with excellent disintegration properties. This phenomenon may be because GL-AG is heavier than GL-FB and does not undergo as much shape deformation as GL-FB, even after compression, making it easier to form channels in the tablet. Using GL-SD prepared by spray-dried granulation, it was possible to produce tablets with moderately consistent tensile strength and disintegration properties.

Thus, we present a selection criterion for GL during tableting by examining the relevance between the type of GL in direct powder compression and the manufactured tablet properties. Additionally, we clarified conditions to optimize manufacturing to achieve the intended tensile strength, disintegration time, and drug loading variability based on the contour plot of the quantity of Mg-S used and blending time, considered essential factors for tablet manufacturing.

In recent years, all companies worldwide have been required to work toward carbon neutrality. The methods include promoting energy conservation, switching to renewable energy, and producing harmful emissions. Carbon offsetting will be the final resort if this does not work. Wet granule compression often requires high amounts of electric energy in the pharmaceutical manufacturing process; therefore, direct powder compression for tablet manufacturing is a great way to achieve the goals required by today's companies. We believe our study can contribute to these goals. This study shows the relevance between the shape of GL (manufacturing method), an essential additive in tablet manufacturing, and product characteristics. The results of our study could facilitate the design of the tablet manufacturing process.

Experimental

Materials Three types of GL, agitated granulation lactose (GL-AG, Tablettose® 80, Meggle, Wasserburg, Germany), spray-dried granulation lactose (GL-SD, FlowLac® 100, Meggle), and fluidized bed granulation lactose (GL-FB, Dilactose® S, Freund Corp., Tokyo, Japan), were used as fillers. The model drug was Paracetamol (AP, Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). AP was obtained by classifying No. 42 (355-μm mesh) and No. 100 (150-μm mesh) sieves using a vibratory sieve shaker (Analysette, Fritsch, Idar-Oberstein, Germany) for 30 min. AP with a particle size of 150 − 355 μm was used in the experiments. Low-substituted hydroxypropyl cellulose (L-HPC, LH-21, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) and maize starch (MS, Nihon Shokuhin Kako Corp., Tokyo, Japan) were used as disintegrants. The lubricant was magnesium stearate (Mg-S, vegetable, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan).

Evaluation of Powder Characteristics

Particle Size Distribution and Mean Particle Size

The particle size distribution of the pure GL powders was analyzed using a laser diffraction particle size distribution analyzer (SALD-2200; Shimadzu Corp., Kyoto, Japan) with a refractive index of $1.60 - 0.10i$. The powder was supplied with compressed air pressure (0.5 MPa). The mean particle size is the median diameter obtained from the particle size distribution.

Particle Shape

The pure GL powders were adhered to the sample stage with conductive double-sided carbon tape and subjected to platinum deposition for 10 s in a vacuum by an ion sputtering device (E-1010; Hitachi High-Technologies Corp., Tokyo, Japan). Their shapes were observed using scanning electron microscopy (SEM, S-3400N; Hitachi High-Technologies Corp.) at an accelerating voltage of 5 kV.

Tap Densities

To determine the tap density, each GL was placed in a dry 100 mL graduated cylinder without consolidation. The volume was measured after dropping the cylinder 50 times from a height of 5 cm to naturally settle the powder. The tap density of each GLs was calculated from the measured volume and weight.

Flowability

The GL powders' repose, compressibility, spatula angle, and cohesion were measured with a powder tester (PT-S; Hosokawa Micron Corp., Osaka, Japan) at 25 ± 2 °C and 35 ± 10% relative humidity. Powder flowability was evaluated according to Carr's index rating for each measurement value (25 points each, 100 points in total), and the flowability index (FI) was obtained from the sum of the values.[39]

Internal Friction

Using a shear tester (NS-V100; Nanoseeds, Aichi, Japan), a shear test was performed at 25 ± 2 °C and 35 ± 10% relative humidity. A shear cell with a shear area of 14.5 cm^2 was

Table 3. Composition of the Blended Powder for Tableting

	Material	Composition (%)								
		Rp 1	Rp 2	Rp 3	Rp 4	Rp 5	Rp 6	Rp 7	Rp 8	Rp 9
Fundamental formulation	GL-AG	61.6	61.6	61.6	—	—	—	—	—	—
	GL-SD	—	—	—	61.6	61.6	61.6	—	—	—
	GL-FB	—	—	—	—	—	—	61.6	61.6	61.6
	MS	26.4	26.4	26.4	26.4	26.4	26.4	26.4	26.4	26.4
	L-HPC	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
	AP	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Lubricant*	Mg-S	0.1	1.0	2.0	0.1	1.0	2.0	0.1	1.0	2.0

GL-AG, agitated granulation lactose; GL-SD, spray-dried granulation lactose; GL-FB, fluidized bed granulation lactose; MS, maize starch; L-HPC, low-substituted hydroxypropyl cellulose; AP, paracetamol; Mg-S, magnesium stearate; Rp, recipe. * Weight percent relative to the total amount of fundamental formulation.

embedded with the powder, loads of 1.38×10^{-2}, 2.76×10^{-2}, and 4.14×10^{-2} MPa were applied, and stress relaxation was performed. The shear stress (τ) was plotted against the vertical load (σ) on the $\sigma-\tau$ coordinate, and the angle formed by the obtained regression line and σ axis was defined as the practical angle of internal friction (AIF).[40–42)]

Compaction Property

The powder bed compression test was performed using a tabletop tension-compression tester (MCT-2150; A&D Co., Ltd., Tokyo, Japan). A mold with a diameter of 8 mm was filled with 250 mg of powder and compressed at a rate of 10 mm/min to evaluate the relevance between the load and volume of the powder bed.

Preparation of Blended Powder for Tableting Table 3 shows the composition of each blended powder for tableting. The fundamental formulation was 2% AP and 10% L-HPC, and the remaining 88% was set to a ratio of GL:MS = 7 : 3. Mg-S was added at 0.1, 1.0, and 2.0%, corresponding with the total amount of the fundamental formulation. A V-type blender (DV-5; Dalton, Tokyo, Japan) blended the fundamental formulation and Mg-S. The total amount of powder added to the device was 500 g. GL, MS, L-HPC, and AP were weighed according to Table 3 and blended for 10 min. Mg-S was added to the blended powder, which was further blended for 10 min to obtain a mixture for tableting. To optimize the Mg-S blending conditions, the blending time of each added amount of Mg-S was varied (5, 10, and 30 min).

Tableting The tablets were manufactured by direct powder compression using a rotary tableting press (VELA 5; Kikusui Seisakusho, Kyoto, Japan). The blended powder for tableting was replenished from a gravity feeder and compressed using a flat pestle with an 8 mm diameter. The tablet's weight was 250 mg, the rotation rate of the turntable was 30 rpm, and the compression pressure was 200 MPa.

Measurement of Tablet Properties After tableting, the tablets were placed in an automatically drying desiccator for ≥24 h and tested for weight and drug loading, tensile strength, friability, and disintegration time variations.

Tablet Weight Variation

Weight variation was evaluated by measuring the weight of 10 arbitrarily selected tablets using an electronic balance and calculating the coefficient of variation (% CV).

Drug Loading Variation

Drug loading variation was determined by measuring the absorbance of the water solution of 10 arbitrarily selected tablets at a wavelength of 237.5 nm to determine the actual AP content per tablet. To avoid drug loading variations due to weight variation, the AP content in each tablet was corrected to the AP content in a 250 mg tablet. The % CV was used as the drug-loading variation.

Hardness and Tensile Strength

The hardness of 10 arbitrarily selected tablets was measured by a tablet hardness tester (PC-30; Okada Seiko Co., Ltd., Tokyo, Japan). Tensile strength was calculated from hardness value using the following formula:

$$\text{Tensile strength (MPa)} = \frac{\text{Hardness (N)}}{\text{Tablet diameter (mm)}\times\text{Tablet thickness (mm)}}$$

Friability

The friability of 26 tablets, equivalent to approximately 6.5 g, was determined by a tablet friability tester (TFT-120; Toyama Sangyo Co., Osaka, Japan). After 100 rotations at a rate of 25 ± 1 rpm, friability was determined from the decrease in weight according to the 18th Japanese Pharmacopoeia.[43)]

Disintegration Time

A disintegration tester (NT-1HM, Toyama Sangyo Co.) measured the disintegration time. Distilled water at 37 ± 2 °C was used as the test medium, and one tablet was placed in one of the tubes in the test container.

Data Analysis

Significance Test

Statistical analysis was carried out *via* one-way ANOVA by Dunnett's test with SigmaPlot 12 (Systat Software Inc., Chicago, IL, U.S.A.). All data are shown as mean ± standard deviation (S.D.). $p<0.001$ or $p<0.05$ were the criteria for statistical significance.

Optimization of Tablet Manufacturing

Contour plots were drawn using Minitab 21 (Minitab, LLC, Pine Hall Rd State College, PA, U.S.A.) to determine correlations between Mg-S added amount, Mg-S blending time, and tablet properties to optimize the manufacturing conditions.

Acknowledgments The authors thank these companies: Meggle for providing lactose in agitated (Tablettose® 80) and spray-dried granulation (FlowLac® 100); Freund Corp. for providing lactose in fluidized bed granulation (Dilactose® S); and Shin-Etsu Chemical Co., Ltd. for low-substituted hydroxypropyl cellulose (LH-21).

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions S. N. prepared the manuscript and designed the experiments. N. I. and A. S. performed tableting experiments. T. S. designed the experiments. All authors have confirmed and approved the final manuscript.

Conflict of Interest The authors declare no conflict of interest.

References

1) Gore A. Y., McFarland D. W., Batuyios N. H., *Pharm. Technol.*, **9**, 114–122 (1985).
2) Shangraw R. F., Demarest D. A. Jr., *Pharm. Technol.*, **32**, 32–44 (1993).
3) Gupta R., *Predictive Modeling of Pharmaceutical Unit Operations*, **2017**, 137–158 (2017).
4) Mahrous G. M., Shaaban D. E. Z., Shazly G. A., Auda S. H., *J. Drug Deliv. Sci. Technol.*, **39**, 192–199 (2017).
5) Ozawa A., Tsani T., Kudoh Y., *Renew. Sustain. Energy Rev.*, **169**, 112943 (2022).
6) Makino T., *Pharm. Tech. Jpn.*, **33**, 2309–2311 (2017).
7) Sun W. J., Aburub A., Sun C. C., *J. Pharm. Sci.*, **106**, 1772–1777 (2017).
8) Yoshida I., Sakai Y., *Chem. Pharm. Bull.*, **47**, 678–683 (1999).
9) Katori N., Aoyagi N., Kojima S., *Chem. Pharm. Bull.*, **49**, 1412–1419 (2001).
10) Hara Y., *Pharm. Tech. Jpn.*, **33**, 2313–2316 (2017).
11) Katayama T., Terasawa K., Takeuchi T., Okuda Y., *Pharm. Tech. Jpn.*, **33**, 2317–2320 (2017).
12) Lukášová I., Muselík J., Franc A., Goněc R., Mika F., Vetchý D., *Eur. J. Pharm. Sci.*, **109**, 541–547 (2017).
13) Furukawa K., *Pharm. Tech. Jpn.*, **34**, 93–97 (2018).
14) Makino T., Hoshino T., Tsuchiya A., Oneda Y., *Pharm. Tech. Jpn.*, **34**, 283–287 (2018).
15) Blanco M., Alcalá M., *Anal. Chim. Acta*, **557**, 353–359 (2006).
16) Moes J. J., Ruijken M. M., Gout E., Frijlink H. W., Ugwoke M. I., *Int. J. Pharm.*, **357**, 108–118 (2008).
17) Goodwin D. J., van den Ban S., Denham M., Barylski I., *Int. J. Pharm.*, **537**, 183–192 (2018).
18) Miller T. A., York P., *Int. J. Pharm.*, **41**, 1–19 (1988).
19) Lerk C. F., Schoonen A. J. M., Fell J. T., *J. Pharm. Sci.*, **65**, 843–847 (1976).
20) De Boer A. H., Bolhuis G. K., Lerk C. F., *Powder Technol.*, **20**, 75–82 (1978).
21) Bolhuis C. K., Lerk C. F., Broersma P., *Drug Dev. Ind. Pharm.*, **6**, 15–33 (1980).
22) Bolhuis G. K., Smallenbroek A. J., Lerk C. F., *J. Pharm. Sci.*, **70**, 1328–1330 (1981).
23) Lerk C. F., Bolhuis G. K., Smallenbroek A. J., Zuurman K., *Pharm. Acta Helv.*, **57**, 282–286 (1982).
24) Johansson M. E., Nicklasson M., *J. Pharm. Pharmacol.*, **38**, 51–54 (1986).
25) Nakamura S., Tanaka C., Yuasa H., Sakamoto T., *AAPS PharmSciTech*, **20**, 151 (2019).
26) Nakamura S., Nakagawa M., Tanaka C., Yuasa H., Sakamoto T., *J. Drug Deliv. Sci. Technol.*, **52**, 386–392 (2019).
27) Nakamura S., Ishii N., Nakashima N., Sakamoto T., Yuasa H., *Chem. Pharm. Bull.*, **65**, 432–441 (2017).
28) Kawakita K., Lüdde K. H., *Powder Technol.*, **4**, 61–68 (1971).
29) Kawakita K., Hattori I., Kishigami M., *J. Res. Assoc. Powder Technol. Jpn.*, **8**, 453–460 (1974).
30) Denny P. J., *Powder Technol.*, **127**, 162–172 (2002).
31) Funakoshi Y., Takeuchi H., "Compression molding technology of powder," Chap. 3, ed. by Division of Particulate Preparation and Design, The Society of Powder Technology, Japan: Nikkan Kogyo Shimbun, Ltd., Tokyo, 1998, pp. 83–96.
32) Kawakita K., *J. Soc. Mat. Sci. Jpn.*, **18**, 460–465 (1969).
33) Kawakita K., Hattori I., Kishigami M., *J. Soc. Powder Technol. Jpn*, **11**, 453–460 (1974).
34) Tanaka K., Saito R., Matsuhama M., Miyazaki S., *Chem. Pharm. Bull.*, **71**, 41–51 (2023).
35) Imai K., Norioka T., Ibuki R., *Pharm. Tech. Jpn.*, **25**, 1747–1753 (2009).
36) Norioka T., Hayashi Y., Onuki Y., Andou H., Tsunashima D., Yamashita K., Takayama K., *Chem. Pharm. Bull.*, **61**, 39–49 (2013).
37) Singh B. N., *AAPS PharmSciTech*, **20**, 313 (2019).
38) Jiwa N., Ozaip Y., Yegen G., Aksu B., *AAPS PharmSciTech*, **22**, 151 (2021).
39) Carr R. L., *Chem. Eng.*, **18**, 163–168 (1965).
40) Jenike A. W., Elsey P. J., Woolley R. H., *Proc. Am. Soc. Test Mat.*, **60**, 1168–1190 (1960).
41) Takao Y., *J. Soc. Powder Technol. Jpn.*, **52**, 530–538 (2015).
42) Shimada Y., Hatano S., Matsusaka S., *J. Soc. Powder Technol. Jpn.*, **54**, 90–96 (2017).
43) Ministry of Health, Labour and Welfare. Tablet friability test. "The Japanese Pharmacopoeia," 18th ed., 2021. p. 2642. ‹https://www.mhlw.go.jp/content/11120000/000788362.pdf›, cited 3 April, 2023.