European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 492–498

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

A comparative study of glycerin fatty acid ester and magnesium stearate on the dissolution of acetaminophen tablets using the analysis of available surface area

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ARTICLE INFO

Article history:
Received 27 October 2010
Accepted in revised form 26 January 2011
Available online 1 February 2011

Keywords:
Glycerin fatty acid esters
Magnesium stearate
Dissolution rate
Available surface area
Extensibility

ABSTRACT

To study the effect of glycerin fatty acid ester (Poem TR-FB) concentrations on the dissolution rate of acetaminophen (APAP), the dissolution and disintegration behaviors of APAP tablets formulated using various lubricants were examined. The change over time in the available surface area of APAP ($S(t)$), which is in direct contact with solvent, was also analyzed using these dissolution data. In the dissolution tests, a retarded dissolution of APAP was not observed with TR-FB, whereas magnesium stearate (Mg-St), which is widely used as a lubricant, retarded the dissolution. However, no significant difference in the disintegration time between the two lubricants was observed. With regard to the time course of the $S(t)$, Mg-St at 0.1% gave a maximum surface area value at 9.19 min (peak time); however, the profiles for APAP with Mg-St at greater than 0.5% showed downward curvature indicating a gradual decrease in surface area over time. Conversely, with TR-FB, even when its concentration was increased, the $S(t)$ profile for APAP had a maximum value that was more than twice that of APAP with that of 0.5–3.0% of Mg-St. Scanning electron microscopy (SEM) observations showed that the differences in the dissolution rate and $S(t)$ patterns between Mg-St and TR-FB could be explained by differences in extensibility deriving from their morphology. Therefore, it was concluded that TR-FB does not cause retardation of drug dissolution and may prove to be a superior alternative lubricant to Mg-St.

1. Introduction

In solid pharmaceutical formulations, magnesium stearate (Mg-St), which is widely used as a hydrophobic lubricant, is considered to cause certain manufacturing problems, such as reduction in tablet hardness [1], prolonged disintegration time [2,3], and retarded drug dissolution [4–6]. Since these problems directly influence the quality of final pharmaceutical products, a variety of substances, including hydrophilic organic materials such as sodium stearyl fumarate [7,8] and magnesium lauryl sulfate [9], and inorganic materials such as hexagonal boron nitride [10] have been evaluated as alternative lubricants to Mg-St thus far.

Recently, we have reported two types of glycerin fatty acid esters (Poem TR-FB (TR-FB) and Poem TR-HB (TR-HB)) as new potential lubricant alternatives to Mg-St [11,12]. Generally, Mg-St is added at 0.5% during the manufacturing process; however, TR-FB and TR-HB at the same concentration of 0.5% had apparently better lubricant performance than that of Mg-St immediately after the initiation of tablet compression. In addition, it was found that TR-FB and TR-HB showed initial lubricant performance equivalent to 0.5% Mg-St even when they were used at concentrations below 0.5%. Furthermore, a prolonged disintegration time and a decreased tensile strength, which are disadvantages of Mg-St, were not observed with TR-FB or TR-HB, even when the lubricant concentration was increased and the mixing time was prolonged. Based on these results, we demonstrated that using TR-FB or TR-HB as lubricants, products with uniform quality could be produced without the pharmaceutical problems associated with Mg-St. However, aside from the advantages of TR-FB and TR-HB with respect to tablet hardness and disintegration time, the effects of TR-FB and TR-HB on drug dissolution rate, which is involved in drug bioavailability *in vivo*, have not yet been clarified. Therefore, to demonstrate the usefulness of TR-FB and TR-HB as alternative lubricants to Mg-St or other lubricants, it is highly desirable to determine whether or not TR-FB and TR-HB cause a retardation of the drug dissolution.

One of the mechanisms for retardation of the dissolution of an active ingredient by Mg-St may involve the strong hydrophobic

Abbreviations: APAP, acetaminophen; L-HPC, low-substituted hydroxypropylcellulose; Mg-St, magnesium stearate; SEM, scanning electron microscopy; TR-FB, triglycerin full behenate; HPC-L, hydroxypropylcellulose (low viscosity).

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doi:10.1016/j.ejpb.2011.01.014

properties reported for Mg-St. Chowhan and Chi [13] reported that when Mg-St was mixed with micronized prednisone and dibasic calcium phosphate dihydrate for 30 min, this prolonged mixing resulted in a decrease in the dissolution rate, and the adhesion of Mg-St flakes to the drug particles as a hydrophobic coating was observed using scanning electron microscope (SEM) analysis. In addition, Shibata et al. [14] clarified the mechanism underlying the effect of Mg-St concentration on ethenzamide dissolution rate using SEM. When 0.5% Mg-St was mixed with glass beads as model host particles for 1, 5, and 30 min, a film of Mg-St was formed on the surface of the glass beads as the mixing time increased. According to other reports, the formation of this hydrophobic film of Mg-St on the surface of host granules and beads can reduce surface wettability [15,16]. This subsequently reduces not only water penetration into a granule or tablet but also contact between drug and solvent [4], consequently resulting in a decrease in the surface area that directly contacts with the outer solvent and a decrease in drug dissolution rate. Therefore, to precisely evaluate the effect of lubricants on the dissolution rate, analyses of the adhesive properties of the lubricant using SEM as well as changes in the available surface area of the drug would be required.

Although the available surface area generally cannot be estimated because it changes continuously, we previously succeeded in designing and deriving an equation that predicts the available surface area [17]. In fact, using the time course of the available surface area, we clearly demonstrated the effect of differences in pharmaceutical processing, such as compression force and formulation, on the dissolution of flufenamic acid [18], suggesting that available surface area can allow us to precisely predict the disintegration, dispersion, and dissolution process of the tablet using just only the result of dissolution test. Therefore, to determine whether or not TR-FB causes a retarded drug dissolution, a comprehensive study analyzing the time-dependent change in the available surface area of the drug as well as evaluating the extensibility of TR-FB with SEM is warranted.

In this study, the effect of the concentration of the lubricants TR-FB and Mg-St on the dissolution rate of acetaminophen (APAP) from tablets was first determined. Next, using the experimental data for the drug dissolution rate of APAP, the time-dependent changes in the available surface area of APAP were analyzed. Finally, SEM morphological study on the adhesive properties of the lubricants was performed to understand the dissolution mechanisms of APAP.

2. Materials and methods

2.1. Materials

Magnesium stearate (specified as a drug additive, listed in the Japanese Pharmacopoeia Fifteenth Edition (JP15th), abbreviated as Mg-St) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Triglycerin full behenate (Poem TR-FB, specified as a food additive, referred to as TR-FB) was kindly provided by Riken Vitamin Co., Ltd. (Tokyo, Japan). The chemical structures and physicochemical properties of these additives, such as particle size, surface area and moisture content, have already been reported in our previous paper [11,12]. Acetaminophen (listed in JP15th, abbreviated as APAP, used as a pharmaceutical ingredient) was kindly provided by Iwaki Seiyaku Co., Ltd. (Shizuoka, Japan). Lactose monohydrate (listed in JP15th, used as a filler) and microcrystalline cellulose (Avicel PH 102, listed in JP15th, used as a filler) were kindly provided by DMV Japan Co., Ltd. (Tokyo, Japan) and Asahi Kasei Co., Ltd. (Tokyo, Japan), respectively. Low-substituted hydroxypropylcellulose (listed in JP15th, used as a disintegrant) and solid-state hydroxypropylcellulose (HPC-L®, listed in JP15th, used as a binder) were kindly provided by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan) and Nippon Soda Co., Ltd. (Tokyo, Japan), respectively. All of the reagents used were of the highest grade available from commercial sources.

2.2. Granulation

Using a mixer (Fuji Medical Equipment Co. Ltd.), 140 g of lactose monohydrate and 60 g of microcrystalline cellulose were mixed for 15 min. Then, 200 g of APAP was added to this powder and mixed for an additional 15 min. A total of 150 g of 5.0% w/v aqueous solution of HPC-L was added to this powder using a syringe (ss-10sz, Terumo Corporation, Tokyo, Japan), and the mixture was subsequently kneaded for 15 min. Granulation was performed using a rotating squeeze-type granulator with a sieve size of 0.8 mm (Hata Iron Work Co., Ltd., Kyoto, Japan). The granules were dried using an oven at 50 °C for 12 h or longer. After drying, they were sieved through a 1680-μm sieve, and the granules that did not pass through a 350-μm sieve were collected. This process was repeated several times, and the resultant granules were then mixed uniformly and subjected to experimental analyses.

2.3. Tablet preparation

A total of 8 g of mixture composed of granules, L-HPC, and lubricant (Mg-St or TR-FB) was mixed in a polyethylene bag manually at a rate of 120 times/min for 2 min. The lubricant concentrations were 0.1%, 0.5%, 1.0%, 2.0%, and 3.0%, which concentrations are often used in pharmaceutical industries, and the L-HPC concentration was 10% [19]. The tablets were prepared using a single punch tablet machine (N30-EX, Okada Seiko Co. Ltd., Tokyo, Japan) with a diameter of 8 mm (flat-faced punch), and the weight of each tablet was 200 mg. The tableting speed was 10 tablets/min, and the tableting force was 10 kN. After the tableting process, the diameter and the thickness of tablets were measured using a micrometer with a precision of 0.01 mm (500–302 CD-20, Mitutoyo Corporation, Kanagawa, Japan), and the value of actual surface area of tablet ($S_{initial}$) was then calculated based on the information of the thickness and diameter of tablets.

2.4. Dissolution study

The dissolution of APAP from tablets was examined in accordance with the paddle method listed in JP15th. The test solution was 900 mL phosphate buffer (pH 6.8) at 37.0 ± 0.5 °C, and the paddle rotation speed was 50 rpm. At 0.5, 1.0, 2.5, 5.0, 7.5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 240, 280, 320, and 400 min, samples (3 mL) were withdrawn. The solution was then filtered through a membrane filter (0.45 μm). Then, the absorbance was determined at 243 nm with a spectrophotometer (UV-mini, Shimadzu Corporation, Kyoto, Japan), and the APAP concentration was calculated from the absorbance of a standard solution.

2.5. Determination of apparent solubility, Cs

Five grams of APAP was added to pH 6.8 phosphate buffer (50 mL) at 37 °C, and the mixture was agitated for 3 h. A 2-mL aliquot of this solution was withdrawn and filtered immediately. After this filtered solution was diluted, the apparent solubility (*Cs*) of APAP was determined in the same manner as described for the dissolution study (Section 2.4). The *Cs* of APAP was found to be 17,945 mg/L.

2.6. Determination of the dissolution rate constant per unit area, k

In order to determine k, the stationary disk method was used [20]. An APAP disk with a diameter of 1.3 cm (surface area = 1.33 cm^2) was prepared by compressing 400 mg of the drug powder at 10 kN. The disk was placed in a JP15th dissolution test apparatus and rotated at 50 rpm in phosphate buffer at pH 6.8 and 37 °C. Solution (5 mL) was withdrawn at appropriate intervals, and after adequate dilution, the APAP concentration was determined in the same manner as described for the dissolution study (Section 2.4).

2.7. Determination of the time course of the available surface area S(t) throughout the dissolution process

To determine the time course of the available surface area $S(t)$ as well as the dissolution rate (C) in relation to $S(t)$, the following equations described by Kouchiwa et al. [17] were used:

$$S(t) = V/k \cdot \ln\{C_s/(C_s - W_0/V)\} \cdot dF(t)/dt \quad (1)$$

$$C = C_s[1 - \exp[-[\ln\{C_s/(C_s - W_0/V)\} \cdot F(t)]]] \quad (2)$$

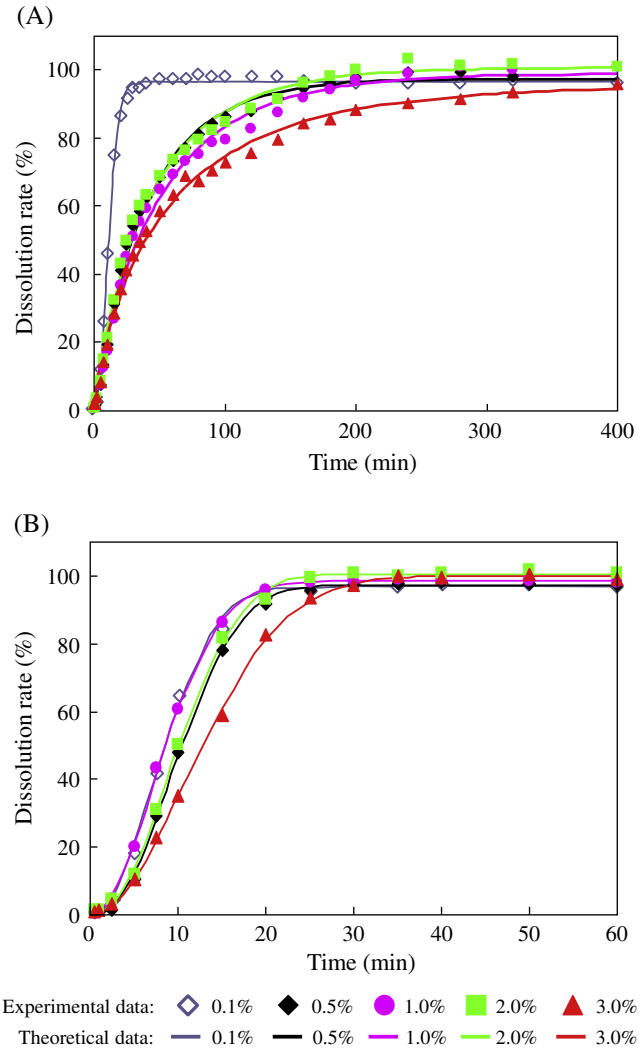

Fig. 1. Effect of lubricant concentration on the dissolution rate of APAP (100 mg) tablets. Figures represent (A) Mg-St and (B) TR-FB. Each point represents an average value of three determinations (Cs = 17,945 mg/L, Wo = 100 mg, V = 900 mL, and $k = 11.5 \times 10^{-2}$ cm/min).

where $F(t)$ is the ratio of the cumulative surface area that has been made available for dissolution up to time t to the total surface area which is made available during the dissolution process. This can be calculated from the experimental data using Eq. (3):

$$F(t) = \ln\{C_s/(C_s - C)\}/\ln\{C_s/(C_s - W_0/V)\} \quad (3)$$

Furthermore, since $F(0) = 0$ and $F(\infty) = 1$, $F(t)$ can be described by a cumulative probability distribution, as shown in Eq. (4):

$$F(t) = \int_0^t \phi(t)dt \quad (4)$$

and if the Weibull distribution is selected, Eq. (4) may be arranged into Eq. (5):

$$F(t) = 1 - \exp\{-(t^b/a)\}. \quad (5)$$

where a and b are the scale parameter and the shape parameter, respectively, namely the scale parameter a and shape parameter b determine the breadth and form of the Weibull distribution, respectively.

In this study, since the dissolution rate did not reach 100% until the end of the dissolution test, a corrected value (c) was used in Eq. (5) (modified to Eq. (6)), and Eqs. (1) and (2) were also modified to Eqs. (7) and (8), respectively.

$$F(t) = c\left(1 - \exp\left(-\frac{t^b}{a}\right)\right) \quad (6)$$

$$S(t) = c \cdot V/k \cdot \ln\{C_s/(C_s - W_0/V)\} \cdot dF(t)/dt \quad (7)$$

$$C = C_s[1 - \exp[-[\ln\{C_s/(C_s - W_0/V)\} \cdot c \cdot F(t)]]] \quad (8)$$

Using this theorem, both the $S(t)$ throughout the dissolution process and the theoretical dissolution rate (C) in relation to the $S(t)$ of a tablet can be determined. In this study, the best-fitting parameters for the probability distribution of the values of $F(t)$ for Eq. (6) could be found by non-linear regression with statistical software (Origin 8, Lightstone Corp., Tokyo, Japan), and the fit of the experimental data was estimated in terms of residual sum of squares (RSS). Also, the peak time (t_{max}) when $S(t)$ was a maximum value (S_{max}) was then determined as shown in Eq. (9).

$$t_{max} = (a(b-1)/b)^{1/b} \quad (9)$$

2.8. Determination of tablet disintegration time

Six tablets each, prepared using either Mg-St or TR-FB as lubricant, were selected randomly, and disintegration tests were performed in accordance with the protocol set out in JP15th using a disintegration tester (Miyamoto Riken Ind. Co., Ltd.). Distilled water at 37 ± 0.5 °C was used as the test fluid.

2.9. Adhesive properties of lubricants

A total of 5 g of glass beads and lubricant were mixed in a vial at a rate of 35 rpm for 2 or 30 min. The lubricant concentrations were 0.1% or 0.5%. The mixtures were fixed onto specimen stubs by

Table 1
The effect of lubricant concentration on disintegration time (min). Each point represents an average value obtained from six determinations (±SD).

Concentration of lubricant (%)	Disintegration time (min)	
	Mg-St	TR-FB
0.1	9.98 ± 0.33	9.55 ± 1.17
0.5	11.52 ± 0.91	11.27 ± 0.64
1.0	13.34 ± 0.65	10.86 ± 0.54
2.0	12.23 ± 0.95	13.22 ± 0.66
3.0	14.03 ± 1.63	12.05 ± 1.00

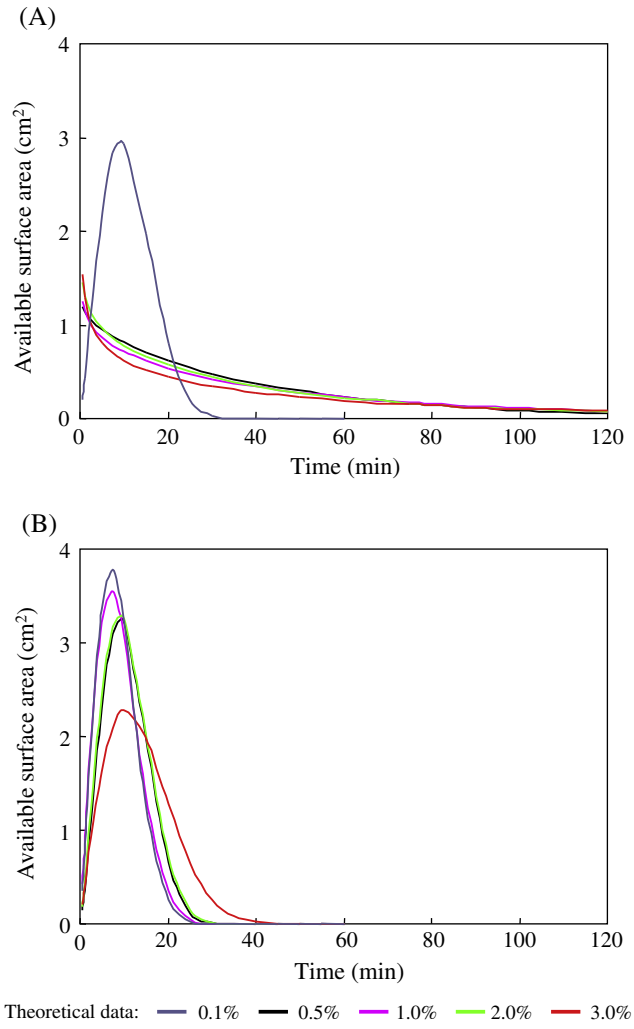

Fig. 2. Effect of lubricant concentration on the available surface area of APAP (100 mg) tablets. Figures represent (A) Mg-St and (B) TR-FB (Cs = 17,945 mg/L, Wo = 100 mg, V = 900 mL, and $k = 11.5 \times 10^{-2}$ cm/min).

means of double-sided carbon conductive adhesive strips and vacuum coated with platinum in a sputter coater (JFC-1600, Japanese Electron Optics Laboratory Co. Ltd., Tokyo, Japan). Images were taken with a scanning electron microscope (JEOL JSM-5200, Japanese Electron Optics Laboratory Co. Ltd., Tokyo, Japan) with an emission of 15 kV or 20 kV and a magnification of 750, 3500, or 7500×.

2.10. Statistical analysis

The Mann–Whitney U-test was used to analyze the differences between the two lubricant groups. A probability value of $p < 0.05$ was considered to indicate statistical significance.

3. Results and discussion

3.1. Effect of lubricant concentration on drug dissolution rate

The experimental data for the drug dissolution rate of an APAP tablet containing each lubricant are shown as plots in Figs. 1A and B. When Mg-St was mixed with APAP granules at a concentration of 0.1%, 80% of the APAP dissolved after 18 min (Fig. 1A). However, as the concentration of Mg-St was increased, a retardation of dissolution was observed; in particular, when the concentration of Mg-St was 2.0% or 3.0%, the times for dissolution of 80% of the APAP were 80 and 140 min, respectively. Therefore, this data suggested that as the concentration of Mg-St increased, Mg-St retarded the dissolution of APAP from the tablets as described previously [4,8,14]. On the other hand, when TR-FB was mixed with APAP granules at a concentration of 0.1%, 0.5%, 1.0%, 2.0%, or 3.0%, the times for dissolution of 80% of the APAP were found to be 13, 15, 13, 15, and 20 min, respectively (Fig. 1B), strongly suggesting that the dissolution rate did not change even when the concentration of TR-FB was increased. In addition, for drug dissolution, a sigmoidal profile was observed for 0.1% Mg-St, while a non-sigmoidal profile was observed as the Mg-St concentration was increased over 0.5% (Fig. 1A). Conversely, for TR-FB, a sigmoidal dissolution profile was observed for each concentration. Previously, when the profile of dissolution rate vs. time is sigmoidal, it is supposed that the tablets disintegrate and disaggregate during the dissolution due to the swelling characteristics of disintegrant L-HPC when L-HPC could adsorb sufficient volume of penetrated water [17]. On the other hand, when the dissolution rate vs. time profile is non-sigmoidal, it is likely that the volume of the tablet is slowly decreased in a similar manner to granules and capsules with no disintegration properties. In this case, the switch in dissolution profile from sigmoid to non-sigmoid was observed with increased Mg-St concentration, but not with increased TR-FB, suggesting that as the concentration of Mg-St increased, the disintegration of the tablet caused by L-HPC could not occur, whereas TR-FB did not have this effect. Therefore, the effect of lubricant concentration on the disintegration time of the tablets was determined (Table 1). Interestingly however, no significant differences among the various concentrations of Mg-St and TR-FB were observed. Therefore, to precisely elucidate the differences in dissolution behavior between Mg-St and TR-FB, we then analyzed the available surface area of APAP using this experimental dissolution data.

3.2. Effect of lubricant concentration on the time course of the available surface area $S(t)$

The theoretical dissolution profiles obtained by Eq. (8) and the theoretical time course of the $S(t)$ obtained by Eq. (7) are shown in Figs. 1 and 2, respectively. There was good agreement between the experimental data (symbols) and the theoretical profile (solid line) for dissolution (Figs. 1A and B), because each residual sum of squares (RSS) had a low value (Table 2). Therefore, the time courses of $S(t)$ (Fig. 2) were also deemed to be rea-

Table 2
Values of dissolution parameters and residual sum of squares.

	Concentration of Mg-St (%)					Concentration of TR-FB (%)				
	0.1	0.5	1.0	2.0	3.0	0.1	0.5	1.0	2.0	3.0
a	187.17	34.85	32.10	27.68	23.26	118.87	266.06	100.33	212.75	207.95
b	2.06	0.955	0.885	0.877	0.775	2.08	2.24	1.99	2.16	1.95
c	0.959	0.974	0.992	1.01	0.955	0.964	0.972	0.985	1.01	1.00
RSS($\times 10^{-3}$)	5.38	13.4	24.3	21.6	15.8	2.89	1.58	0.859	1.37	1.33

a: scale parameter, b: shape parameter, c: corrected value.

Table 3
Peak time (t_{max}) to maximal available surface area (S_{max}) after start of dissolution test.

	Concentration of Mg-St (%)					Concentration of TR-FB (%)				
	0.1	0.5	1.0	2.0	3.0	0.1	0.5	1.0	2.0	3.0
S_{max} (cm^2)	2.90	1.19	1.26	1.45	1.54	3.78	3.26	3.55	3.25	2.29
t_{max} (min)	9.19	0.5	0.5	0.5	0.5	7.24	9.26	7.16	8.97	10.67

sonable. As shown in Fig. 2, substantial differences in the profiles of the S(t) were observed between Mg-St and TR-FB. For Mg-St, at the lowest concentration of 0.1%, a shape parameter $b > 1$ was observed (Table 2) and $S(t)$ initially increased and then reached a maximum and decreased (Fig. 2A). However, as the concentration was increased to greater than 0.5%, a shape parameter $b < 1$ was observed (Table 2), and the $S(t)$ profiles showed a downward curvature (Fig. 2). Generally, when the value of b is more than 1, the Weibull distribution has a distinct maximum value, namely it shows like a normal probability distribution. On the other hand, when the value of b is less than 1, the Weibull distribution shows a downward curvature, having a maximum value at the start of experiments. Our previous paper also demonstrated that when analyzing the available surface area of granules, which already had a maximum surface area unlike the tablets, a shape parameter b was less than 1 and a downward curvature of available surface area was observed [18], suggesting that if the value of b is less than 1, a slow decrease in the available surface area would be observed because tablets or granules themselves do not collapse and gradually become smaller; whereas if the value of b is more than 1, tablets collapse to be granules, available surface area explosively increases and then decreases. Therefore, this result suggests that when the concentration of Mg-St was increased, APAP gradually dissolved into the solvent from the surface of the tablet, since the tablet itself did not collapse [17]. In contrast, for TR-FB, a shape parameter $b > 1$ was observed at each concentration (Table 2) and $S(t)$ initially increased, reached a maximum, and then decreased (Fig. 2), suggesting that tablet collapsed to be granules because the disintegration and disaggregation of the tablet might be induced by L-HPC swelling, and subsequently APAP may rapidly dissolve into the solvent from the surface of granules [17,18].

Table 3 shows the maximum value of $S(t)$ (S_{max}) and the peak time when the $S(t)$ is a maximum (t_{max}), which can be determined by Eq. (9), for both lubricants. At a concentration of 0.1% Mg-St, S_{max} and t_{max} were 2.90 cm^2 and 9.19 min, respectively. From the viewpoint of dimension such as the thickness and diameter of tablets, the value of actual surface area of tablet ($S_{initial}$) was found to be 1.77 cm^2. Since tablets themselves were constructed from 50% APAP, the surface area of APAP on the tablet was turned out to be lower than 1.77 cm^2 ($S_{initial}$). Therefore, since the S_{max} was significantly larger than $S_{initial}$, tablets practically collapsed as we expected above based on the value of b. When the concentration of Mg-St was 0.5–3.0%, S_{max} was decreased to 1.19–1.54 cm^2 and t_{max} was 0.5 min, which was the start time of the dissolution test, proving the phenomenon that the tablets practically did not collapse. On the other hand, at a concentration of 0.1–2.0% TR-FB, the S_{max} was 3.25–3.78 cm^2, which was more than twice that of $S_{initial}$ or 0.5–3.0% of Mg-St where the switch in dissolution profile from sigmoid to non-sigmoid occurred as shown in Fig 1A, and t_{max} was 7.16–9.26 min, indicating that the practical disintegration of tablets would be occurred. However, at a concentration of 3.0%, S_{max} was decreased to 2.29 cm^2 and t_{max} was prolonged to 10.67 min. This may be explained by the increase in the surface coverage of TR-FB on the granules and/or tablets.

3.3. SEM morphological study on the adhesive properties of the lubricants

In order to compare the surface coverage of the lubricants on granules, the adhesion of the lubricants to glass beads as model granules was studied by varying the lubricant concentration (Fig. 3) and mixing time (Fig. 4), because many researchers use this technique to examine the extensibility of lubricants [13,14,21]. Besides, Ebba et al. demonstrated that mechanical shearing generally generated in the compression process was significantly involved in the formation of Mg-St film [22]; therefore, in this experiment, the lubricants were mixed with glass beads until 30 min to assume the situation. As the lubricant concentration was increased, the amount of lubricant that adhered to the surface of the glass beads was increased for both lubricants, and there were no significant differences between Mg-St and TR-FB in the amount of lubricant adhered to the glass beads (Fig. 3). When the glass beads were mixed for long periods (30 min), a film of Mg-St, generated by mechanical shearing of the Mg-St particles during mixing, was formed on the surface of the glass beads, whereas interestingly, despite the same prolonged mixing time, an increase in coverage on

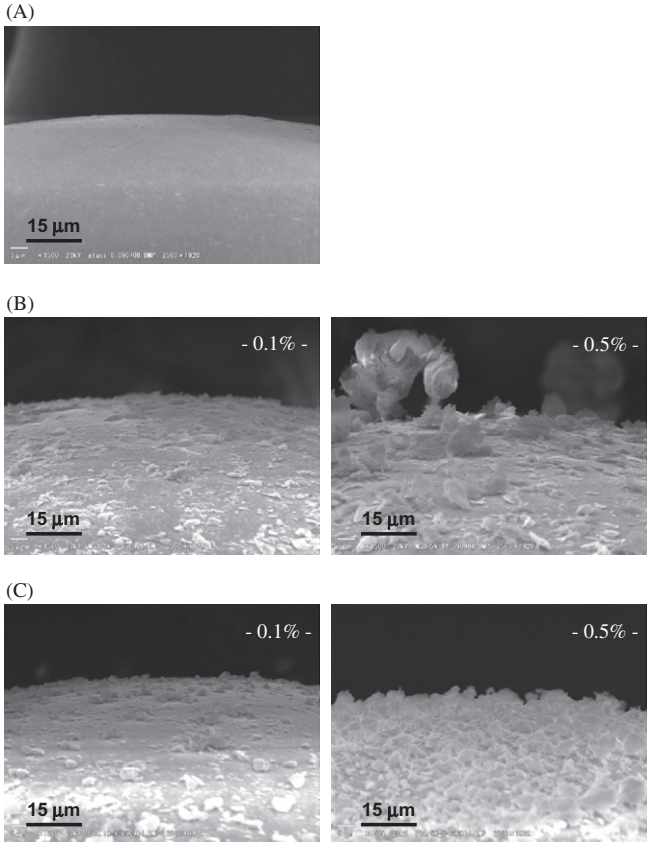

Fig. 3. SEM photographs of the treated surface of glass beads with various lubricant concentrations. (A) No lubricant, (B) Mg-St, and (C) TR-FB.

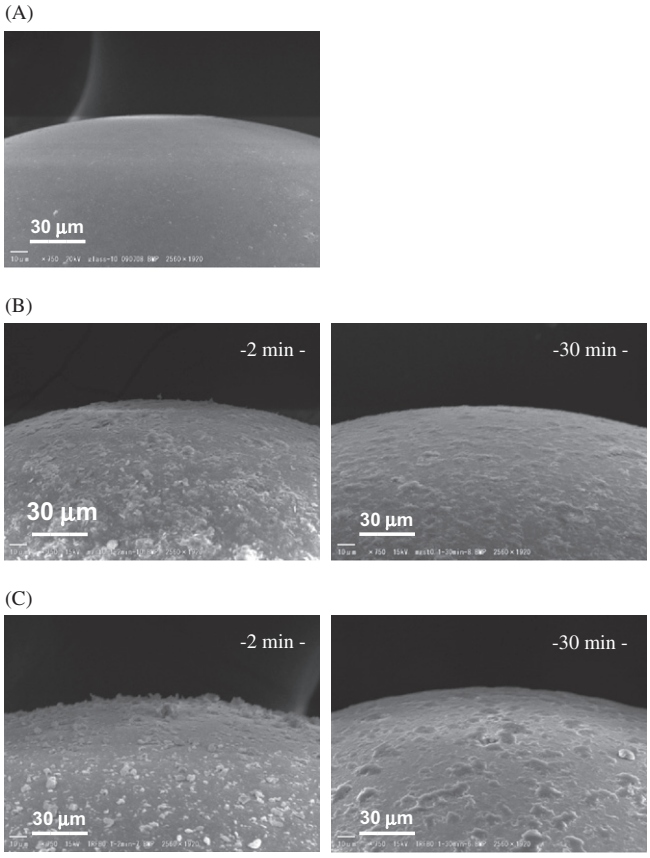

Fig. 4. SEM photographs of the treated surface of glass beads with various mixing times. (A) No lubricant, (B) Mg-St, and (C) TR-FB.

the surface of the glass beads was not observed with TR-FB. This difference in extensibility between Mg-St and TR-FB might be explained by their morphological properties. Therefore, SEM photographs of Mg-St and TR-FB particles alone were taken to observe their morphology as shown in Fig. 5. As shown in Fig. 5A, the Mg-St used in this study forms thin layers and plates that are scaly and laminar (Fig. 5A). These thin, scaly, laminar plates might be

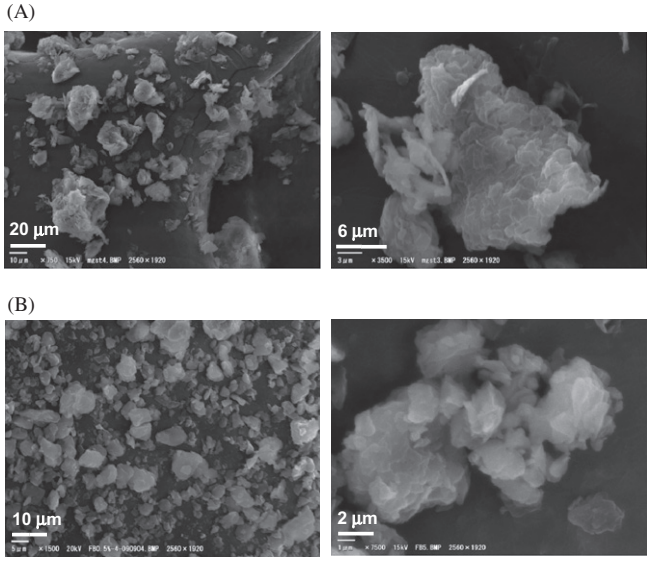

Fig. 5. Morphology of the lubricants. (A) Mg-St and (B) TR-FB.

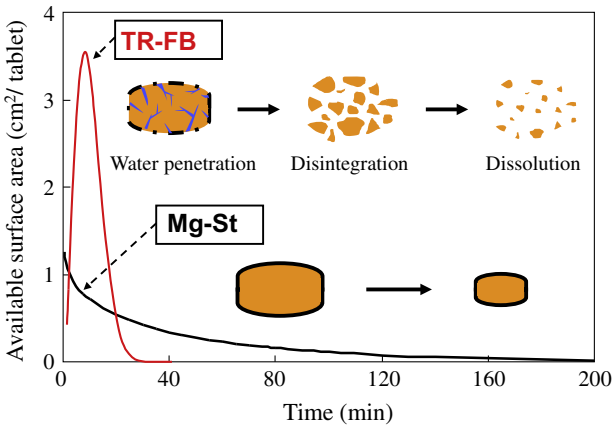

Fig. 6. Schematic illustration of the relationship between the mechanism of tablet disintegration and the available surface area.

easily broken and become extensively coated onto the surface of the glass beads as the mixing time increases (Fig. 4B). In contrast, SEM revealed the TR-FB to be composed of comparatively fine, irregular shaped particles (Fig. 5B): thus, even if the mixing time was prolonged, complete coverage of the surface of the glass beads would not be observed with TR-FB as it would be for Mg-St (Fig. 4C). In the near future, an evaluation of hardness of these primary particles using dynamic ultra-micro hardness tester (DUH-W201S, Shimadzu, Kyoto, Japan) would shed a light on the differences of lubrication mechanism caused by Mg-St and TR-FB.

3.4. The differences in dissolution mechanisms of APAP

Based on these findings, we devised the schematic shown in Fig. 6. In this study, as Mg-St concentration was increased from 0.1% to 3.0%, hydrophobic films of Mg-St formed readily during mixing, and it is likely that this interfered with water penetration into the tablets. As a result, this film formation inhibited the disintegration of the tablet (which is related to the swelling of L-HPC), and the time course profile of the $S(t)$ showed no peak time and a small S_{max}. Therefore, with the higher concentrations of Mg-St, the APAP might have gradually dissolved into the solvent from the tablet (Fig. 6). On the other hand, since TR-FB particles, unlike those of Mg-St, were scattered diffusely on the surface of the granules, water readily penetrated into the tablets, and a sharp increase and then decrease in the time course of the $S(t)$, which is likely related to the swelling of L-HPC, occurred. Also, due to the swelling of L-HPC with water penetration, the S_{max} for TR-FB was larger than that of Mg-St, indicating that the dissolution of APAP with TR-FB might be faster than that with Mg-St (Fig. 6).

4. Conclusions

Mg-St is widely used as a lubricant, but it can also retard the drug dissolution, which affects the bioavailability of a drug. In this study, we have examined the effect of TR-FB concentrations on the dissolution rate of APAP and determined the mechanism of dissolution of APAP from tablet form on the basis of the available surface area of APAP. With regard to the dissolution rate, the time at which 80% of the APAP had dissolved from tablets prepared with 3.0% TR-FB was shorter than that for tablets prepared with 0.5% Mg-St. However, no significant difference in disintegration time was observed between the two lubricants. Therefore, in order to investigate whether disintegration time correlated with the results of the dissolution tests, we focused on the time course of the $S(t)$ of APAP during the dissolution tests. At a concentration of 0.1% Mg-St, the $S(t)$ had a maximum value at 9.19 min. However, as the con-

centration of Mg-St was increased (to greater than 0.5%), the time course profile of the $S(t)$ of APAP showed a downward curvature without a peak time. On the other hand, even when the concentration of TR-FB was increased from 0.1% to 2.0%, the $S(t)$ had a maximum value that was more than twice that of $S_{initial}$ or 0.5–3.0% of Mg-St. In addition, from the results of the SEM photographs, these differences in dissolution rates and $S(t)$ profiles were explained by their differing extensibility deriving from their morphology, namely for Mg-St, a hydrophobic film of Mg-St was formed during mixing and this film decreased the available surface area of APAP, thus resulting in a retarded drug dissolution of APAP. However, since TR-FB particles were scattered diffusely on the surface of the granules, a peak in the time course of the $S(t)$ related to the swelling of L-HPC was observed, and there was no retardation of the dissolution of APAP. Based on these results, it can be concluded that TR-FB, in contrast to Mg-St, does not affect the dissolution rate of APAP. It was also shown that analysis of the available surface area of the active ingredient could be a useful tool for predicting whether a lubricant might retard the dissolution of a drug.

Acknowledgments

The authors' sincere thanks are due to the following companies; Riken Vitamin Co. Ltd., DMV Japan Co., Ltd., Asahi Kasei Co., Ltd., Shin-Etsu Chemical Co., Ltd., Nippon Soda Co., Ltd., and Iwaki Seiyaku Co., Ltd. for kindly providing reagents for this study.

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