Graphical Abstract

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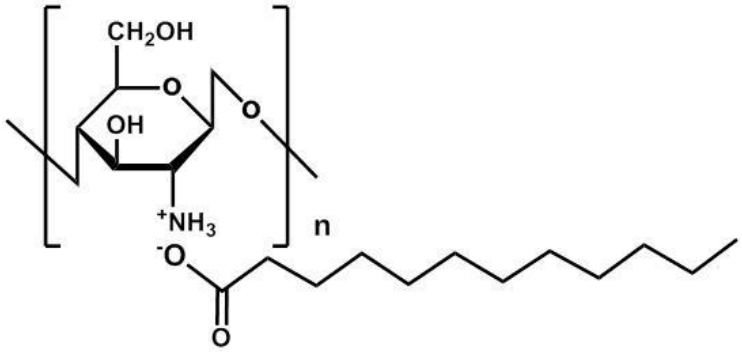
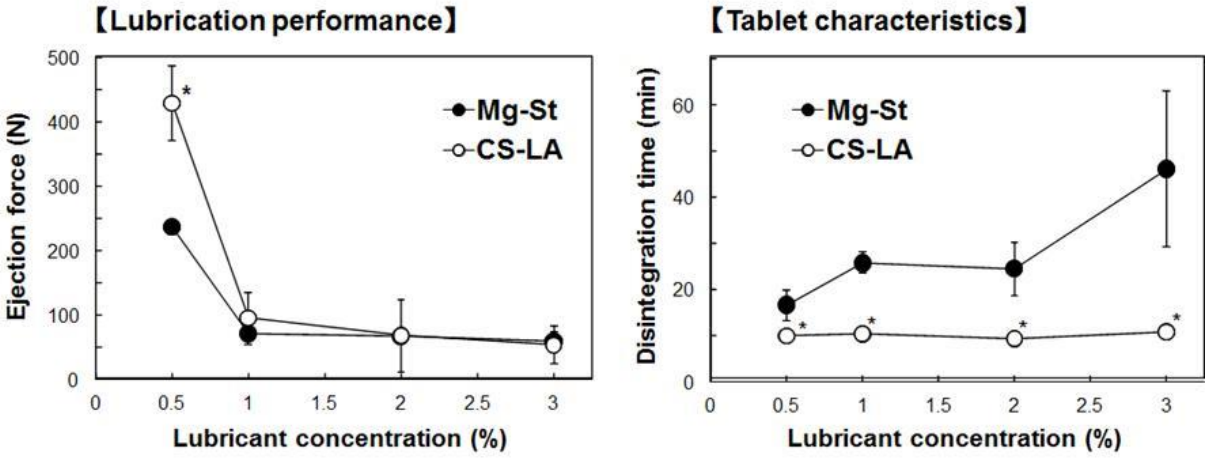
Chitosan laurate (CS-LA),
a newly developed lubricant





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A newly developed lubricant, chitosan laurate, in the manufacture of acetaminophen tablets

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Abstract

To study the usefulness of chitosan laurate (CS-LA), a newly developed chitosan salt, as a lubricant, lubrication properties such as the pressure transmission ratio and ejection force were determined at different concentrations of CS-LA in tableting. In addition, tablet properties such as the tensile strength, disintegration time, and dissolution behavior, were also determined. When CS-LA was mixed at concentrations of 0.1% to 3.0%, the pressure transmission ratio was increased in a concentration-dependent manner, and the value at a CS-LA concentration of 3% was equal to that of magnesium stearate (Mg-St), a widely used lubricant. Additionally, a reduction in the ejection force was observed at a concentration from 1%, proving that CS-LA has good lubrication performance. A prolonged disintegration time and decreased tensile strength, which are known disadvantages of Mg-St, were not observed with CS-LA. Furthermore, with CS-LA, retardation of dissolution of the drug from the tablets was not observed. Conjugation of CS with LA was found to be quite important for both lubricant and tablet properties. In conclusion, CS-LA should be useful as an alternative lubricant to Mg-St.

Abbreviations: *CS-LA, chitosan laurate; D_{50}, median particle diameter; HPC-L, hydroxypropylcellulose (low viscosity); L-HPC, low-substituted hydroxypropylcellulose; Mg-St, magnesium stearate; SEM, scanning electron microscope; TR-FB, triglycerin full behenate.*

1. Introduction

Magnesium stearate (Mg-St) is widely used as a lubricant in solid pharmaceutical formulations **(Fig. 1A)**. However, as the concentration of Mg-St in a formulation increases, it causes manufacturing problems, such as a reduction in tablet mechanical strength (Strickland et al, 1956), prolonged disintegration time (Strickland et al, 1956; Udeala et al, 1980; Flores et al, 2000; Uğurlu and Turkoğlu, 2008) and retarded dissolution (Levy and Gumtow, 1963; Murthy and Samyn, 1977). Additionally, to assure the uniform quality of pharmaceutical products with Mg-St, it is necessary to discard the initial tablets after starting compression until a uniform lubrication effect takes place.

To overcome these disadvantages, a variety of substances, including hydrophilic organic materials, such as sodium stearyl fumarate (Hölzer and Sjögren, 1979; Chowhan and Chi, 1986.), sucrose fatty acid esters (Shibata et al, 2002), glycerin dibehenate (Compritol®)(N'Diaye et al, 2003), magnesium lauryl sulfate (Salpekar and Augsburger, 1974), and hexagonal boron nitride (Uğurlu and Turkoğlu, 2008); hydrophobic organic materials; and inorganic materials have been evaluated to date as alternative lubricants to Mg-St. Additionally, the effect of co-treatment with these evaluated lubricant and Mg-St on lubrication properties has also been evaluated (Wang and Chowhan, 1990; Adeagbo and Alebiowu, 2008). Recently, we reported two types of glycerin fatty acid esters [Poem TR-FB® (TR-FB) and Poem TR-HB®

(TR-HB)] as alternatives to Mg-St (Aoshima et al, 2005; Uchimoto et al, 2010; Uchimoto et al, 2011; Uchimoto et al, 2013). These materials were found to show excellent lubrication performance immediately after the start of compression.

Mg-St has a lamellar structure and a high hydrophobicity derived from long fatty acids, such as stearic acid. Because of breakage of the lamellar structure by even weak forces (tangential forces) during mixing conditions, Mg-St deformation easily occurs and Mg-St spreads better over the entire surface of the granules and tablets (i.e. film formation). This explains why Mg-St exerts lubrication effects, as well as causes the adverse effects mentioned above. Conversely, the recently-discovered new lubricants, TR-FB and TR-HB do not have a lamellar structure and cannot easily be spread over the entire surface of granules and tablets, because of the quite hard nature of the primary particles; hence, they did not show any adverse effects even if the concentration and mixing times of the lubricants were increased (Uchimoto et al, 2010; Uchimoto et al, 2011). Therefore, we speculated that a compound with a high hydrophobicity, as well as a bulky structure, in which easy extensibility does not occur, might have potential as an alternative lubricant to Mg-St.

Recently, we prepared a chitosan derivative, chitosan conjugated with lauric acid (CS-LA), (**Fig. 1B)** and successfully obtained a CS-LA tablet with gastro-retained properties, because one half of the amino residues of CS was modified and CS-LA could not completely

dissolve in the low pH conditions of the gastro fluids (Bani-Jaber et al, 2012). Basically, CS is a partially deacetylated form of chitin and it has recently received much attention as a new excipient and/or functional material with potential in the pharmaceutical and food industry (Illum, 1998). CS has excellent material properties, including biocompatibility, biodegradability, and non-toxicity, as well as chemical and physical stability. Interestingly, Mir et al. (2008) reported that CS was bulky in structure and resistant to deformation against strong forces because of the hardness of the primary particles. Lauric acid is a saturated fatty acid with a 12-carbon chain, which has been reported to show low toxicity and have good lubricating performance. We speculated that CS-LA might have better lubricant properties, without causing any adverse effects derived from a better spread of material over the entire surface of the granules or tablets compared with Mg-St.

In this study, we determined the lubricant properties of CS-LA by measuring the pressure transmission ratio and the ejection force, as representative lubricant properties; and the tensile strength and disintegration time, as well as the dissolution behavior, as tablet characteristics, compared with those of Mg-St.

2. Materials and methods

2.1. Materials

Magnesium stearate [(Mg-St) vegetable origin, pharmaceutical grade additive, listed in the Japanese Pharmacopoeia Sixteenth Edition (JP16th), lot number: WAN 0484] was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). The median particle diameter (D_{50}) of Mg-St was 11.5 μm, measured by a laser diffraction method [LS 13 320, Beckman Coulter (Tokyo, Japan)]. High molecular weight CS (600,000) with more than 75% deacetylation (Brookfield viscosity 800,000 cps in 1% solution with 1% acetic acid), and lauric acid (LA) were purchased from Sigma-Aldrich. Lactose monohydrate (Pharmatose 200M, listed in JP16th, used as a filler, lot number: 10686010), microcrystalline cellulose (Ceolus PH-102, listed in JP16th, used as a filler, lot number: 2173 BAG), and hydroxypropylcellulose [(HPC-L) listed in JP16th, used as a binder, lot number: NCI-1411] were kindly provided by DFE Pharma (Tokyo, Japan), Asahi Kasei Chemicals Corp. (Tokyo, Japan), and Nippon Soda Co., Ltd. (Tokyo, Japan), respectively. Acetaminophen (APAP) was kindly provided by Iwaki Pharmaceutical Co. Ltd. (Shizuoka, Japan). Low-substituted hydroxypropylcellulose LH-21 [(L-HPC), listed in JP16th, Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan)] was used as a disintegrant. All other reagents used were of the highest grade available from commercial sources and all solutions were prepared with deionized water.

2. 2. Preparation and physicochemical properties of lauric acid salt of chitosan (CS-LA)

CS-LA was prepared as previously described (Bani-Jaber et al, 2012). Briefly, saturated CS solutions in 0.18% acetic acid (400 mL) were combined with sodium LA solutions equivalent to 1.5% fatty acid (200 mL) and 400 mL distilled water. The mixtures were incubated and shaken, with subsequent filtration and two distilled water washes of the obtained precipitates. The precipitates were left to dry at room temperature in glass petri-dishes, and then ground into powders using a mortar and pestle and passed through a 250-µm sieve. The D_{50} values of CS-LA, as well as other compounds, were measured by image analysis using WinROOF image analysis software (Version: 5.5, MITANI Co., Ltd., Tokyo, Japan). The materials were fixed onto specimen stubs by means of double-sided carbon conductive adhesive strips and coated with platinum in a sputter coater under vacuum at 8 Pa for 90 s (JFC-1600, Japanese Electron Optics Laboratory Co. Ltd., Tokyo, Japan). Images were taken with a scanning electron microscope (SEM, JEOL JSM-5200, Japanese Electron Optics Laboratory Co. Ltd., Tokyo, Japan) with an emission of 15 kV and a magnification of 350 times.

2.3. Preparation of 50% acetaminophen granules

Lactose monohydrate and microcrystalline cellulose were dried using an oven at 50 °C for 12 h. Using a mixer (Fuji Medical Equipment Co. Ltd., Tokyo, Japan), 105 g of lactose monohydrate and 45 g of microcrystalline cellulose were mixed for 15 min. APAP (150 g) was then added to this powder and mixed for an additional 15 min. A total of 112.5 g of 5.0% w/w 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.

2.4. Tablet preparation and determination of the pressure transmission ratio and the ejection force

A total of 8 g of mixture composed of granules, L-HPC, and lubricant (Mg-St or CS-LA) was mixed in a polyethylene bag manually at a rate of 120 times/min for 2 min. The lubricant concentrations were 0.5%, 1.0%, 2.0%, and 3.0%, which are concentrations often

used in the pharmaceutical industry, and the L-HPC concentration was 2.5%. The tablets were prepared using a single punch tablet machine (TabAll 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. Tablet preparation was carried out under a relative humidity (RH) of 60 ± 5% at room temperature. The tableting speed was 10 tablets/min and the tableting force was 10 kN. The pressure transmission ratio was calculated as the ratio of the maximum pressure of the lower punch to the maximum pressure of the upper punch. The ejection force (i.e. the force applied to the lower punch during tablet ejection) was measured by a 2 kN load cell. Upper punch force, lower punch force, and ejection force data were recorded using DAATSU II software (Okada Seiko Co. Ltd., Tokyo, Japan).

2.5. Determination of tablet disintegration time and tensile strength

Six tablets were selected at random from the tablets prepared, and the disintegration tests were performed according to the JP16th disintegration test using a disintegration tester (Toyama Sangyo Co., Ltd., Osaka, Japan). Distilled water at 37 ± 0.5 °C was used as the test fluid. For the tensile strength measurements, ten tablets were selected at random. The tensile strength of the tablets was determined by diametrical compression tests, which were performed using a hardness meter with a 300 N load cell (precision of 1 N, PC-30, Okada

Seiko Co., Ltd.) to accurately measure the maximal diametrical crushing force (*F* (N)). 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). The tensile strength (σ) (MPa) was calculated by the following formula (Fell and Newton, 1970):

$$\sigma = \frac{2F}{\pi D t} \quad (1)$$

where *D* (mm) and *t* (mm) are the diameter and the thickness of the tablets, respectively.

2.6. Dissolution study

The dissolution of APAP from tablets was examined in accordance with the paddle method listed in JP16th. The test solutions were 900 mL JP16th first fluid (pH 1.2) and JP16th second fluid (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, and 120 min, samples (5 mL) were withdrawn. The solution was then filtered through a membrane filter (cellulose acetate, pore size: 0.45 μm, Toyo Roshi Kaisha Ltd., Tokyo, Japan). 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.

2.7. Adhesive properties of lubricants

A total of 5 g of glass beads with particle diameters from 500–610 μm and Mg-St or CS-LA were mixed in a vial at a rate of 35 rpm for 15 min. The lubricant concentration was 3%. Images of the mixtures were taken with a SEM, following similar protocols as mentioned above (Section 2.2).

2.8. Measurement of the contact angle of water on the tablet surface and water penetration time

A 10 μL droplet of phosphate buffer (pH 6.8) was placed on the surface of a 50% APAP tablet containing Mg-St or CS-LA, and an image of the droplet was taken with a digital camera. The static apparent contact angle was measured by the θ/2 method. Additionally, the time required for the phosphate buffer to completely penetrate into the tablets was determined.

2.9. Statistics

Statistical analyses were performed using the Student's t-test; a probability value of $p < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. Physicochemical properties of the lubricants

Table 1 shows the mean particle sizes of Mg-St, CS, LA, and CS-LA. Lubricants are generally considered to have a greater surface area and to provide better lubrication as the particle size gets smaller (Leinonen et al, 1992; Baichwal and Augsburger, 1987). The particle size of CS-LA (79.2 μm) is larger than that of Mg-St (11.5 μm). Additionally, according to SEM observations (**Fig. 1C**), CS has a cubed and bulky structure with a smooth surface, LA has thin plates, and CS-LA, prepared in this study, has a scaly cubed and bulky structure. Previously, it has been reported that Mg-St forms thin layers and plates which are scaly and laminar, and these thin, scaly, and laminar plates might be easily broken and become extensively coated onto the surface of the granules, giving good lubrication performance (Uchimoto et al, 2011). Therefore, it is possible that CS-LA might be considered to have less lubrication properties, compared with Mg-St, because of the smaller surface area of the particles.

3.2. Effects of CS-LA concentration on lubricant properties

The relationship between the concentrations of CS-LA and Mg-St and the pressure transmission ratio is shown in **Fig. 2A**. Although the average pressure transmission ratio was 65% when granules without lubricant were compressed, it was found that when Mg-St was

mixed with those granules at a concentration of 0.5%, the pressure transmission ratio was 91.8%. As the concentration increased, the pressure transmission ratio also gradually increased at concentrations of 1–3%, and the pressure transmission ratio reached the maximal value, 93.2%, at a concentration of 3%. For CS-LA, the pressure transmission ratio at a concentration of 0.5% was approximately 80%, which was significantly lower than that of Mg-St at the same concentration ($p < 0.01$). However, as the CS-LA concentration increased, the pressure transmission ratio appreciably increased, and the pressure transmission ratio reached the maximum value, approximately 90%, at a concentration of 3%. The relationship between lubricant concentration and ejection force is shown in **Fig. 2B**. When granules without lubricant were compressed, the average ejection force was 1875 N, and tableting problems, such as capping and lamination, occurred. By addition of 0.5% Mg-St or CS-LA, the ejection force was significantly reduced. When Mg-St was added, the ejection force at a concentration of 0.5% was approximately 250 N, and this significantly decreased to less than 100 N when the concentration reached 1%. For CS-LA, the ejection force at a concentration of 0.5% was approximately 430 N, which was significantly higher than that of Mg-St at the same concentration ($p < 0.01$). However, the ejection force also significantly decreased, similar to Mg-St, at concentrations of 1–3%. Previously, an ejection force value of less than 100 N was found to correspond to good lubrication properties (Uchimoto et al, 2013). Taken together,

these pressure transmission ratio and ejection force data demonstrate that CS-LA, at concentrations over 1%, has similar lubrication properties as Mg-St.

3.3. Effects of CS-LA concentration on tablet properties

Figure 3A shows the effects of the lubricant concentration on the tensile strength of tablets. The tensile strength with Mg-St was 2.0 MPa at a concentration of 0.5%. As the concentration was increased, the tensile strength gradually decreased, and the value at a concentration of 3.0% was reduced to 1.54 MPa. With CS-LA, it was found that the tensile strength was higher than that of Mg-St for every concentration ($p < 0.01$); the values at all concentrations ranged from 2.24 to 2.4 MPa, indicating that the tensile strength was not concentration dependent with CS-LA. **Fig. 3B** shows the tablet disintegration time versus the concentration of the lubricants. While the tablets disintegrated in 20 min at a concentration of 0.5% Mg-St, the disintegration time was significantly prolonged as the concentration of Mg-St increased. Conversely, the disintegration time was similar for all concentrations of CS-LA tested ($p < 0.01$, compared with Mg-St at the same concentration). Therefore, it was concluded that CS-LA does not cause any adverse effects with regard to tablet properties.

Generally, Mg-St has high water repellency, and as an increase in the concentration and/or a prolongation in the mixing time of Mg-St, a hydrophobic film is formed on the particle

and/or tablet surfaces. As a result, the disintegration time is prolonged accordingly (Uchimoto et al, 2011; Shah and Mlodozeniec, 1977; Ragnarsson et al, 1979; Bolhuis et al, 1981). Considering these reports, we assumed that CS-LA would have low water repellency compared with Mg-St, and be unable to spread well, because of the bulky structure of CS-LA as shown in **Fig. 1C**, and consequently no hydrophobic film would be observed to form on the particle or tablet surfaces. To compare the surface coverage of the lubricants on granules, the adhesion of the lubricants to glass beads as model granules was studied (**Fig. 4A**). When 3% Mg-St or CS-LA was mixed with glass beads, a kind of Mg-St film, generated by mechanical shearing of the Mg-St particles during mixing, was formed on the surface of the glass beads; whereas, despite the same mixing conditions, no coverage on the surface of the glass beads was observed with CS-LA. This difference in extensibility between Mg-St and CS-LA might be explained by their morphological properties. Because Mg-St has thin layers and plates which are scaly and laminar as mentioned above, these thin and laminar plates might be easily broken and become extensively coated onto the surface of the glass beads. In contrast, SEM revealed CS-LA to be composed of comparatively fine, bulky, and irregular shaped particles (**Fig. 1C**), thus complete coverage of the surface of the glass beads was not observed with CS-LA (**Fig. 4A)**. Additionally, significant increases in the contact angle and prolonged water penetration times were observed for Mg-St in a concentration-dependent manner, whereas

changes in these parameters were not observed with changes in the concentration of CS-LA (**Fig. 4B and 4C)**, suggesting that based on the differences in extensibility between Mg-St and CS-LA, the wettability for Mg-St tablets is quite poor, while for CS-LA wettability does not change even when the concentrations are increased. In addition, as another reason, we speculated that because, from a structural perspective, CS-LA is a kind of surfactant, the wettability might be increased. Therefore, these results demonstrate that CS-LA may give a better tablet performance than Mg-St.

3.4. Effects of CS-LA concentration on dissolution behavior

The drug dissolution rates of an APAP tablet containing each lubricant are shown as plots in **Figs. 5A and B**. When Mg-St was mixed with APAP granules at a concentration of 0.5%, it took approximately 120 min until 80% of the APAP dissolved in both pH 1.2 and pH 6.8 solutions (**Fig. 5A**). Additionally, as the concentration of Mg-St was increased, a retardation of dissolution was observed. In particular, when the concentration of Mg-St was 3.0%, only 70% and 65% APAP dissolved after 120 min, in pH 1.2 and 6.8 solutions, respectively, indicating that as the concentration of Mg-St increased, Mg-St retarded the dissolution of APAP from the tablets as described previously (Levy and Gumtow, 1963; Murthy and Samyn, 1977; Uchimoto et al, 2011). However, when CS-LA was mixed with APAP granules, at all tested

concentrations, the times for dissolution of 80% of the APAP were found to be under 120 min for both pH 1.2 and 6.8 solutions (**Fig. 5B**), strongly suggesting that the dissolution rate did not change even when the concentration of CS-LA was increased. This effect is also explained by the surfactant structure of CS-LA, meaning that because of the presence of CS-LA, the wettability might be increased and retarded dissolution is not observed. Additionally, fast APAP release from CS-LA tablets was observed at pH 1.2 compared with pH 6.8. This is explained by the remaining amino groups in CS-LA, which are ionized under low pH conditions allowing CS-LA to dissolve, resulting in the fast release of APAP.

3.5. Effects of CS-LA components on lubricant and tablet characteristics

It was found that CS-LA shows good lubrication properties during compression and does not cause any adverse tablet characteristics. To investigate what components of CS-LA, CS, LA, as well as the physical mixture (PM) of CS and LA, are involved in these properties, we determined the effect of CS-LA components on the pressure transmission ratio and the ejection force as well as the tensile strength, disintegration time, and dissolution behavior (**Figs. 6 and 7**). The concentration of CS-LA components was fixed at 3.0%, because CS-LA showed good lubrication properties at 3% (**Fig. 2**). As shown in **Fig. 6A**, the values of the pressure transmission ratios for CS, LA, and PM were 79.7%, 89.0%, and 82.3%, respectively.

311 The ejection force values for CS, LA, and PM were 369, 153, and 163 N, respectively (**Fig. 6B**).
312 Because the pressure transmission ratio and ejection force values for LA were almost the
313 same as that for 3% CS-LA, it is thought that LA is involved in the superior lubrication
314 properties of CS-LA. Although PM gave almost the same value for the pressure transmission
315 ratio as that observed for 3% CS-LA, the value of the ejection force was slightly higher,
316 indicating that the conjugation of CS with LA might be important for lubrication performance.
317 The values for tensile strength for CS-LA and CS were 2.23 and 2.70 MPa, respectively, while
318 the values for LA and PM were 1.89 and 1.86 MPa, respectively (**Fig. 6C**), suggesting that
319 owing to the lower extensibility of CS-LA and CS, these compounds did not completely cover
320 the surface of the granules, allowing cohesion of the granules, and resulting in a high tensile
321 strength compared with LA and PM. The disintegration time for CS-LA was longer than 10 min,
322 while the times for CS, LA, and PM were under 3 min (**Fig. 6D**), indicating that even if
323 hydrophilic coverage on the granules occurred for LA and PM, as mentioned above (**Fig. 6C)**,
324 water penetration into the tablets was not prevented and rapid disintegration occurred. Finally,
325 the drug dissolution rates of an APAP tablet containing each component are shown as plots in
326 **Fig. 7**. In a pH 1.2 medium, the times for dissolution of 80% of the APAP from CS, LA, and PM
327 tablets were found to be under 40 min (**Fig. 7A**), indicating that all formulations showed rapid
328 drug release compared with CS-LA. In a pH 6.8 medium, similar tendencies were observed

329 (**Fig. 7B**). Additionally, only drug release in CS-LA occurred in a pH-dependent manner,
330 meaning that in the chitosan salt, conjugation of CS with LA caused more rapid drug release in
331 an acidic medium because of the amino acid residues remaining in the structure.

332 Although the CS-LA components CS, LA, and PM themselves gave good lubrication or
333 good tablet properties, only the CS salt (conjugation of CS with LA) showed improvement in
334 both characteristics, indicating that CS-LA might be a good lubricant in the tableting process
335 as an alternative Mg-St.
336

4. Conclusions

Traditionally, Mg-St has been widely used as an inexpensive lubricant having excellent lubrication effects, but it also has disadvantages, such as a reduction in tablet mechanical strength and prolonged disintegration time. In this study, we determined whether CS-LA, a newly developed CS salt, worked as a potential alternative lubricant to Mg-St. The lubrication properties for CS-LA were examined, as well as the tablet properties, in comparison to those of Mg-St. The pressure transmission ratio was significantly improved in a concentration-dependent manner and the ejection force prominently decreased for CS-LA; the pressure transmission ratio for 3% CS-LA was similar to that of Mg-St. Additionally, even when the lubricant concentration was increased, adverse characteristics such as a reduction in tablet mechanical strength, prolonged disintegration time, or retarded dissolution behavior were not observed with CS-LA, unlike with Mg-St. Furthermore, as a result of the CS-LA components, conjugation of CS with LA was found to be quite important for both lubricant and tablet properties. Based on these results, CS-LA may be useful as an alternative lubricant to Mg-St.

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419
420

421 **Table**

422 **Table 1.** The median diameter of Mg-St, CS, LA, and CS-LA

	Mg-St	CS	LA	CS-LA
Median diameter (μm)	11.5±5.7*	96.5±24.2[#]	74.7±7.9[#]	79.2±9.73[#]

423 *: Data expressed as mean ± S.D. (*n*=3). [#]: Data expressed as mean ± S.D. (*n*=20).

424

425

426 **Figure legends**

427 **Figure 1. Chemical structures of Mg-St (A) and CS-LA (B), and SEM images of CS, LA,**
428 **and CS-LA (C).**

429 Each bar scale represents 50 μm (a), 50 μm (b) and 20 μm (c).
430

431 **Figure 2. Effect of Mg-St and CS-LA concentrations on the pressure transmission ratio**
432 **(A) and ejection force (B).**

433 The lubricant concentration ranged from 0.5% to 3.0%. Each point represents an average
434 value obtained from ten determinations (± S.D.). *, $p < 0.01$, compared with each lubricant at
435 the concentration of 0.5%.

436

437 **Figure 3. Effect of Mg-St and CS-LA concentrations on the tensile strength (A) and**
438 **disintegration time (B).**

439 The lubricant concentration ranged from 0.5% to 3.0%. Each point represents an average
440 value obtained from six determinations (± S.D.). *, $p < 0.01$, compared with Mg-St at the same
441 concentration.
442

443 **Figure 4. SEM images of the surface of glass beads treated with 3% Mg-St and CS-LA**
444 **(A), effect of Mg-St and CS-LA concentrations on contact angle (B) and water**
445 **penetration time into tablet (C).**

446 In (B) and (C), the lubricant concentration ranged from 0.5% to 3.0%. Each column represents
447 an average value obtained from four determinations (± S.D.). *, $p < 0.05$ and **, $p < 0.01$,
448 compared with each lubricant at the concentration of 0.5%.
449

450 **Figure 5. Effect of Mg-St and CS-LA concentrations on the dissolution behavior of**
451 **acetaminophen from tablets.**
452 (A) Mg-St and (B) CS-LA. Each point represents an average value obtained from three
453 determinations (± S.D.).

Figure 6. Effect of CS-LA components on the lubricant and tablet properties.

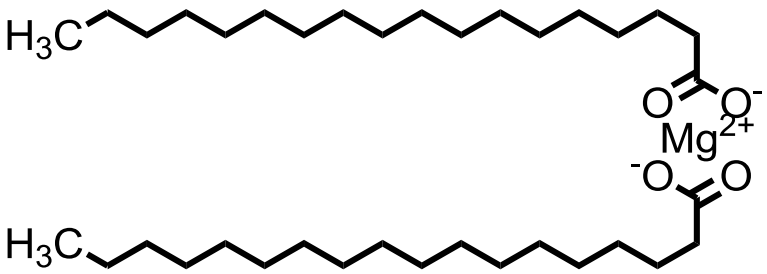
Each CS-LA component concentration was fixed at 3.0% and the Mg-St concentrations were 0.5% and 3.0%. (A) pressure transmission ratio, (B) ejection force, (C) tensile strength, and (D) disintegration time. Each column represents an average value obtained from ten determinations (A and B) and six determinations (C and D) (± S.D.).*, $p < 0.05$ and **, $p < 0.01$, compared with CS-A at the concentration of 3.0%.

Figure 7. Effect of Mg-St and CS-LA components on the dissolution behavior of acetaminophen from tablets.

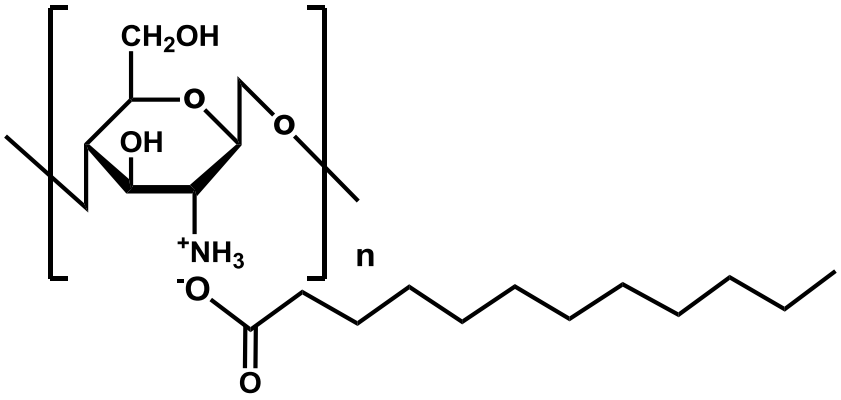
(A) pH 1.2 medium and (B) pH 6.8 medium. Each point represents an average value obtained from three determinations (± S.D.).

Fig. 1.

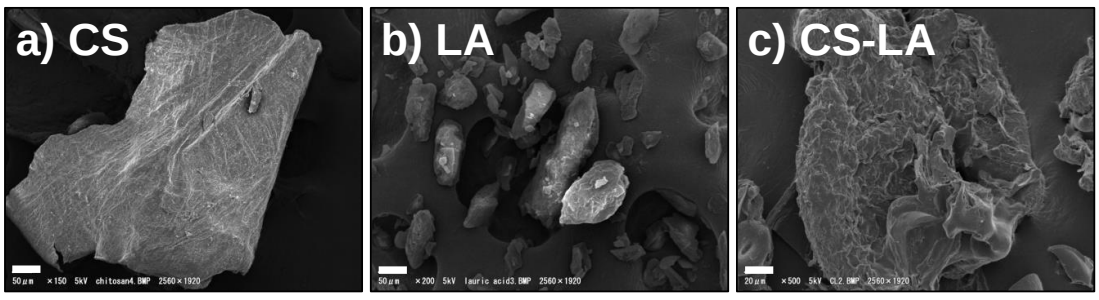
A)



B)

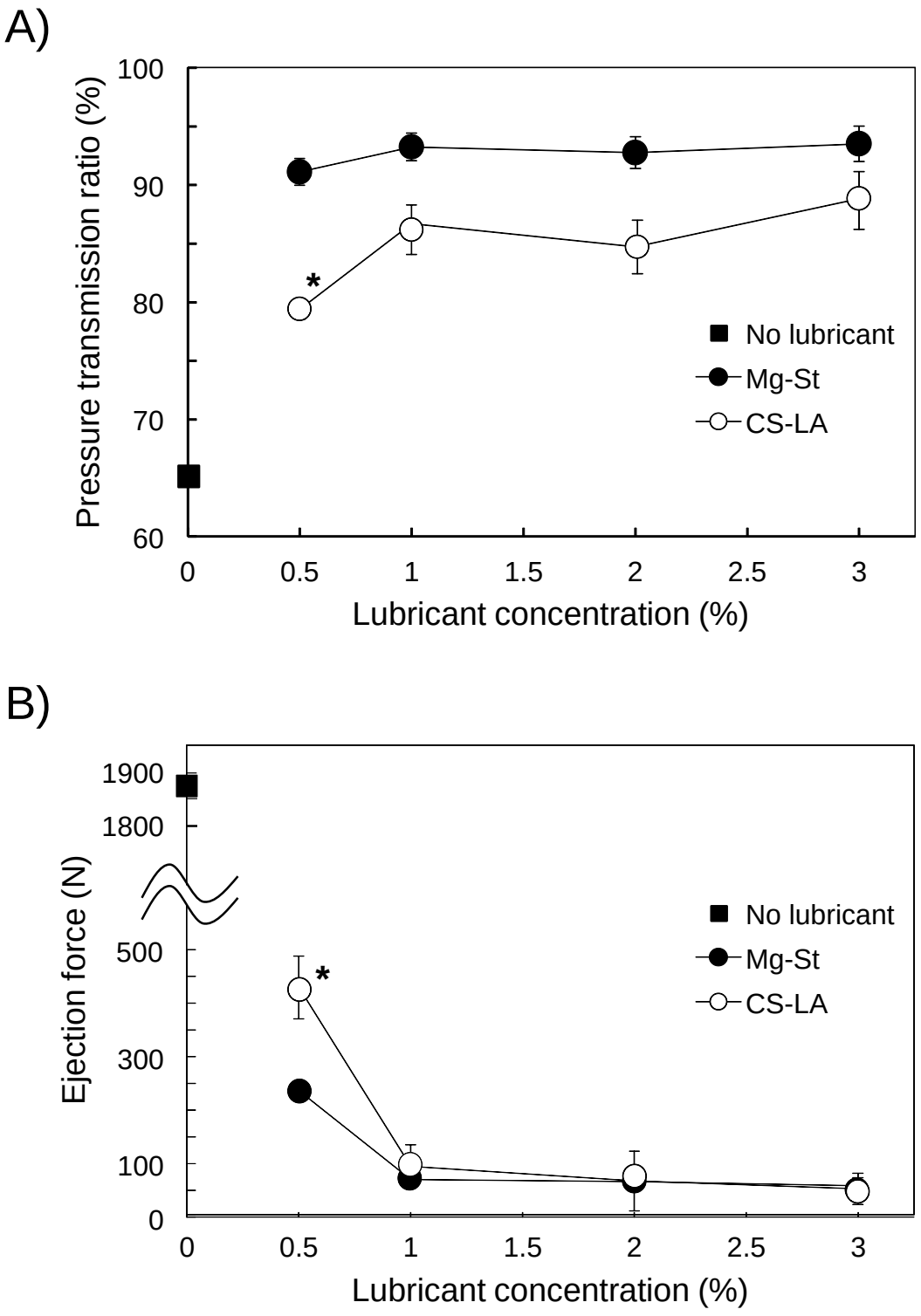


C)



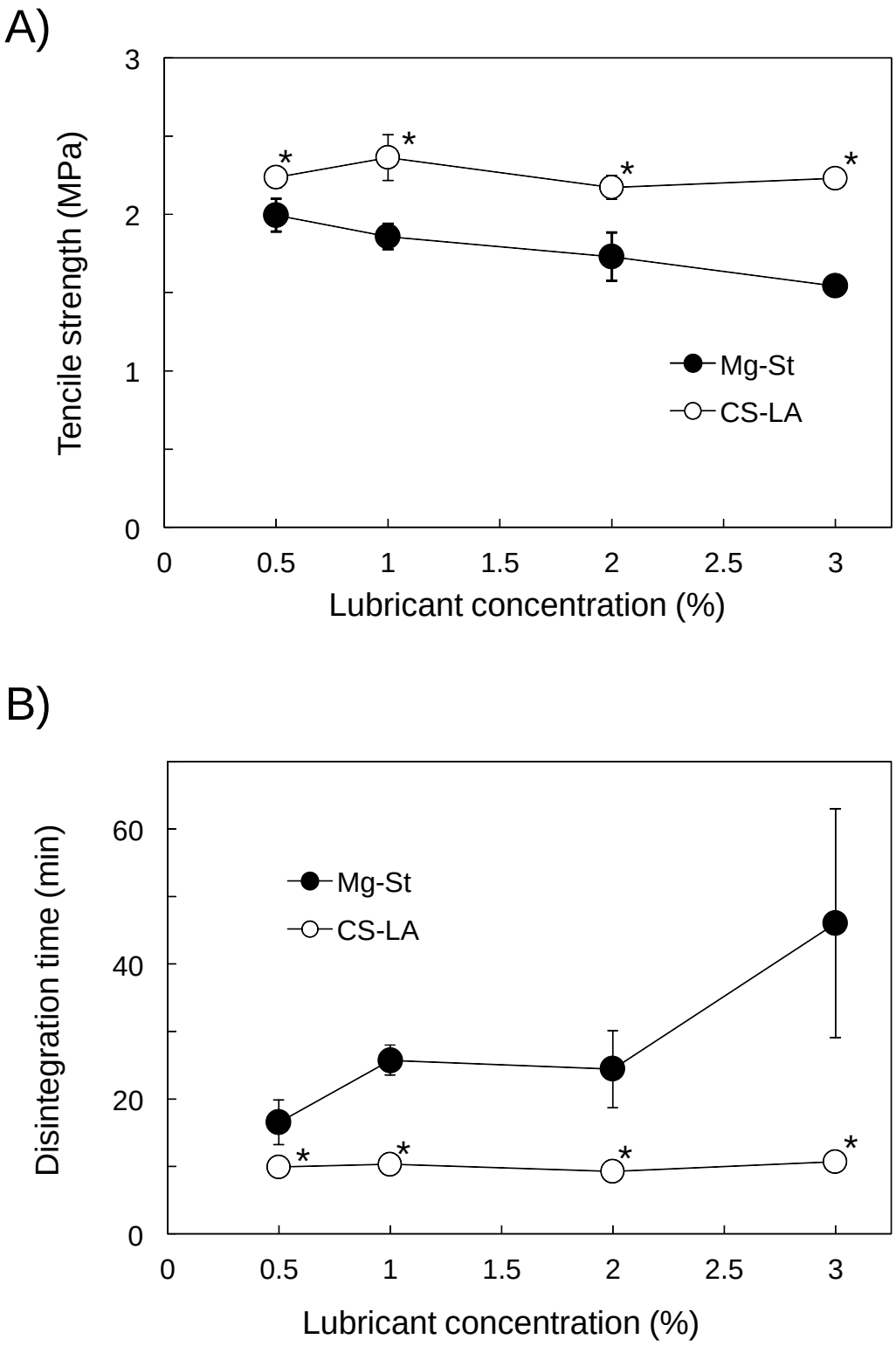
467

Fig. 2.


A)
Pressure transmission ratio (%)
100
90
80
70
60
0
0.5
1
1.5
2
2.5
3
Lubricant concentration (%)
*
No lubricant
Mg-St
CS-LA
B)
Ejection force (N)
1900
1800
500
300
100
0
0
0.5
1
1.5
2
2.5
3
Lubricant concentration (%)
*
No lubricant
Mg-St
CS-LA

468

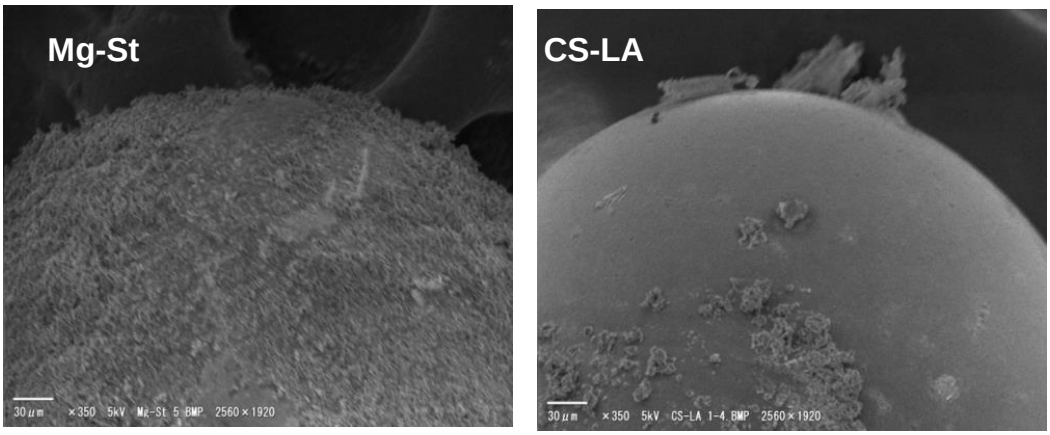
Fig. 3.


A)
Tencile strength (MPa)
3
2
1
0
0
0.5
1
1.5
2
2.5
3
Lubricant concentration (%)
Mg-St
CS-LA
*
B)
Disintegration time (min)
60
40
20
0
Lubricant concentration (%)
Mg-St
CS-LA

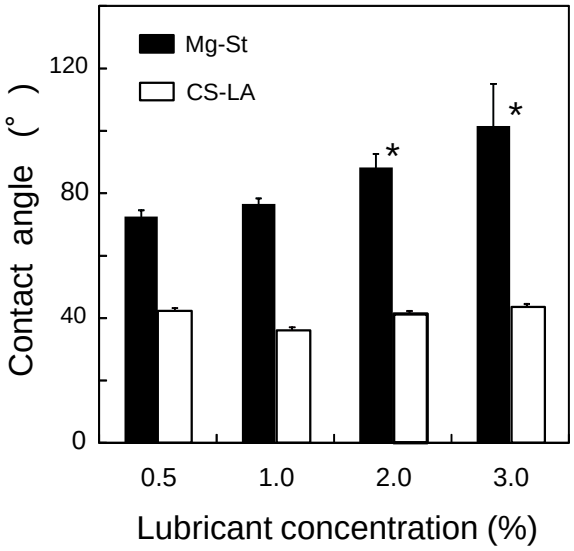
469

Fig. 4.

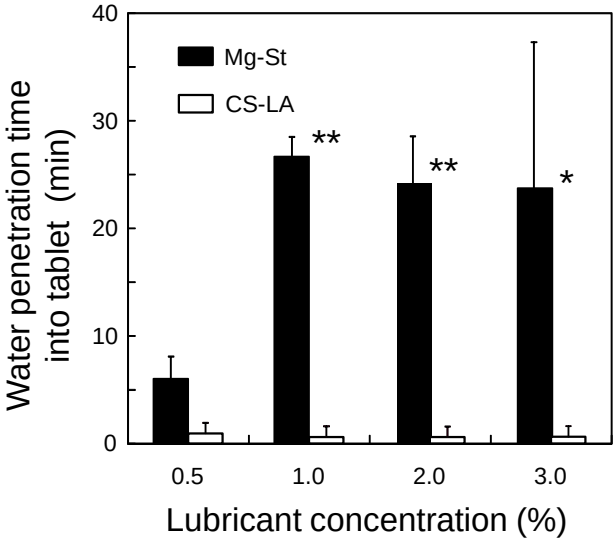
A)


Mg-St
CS-LA

B)

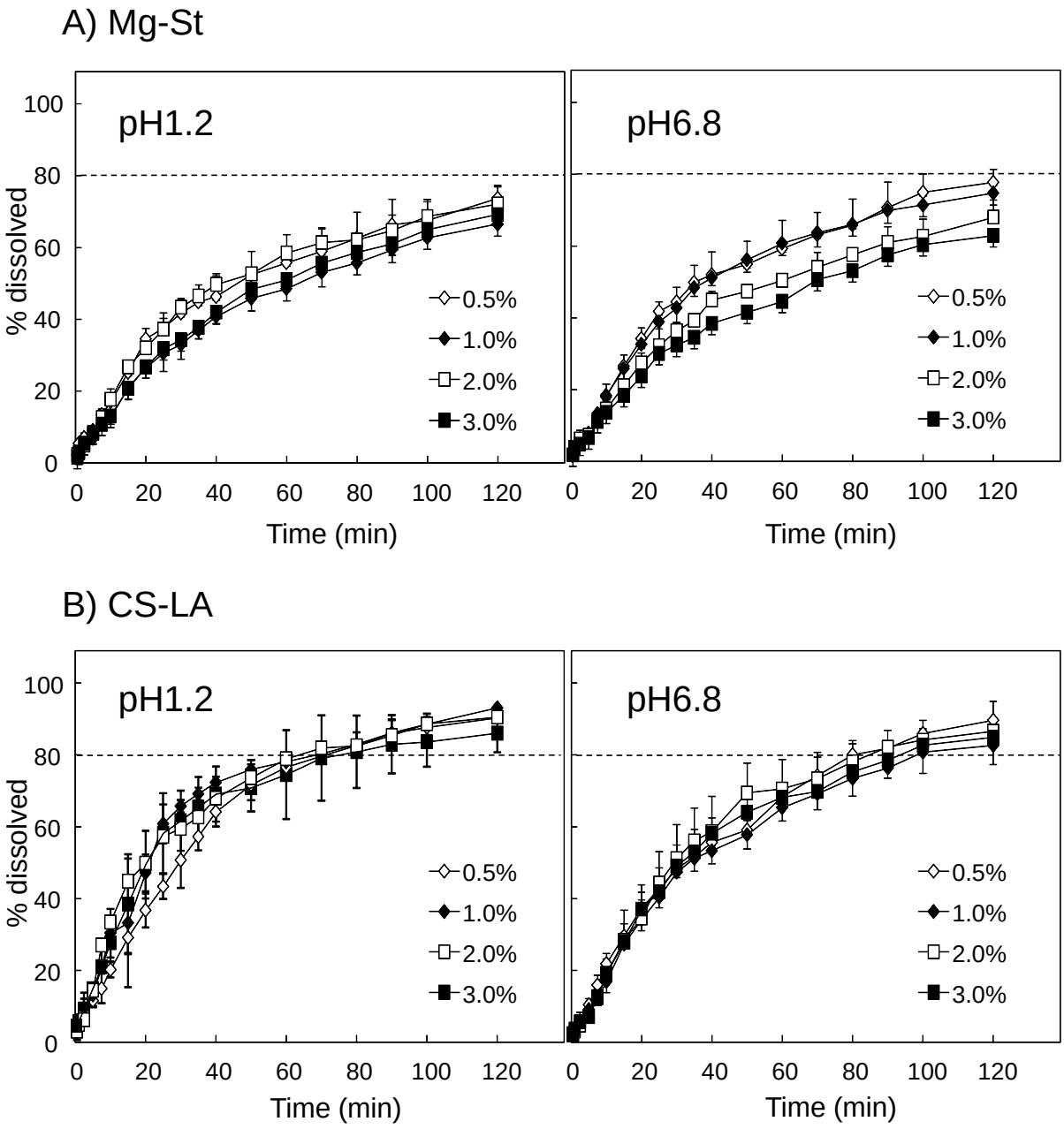

Mg-St
CS-LA
Contact angle (°)
120
80
40
0
*
*
*
0.5
1.0
2.0
3.0
Lubricant concentration (%)

C)


Mg-St
CS-LA
Water penetration time into tablet (min)
40
30
20
10
0
**
**
*
0.5
1.0
2.0
3.0
Lubricant concentration (%)

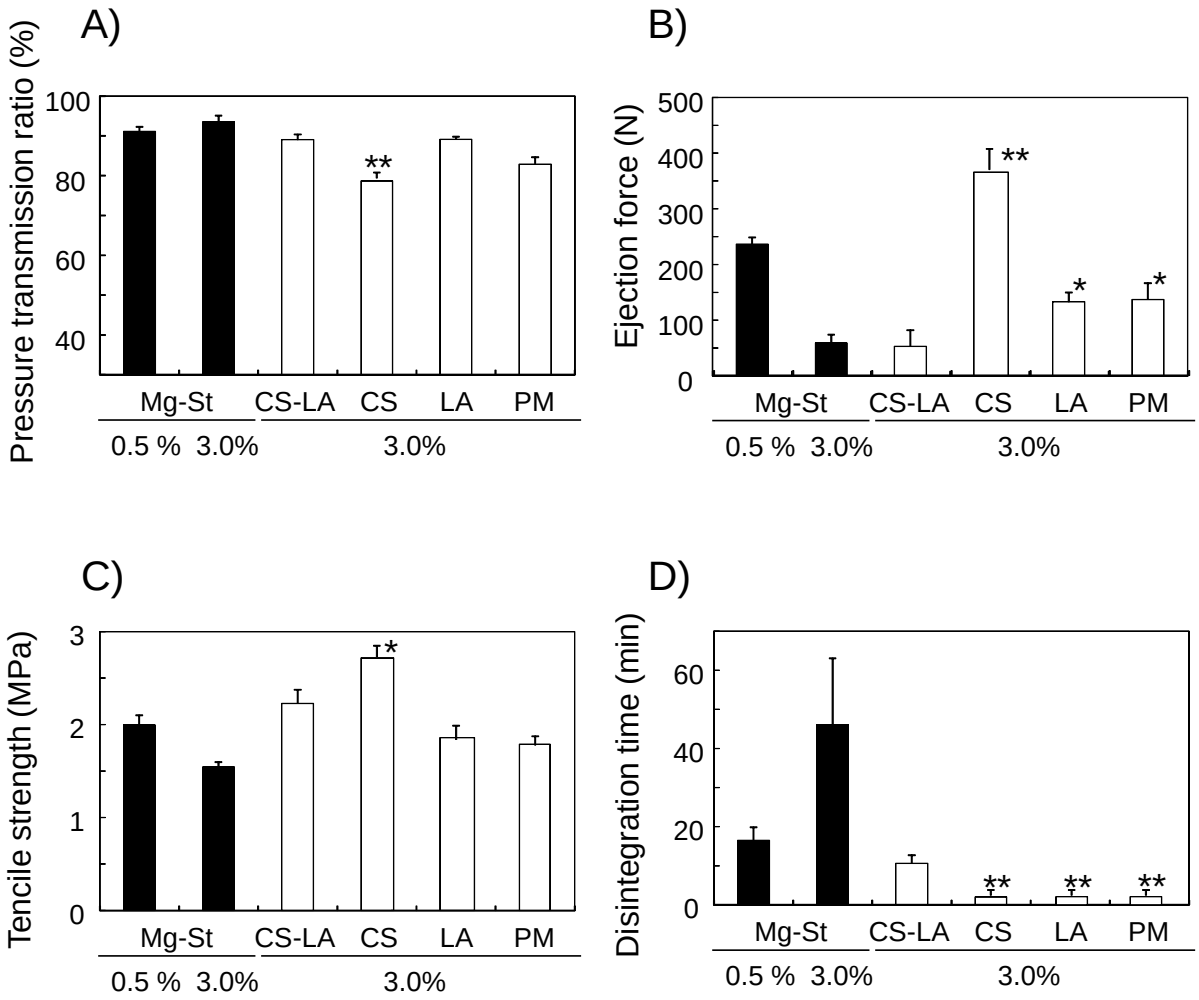
470

Fig. 5.


A) Mg-St
pH1.2
pH6.8
% dissolved
Time (min)
0.5%
1.0%
2.0%
3.0%
B) CS-LA
pH1.2
pH6.8
% dissolved
Time (min)
0.5%
1.0%
2.0%
3.0%

471

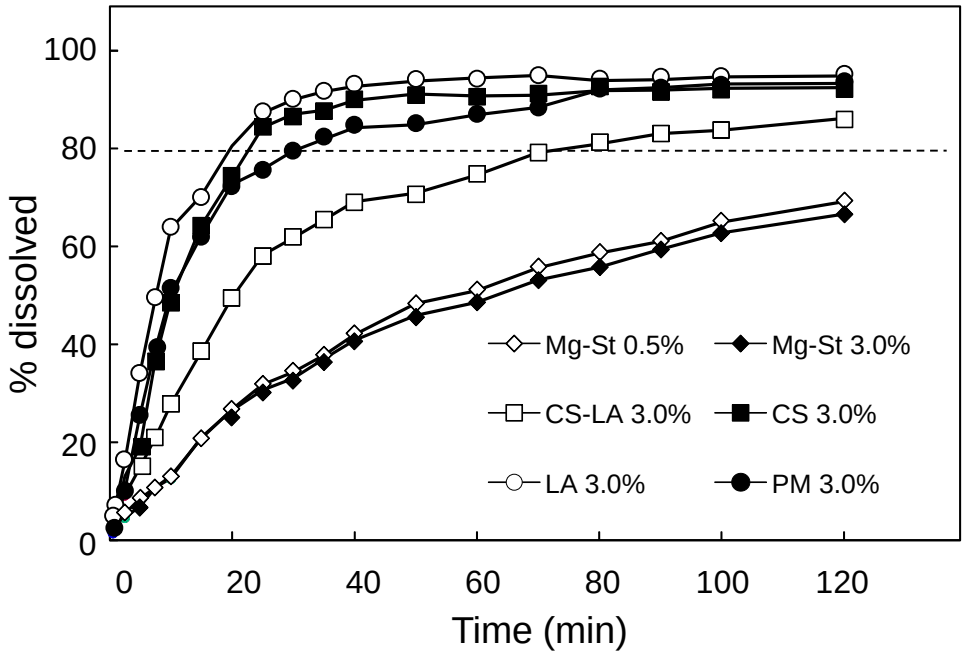
Fig. 6.


A)
Pressure transmission ratio (%)
100
80
60
40
**
Mg-St
CS-LA
CS
LA
PM
0.5 %
3.0%
3.0%
B)
Ejection force (N)
500
400
300
200
100
0
**
*
*
Mg-St
CS-LA
CS
LA
PM
0.5 %
3.0%
3.0%
C)
Tencile strength (MPa)
3
2
1
0
*
Mg-St
CS-LA
CS
LA
PM
0.5 %
3.0%
3.0%
D)
Disintegration time (min)
60
40
20
0
**
**
**
Mg-St
CS-LA
CS
LA
PM
0.5 %
3.0%
3.0%

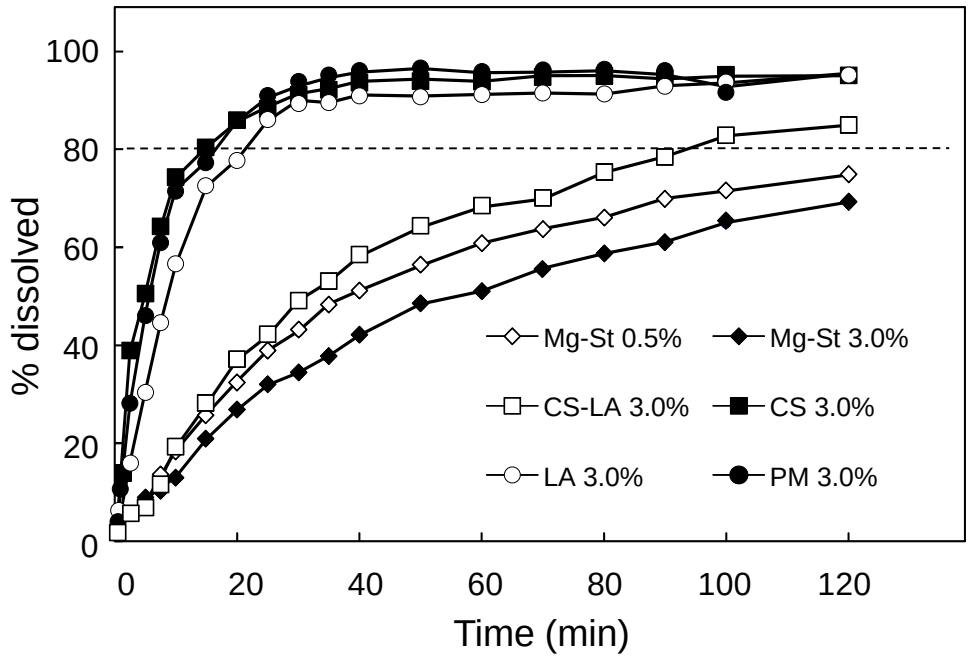
472

Fig. 7.

A) pH1.2



B) pH6.8



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