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Glycerin fatty acid esters as a new lubricant of tablets

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Abstract

Lubrication properties were compared among glycerin fatty acid esters (Poem TR-FB® and Poem TR-HB®), magnesium stearate (Mg-St), and a sucrose fatty acid ester (RYOTO SUGAR ESTER S-370F®: SSE). Granules containing 50% acetaminophen were prepared, and improvements in their fluidity by the lubricants were compared. The lubricant effects of TR-FB and HB during tablet punching (pressure transmission ratio, ejection force) were similar to those of Mg-St and were better than those of SSE. When the lubricant content, mixing time, and tabletting pressure were changed, TR-FB® and TR-HB® provided better tablet hardness than Mg-St. TR-FB® and TR-HB® made tablets more disintegratable than Mg-St. When the effects of these lubricants on the stability of acetylsalicylic acid (ASA) were compared, Mg-St promoted its hydrolysis, but TR-FB® or TR-HB® did not affect its stability.

Keywords: Lubrication properties; Glycerin fatty acid esters; Tablet characteristics; Fluidity; Acetaminophen; Tabletting

1. Introduction

Lubricants are pharmaceutical excipients that improve the fluidity, filling properties, adhesiveness, and plasticity of powders and are indispensable for improving the quality and manufacturing efficiency of solid preparations (Miller and York, 1988). Insufficient fluidity of the bulk powder in the tabletting process causes problems such as an increase in the variability of the tablet weight, impairment of content uniformity, and deterioration of the product quality. Also, inadequate plasticity due to friction and adhesion among powder particles or between the particles and the punch and die directly leads to troubles in the manufacturing process and deterioration of the productivity. Lubricants are effective for avoiding such troubles.

Magnesium stearate (Mg-St) is the most widely used lubricant today, and various studies of its physicochemical properties and lubrication properties, and their relationships with tablet characteristics (Ertel and Carstensen, 1988; Leinonen et al., 1992; Ribet et al.,

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2003), as well as those comparing them with those of other lubricants (Salpekar and Augsburger, 1974; Iranloye and Parrott, 1978; Baichwal and Augsburger, 1987; Shibata et al., 2002), have been performed. These studies have shown that Mg-St has demerits as well as merits as a lubricant. In particular, there have been a number of studies concerning a delay of tablet disintegration (dissolution of the active ingredient) and a decrease in the tablet hardness (Shah and Mlodozeniec, 1977; Bolhuis et al., 1981; Flores et al., 2000; Eissens et al., 2002). The delay of disintegration of tablets due to Mg-St has been shown to affect the bioavailability of the active ingredient (Rubinstein and Eastwood, 1978). Usually, a lubricant is used at 0.2–2% of the total weight of tablet, but it exerts a very large effect on the pharmaceutical characteristics. In addition to Mg-St, magnesium lauryl sulfate (Salpekar and Augsburger, 1974), sodium lauryl sulfate(Tsumamoto et al., 2002), glycerin bibehenate (Compritol®) (Diaye et al., 2003), and sucrose fatty acid esters (Shibata et al., 2002) have been evaluated as lubricants. These lubricants are used instead of Mg-St when Mg-St may be incompatible with the active ingredient or other additives.

Most recently, there are growing concerns for safety on pharmaceutical excipients derived from animal resources including magnesium stearate and gelatin. This study focuses on glycerin fatty acid esters as possible substitutes for Mg-St. Glycerin fatty acid esters are used primarily as emulsifiers in the food industry, and those with diverse properties can be obtained by adjusting the combination of the degree of glycerin polymerization, the kinds of fatty acid, and the degree of esterification. Lately, some of them were reported to be useful for tabletting lubricants (N'Diaye et al., 2003). In this study, two types of triglycerin behenate that differ in the degree of esterification (Poem TR-FB® and Poem TR-HB®) were compared with Mg-St and a sucrose fatty acid ester with regard to lubrication properties, tablet characteristics, and stability of the preparation.

2. Materials and methods

2.1. Materials

Magnesium stearate (Merck Ltd., JP14; abbreviated as Mg-St), triglycerin full behenate (Poem TR-FB®, Riken Vitamin Co. Ltd., specifications as a food additive; referred to as TR-FB), triglycerin half behenate (Poem TR-HB®, Riken Vitamin Co. Ltd., specifications as a food additive; referred to as HB), and a sucrose fatty acid ester (RYOTO SUGAR ESTER S-370F®, MITSUBISHI-KAGAKU FOODS CORPORATION, specifications as a drug additive; referred to as SSE) were used as lubricants.

For the preparation of granules, acetaminophen (Iwaki Seiyaku Co. Ltd., JP14), which has a poor compression plasticity and a high content, was used as the active component, lactose (DMV Japan Co. Ltd., JP14) and corn starch (Nihon Shokuhin Kakou Co. Ltd., JP14) were used as fillers, and hydroxylpropyl cellulose (HPC-L®, Nippon Soda Co. Ltd., JP14) was used as a binder.

To determine the moisture content, potassium carbonate (Wako Pure Chemical Industries, Ltd., 1st grade reagent) and monobasic calcium phosphate (Wako Pure Chemical Industries Co. Ltd., 1st grade reagent) were used to adjust the ambient humidity, and phosphorus oxide (Wako Pure Chemical Industries, Ltd., 1st grade reagent) was used as a desiccating agent.

For stability testing, acetylsalicylic acid (Wako Pure Chemical Industries, Ltd., special grade reagent; ASA) was used as the active ingredient, salicylic acid (Wako Pure Chemical Industries, Ltd., special grade reagent; SA) was used as a standard of a degradation product, sodium chloride (Wako Pure Chemical Industries, Ltd., 1st grade reagent) was used to adjust the humidity, and acetonitrile (Wako Pure Chemical Industries, Ltd., special grade reagent) and phosphoric acid (Wako Pure Chemical Industries, Ltd., 1st grade reagent) were used for the preparation of the mobile phase of HPLC.

2.2. Physicochemical properties of lubricants

The measurement of the particle size of TR-FB, HB and SSE was carried out by a laser diffraction method (Microtrac® MT-3000, Nikkiso Co. Ltd.). The moisture contents of various lubricants were determined after storage at 25 °C 43% RH and 97% RH for 1 week, and about 2 g of each lubricant was placed in a weighing bottle and vacuum-dried for 24 h in a desiccator containing phosphorus oxide. The relative humidity values of saturated water solutions of potassium carbonate and monobasic calcium phos-

phate at 25° were 43% and 96%, respectively. Thermal analysis was carried out by a differential scanning calorimeter (DSC100®, Seiko Instruments, Inc.) using 10 mg of a sample, at a temperature increase rate of 10 °C/min, and in measured temperature ranges of 30–150 °C for Mg-St and 30–120 °C for the other lubricants.

2.3. Granulation and lubrication

Using a mixer (Fuji Medical Equipment Co. Ltd.), 175 g of lactose and 75 g of corn starch were mixed for 10 min, 250 g of acetaminophen was added, and the components were mixed for another 10 min. To this mixed powder, 100 g of a 4% water solution of HPC-L was added by spraying, and the mixture was kneaded for 10 min. Granulation was performed using a rotating squeeze type granulator (Hata Iron Work Co. Ltd.) by squeezing the paste through a screen with a sieve size of 0.8 mm. The granules were dried at 25 °C and 40% RH for 24 h or longer. After drying, they were sieved through a 1680-μm sieve, and those that passed the sieve were collected. This process was repeated several times, and the resultant granules were mixed uniformly and used for the experiment. Each lubricant and the granules were mixed by trituration. They were mixed in a polyethylene bag manually for about 1 min. The lubricant concentrations were 0.5%, 1%, 2% and 3%.

2.4. Measurement of powder fluidity

Using a general powder property measurement apparatus (Powder Tester®, Hosokawa Micron Co. Ltd.), the angle of repose, bulk density and tapped density were measured. The measurements were carried out at 25 °C and 60 ± 5% RH.

2.5. Tablet preparation and lubrication effects

2.5.1. Method A

Tablets prepared using a single punch tablet machine (N20-E®, Okada Seiko Co. Ltd.) were of a diameter 8 mm, 10*R* (radius of curvature, 10 mm), and of a weight 200 mg. The pressure of punch during tabletting was measured using load cells with a mobile type data recorder (NR-1000, Keyence), and it was converted to the force applied to the die. The pressure transmission ratio $P(r)$ was calculated by the following formula

$$P(r) = \frac{P_L}{P_U} \times 100$$

in which P_L is maximum pressure of the lower punch and P_U, the maximum pressure of the upper punch.

As the ejection force, the force applied to the lower punch during tablet ejection was measured by the same method used for the measurement of the punching pressure.

2.5.2. Method B

Tablets prepared using an oil press (Japan Spectroscopic Co. LTD.) with a flat punch and a die were of a diameter 13 mm and of a weight 400 mg. The pressure was applied for 3 s.

2.6. Measurement of the tablet weight, hardness, and disintegration time

Twenty tablets were selected at random from the tablets prepared, each was weighed carefully, and the hardness (*N*) along its diameter was measured using a Monsanto type hardness meter (Kayagaki Irika Kogyo). Six other tablets were selected, and disintegration tests were performed according to the JP14 disintegration test. Distilled water at 37 ± 0.5 °C was used as the test fluid.

2.7. Effects of the mixing time of lubricants

The lubricants and granules were mixed in a V-shaped mixer (Microtype Transparent Mixer S-3, Tsutsui Rikagaku Kikai Co. Ltd.) at a rotation rate of 30 rpm. Two grams of a lubricant was mixed with 200 g of granules (1%) for 5 min, 10 min, 30 min or 60 min. After mixing, tablets 13 mm in diameter with a mass of 500 mg were prepared using a hydraulically-operated tablet puncher at a punching pressure of 10 kN (JASCO Co.). The tablet hardness was measured using a tablet hardness measurement apparatus (TS-50N®, Okada Seiko Co. Ltd.).

2.8. Effects on the stability of acetylsalicylic acid

The stability test of ASA was performed by placing 2 g of ASA and 60 mg of a lubricant in a vial, mixing them manually, and storing the mixture at 50 °C

and 75% RH in a desiccator, in which the humidity was adjusted with a saturated water solution of sodium chloride. After 10, 20 and 30 days, 10 mg of the sample was collected, dissolved with 100 mL of a mixture of acetonitrile and 0.1% water solution of phosphoric acid (25:75), and passed through a 0.45-μm membrane filter (Millex-HV®, Millipore Co.), and the filtrate was analyzed by high pressure liquid chromatography.

Analytical equipment and chromatographic conditions

High pressure liquid chromatograph: Model 510®, Waters Co. Ltd.
Detector: S-310A model II®, Soma Chemical Co. Ltd.
Data processing system: Chromatocorder 12, System Instruments.
Column: Lichrospher100®, Rt250-4, RP18; Kanto Kagaku Co. Ltd.
Mobile phase: Acetonitrile/0.1% water solution of phosphate (25:75).
Flow rate of mobile phase: 1.0 mL/min.
Measuring wavelength: 285 nm.

3. Results and discussion

3.1. Physicochemical properties of lubricants

Fig. 1 shows the structural formulas of the lubricants used. Behenic acid is esoterically bound to 4–5 of the hydroxy groups of triglycerin for TR-FB and to 2–3 of those of triglycerin for HB. In SSE, stearic acid is bound to sucrose by ester bonds. These structures suggest that HB and SSE are more hydrophilic and allow the preparation of more favorable disintegrating tablets than TR-FB.

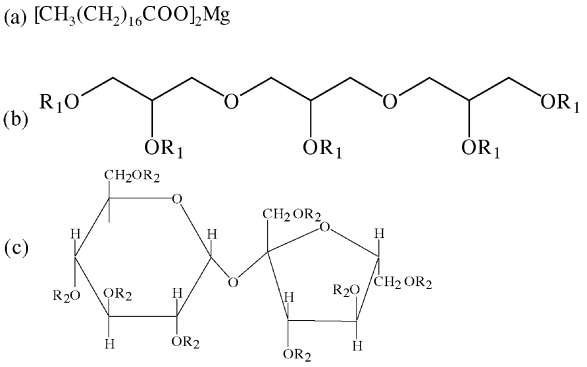

Fig. 1. Chemical structure of lubricants. (a) Magnesium stearate. (b) Glyceryl fatty acid esters; $R_1 = CH_3(CH_2)_{20}CO$ or H for TR-FB® and TR-HB®. (c) Sucrose fatty acid ester; $R_2 = CH_3(CH_2)_{16}CO$ or H for SSE.

Table 1 shows the mean particle sizes, moisture contents, and melting points of the lubricants. 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). Since the particle sizes of TR-FB and HB (4.1 μm and 5.8 μm, respectively) are smaller than those of Mg-St and SSE (9.5 μm and 22.2 μm, respectively), they are considered to have larger surface areas and better lubrication properties. TR-FB had a low moisture content of 0.25%, even at 97% RH, compared with other lubricants, probably because most of its hydroxyl groups are bound to behenic acid. Therefore, the tablets prepared using TR-FB were expected to be poorly hydrophilic, and their disintegration to be delayed similarly to those prepared using Mg-St. The moisture contents of Mg-St and HB were similar, but the moisture content of SSE showed 6.22% at 97% RH and more notable increases with increases in the ambi-

Table 1
Mean particle size, moisture content and melting point of lubricants

	Particle diameter (μm)	Melting point (°C)	Moisture content (%)	
			Storage condition	
			25 °C, 43% RH	25 °C, 97% RH
Mg-St	9.5	109.9	1.09 ± 0.01	3.07 ± 0.06
TR-FB	4.1	69.8	0.14 ± 0.01	0.25 ± 0.01
HB	5.8	72.0	0.87 ± 0.02	3.91 ± 0.21
SSE	22.2	47.5, 59.0	1.63 ± 0.02	6.22 ± 0.05

Moisture contents were determined at 25 °C and expressed as mean ± S.D. of three determinations.

Table 2
Physical Characteristics of Lubricated Granules

		Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility
Unlubrioated		39.2 ± 0.3	48.3 ± 0.5	57.3 ± 0.2	15.6 ± 0.8
Lubricant (%)					
Mg-St	0.5	38.3 ± 0.3	51.0 ± 0.2	58.9 ± 0.3	13.3 ± 0.6
	1	37.5 ± 0.5	50.9 ± 0.1	58.6 ± 0.3	13.1 ± 0.3
	2	38.5 ± 0.5	51.3 ± 0.3	59.5 ± 0.3	13.8 ± 0.9
	3	37.8 ± 1.0	51.5 ± 0.2	59.8 ± 0.4	13.9 ± 0.9
TR-FB	0.5	37.7 ± 0.8	49.1 ± 0.3	58.1 ± 0.2	15.4 ± 0.4
	1	38.0 ± 0.6	49.0 ± 0.1	58.3 ± 0.2	15.8 ± 0.4
	2	38.2 ± 1.2	50.5 ± 0.4	59.3 ± 0.4	14.8 ± 0.8
	3	37.5 ± 0.5	50.2 ± 0.1	59.3 ± 0.2	15.2 ± 0.2
HB	0.5	37.3 ± 0.3	48.8 ± 0.2	57.3 ± 0.1	14.8 ± 0.4
	1	38.0 ± 0.5	49.0 ± 0.1	57.9 ± 0.2	15.4 ± 0.4
	2	38.3 ± 0.6	49.2 ± 0.2	58.3 ± 0.2	15.6 ± 0.3
	3	38.0 ± 0.5	49.4 ± 0.2	58.4 ± 0.1	15.4 ± 0.4
SSE	0.5	37.3 ± 0.3	50.3 ± 0.3	58.2 ± 0.1	13.6 ± 0.4
	1	37.8 ± 0.3	50.4 ± 0.2	58.6 ± 0.2	14.0 ± 0.5
	2	37.8 ± 0.6	51.0 ± 0.1	59.0 ± 0.1	13.5 ± 0.3
	3	37.5 ± 0.5	51.5 ± 0.2	59.3 ± 0.1	13.0 ± 0.3

All values are mean ± S.D. of three determinations.

ent humidity than those of the other lubricants. According to the results of differential scanning calorimetry, the melting points were 109.9 °C in Mg-St, 69.8 °C in TR-FB, and 72.0 °C in HB. In SSE, peaks considered to be due to melting were observed at 47.5 °C and 59.0 °C.

During tablet punching, heat is generated due to friction between the powder and the die wall. In continuous punching, this heat is considered to accumulate and to increase the temperature of the punch to a considerable level. Since lubricants reduce friction, they prevent generation of this heat. However, as SSE has a lower melting point than other lubricants, it may melt due to frictional heat and cause problems in the molding of tablets. On the other hand, Mg-St, TR-FB, and HB have higher melting points.

3.2. Improvements in the fluidity by lubricants

Table 2 shows the powder characteristics of granules with and without the addition of various lubricants. The angle of repose of the granules was 39.2° without lubricants but was 37.3–38.5° with lubricants, indicating slight improvements in the fluidity by the addition of lubricants. The bulk density and tapped density were 48.3 g/cm^3 and 57.3 g/cm^3, respectively, without lubricants, but they were increased by the addition of each lubricant, probably because small particles of the lubricants entered the space among the granules. In association, the compressibility was also improved by the addition of the lubricants under most conditions. Lubricants improve the fluidity of powders, but they may not linearly improve or may deteriorate the fluidity when added in excess (Danish and Parrott, 1971; Podczeck and Newton, 2000). In this study, the fluidity is considered to have been improved sufficiently by granulating the experimental powder, therefore the lubricants are considered to have caused no marked additional improvement in the fluidity. However, no decrease in the fluidity with increases in the lubricant concentration was observed with any lubricant.

3.3. Lubricating effects

Table 3 shows the maximum upper punch force during tabletting by the Method A at various concentrations of each lubricant, and Table 4 shows the weights of the tablets prepared under various conditions. There was a variation in the tablet punching force, because the quantity of the granules placed in the die (tablet weight) was not uniform. The fluidity of granules is considered to be a factor that may affect the quantity of granules placed in the die. However, the fluidity is

Table 3
Maximal upper punch forces (kN)

	Lubricant concentration (%)			
	0.5	1	2	3
Unlubricated		20.09 ± 0.63		
Mg-St	19.89 ± 0.86	21.34 ± 0.70	20.10 ± 0.70	19.77 ± 0.98
TR-FB	18.99 ± 0.78	17.73 ± 0.79	19.02 ± 1.03	20.37 ± 0.80
HB	17.73 ± 0.69	18.09 ± 1.08	22.29 ± 0.44	19.41 ± 0.92
SSE	20.46 ± 0.75	19.63 ± 0.67	19.26 ± 0.81	19.56 ± 0.74

All values are mean ± S.D. of 20 determinations. Tablets were compressed by the Method A.

Table 4
Weight (mg) variation of tablets

	Lubricant concentration (%)			
	0.5	1	2	3
Unlubricated		202.4 ± 4.2		
Mg-St	205.7 ± 6.7	214.1 ± 4.4	208.4 ± 4.9	204.8 ± 7.7
TR-FB	201.6 ± 6.5	197.5 ± 8.0	196.7 ± 7.0	206.3 ± 6.5
HB	194.6 ± 7.1	196.6 ± 7.0	212.8 ± 5.3	203.6 ± 4.9
SSE	205.7 ± 6.2	202.6 ± 6.6	201.6 ± 6.0	202.1 ± 6.9

All values are mean ± S.D. of 20 determinations. Tablets were compressed at 20 kN. By the Method A.

not considered to be responsible for the variation in the weight, because it was nearly the same among all mixtures.

Fig. 2 shows the relationship between the lubricant concentration and pressure transmission ratio. Part of the force delivered by the upper punch in the process of powder compression is lost due to friction between the powder and the die wall before it is transmitted to the lower punch. A lubricant mitigates friction among particles or between particles and the die wall by attaching to the particle surface. Therefore, the lubricant equalizes the pressure distribution in the powder layer, thus facilitating changes in the shape of the powder layer, and improves its compressibility. In this experiment, the pressure transmission ratio during tabletting was 79.8% without the addition of a lubricant but was improved to 90% or higher by the addition of a lubricant. Among the four lubricants tested, the pressure transmission ratio was highest with Mg-St, being nearly 100% at all concentrations. It was about 97% with both TR-FB and HB, being sufficiently high though inferior to the value with Mg-St. The pressure transmission ratio was lower with SSE than with the other lubricants but was improved from 92.1% to 97.8% by increasing the concentration from 0.5% to 3%. Although SSE provided a pressure transmission ratio similar to those obtained with TR-FB and HB at concentrations of 2% or above, it caused no sufficient improvements in the pressure transmission ratio at lower concentrations. Little change was observed in the pressure transmission ratio when the concentration of Mg-St, TR-FB, or HB was

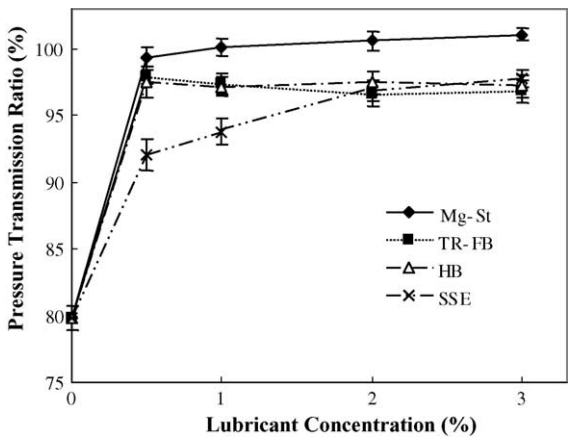

Fig. 2. Relationship between lubricant concentration and pressure transmission ratio. Tablets were compressed at 20 kN by the Method A ($n = 20$).

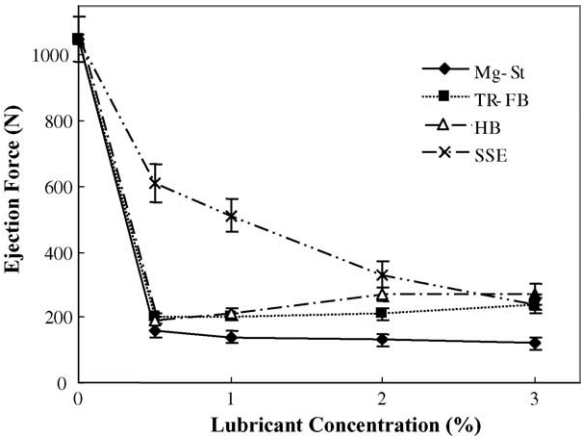

Fig. 3. Relationship between lubricant concentration and ejection force. Tablets were compressed at 20 kN by the Method A ($n = 20$).

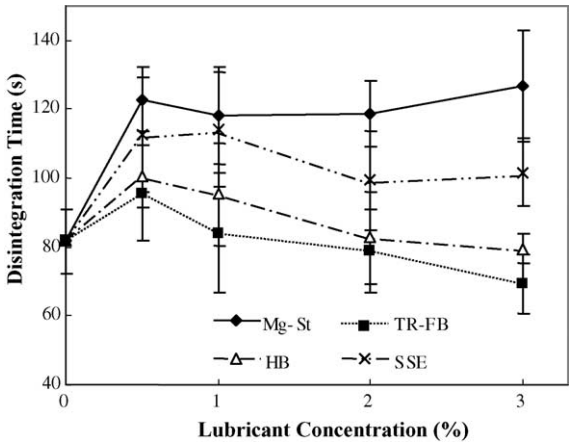

Fig. 4. Relationship between lubricant concentration and disintegration time. Tablets were compressed at 20 kN by the Method A ($n = 6$).

increased. Since these three lubricants have small particle sizes and good extensibility, they are considered to be able to sufficiently cover the granule surface even at a low concentration. On the other hand, SSE with a larger particle size is considered not to be able to completely cover the granule surface at a low concentration but to have improved the pressure transmission ratio when added at high concentrations.

Fig. 3 shows the relationship between the lubricant concentration and ejection force. One of the effects of a lubricant is to reduce friction between the sides of the tablet and the die wall during ejection after compression of the powder. High friction between the side of the tablet and the die wall may cause damage to the tablet or break its margins. In continuous tablet punching, frictional heat accumulates and may cause melting of low-melting-point materials. The addition of a lubricant is indispensable in preventing such problems. The ejection force during tablet punching without a lubricant was 1.05 kN. It was reduced slightly from 160 N to 120 N by increasing the concentration of Mg-St from 0.5% to 3%, but it was increased from 200 N to 240 N by increasing the concentration of TR-FB and from 190 N to 270 N by increasing the concentration of HB. These results were contradictory to the common knowledge that the ejection force decreases with increases in the lubricant concentration (Matsuda et al., 1976), and suggest that TR-FB and HB have optimal concentrations and should not be added in excess quantities. The ejection force decreased from 610 N to 240 N with increases in the concentration of SSE, but SSE must be added in a large quantity to sufficiently reduce the ejection force.

3.4. Effects on the disintegration time of tablets

Fig. 4 shows the relationship between the lubricant concentration and disintegration time of tablets prepared by the Method A. Mg-St delays the disintegration of tablets by forming a hydrophobic membrane on the surface of powder particles. Disintegration is delayed more markedly as the Mg-St concentration is higher (Durig and Fassihi, 1997). In this study, the disintegration time with Mg-St was about 120 s, which was longer than those with the other lubricants and was unrelated to its concentration. The disintegration time was 96 s, 84 s, 79 s, and 69 s with TR-FB at 0.5%, 1%, 2% and 3%, 101 s, 95 s, 83 s and 80 s with HB, and 113 s, 114 s, 99 s and 102 s with SSE, respectively. Since TR-FB has no hydroxyl group, it was expected to delay the disintegration more than the other lubricants, but the disintegration time was the shortest with TB-FB among the four lubricants. Also, in consideration of the chemical structures and moisture contents, we expected the disintegration time to be shortest with SSE, followed by HB, and longest with TR-FB, when Mg-St was excluded, but the results were completely opposite to our expectation. Both glycerin fatty acid ester TR-FB and HB are speculated to have an effect that promotes tablet disintegration.

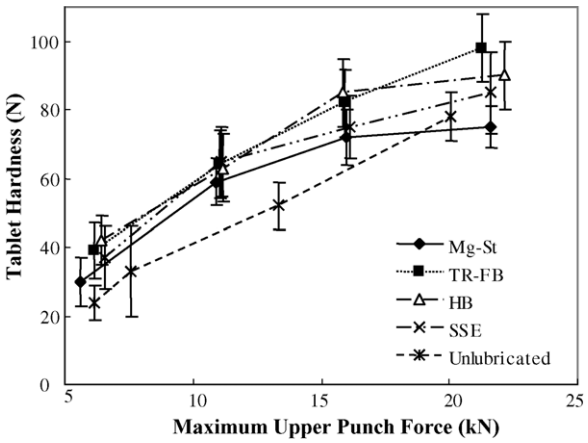

Fig. 5. Relationship between maximal upper punching force and tablet hardness. Lubricant concentration is 1% and tablets were prepared by the Method A ($n = 20$).

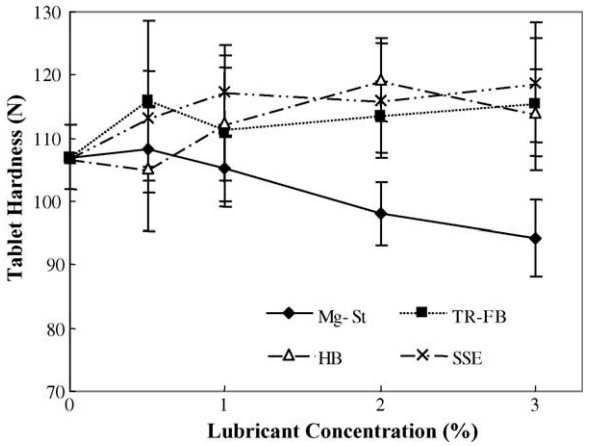

Fig. 6. Relationship between lubricant concentration and tablet hardness. Tablets were compressed at 20 kN by the Method B ($n = 20$).

3.5. Effects on the tablet hardness

Fig. 5 shows the relationship between the maximum upper punch force and hardness of tablets prepared by the Method A. Generally, the tablet hardness increases with the maximum upper punch force, and this relationship was also observed in this study. However, while the tablet hardness was similar among the lubricants used when the maximum upper punch force was low, the tablet hardness decreased with Mg-St compared with the other lubricants when the maximum upper punch force was increased. The tablet hardness at a maximum upper punch force of 20 kN was 75 N with Mg-St but was 98 N with TR-FB, 90 N with HB, and 85 N with SSE. While Mg-St prevents bonding among powder particles because of its high extensibility, TR-FB and HB have little such property, so they provided greater tablet hardness than Mg-St.

Fig. 6 shows the relationship between the lubricant concentration and hardness of tablets prepared by the Method B. The tablet hardness is known to decrease with increases in the Mg-St content (Williams and Mcginity, 1989). In this study, also, the tablet hardness decreased from 108 N to 94 N as the Mg-St concentration was increased from 0.5% to 3%. It was nearly the same, at about 115 N, with the other lubricants, regardless of their concentration. Mg-St is considered to reduce the tablet hardness because of its weak binding force with other particles. Shibata et al. (2002) prepared tablets made only of lubricants and compared their tensile strength. They observed that tablets made of Mg-St had a low tensile strength and considered it to be the cause of the low hardness of tablets containing Mg-St. Though the lubricant contents of tablets are a small percent, it is important to see to what extent they are extended on the granules surface at the mixing procedure. Mg-St has apparently the largest extendability and the lowest tensile strength among the lubricants, which eventually causes a decrease of tablet hardness with an increase of the concentration.

Fig. 7 shows the relationship between the mixing time and hardness of tablets prepared by the Method B. Similarly to the results of the experiment by Shah and Mlodozeniec (1977) the tablet hardness decreased with prolongation of the mixing time with Mg-St. The hardness of tablets containing Mg-St was 101 N when the mixing time was 5 min but decreased to 91 N, 85 N and 84 N after mixing for 10 min, 30 min and 60 min, respectively. There was little difference in the tablet hardness when the mixing time was 30 min and 60 min, and the tablet hardness scarcely decreased with mixing time when the mixing time exceeded 30 min. The hardness is considered to have decreased with the mixing time, probably because Mg-St spread over the surface of the granules with prolongation of mixing, and this spread has been observed by SEM (Miyake et al., 1970; Chowhan and Chi, 1986a,b). On the other hand, the tablet hardness with TR-FB, HB, or SSE was nearly the same at about 110 N, and was not affected by the

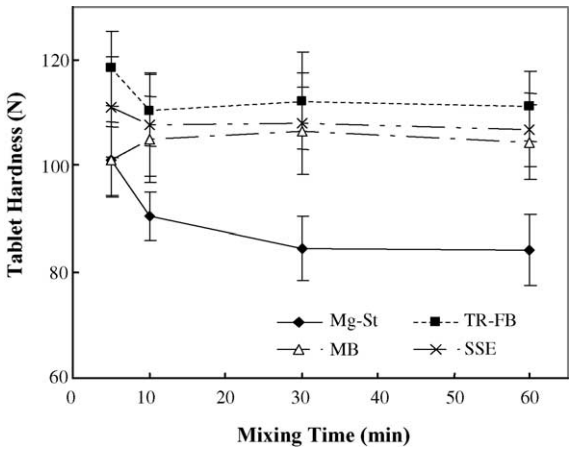

Fig. 7. Influence of mixing time on tablet hardness. Each lubricant concentration is 1% and tablets were compressed at 10 kN by the Method B ($n = 10$).

mixing time. The change in the tablet hardness between the mixing times of 5 min and 10 min is considered to be due to insufficient mixing of the lubricant and granules.

3.6. Effects on the stability of acetylsalicylic acid

Mg-St is known to affect the stability of various drugs including acetylsalicylic acid (ASA), ketoprofen, indomethacin, and picotamide (Mroso et al., 1982; Mura et al., 1995, 1998; Venkataram et al., 1995). These effects of Mg-St on the stability of drugs are considered to be due to the formation of eutectic mixtures. In this study, the ASA contents in its mixtures with various lubricants stored under the accelerated conditions (50 °C, 75% RH) were determined serially to compare the effects of the lubricants on the stability of ASA.

Table 5 shows serial changes in the ASA content. It was 92.2% after ASA was stored alone for 30 days, and no peak other than that of ASA was detected by HPLC. In a mixture of ASA with Mg-St, it decreased to 21.5%, and a new peak of salicylic acid (SA) was noted. Salicylsalicylic acid and acetylsalicylsalicylic acid as well as SA are known to be degradation products of ASA (Reepmeyer and Kirchhoefer, 1979), but no peak of other degradants than that of SA was noted in this study. In mixtures of ASA with TR-FB or HB, no peak other than that of ASA was noted, and the ASA content was more than 90%, which did not markedly differ from that after storage of ASA alone.

Table 5
Residual content (%) of ASA-lubricant mixture exposed to 50 °C, 75% RH

	10 days	20 days	30 days
ASA	92.6 ± 0.8	95.6 ± 3.3	92.2 ± 5.8
ASA-Mg-St	53.6 ± 1.0	33.7 ± 2.0	21.1 ± 0.4
ASA-TR-FB	99.3 ± 1.2	97.9 ± 1.2	95.1 ± 3.4
ASA-HB	95.2 ± 1.8	96.3 ± 1.6	90.8 ± 2.0

All values are mean ± S.D. of three determinations and normalized as initial contents are 100%.

4. Conclusions

TR-FB and HB showed lubricant characteristics similar to those of Mg-St, and tablets superior to those with Mg-St in hardness, disintegration and stability can be prepared with these lubricants. Also, the lubricant characteristics of TR-FB and HB were shown to be better than those of SSE. TR-FB and HB are free of biological problems including viral like contamination and be promising alternatives to Mg-St.

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