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Effects of automated external lubrication on tablet properties and the stability of eprazinone hydrochloride

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ABSTRACT

We investigated the advantages of an external lubrication technique for tableting. A newly developed external lubricating system was applied to tableting in a rotary tablet press using magnesium stearate. The resulting tablets were compared with tablets produced by the conventional internal lubrication method, in which lubricant is blended before tableting. As a model API, we chose eprazinone hydrochloride, because it is easily hydrolyzed by alkaline lubricant. The amount of lubricant required to prevent sticking with external lubrication was only 1/13th of that required with internal lubrication. External lubrication increased tablet crushing strength by 40%, without prolonging tablet disintegration time, and improved the residual ratio of eprazinone hydrochloride in tablets stored under stress conditions for 4 weeks by 10%. The distribution of lubricant on the surface of externally lubricated tablets was observed by scanning electron microscopy after the preparation by focused ion beam milling. The lubricant had formed a layer on the tablet surface. At the central part of the tablet surface, this layer was much thinner than at the edges, and remained extremely thin even when there was excess magnesium stearate. This is the first report to describe the distribution of lubricant on the surface of externally lubricated tablets.

1. Introduction

Lubricants are essential ingredients in tablet formulations. Lubricants reduce the adhesion force and friction between punches, dies and tablets and prevent tableting problems such as sticking, capping and lamination. Conventionally, lubricants have been mixed with the other powdered or granulated ingredients internally (internal lubrication) prior to tableting. However, lubricants tend to coat the powder or granules because of excessive dose and/or mechanical stress (Mehrotra et al., 2007) caused by overmixing; such coating has two main negative effects. One negative effect is decrease in tablet crushing strength: bonding between particles in the tablet is reduced because the surfaces of the powder or granules are covered with lubricant (Mollan and Çelik, 1996; Otsuka and Yamane, 2006). The other negative effect is the prolongation of tablet disintegration time: the lubricant coating the particles in the tablet is hydrophobic, so the water penetration rate and/or wetting characteristics of the active pharmaceutical ingredients (APIs) are decreased, and the disintegration and/or dissolution time of the APIs is delayed (Bolhuis et al., 1981; Lerk et al., 1982; Desai et al., 1993). Moreover, the physical properties of the lubricant vary subtly from batch to batch (Billany and Richards, 1982; Barra and Somma, 1996), and this makes it very difficult to set specific conditions for lubricant blending. To solve these problems, external lubrication was invented.

External lubrication refers to the application of lubricant to the tablet surface only, without blending (Gruber et al., 1991). Otsuka et al. (2001) reported that manual external lubrication using a compression tester produced a fast-dissolving tablet. This method has advantages for a pressure-sensitive API with enzymatic activity. Takeuchi et al. (2005) reported that data for maximum and residual die wall forces showed that external lubrication inhibited capping tendencies more than internal lubrication, and that this effect was particularly useful when tableting plastically deformable powders. Recently, automated external lubrication systems have been developed for rotary tablet presses. The main mechanism is to spray on a powdered lubricant, which enables the amount of a lubricant to be reduced to the minimum necessary (Jahn and Steffens, 2005). With an up-to-date machine that applies an electric charge to the lubricant, the amount of lubricant in the tablet can be accurately controlled and can be increased to over 1.0%, the level usually required for internal lubrication, enabling comparison at the same concentration.

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In this study, tablet properties and the stability of an API that is incompatible with alkaline lubricant was evaluated to demonstrate the novel advantages of using an external lubrication system installed to a rotary tablet press. The model API used was eprazinone hydrochloride (EH), which is degraded by base-catalyzed hydrolysis, and the representative lubricant used was magnesium stearate, which is alkaline in nature.

Furthermore, in order to investigate the distribution of excess magnesium stearate on the surfaces of externally lubricated tablets, tablet samples prepared by focused ion beam (FIB) milling were observed by scanning electron microscopy (SEM). FIB milling uses a finely focused beam of metal ions (usually gallium) to sputter a small amount of material. The beam can be focused to a diameter of approximately 5 nm, and the signal from the sputtered ion or secondary electrons can be collected by SEM or scanning ion microscopy (SIM). FIB milling is capable of cross-sectioning samples at a specific position with high accuracy (100 nm or less). FIB has been used in the semiconductor industry for many years as a useful tool for failure analysis and device development (Melngailis, 1987). Recently, this technique has been applied to biological materials (Young et al., 1993) and to pharmaceutical sciences (Moghadam et al., 2006; Heng et al., 2007). We attempted to use this novel technology to observe an extremely thin layer of magnesium stearate on the tablet surfaces.

2. Materials and methods

2.1. Materials

Table 1 shows the formulation used in this study. All excipients conformed to the Japanese Pharmacopoeia 14th edition (JP14). Eprazinone hydrochloride (Kongo Chemical Co., Ltd., Japan) was used as a model API. It has been confirmed that EH (MW: 453.5) degrades into 1-(2-phenyl-2-ethoxyethyl)-piperazine (MW: 307.3) and α-methylacrylophenone (MW: 146.2) on hydrolysis catalyzed by alkaline lubricants. The excipients used were lactose monohydrate (Pharmatose® 200M, DMV Japan, Japan) as a filler, corn starch (Nihon Shokuhin Kako Co., Ltd., Japan) as a binder, microcrystalline cellulose (Ceolus® PH-101, Asahi Kasei Chemicals, Japan) as a disintegrant, and magnesium stearate (Nitto Kasei Kogyo, K.K., Japan) as a lubricant. A portion of the corn starch was gelatinized with water before use as a binder.

2.2. Equipping the tablet press

A 12-punch rotary tablet press (Aquarius 3, Kikusui Seisakusho, Ltd., Japan) was equipped with an external lubrication system (ELS-P2, Kikusui Seisakusho, Ltd., Japan). The structure of the ELS-P2 system is illustrated in Fig. 1. Powdered lubricant is conveyed to the supply part and filled into a narrow channel in the supply rotor. The lubricant is then aspirated from the rotor channel by a pressure differential and supplied via a branching line to two nozzles in the dust-chamber by air pressure, one for the upper punches and one for the lower punches. The lubricant spraying rate is controlled by the supply rotor speed and channel size. The nozzles are equipped with an electrode to electrically charge the lubricant particles. Since strongly charged lubricant powder adheres more strongly to the punches and die walls, a high load voltage was applied to the nozzle electrodes to enable a large amount of lubricant to be delivered to each tablet. Surplus lubricant is diffused in the dust-chamber and collected by a vacuum aspirator in the dust-collecting unit to avoid contamination of other tablets. In addition, the supply unit and the dust-collecting unit are placed on separate balances, and the weights are monitored as indicators of the amount of lubricant sprayed and the amount of surplus lubricant collected.

Table 1
Composition (%) of the master mixture.

Eprazinone hydrochloride (EH)	10
Lactose monohydrate	55
Corn starch	10
Corn starch (for gelatinized binder)	2
Microcrystalline cellulose	23
Purified water (for gelatinized binder)[a]	16
Total (master mixture)	100

[a] Essentially removed during processing.

2.3. Manufacturing the master mixture

A mixture of granules and microcrystalline cellulose was used as the master mixture. The granules were manufactured as follows, with a batch size of 100 kg. Eprazinone hydrochloride, lactose monohydrate, corn starch and gelatinized corn starch were granulated using a high-shear mixer (VG-400, Powrex Corp., Japan) and dried using a fluidized bed dryer (NFLO-120, Freund Corp., Japan). The dried granules were milled in a screening mill (U-20, Powrex Corp., Japan) with a pore size of 1.4 mm. The screened granules were mixed with microcrystalline cellulose for 10 min at 15 rpm in a 60-L V-shaped blender (V-60, Tokuju Corp., Japan).

2.4. Tableting on a rotary tablet press

To prepare externally lubricated tablets, the external lubrication system was used to supply magnesium stearate to the dies and punches during tableting to give five concentrations of lubricant in the tablets: 0.06, 0.08, 0.12, 0.25 and 1.27% (w/w). The spraying rate of magnesium stearate was varied from 6.1 to 104.0 g/h. The spraying air volume, the dust-collecting pressure and the electrode voltage was fixed at 12 L/min, 0.5 ± 0.1 kPa and 40 kV, respectively.

To prepare internally lubricated tablets, a 10-L V-shaped blender (V-10, Tokuju Corp., Japan) was used to blend magnesium stearate with the master mixture for 1 min before tableting at four concentrations: 0.12, 0.27, 0.55 and 1.06% (w/w).

The tableting conditions were a compression force of 10 kN/punch and a turntable rotation speed of 30 rpm. The punch set was round-faced with a 7.5-mm radius of curvature and a 9-mm diameter. The target tablet weight was 300 mg. The press was run in automatic mode for at least 30 min to allow time for problems to manifest, and the last 100 tablets were obtained as samples.

2.5. Evaluation of tablet sticking and tablet properties

After tableting, sticking problems were classified using three categories, based on damage to the last 100 tablets and adhesion of particles to the surface of all punches. Because the sticking problems in this study were readily detectable by visual inspection, we did not evaluate them by quantitative methods such as the measurement of ejection force (Jahn and Steffens, 2005) or scraper pressure (Danjo et al., 1993). The criteria for sticking problems were as follows. Only "No defect" was judged acceptable.

- *Severe sticking*: Tableting could not be continued because of severe sticking.
- *Sticking*: Sticking of tablet material to the punches was observed after tableting, and the adhered material could not be removed easily by swabbing with wipes.

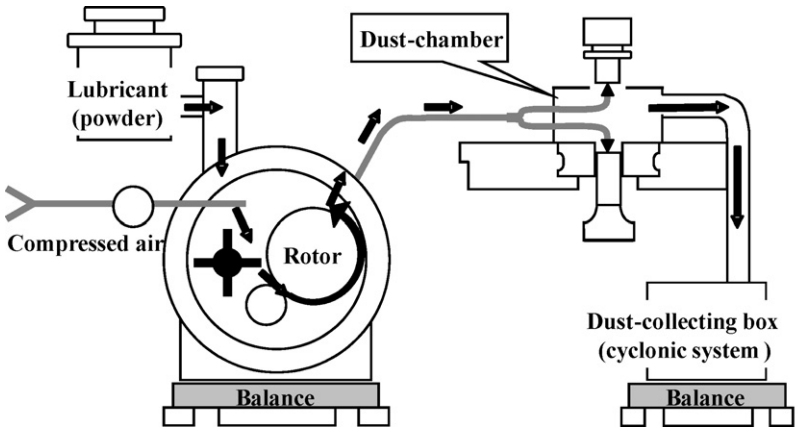

Fig. 1. Structure of external lubrication system (ELS).

- *No defect*: No defects were observed on the tablets or punches after tableting.

The weight and diametrical crushing strength of 20 tablets from each batch were measured using a fully automated tablet testing system (WHT-2, Pharma Test, Germany). Tablet disintegration time was evaluated according to the method of JP14.

2.6. Quantitative analysis of magnesium stearate

Based on previous reports (Dunn et al., 1995; Ikem et al., 2002), we developed an inductively coupled plasma atomic emission spectroscopy (ICP-AES) method for the accurate, precise measurement of an extremely small amount of magnesium stearate in a single tablet. The measurements were carried out using an ICP-AES (ICPS-8100, Shimadzu Corp., Japan). Each tablet was weighed and added to 7 mL of concentrated nitric acid (atomic absorption spectrochemical analysis grade, Wako Pure Chemical Industries, Ltd., Japan). The samples were digested using an Ethos Plus microwave lab-station with computer control (Milestone Inc., CT) (900 W, 220 °C for 22 min). After cooling, the solution was diluted to 30 mL with ultrapure deionized water. The concentration of magnesium atoms was determined from the absorbance at 280.270 nm using a calibration curve, and the magnesium stearate content was calculated. The calibration standard solutions were prepared daily by appropriate dilution of a standard solution (Mg-1000, Kanto Chemical Co., Inc., Japan), and a calibration curve was constructed daily. The quantification limit of this method was 4.69 ppb, which corresponds to 0.14 μg of magnesium stearate per tablet.

2.7. Accelerated stability test

To evaluate the effect of stress conditions on the chemical stability of EH, tablets were stored at 40 °C and 75% relative humidity (RH) and withdrawn after 5 days, 2 weeks and 4 weeks. The amount of EH in the tablets was determined by HPLC, and the ratio of EH in the tablets before and after storage was calculated as the residual ratio. Three independent measurements were conducted for each storage period. Under the assumption that the hydrolysis reaction of EH with magnesium stearate obeys first-order kinetics, first-order rate constants were calculated from the slopes of the logarithm of intact EH–time curve based on Eq. (1):

$$\ln[C] = \ln[C_0] - kt \quad (1)$$

where C_0 is the initial concentration of EH, C is the time-dependant concentration of EH, and the rate constant (k) was obtained by linear regression.

2.8. Scanning electron microscopy using focused ion beam milling

Lubricant distribution on the tablet surface was observed by scanning electron microscopy (S-4800, Hitachi, Japan) with an accelerating voltage of 800 V. Tablets were cleaved with a razor and then a precise cross-section was prepared by FIB milling (FB-2100, Hitachi, Japan) up to 100 μm down from the surface. To prevent charge-up of samples and to protect the cross-section after FIB milling, platinum coating and carbon vapor deposition were performed, respectively.

3. Results and discussion

3.1. Concentration of magnesium stearate in tablets

Results of quantitative analysis of the magnesium stearate concentrations in tablets manufactured with external and internal lubrication are shown in Table 2. With both types of lubrication, the standard deviation decreased as the amount of magnesium stearate decreased. With external lubrication, the relative standard deviations were relatively large at low concentrations of magnesium stearate.

3.2. Effect of external lubrication on sticking problems

Fig. 2 shows the effects of magnesium stearate concentration on the degree of sticking with external and internal lubrication. With both types of lubrication, the degree of sticking increased as the amount of magnesium stearate decreased. With internal lubrication, slight sticking was confirmed at 0.55% magnesium stearate, so the minimum concentration for proper internal lubrication was 1.06% magnesium stearate. On the other hand, with external lubrication, there was no indication of sticking down to 0.08%, and sticking was observed at 0.06% magnesium stearate,

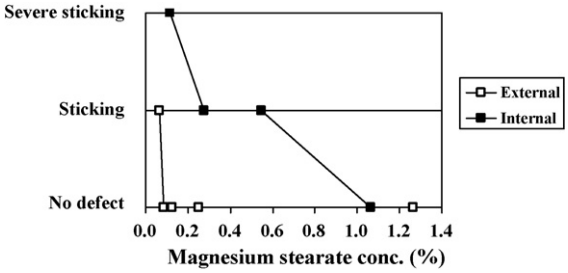

Fig. 2. Effect of magnesium stearate concentration on sticking during 30 min tableting process.

Table 2
Results of quantitative analysis of magnesium stearate concentration.

Lubrication type	Average (%)	Concentration of each sample (%)			S.D. (%)	R.S.D. (%)
		Tablet 1	Tablet 2	Tablet 3		
Internal	1.06	1.042	1.085	1.066	0.0219	2.06
	0.55	0.529	0.555	0.558	0.0164	3.00
	0.27	0.274	0.274	0.274	0.0002	0.06
	0.12[a]	0.118	0.119	0.116	0.0015	1.28
External	1.27	1.283	1.253	1.263	0.0149	1.18
	0.25	0.251	0.266	0.242	0.0121	4.78
	0.12	0.120	0.123	0.129	0.0044	3.53
	0.08	0.080	0.085	0.087	0.0032	3.82
	0.06	0.060	0.068	0.062	0.0041	6.75

R.S.D.: relative standard deviation.
[a] Samples at the beginning of a process were used because tableting could not be continued.

so the minimum concentration for proper external lubrication was 0.08% magnesium stearate. Although intermediate concentrations need to be tested to identify the minimum concentration for proper internal lubrication more accurately, these results show that proper external lubrication required only about 1/13th the amount of magnesium stearate required for proper internal lubrication. This information should be useful when developing new APIs with strong sticking tendencies because of a low melting point and/or fine particle size (Danjo et al., 1993).

3.3. Effects of external lubrication on tablet properties

Table 3 shows the effects of type of lubrication and lubricant concentration on tablet crushing strength and disintegration time. With external lubrication, crushing strength increased as the amount of lubricant decreased, and the highest value was 92.2 N (with 0.08% magnesium stearate). By contrast, with internal lubrication, the crushing strength was 66.0 N (with 1.06% magnesium stearate). So external lubrication gave 40% higher crushing strength than internal lubrication when 1/13th the amount of magnesium stearate was used. It is well known that the crushing strength of internally lubricated tablets often decreases as the scale increases because of lubricant over-mixing due to the increased mechanical stress caused by larger blenders (van der Watt and de Villiers, 1997). This decrease in strength on scale-up should not occur with external lubrication, because magnesium stearate is not blended with the other ingredients. As a result, the superiority in crushing strength with external lubrication relative to internal lubrication is expected to be even more marked at industrial scale.

With regard to disintegration time, despite the large increase in crushing strength when the minimum effective concentration of lubricant (0.08%) was applied externally, tablet disintegration was not delayed. On the other hand, with internal lubrication, tablet disintegration may be delayed when the process is scaled-up (Bolhuis et al., 1981). It is therefore expected that external lubrication will have the advantage of avoiding the prolongation of tablet disintegration time at industrial scale.

3.4. Effect of external lubrication on stability of EH in tablets

The relationship between the magnesium stearate concentration and the residual ratio of EH in tablets stored under stressed conditions for 4 weeks is shown in Fig. 3. With external lubrication, the highest residual ratio observed was 93.6% with 0.12% lubricant, and the residual ratio decreased as the concentration of lubricant increased. In contrast, with internal lubrication the residual ratio was 83.0% with 1.06% lubricant. These results clarified that external lubrication has the advantage of improving the stability of EH (which is hydrolyzed by magnesium stearate). It has been reported

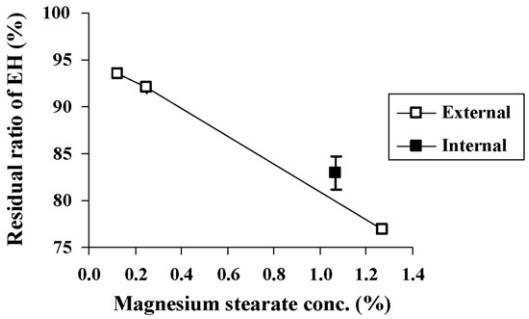

Fig. 3. Effect of magnesium stearate concentration on the residual ratio of EH in tablets stored at 40 °C and 75% RH for 4 weeks (n = 3 tablets).

that a large number of APIs are susceptible to pH-dependent hydrolysis; these include salicylic acid derivatives (Leeson and Mattocks, 1958; Hasegawa et al., 1975; Mroso et al., 1982; Du and Hoag, 2001), benzodiazepines (Mayer et al., 1972) and N-carboxyalkyl dipeptide analogs (Al-Omari et al., 2001). External lubrication should therefore be a useful technology for the development of new APIs that may have hydrolysable functional groups (Waterman et al., 2002) in their chemical structures.

For further comparison, we investigated the degradation kinetics of EH in externally and internally lubricated tablets, including internally lubricated tablets that showed sticking (0.27 and 0.55%). As shown in Fig. 4, an approximately linear relationship was observed between the natural logarithm of EH residual ratio and storage time. First-order rate constants were calculated by linear regression (Table 4). The effects of lubrication-type and magnesium stearate concentration on the first-order rate constant are shown in Fig. 5. We had expected that external lubrication would dramatically decrease the first-order rate constant because the lubricant

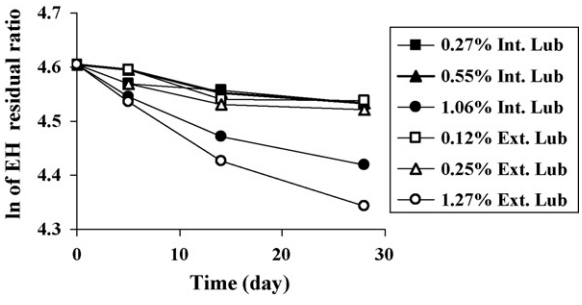

Fig. 4. First-order plots for the degradation of EH in tablets stored at 40 °C and 75% RH for 0 to 4 weeks (n = 3 tablets). The abbreviations, "% Int. Lub" and "% Ext. Lub", indicate the magnesium stearate concentration in internally and externally lubricated tablets, respectively.

Table 3
Effect of magnesium stearate concentration on the physical properties of tablets.

Lubrication type	Concentration of magnesium stearate (%)	Weight ($n = 20$)		Crushing strength ($n = 20$)		Disintegration time ($n = 6$) (s)
		mg	R.S.D. (%)	N	R.S.D. (%)	
Internal	1.06	303.0	0.3	66.0	4.1	26–34
	0.55	301.5	0.3	–[a]		–[a]
	0.27	300.3	0.4	–[a]		–[a]
	0.12	–[b]		–[b]		–[b]
External	1.27	301.2	0.6	66.9	5.1	24–40
	0.25	300.5	0.4	77.8	3.6	–
	0.12	299.7	0.4	78.4	4.5	20–42
	0.08	300.8	0.6	92.2	5.8	23–36
	0.06	299.2	0.6	–[a]		–[a]

R.S.D.: relative standard deviation.
[a] Not performed because of sticking.
[b] Not performed because tableting could not be continued.

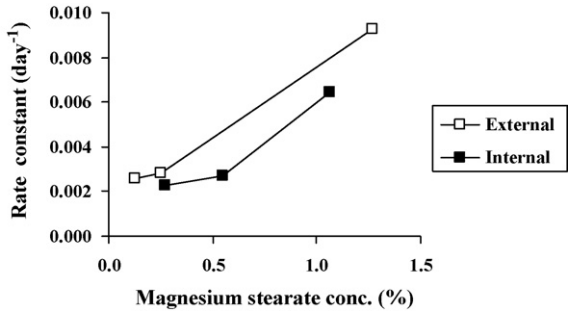

Fig. 5. Effect of magnesium stearate concentration on first-order rate constant for the degradation of EH in tablets stored at 40 °C and 75% RH.

is localized on the surface of the tablet, decreasing its contact with most of the EH in the tablet. However, the rate constants for externally lubricated tablets were actually slightly higher than those for internally lubricated tablets with similar concentrations of magnesium stearate.

As reasons for the slightly higher rate constants with external lubrication, we conjectured two hypotheses. First, EH may have been hydrolyzed mainly near the surface of the tablets because moisture was absorbed from the surface of tablets. This would make the hydrolysis reaction more responsive to lubricant concentration in externally lubricated tablets because the lubricant is localized on the surface of the tablet. Second, we hypothesized that more strongly alkaline microenvironments may have occurred and/or that moisture uptake by magnesium stearate may have been higher in the externally lubricated tablets. During external lubrication in this study, the lubricant was electrically charged, and spark discharges between lubricant and punches were observed. These spark discharges may have oxidized the magnesium stearate to generate alkaline impurities such as magnesium oxide (which already constitutes about 8% of commercially available magnesium stearate [Dansereau and Peck, 1987]), so the basicity of the magnesium stearate may have been increased by the external lubrication process. Alternatively, the spark discharges may have converted some of the crystalline magnesium stearate into amorphous magnesium stearate, so it is possible that the moisture uptake of the magnesium stearate was increased because, as has been reported (Swaminathan and Kildsig, 2001), at 25 °C and 70% RH, water is more readily absorbed by amorphous than by crystalline magnesium stearate. These hypotheses need further study.

3.5. Observation of the lubricant by scanning electron microscopy

One of the undesirable side effects of lubricant is the prolongation of disintegration time. The novel external lubrication system enabled the application of over 1.0% lubricant onto the surface of 300-mg tablets, but there was great concern about retarding disintegration time by coating tablets with excess lubricant. However, our results above show that tablets externally lubricated with 1.27% magnesium stearate had the same disintegration times as tablets externally lubricated with 0.12% magnesium stearate (Table 3). We therefore used SEM observation of tablet cross-sections to examine the distribution of the hydrophobic lubricant on the surface of tablets because this has implications for water penetration and disintegration as well as for the mechanism of the lubricant effect in external lubrication. Because of the friability of the tablets and the thinness of the magnesium stearate layer, it was impossible to prepare adequate cross-sections for SEM observation using an ultramicrotome. We were, however, able to prepare precise cross-sections by FIB milling.

Fig. 6 shows cross-sections of the surfaces of externally lubricated tablets with magnesium stearate contents of 1.27 and 0.12%. In each photograph, the whitish part under the even white surface layer (the platinum coating) is the magnesium stearate layer. The thickness of the magnesium stearate layer at the edges of the tablets was quite variable, reaching 4.5 μm (1.27%) and 7 μm (0.12%), at most. The thickness of the magnesium stearate layer on the central part of the tablets was relatively uniform and much

Table 4
Linear regression results of first-order rate constants for the degradation of EH in tablets stored at 40 °C and 75% RH for 0–4 weeks.

Lubrication type	Concentration of magnesium stearate (%)	First-order rate constant (day^{-1})	Log natural of EH residual ratio			r^2 value
			5 days ($n = 3$)	14 days ($n = 3$)	28 days ($n = 3$)	
Internal	1.06	0.00645	4.54	4.47	4.42	0.939
	0.55	0.00272	4.59	4.55	4.53	0.937
	0.27	0.00227	4.57	4.56	4.53	0.874
External	1.27	0.00926	4.54	4.43	4.34	0.962
	0.25	0.00282	4.57	4.53	4.52	0.816
	0.12	0.00258	4.60	4.54	4.54	0.787

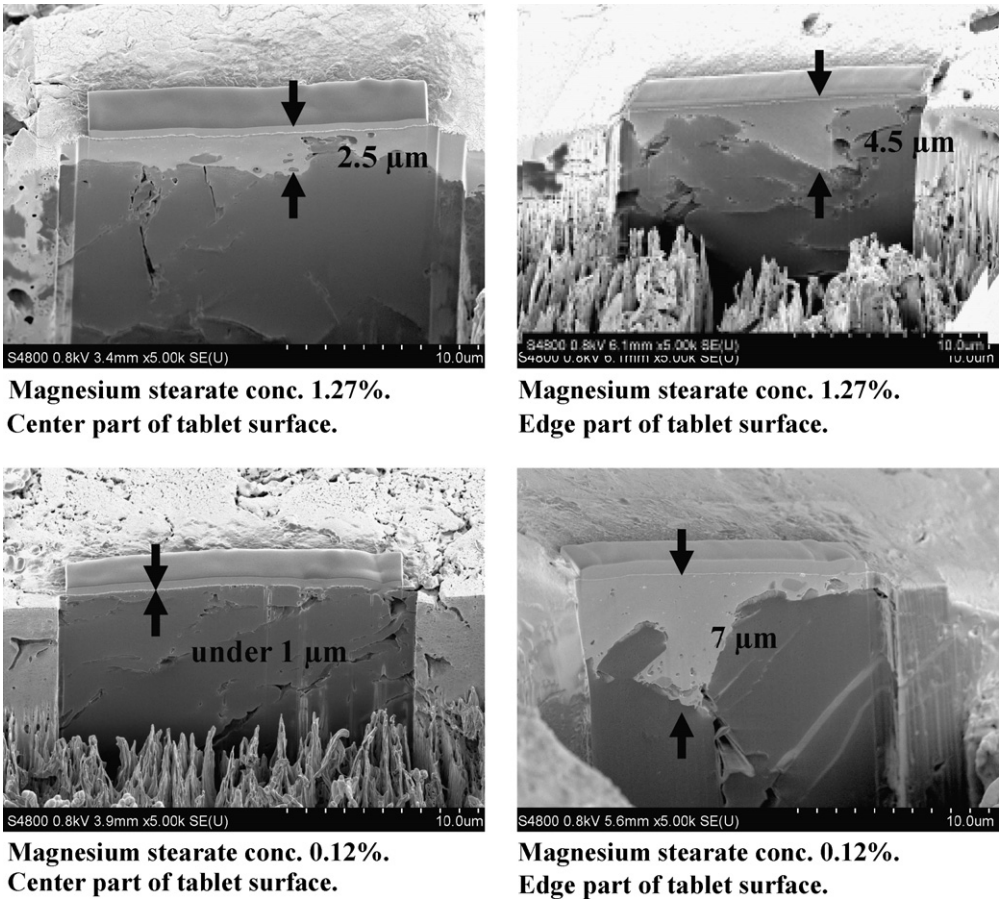

Fig. 6. Distribution of magnesium stearate on the surface of externally lubricated tablets. In each photograph, the magnesium stearate layer is the whitish part under the even white surface layer (the platinum coating).

thinner than at the edges: 2.5 μm (1.27%) and under 1 μm (0.12%). The magnesium stearate layer became thicker as the amount of lubricant increased, but the layer on the central part of the tablet remained extremely thin even when the magnesium stearate concentration was higher than necessary (1.27%). The formation of a magnesium stearate film on the surface of the tablets with external lubrication is a risk because the hydrophobic lubricant film could prevent the penetration of water into the tablet. Based on the SEM images, however, we concluded that water can penetrate into the tablet, at least at the central part of the tablet surface. The SEM images showing the distribution of lubricant on the surface of externally lubricated tablets provide information that is helpful for understanding the process of tableting with external lubrication and establish the usefulness of SEM with FIB milling for such investigations.

4. Conclusion

The advantages of the external lubrication technique were demonstrated by comparison with conventional internal lubrication. With external lubrication, only 1/13th the amount of lubricant was required to produce tablets without any indications of sticking problems. External lubrication increased tablet crushing strength by up to 40% without prolonging the disintegration time. Although the degradation rate constant observed for externally lubricated tablets was slightly higher than that observed for internally lubricated tablets at the same concentration of magnesium stearate, external lubrication was clearly shown to improve the stability of EH at the optimal lubricant concentration. These results therefore present one example where external lubrication showed advantages in relation to drug substance stability and crushing strength, as well as preventing sticking problems without prolonging disintegration time.

In order to investigate why even an excess concentration of externally applied lubricant had no impact on disintegration time, the distribution of lubricant on the tablet surface was observed by SEM of tablets prepared by FIB milling. Externally applied magnesium stearate had formed a layer on the outside of the tablets. The lubricant layer at the central part of the tablet surface was much thinner than at the edges, and was extremely thin even when there was excess magnesium stearate. This is the first report to describe the distribution of lubricant on the surface of externally lubricated tablets and the data obtained is helpful for understanding the process of tableting with external lubrication.

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