Comparative Evaluation of Tableting Compression Behaviors by Methods of Internal and External Lubricant Addition: Inhibition of Enzymatic Activity of Trypsin Preparation by Using External Lubricant Addition During the Tableting Compression Process

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ABSTRACT This study evaluated tableting compression by using internal and external lubricant addition. The effect of lubricant addition on the enzymatic activity of trypsin, which was used as a model drug during the tableting compression process, was also investigated. The powder mixture (2% crystalline trypsin, 58% crystalline lactose, and 40% microcrystalline cellulose) was kneaded with 5% hydroxypropyl cellulose aqueous solution and then granulated using an extruding granulator equipped with a 0.5-mm mesh screen at 20 rpm. After drying, the sample granules were passed through a 10-mesh screen (1680 μm). A 200-mg sample was compressed by using 8-mm punches and dies at 49, 98, 196, or 388 MPa (Mega Pascal) at a speed of 25 mm/min. The external lubricant compression was performed using granules without lubricant in the punches and dies. The granules were already dry coated by the lubricant. In contrast, the internal lubricant compression was performed using sample granules (without dry coating) containing 0.5% lubricant. At 98 MPa, for example, the compression level using the external lubricant addition method was about 13% higher than that for internal addition. The significantly higher compressing energy was also observed at other MPas. By comparison, the friction energy for the external addition method calculated based on upper and lower compression forces was only slightly larger. The hardness of tablets prepared using the internal addition method was 34% to 48% lower than that for the external addition

method. The total pore volume of the tablet prepared using the external addition method was significantly higher. The maximum ejection pressure using the no-addition method (ie, the tablet was prepared using neither dry-coated granules nor added lubricant) was significantly higher than that of other addition methods. The order was as follows: no addition, external addition, and then internal addition. The ejection energy (EE) for internal addition was the lowest; for no addition, EE was the highest. In the dissolution test, the tablets obtained using external addition immediately disintegrated and showed faster drug release than those prepared using internal addition. This result occurred because the water penetration rate of the tablet using the external addition was much higher. The trypsin activity in tablets prepared using the external addition method was significantly higher than that produced using the internal addition method at the same pressure. All these results suggest that the external addition method might produce a fast-dissolution tablet. Because the drug will be compressed using low pressure only, an unstable bulk drug may be tableted without losing potency.

Key Words: Tableting, Trypsin, Preparation, Compression, Dissolution.

INTRODUCTION

Nelson et al¹ and subsequent investigators²⁻⁵ have reported on the role of lubrication in the tableting process. Recent studies⁶⁻¹⁰ have indicated that bulk drug powders and magnesium stearate, a lubricant, interact with each other when thoroughly mixed before tablet compression. As a result, incomplete dissolution of tablets or decreased tablet hardness may occur⁶⁻¹⁰; the particles coated with magnesium stearate become

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smooth and less wettable. However, a lubricant is a necessary additive for tablet compression. Many formulation scientists, therefore, have studied lubricants and their addition in tableting. Many studies have been published on the work of compression in the dynamic compression behavior of homogeneous mixtures of bulk powders and lubricants⁶⁻¹⁰. However, the addition of a lubricant to bulk mixture powders has not been proven to be the best way for preparing high-quality pharmaceuticals. Several attempts^{11,12} to direct lubricants onto the punches and dies in industrial-scale tableting compression were performed. Gruber et al¹³ reported on the direct-lubrication effect on tablet characteristics. There were indications¹³ that direct lubrication produced tablets with good binding properties and improved disintegration time and dissolution. Nonetheless, manufacturing tablets using direct lubrication has been tried in the pharmaceutical industry, but not on products intended for the market.

Polypeptide and enzymatic drugs may be inactivated in their solid state by either heat or pressure¹⁴. It is necessary, therefore, to design a solid-dosage form of these drugs that is suitable for pharmaceutical applications¹⁵. The purpose of this study was to elucidate the effect of lubricant addition on the compression process and the effect on the enzymatic activity of trypsin, a model drug.

MATERIALS AND METHODS

Materials

Crystalline trypsin (lot number KCN4209; activity 5000 ± 500 USP U/mg) was obtained from Wako Chem Co Ltd, Tokyo, Japan. Microcrystalline cellulose (Avicel, PH102, lot number 2012) was supplied by Asahikasei Ind Co Ltd, Tokyo, Japan. Crystalline α -lactose monohydrate (Pharmatose 200M, lot number 24521) was provided by the DMV Co (Veghel, The Netherlands). Hydroxypropyl cellulose (HPC-L, lot number EB-0711) was obtained from Nihonsoda Co (Tokyo, Japan). Magnesium stearate (lot number 238) was purchased from Sakai Chem Co (Sakai, Japan). All other chemicals used were of analytical grade.

Density determination

True powder density was determined using an air comparison pycnometer (Beckman-Toshiba Ltd, Tokyo, Japan, model 930).

Granulation process

Twenty grams of crystalline trypsin, 580 g of crystalline lactose, and 400 g of microcrystalline cellulose were mixed in a twin-shell mixer (Model 5DMr, Sanei Ind Co, Osaka, Japan; capacity, 4.7 L; mixing speed, 24 rpm) for 10 minutes. After the addition of 200 mL/kg of 5% hydroxypropyl cellulose aqueous solution, the mixed powder was kneaded for 10 minutes in a multipurpose mixer (Sanei Ind Co; capacity, 2.0 L; mixing speed, 107 rpm) at 25 C and at 50% relative humidity. The wet mass was immediately transferred to an extruding granulator equipped with a 0.5-mm mesh screen (Dorm Gran, type DG-L1, Fuji Powdal Co, Osaka, Japan), through which the wet mass was extruded at 20 rpm. Processed granules were dried under vacuum for 24 hours at room temperature. Dried granules were then sieved through a 10-mesh screen (1680 μ m).

Tableting apparatus and procedure

A compression/tension tester (Autograph, model IS-5000, Shimadzu Co, Kyoto, Japan) with 2 load cells (upper and lower punches) and a displacement transducer were used to measure the upper and lower pressure and distance between the punches at 25 ± 1 C. An 8-mm punch and die with flat surfaces was used to compress 200 mg of a sample at 49, 98, 196, or 388 (maximum upper punch pressure) MPa at a speed of 25 mm/min. Sample tablets were ejected from the punch and die at 300 mm/min. The pressure and thickness data of tablets during compression were converted digitally and stored directly to a computer system by using the software "Super Scope" (Somerville Co, Boston, MA). A brief description of the external lubricant addition method is discussed below. After sealing the lower die cavity with a plastic film (parafilm), about 500 mg of magnesium stearate powder was filled into the die. The upper die cavity was then sealed and shaken 50 times by hand. The die was tapped on the steel block to remove an excess

amount of lubricant from the die surface. In addition, the punch was inserted into magnesium stearate powder. The excess amount of lubricant was removed from the punch by tapping it 20 times. The compression was performed using sample granules that had been coated by the lubricant powder.

In contrast, the sample granules for using the internal addition method were mixed with 0.5% of magnesium stearate in a twin-shell type mixer for 3 minutes. Tableting compression was performed using a punch and die without a lubricant coating. The punches and dies were washed with 3 mL of chloroform and wiped with wiping paper (s-200 Kimwipes, Kimberly-Clark Co, Tokyo, Japan); this process was repeated three times.

Determination of magnesium stearate

a) Measurement of the amount of magnesium stearate coated on the surface of the punches and dies was accomplished as follows. After performing the coating procedure on the punches and dies as described above, the punch and die were washed 3 times with 3 mL of chloroform solution; the washed solution was then collected. The amount of magnesium stearate in the sample solution was determined by using the titration method in Japanese Pharmacopoeia XIII Edition (JPXIII). After the sample solution was evaporated, it was transferred to a flask. A mixture of n-butanol and dehydrate ethanol (1:1), strong ammonia water and ammonium chloride buffer solution at pH 10, 0.1 mol/L disodium ethylenediaminetetraacetate versus, and 1 drop of eriochrome black T TS were mixed and added at 45 C. The resulting solution was clear. After cooling, the solution was titrated with the disodium ethylenediaminetetraacetate with 0.1 mol/L zinc sulfate. The sample solution was titrated photometrically at 650 nm using an autotitration instrument (Comtite-101, Hiramuma Sanjyou Co, Mito, Japan).

b) Measurement of the amount of magnesium stearate in the tablets was performed as follows. Five sample tablets were obtained by compressing them at 189 MPa. Each tablet was divided into an upper and lower part with a razor

and then triturated to make the sample powder. After heating at 500 C for 8 hours in a ceramic crucible containing the sample powder, the sample was transferred to a flask. The magnesium content was determined by the JPXIII method.

Dissolution tests

The drug dissolution tests for the tablets and granule powders were outlined in JPXIII, second fluid (phosphate buffer, pH 6.8). A sample tablet was introduced into 200 mL of dissolution medium at 37 ± 0.5 C. The test solution was stirred with a paddle (JPXIII) at 100 rpm. Aliquots (3 mL) of the solution were withdrawn through a 0.8- μ m membrane filter (cellulose nitrate, Advantec, Toyo Co, Ltd, Tokyo, Japan) at appropriate time intervals using a syringe and was suitably diluted with dissolution medium for measurement of trypsin concentration. The concentrations of trypsin were measured using the protein assay kit (BIO-RAD Co Ltd, Richmond, VA) by ultraviolet-visible spectrometer at 595 nm¹⁶. All values reported were reproducible and represented the average of 3 independent dissolution experiments.

Tablet disintegration test

The tablet disintegration test was performed using the disintegration tester (Toyama Inc, Osaka, Japan) as described in JPXIII using distilled water at 37 ± 2 C. The time required for tablet disintegration (DIT) was measured by observation. Each value reported is an average of 6 independent measurements.

Assay of enzymatic activity of trypsin

The compressed tablet was carefully ground with a mortar and pestle 50 times. The enzymatic reduction during tablet grinding was negligible. The enzymatic activity of trypsin was assayed according to the US Pharmacopoeia¹⁷. The sample solution involved in the dissolution of the ground tablet powder was weighed and then diluted in 10 mN hydrochloric acid. After removing 200 μ L of the sample solution via a pipette into a 1-cm quartz cell, 3 mL of substrate solution containing n-benzoyl-L-arginine ethyl ester hydrochloride was added. The absorbance at

252 nm was measured at 30-second intervals for 5 minutes. The trypsin unit concentration was calculated from the slope of the absorbance profiles using equation 1¹⁷. The residual activity of trypsin was calculated based on that of the intact granules as 100% activity.

$$= \left(\frac{1 - 2}{0.003} \right) \quad (1)$$

$$= \text{---} \times 100 \quad (2)$$

The term C_t is trypsin unit concentration. A_1 is the absorbance straight-line final reading. A_2 is the absorbance straight-line initial reading. t is the elapsed time. W_t is the weight of trypsin C_1 i (before the experiment). C_1 and C_2 are the trypsin unit concentrations before and after compression, respectively. $\%A$ is the percent activity of trypsin.

All values reported are reproducible and represent the average of 3 runs.

Statistical analysis

A Student t test was used for statistical determination, and a p value of .05 or .01 was considered significant.

Tablet hardness

The hardness of the tablets was measured 3 times using a hardness tester (Toyama Co).

Micropore distribution measurement

The micropore distribution of a tablet was measured by mercury porosimetry (type 2000, Carlo Erba Co Ltd, Strumentazione, Italy). The contact angle and surface tension of mercury were 141.3 degrees and 480 dyne/cm, respectively. The pore radius ranged from 6×10^{-3}

μm to $300 \mu\text{m}$. The mean micropore size was evaluated based on 50% volume on the plot for the cumulative volume against the pore radius.

Water penetration into tablet

The tablet's water absorption was measured using a modified glass pipette at 25 °C; this method was reported by Takayama et al¹⁸. The penetration solution was distilled water. The modified glass pipette had a glass filter that was filled with distilled water. After the tablet was placed on the glass filter, the amount of absorbed water was measured at suitable time intervals.

RESULTS

Effect of lubricant addition on the compression process of trypsin tablets

Table 1 shows the amount of magnesium stearate inside and outside a tablet. The tablet was prepared using the external addition method, in which the absolute amount of lubricant added was almost the same as that introduced using internal addition (0.5%). In the present study, the powder treatment was performed manually; therefore, the total amount was not controlled. However, it may be possible to reduce the amount by using a powder spray instrument^{11,12} in the future.

Figure 1 shows the compression process of trypsin granules at 196 MPa using different lubricant addition methods. The pressure-thickness curves of powder beds using various lubrication additions showed hysteresis. The profiles for the internal and external addition methods shifted slightly left when compared with that of the no-addition method. The order of the powder bed's thickness during dynamic

Table 1. Amount of Magnesium Stearate on Punches and Dies After Tableting Compression of Trypsin Tablets*

Amount of Magnesium Stearate on Tool Surface (mg/Compression)			
Upper Punch	Lower Punch	Die	Total
0.592 ± 0.78	0.430 ± 0.22	1.132 ± 0.288	2.154
Amount of Magnesium Stearate in Tablet (mg/Tablet)			
Upper Tablet Surface	Lower Tablet Surface	Around Tablet Surface	Total
0.172 ± 0.042	0.284 ± 0.026	0.664 ± 0.116	1.12
Transfer Percent of Magnesium Stearate from Tool Surface			
From Upper Punch	From Lower Punch	From Die	Total
29.2	66.1	58.6	44.1

* The amount of magnesium stearate of the tablet obtained by 0.5% internal lubricant is 1 mg/tablet.

compression was as follows: internal addition < external addition < no addition. This might be related to the hypothesis that powder flowability using the internal addition method during tablet compression was better than that for the external addition method.

To evaluate the work of compression for the tableting processes, we followed integration from zero to a maximum pressure, as shown in equation 3. The results are summarized in Figure 2.

$$W = \int_0^{P_{up}} P \, dL \quad (3)$$

In this equation, W is the work of compression per gram, P_{up} is the pressure by the upper punch, L_m is the powder bed thickness at maximum pressure, L_0 is the powder bed thickness at pressure zero, and L is the thickness of the powder bed.

The work of compression for the external addition and no-addition methods was significantly higher than that for the internal addition in all compression ranges. The differences in the work of compression using the external and internal addition methods increased with increasing pressure. However, the difference

Figure 1. Effect of lubricant addition methods on compression process of trypsin tablet. closed circle, no addition; open triangle, external addition; open circle, internal addition.

at 98 MPa, which is the practical pressure used in the pharmaceutical industry, was only 13%. The addition of a lubricant in a tablet formulation decreases friction between the surface of the punch or die and the powder during compression. The friction during tableting is an important factor when producing tablets on a commercial scale. The friction energy during tableting compression was evaluated by the Jenin equation (equation 4)¹⁹.

$$E_f = \frac{P_{up} - P_{lp}}{\log\left(\frac{L_m}{L_0}\right)} \quad (4)$$

E_f is the friction energy during compression, P_{up} is the pressure exerted by the upper punch, P_{lp} is the pressure exerted by the lower punch, L is the thickness of the powder bed, L_0 is the thickness of the initial powder bed, and L_m is the thickness of the final powder bed.

Figure 3 shows the effect of lubricant addition on the friction energy during tablet compression. The friction energy significantly increased with increasing pressure. The different addition methods significantly affected the friction energy. The friction energy values for the external addition method were much lower than those for the no-addition method, but were slightly higher than those for internal addition.

Figure 2. Effect of lubricant addition methods on work of compression of trypsin tablet

Figure 3. Effect of lubricant addition methods on friction energy of trypsin tablet.

Figure 4. Effect of lubricant addition methods on tablet hardness of trypsin tablet.

Figure 5. Effect of lubricant addition methods on availability of work of compression (CEA) of trypsin tablet.

Figure 4 shows the effect of lubricant addition on tablet hardness. The tablet hardness for the external addition and no-addition methods was significantly higher than that for the internal addition. The hardness values for the tablets obtained using the internal addition at 186 and 388 MPa were 34% and 48% lower than those obtained using the external addition method. These results suggested that mixing drug powder with magnesium stearate powder improved powder flowability and reduced die friction, thereby decreasing the work of compression. However, the mixture inhibited particle binding and the tablet mechanical strength decreased, as reported previously⁶⁻¹². Therefore, we used equation 5 to evaluate the work efficiency of tablet compression. Equation 5 determines the availability of work of compression (CEA).

$$= \frac{H}{W} \quad (5)$$

is the availability of work of compression, H is the hardness of a tablet 8 mm in diameter, and W is work of compression.

Figure 5 shows the effect of lubricant addition on the CEA during tablet compression. The CEA values for the internal addition at all compression pressures were significantly higher than those for the external addition. The results indicated that compression using the internal addition method required more work of compression to provide sufficient hardness than that using external method. Mixing magnesium stearate into the formulation inhibited the interparticle bond between lactose and microcrystalline cellulose particles-the main component-because magnesium stearate is hydrophobic. Lactose and microcrystalline cellulose particles, however, possess hydrophilic characteristics.

Figure 6 shows the pore distribution of tablets using various lubricant addition methods. The total pore volume of the tablet produced using internal addition was lower than when using other methods of addition. The order of total pore volume is no addition > external addition > internal addition. The results suggested that compression using internal addition had better powder flow during compression when compared

with the other methods. The powder flow during compression was improved by adding lubricant because lubricant particles decreased friction between lactose particles.

Effect of lubricant addition on the ejection process of trypsin tablets

Figure 7 shows the effect of lubricant addition on the tablet ejected from the die after compression at 196 MPa. The ejection force (F_e) was related to the surface friction coefficient between the tablet and die wall and the tablet residual stress. The maximum F_e using the no-addition method was significantly higher than when using other additions. The order was no addition > external addition > internal addition. The EE is calculated by integrating F_e and range of movement distance into tablet ejection.

$$= \mu \bullet \quad (6)$$

$$= \int_0^e \quad (7)$$

The term F_e in equations 5 and 6 is ejection force, μ is the friction coefficient between die wall and tablet, σ is residual stress in the tablet, E is the ejection energy, d is movement distance for tablet ejection, x_0 is initial displacement, and x_e is displacement at tablet ejection.

Figure 8 shows the effect of lubricant addition on the EE of trypsin tablets. The EE for internal addition was the lowest; that for no addition was the highest. Because the EE for the tablet was related to F_e during the tablet ejection, the order was the same as that for the F_e . The increasing F_e and EE for the external addition as compared with those for the internal addition are related to the increase of the residual tablet stress, σ , during the tablet ejection process, as shown in Equation 5. Tablet hardness might be linked to the residual tablet stress, σ . The hardness of the tablet prepared using the external addition method was 10% to 30% higher than that prepared using internal addition. However, the difference in EE between the external and internal additions might be related to the fact that the tablets were weaker because lubricant powder was added. The residual die wall pressure, P , was lowered and, therefore, the die wall friction would also be decreased.

Figure 6. Effect of lubricant addition methods on micropore distribution of trypsin tablet (closed circle no addition tablet; open triangle, external addition tablet; open circle, internal addition tablet; closed triangle, granules).

Figure 7. Effect of lubricant addition methods on ejection processes of trypsin tablet (closed circle no addition tablet; open triangle, external addition tablet; open circle, internal addition tablet; closed triangle, granules).

Figure 8. Effect of lubricant addition methods on ejection energy availability of trypsin tablet.

Dissolution Profiles

Figure 9. Effect of lubricant addition methods on dissolution of trypsin tablet (closed circle no addition tablet; open triangle, external addition tablet; open circle, internal addition tablet; closed triangle, granules).

Effect of lubricant addition on the dissolution behaviors of trypsin tablets

Figure 9 shows the dissolution behaviors of trypsin tablets that were compressed at 196 MPa. The tablets obtained by using the external addition method showed an immediate disintegration and rapid drug release, as observed with the granule powder. Almost 100% of drug was released from the tablets within 7 minutes. In contrast, the tablet prepared using the internal addition method did not disintegrate. Dissolution from the tablet surface was slow, and the amount of drug released was less than 20% after 20 minutes. The time required for tablet disintegration (DIT) was measured independently. DIT of the internal method was significantly larger than that of the external method, as shown in Table 2. This suggests that the disintegration time determines the tablet dissolution rate of the trypsin tablet.

Drug dissolution involves both the disintegration of the tablet and then dissolution of the drug particles. It was assumed that the tablet first disintegrated to produce the primary drug particles, which then dissolved. The drug release profiles for trypsin tablets, therefore, were analyzed based on the above dissolution model by using the moment analysis method²⁰ as shown in equations 8 and 9.

$$= \frac{(\infty)}{(\infty)} \quad (8)$$

$$= \quad + \quad (9)$$

and t_{gra} are the mean drug release time for tablet and granule powder, respectively. t_{tab} is the mean disintegration time for tablet, (∞) is the total drug content, and (∞) is the amount of drug released at time t . The granular powder was triturate in a mortar by a pestle.

t_{tab} and t_{gra} were estimated by using moment analysis²⁰; the results are summarized in Table 2. MDIT of the internal addition method was more than 100 times longer than for the external addition method. However, MDIT of the granular powder was almost the same as for tablets containing lubricant. This suggested that the presence of lubricant did not affect the powder dissolution; however, it did affect tablet disintegration. The disintegration time of the tablet governed the dissolution rate of the tablet.

Because the disintegration time of a tablet is related to the water penetration rate of a tablet, the water penetration in the tablets was measured and is shown in Figure 10. The water absorption rate in the micropore followed Washburn's equation²¹ (equations 10-13).

$$(\quad)^2 = \frac{\gamma \cos(\theta)}{2\eta} \quad (10)$$

$$(\quad) = \left(\frac{\gamma \cos(\theta)}{2\eta} \right)^{1/2} \quad (11)$$

$$(\quad) = \quad^{1/2} \quad (12)$$

Both η and γ are constants, r is the penetration length through the micropore, R is the radius of the capillary tube, γ is the surface tension of liquid, θ is the contact angle, k is the water absorption rate constant, and η is the viscosity of liquid.

$$\cos(\theta) = \frac{2}{\quad} \approx \frac{2}{\quad} \quad (13)$$

Table 2. Effect of Lubricant Additions on the Dissolution Behaviors of Trypsin Tablets

Samples	MDT (min)	MDIT (min)	DIT $\pm$ SD (min)
Tablet of internal addition	214.2	213.7	35 $\pm$ 6
Tablet of external addition	2.1	1.8	0.9 $\pm$ 0.8
Granule powder with 0.5% lubricant	0.5	-	-
Granule powder lubricant	0.3	-	-

DIT indicates disintegration time for tablet; MDIT, mean disintegration time for tablet; MDT, mean drug release time; SD, standard deviation.

Table 3. Effect of Lubricant Additions on the Water Penetration Behaviors of Trypsin Tablets

Samples	r (μm)	K ($\text{cm}^3/\text{min}^{1/2}$)	k ² /r (cm^5/min)
Tablet of internal addition	0.150	6.1 $\times 10^{-3}$	2.5
Tablet of external addition	0.280	22.3 $\times 10^{-3}$	17.8
Tablet of no addition	0.299	27.2 $\times 10^{-3}$	24.7

r indicates the radius of the micropore evaluated on the basis of data in ; k, water-penetration rate constant estimated on the basis of the data in the initial stage in by the least squares method.

Figure 10 shows the relationship between the water absorption of the tablet and the root square of the amount of time necessary for dissolution. The water absorption profiles for all tablets were linear at the initial absorption stage on the plot. However, the absorption rates were reduced after 1 minute because of the change in the geometrical structure of the micropores and because of the viscosity of the solution. The water penetration rate was evaluated on the basis of the initial water absorption (0-1 minute) by the least squares method and is summarized in Table 3. The water penetration rates, k , for the no-addition and external addition methods were much higher than those for the internal addition method. The order is no additive > external > internal. The k^2/r is evaluated as a wettability parameter and is summarized in Table 3. The k^2/r for no addition exhibited the best score. The external addition and no-addition k^2/r scores were much higher than that for the internal addition. This suggested that the tablet's micropore of the internal addition had poor wetting characteristics as compared with the others. As expected, the added magnesium stearate was hydrophobic. This indicated that the external addition method had an advantage on tablet disintegration process as explained by the total porosity and the wettability of the micropore.

Figure 10. Effect of lubricant addition methods on water absorption of trypsin tablet (closed circle, no addition tablet; open triangle, external addition tablet; open circle, internal addition).

DISCUSSION

Effect of lubricant addition on the enzymatic activity of trypsin tablets

The drug activities for polypeptides could be reduced during the tablet compression process by mechanical stress. Morii et al¹⁴ reported the relationship between the pressure and reduction of alkaline protease activity. The study concluded that the enzymatic activity reduction depended on the maximum pressure but not on the

compression time. Figure 11 shows the effect of tablet work of compression on the trypsin activity. The reduction of enzymatic activity for all tablet formulations was related to the increase in the pressure and energy. However, the activity of trypsin in tablets prepared using the external and no-addition methods at the same pressure were significantly higher than those prepared using the internal addition. Because enzymatic activity of the internal addition sample was only about 3% reduced after 7 days of storage at 50% relative humidity and 25 C, the interaction between trypsin and magnesium stearate was not significant. This might be related to the total porosity and micropore distribution of the tablets; the tablet prepared using internal addition contained 30% less space than that of the external addition, as shown in the previous section. Horikoshi et al¹⁵ reported that the geometrical structure of a convex tablet affected the enzymatic activity because the stress distribution of the tablet depended on the geometrical structure. In the present study, the high pressure experienced for trypsin particles was more heterogeneous in external addition than in internal addition. In other words, it seemed that the external lubricant addition induced heterogeneous stress distribution in the tablet. Consequently, inactivation by high pressure during tableting was reduced.

Figure 12 shows the effect of tablet hardness and trypsin activity. The enzymatic activity of all tablet formulations was reduced with increasing tablet hardness. However, the trypsin activity in tablets prepared using the external addition method was the highest; the ranking was external addition > no addition > internal addition. In practical terms, the tablet hardness is required to be around 50 to 80 N to prevent tablet breakage during transportation. With a tablet hardness of approximately 70 N produced by using the external addition method, the enzymatic activity of the tablet was 15% more than for internal addition because the tablets prepared using this external addition method had sufficient mechanical strength. This novel lubricant addition method has the advantage of being able to make a tablet from an unstable drug because it is exposed to lower pressure.

Figure 11. Effect of availability of work of compression (CEA) on enzymatic activity of trypsin tablet (closed circle, no addition tablet; open triangle, external addition tablet; open circle, internal addition).

Figure 12. Relationship between tablet hardness and enzymatic activity of trypsin tablet (closed circle, no addition tablet; open triangle, external addition tablet; open circle, internal addition).

CONCLUSION

The compression parameters, which were compression pressure and friction and ejection energies, indicated that tablet compression after using the external addition method was slightly higher than after using internal addition. However, the differences were not significant. The tablets obtained by using external addition were significantly different from those made using internal addition with regard to geometrical

and interfacial characteristics. In another words, the tablet obtained by external addition might have been more porous and wettable. The pharmaceutical characteristics of the tablet reflect the dissolution behavior through shortening of the tablet disintegration time. The fast-dissolving tablet could therefore be obtained by using this external addition method without any special additives and instruments. The lower compression pressure associated with the external lubricant addition method enabled tablets made of labile drugs to be manufactured without a loss in activity.

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