In-Die Evaluation of Capping Tendency of Pharmaceutical Tablets Using Force-Displacement Curve and Stress Relaxation Parameter

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A novel in-die evaluation method of tablet capping tendency was proposed based on a force-displacement curve and stress relaxation parameter in a tableting process. In our previous study (*Chem. Pharm. Bull.*, 59, 2011, Nakamura *et al.*), the phase diagram consisting of elastic recovery energy (E_c) and plastic deformation energy (E_p) of compressed powder, named as the E_c – E_p diagram, was proposed. However, it was found that capping tendency of tablets prepared by double-compression with multi-component powder formulations cannot be discriminated using the E_c – E_p diagram. To improve the capping discrimination ability, we here proposed a novel corrected phase diagram consisting of the E_c and an interparticle bonding parameter $E_b(t)$, named as the E_c – $E_b(t)$ diagram. The $E_b(t)$ was proposed as a new parameter expressing strength of the interparticle bonding formed by the stress relaxation inside compressed powder. The $E_b(t)$ was defined as a product of the E_p and the stress relaxation parameter $Y(t)$, estimated from the force-displacement curve and the stress relaxation test. The capping discrimination ability of the diagrams was evaluated using a hierarchical-clustering analysis. The results exhibited that the capping tendency could be clearly discriminated using the proposed E_c – $E_b(t)$ diagram at the double-compression and the multi-component powder formulations, as compared to the E_c – E_p diagram. This proposed diagram can be used for screening of the powder formulations to avoid the capping.

Key words tableting; capping; stress relaxation; force-displacement curve; hierarchical-clustering analysis

When pharmaceutical powders are compressed into tablets, cracking or lamination sometimes occurs inside the tablets. This phenomenon is well known as capping. The capping is one of the most common tableting troubles. Although many efforts have been made to overcome the trouble, the capping has still been an unsolved issue. Thus, a methodology to evaluate and avoid the capping has been a strong interest in pharmaceutical industries.

Generally, capping tendency can be evaluated by out-of-die or in-die evaluation methods. In the out-of-die evaluation methods the capping tendency is evaluated after ejection of the tablet from a die, whereas in the in-die evaluation methods the capping tendency is evaluated during preparation of the tablet.

As an out-of-die evaluation method of the capping tendency, visual inspection after a friability test¹⁾ is widely accepted. An indentation fracture test²⁾ has been proposed as an out-of-die evaluation method, in which the capping tendency was evaluated by making a small indentation fracture on the tablet. An X-ray microtomography,^{3,4)} by which cracks inside a tablet can be directly visualized noninvasively, has also been employed as an out-of-die evaluation method. However, the out-of-die evaluation methods are cumbersome, because they need to handle tablets after their preparation.

By contrast, in-die evaluation methods can evaluate the capping tendency using data monitored during preparation of the tablet without any need to handle the tablet after its preparation. Sugimori *et al.*^{5–7)} proposed an in-die evaluation method of the capping by monitoring of residual die wall pressure at decompression stage in the tableting process. They proposed the capping index, which is a ratio of residual die wall pressure to axial crushing strength of the tablet, as a quantitative indicator of the capping tendency. However, as

pointed out by Takeuchi *et al.*,⁸⁾ their work was conducted under quasi-static compression/decompression conditions, and an in-die evaluation method of the capping under dynamic compression/decompression conditions has not been proposed yet.

In our previous study,⁹⁾ a novel single punch tablet machine for a tiny amount of powder sample was developed, and a novel in-die evaluation method of the capping tendency under the dynamic tableting conditions was proposed. Basically, occurrence of the capping can be determined by the balance between the interparticle bonding and the elastic recovery of compressed powder.^{10,11)} Based on this mechanism, we proposed a new phase diagram consisting of elastic recovery energy (E_c) and plastic deformation energy (E_p) of the compressed powder, named as the E_c – E_p diagram. The E_p was used as a factor of the interparticle bonding with an assumption that the E_p can be well correlated with the energy of interparticle bonding formed by compressing the powder. The E_c and E_p were calculated from a force-displacement curve during compression/decompression of the powder. Because the E_c – E_p diagram expresses the balance between the elastic recovery and the interparticle bonding of compressed powder, the capping tendency could be evaluated using the E_c – E_p diagram.⁹⁾

However, applicability of the E_c – E_p diagram was confirmed in the tablets prepared solely by the single-compression, in which the powder is compressed once. In manufacturing processes, most of the pharmaceutical tablets are produced by the double-compression, in which the powder is compressed twice.¹²⁾ Many previous works^{12–14)} reported that mechanism of the double-compression is significantly different from that of the single-compression due to relaxation of the stress accumulated inside the compressed powder. Therefore, applicability of the E_c – E_p diagram to evaluate the tablets prepared by the double-compression needs to be studied.

Moreover, the tablets prepared with single component

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powders were solely evaluated in our previous study.⁹⁾ Most of the pharmaceutical tablets are prepared with granules or physical mixtures of multi-component powders. Thus, applicability of the E_c-E_p diagram to evaluate the tablets prepared with the multi-component powder mixtures should also be investigated.

In this paper, capping tendency of the tablets prepared by the double-compression with various powders including multi-component powder formulations was evaluated using the E_c-E_p diagram. The capping discrimination ability of the diagram was evaluated using a hierarchical-clustering analysis.¹⁵⁾ We then corrected the E_c-E_p diagram by taking into account the stress relaxation effect, and discussed applicability of the corrected diagram to evaluate the capping tendency.

Experimental

Equipment Tablets were prepared using a developed single punch tablet machine reported in our previous study.⁹⁾ This machine enables us to prepare tablets with a tiny amount of powder sample under any operating conditions. The upper and lower punches are independently driven by electric servo motors, allowing us to set motions of both upper and lower punches arbitrarily. Thus, tablets can be prepared by the double-compression under various compression loads and compression/decompression velocities. Loads and displacements of the upper and lower punches during the tableting can be monitored in real-time.

Powder Samples Table 1 lists formulation of model

powders used in this study. Nine kinds of powder formulations including single component powders ((A) to (E)), granules ((F), (G), and (H)) prepared by a fluidized bed granulation, and a physical mixture (I) were used. The granules (F) and (G) were prepared in our laboratory using a fluidized bed granulator (NQ-125, Fuji Paudal, Co., Ltd.). Table 2 shows operating parameters of the fluidized bed granulator. Figure 1 indicates SEM images of the model powders of (A) to (H). Mean particle diameter (D_{50}) and geometric standard deviation (σ_g) of the model powders were measured using a laser diffraction particle size analyzer (SALD-2100, Shimadzu Co., Ltd.). Magnesium stearate (Kishida Chemical Co., Ltd.) was used as a lubricant which was added by an external lubrication method in all of the experiments. Amount of the lubricant was approximately 2mg. Sticking of the powders to the punches and the die was not observed.

Tableting Table 3 summarizes operating parameters in the tableting. A convex-shaped tablet with a diameter of 8 mm (6.5 mm radius of curvature) was prepared under various compression loads and compression/decompression velocities. Compaction of the powders was conducted by the double compression, which is the same compression method as the conventional rotary tablet machines. Mass of the tablets was set at 195 mg. Crushing strength of the tablet was measured using a tablet hardness tester (TH203-RP, Toyama Sangyo Co., Ltd.) with loading rate of 15 N/s.

Analysis of Force-Displacement Curve A force-dis-

Table 1. Formulation of Model Powders (wt%)

	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)
Corn starch ^{a)}	100	0	0	0	0	14	14	0	14
Hydroxypropyl cellulose (L-HPC) ^{b)}	0	100	0	0	0	3	3	0	3
Lactose ^{c)}	0	0	100	0	0	34	34	100	34
Micro crystalline cellulose (MCC) ^{d)}	0	0	0	100	0	0	0	0	0
Acetaminophen ^{e)}	0	0	0	0	100	49	0	0	49
Ethenzamide ^{f)}	0	0	0	0	0	0	49	0	0

(A), (B), (C), (D), and (E): Single component. (F), (G), and (H): Granules prepared by fluidized bed. (I): Physical mixture. ^{a)} Corn starch W, Nihon Shokuhin Kako Co., Ltd. ^{b)} LH22, Shin-Etsu Chemical Co., Ltd. ^{c)} 200M, DMV Pharmatose, in formulations of (C), (F), (G); Dilactose S, FREUND, in formulation of (H). ^{d)} Ceolus PH101, Asahika-sei Chem. Ind. Co., Ltd. ^{e)} Iwaki Seiyaku Co., Ltd. ^{f)} API Co., Ltd.

Fig. 1. SEM Images of Model Powders of (A) to (H). D_{50} and σ_g Indicate the Mean Particle Diameter and the Geometric Standard Deviation, Respectively

placement curve during the tableting was used to calculate the elastic recovery energy E_e and the plastic deformation energy E_p as previously reported.⁹⁾ Figure 2 shows a typical force-displacement curve in the compression and decompression stages during tableting. The area under the decompression curve (ADCA) is equivalent to the E_e .¹⁶⁾ The area of OBDO, enclosed by the compression curve of the upper punch and the decompression curve of the lower punch, is equivalent to the E_p .¹⁶⁾ In the double-compression, the E_e and E_p were defined as a summation of the energies in the pre-compression stage (1st compression) and the main-compression stage (2nd compression).

Evaluation of Capping Discrimination Ability Figure 3 shows evaluation procedure of the proposed in-die evaluation method. The capping discrimination ability of the proposed method was evaluated by comparing with the results obtained by an out-of-die evaluation. The procedure was as follows. First of all, tablets were prepared while monitoring the force-displacement curves. Each tablet was prepared at different conditions. Capping tendency of each tablet was then evaluated by the out-of-die evaluation, in which thirty-two tablets were tumbled in a friabilator¹⁾ at 25 rpm for 4 min. After the tumbling, each tablet was visually inspected one by one, and the tablet exhibiting significant cracks was identified as having capping. The proposed in-die evaluation was then conducted as follows. From the force-displacement curves monitored during tableting, the E_e and E_p of each tablet were calculated. The individual tablets were then classified into two groups based on the E_e and E_p using a hierarchical clustering analysis (HCA),¹⁵⁾ which is a multivariate analysis technique to classify data sets into groups according to an unsupervised classification procedure. The classified two groups mean that the tablets can be discriminated into two categories (with and without capping) based on the E_e and E_p . Finally, the classified two groups were compared with the capping tendency obtained by the out-of-die evaluation, and the capping discrimination ability of the proposed in-die evaluation method was evaluated.

Hierarchical Clustering Analysis In order to classify the tablets based on the E_e and E_p , a hierarchical clustering analysis (HCA)¹⁵⁾ was used. The HCA is a multivariate analysis technique that is used to classify data sets into groups. This technique is based on an unsupervised classification procedure. Thus, there is no artifact when data sets are classified. The classification was conducted as follows: (1) the dissimilarity between each tablet was quantified based on the values of E_e and E_p , (2) the pair of tablets having the minimum

dissimilarity was merged into the same group, and (3) these two steps were repeated until all tablets were classified into two groups. The dissimilarity between two groups was quantified using a Ward's method,¹⁷⁾ where the dissimilarity between group A and B (d_{AB}) was defined as follows:

$$d_{AB} = \frac{n_A n_B}{n_A + n_B} \left\{ \left(\frac{\overline{E_{e,A}} - \overline{E_{e,B}}}{\sigma_{E_e}} \right)^2 + \left(\frac{\overline{E_{p,A}} - \overline{E_{p,B}}}{\sigma_{E_p}} \right)^2 \right\} \quad (1)$$

where the subscripts A and B indicate the group A and B, respectively. n is the number of tablets within the group. $\overline{E_e}$ and $\overline{E_p}$ are the averaged E_e and E_p within the group, respectively. σ_{E_e} and σ_{E_p} are the standard deviation of all the data of E_e and E_p , respectively.

Results and Discussion

Applicability of the E_e - E_p Diagram to the Double-Compression and Multi-Component Powder Formulations

Figure 4 shows the E_e - E_p diagram obtained in this study. Each plot expresses the E_e and E_p of each tablet prepared under different tableting conditions. The closed plots indicate the tablets judged as having capping by the out-of-die evaluation, while the open plots indicate the tablets without capping. The two frames in Fig. 4 show the two groups determined by the HCA. The tablets within the same frame can be regarded as

Fig. 2. Force-Displacement Curve during Tableting

Fig. 3. Evaluation Procedure of Proposed In-Die Evaluation Method

Table 2. Operating Parameters of Fluidized Bed Granulator

Total amount of powder	600 g
Air flow velocity	0.8–1.0 m/s
Air temperature	333 K
Feed rate of binder (water)	10 g/min
Total amount of binder (water)	360 g
Spray air pressure	1.6 kg/cm ²

Table 3. Operating Parameters in Tableting

Pre-compression load	1.0–9.0 kN
Main-compression load	5.0, 10.0 kN
Compression velocity	1.0–10.0 mm/s

the similar tablets in terms of the E_c and E_p . Thus, the two groups mean that the tablets can be classified into two groups (with and without capping) by the E_c - E_p diagram.

Tablets with capping were mainly plotted in the upper-left region (lower E_p and higher E_c region), while tablets without capping were in the lower-right region (higher E_p and lower E_c region). This implies that the capping tendency was roughly discriminated using the E_c - E_p diagram. However, plots of tablets without capping prepared with granules (F) and (G) showed overlapping with plots of the tablets with capping. The HCA result also showed that the tablets without capping prepared with granules (F) and (G) were classified into the same group as the tablets with capping. This means that the tablets without capping were deemed similar to the tablets with capping by the E_c - E_p diagram.

Accordingly, it was found that the capping discrimination ability of the E_c - E_p diagram is insufficient in case of the double-compression and the multi-component powder formulations. Thus, a few corrections of the E_c - E_p diagram are required to improve its capping discrimination ability.

Correction of the E_c - E_p Diagram by the Stress Relaxation Parameter A major difference between the single-compression and the double-compression is the total compression/decompression time. By using the double-compression, the total compression/decompression time can be prolonged longer than the single-compression. This longer compression/decompression time leads to decrease in the stress accumulated inside the compressed powder, *i.e.*, the stress relaxation. The stress relaxation increases the interparticle bonding strength, resulting in prevention of the capping.¹²⁻¹⁴⁾

Figure 5 shows effect of the decompression time on crushing strength of tablets prepared with corn starch and lactose powders. The tablets were prepared by the single compression under different decompression velocities, while the compression velocity was kept constant at 3.0 mm/s. The compression load was set at 10 kN. In both powder samples, crushing strength of the tablets increased with an increase in the decompression time, because longer decompression time leads to the stress relaxation, resulting in an increase in the interparticle bonding strength. However, as shown in Fig. 6, the E_p and E_c were almost unchanged with the decompression time. This means that the E_p and E_c are less sensitive to the stress relaxation. In our previous study,⁹⁾ the E_p was used as a factor of the interparticle bonding of compressed powder, because the E_p could be well correlated with energy of the interparticle bonding formed by compressing the powder. However, the results in Figs. 5 and 6 suggest that strength of the interparticle bonding cannot be correlated solely by the E_p under different stress relaxation conditions. Therefore, a new parameter which takes into account the stress relaxation effect needs to be proposed.

The stress relaxation can be expressed by the stress relaxation parameter $Y(t)$ defined as follows¹⁸⁾:

$$Y(t) = (F_0 - F(t)) / F_0 \quad (2)$$

where F_0 and $F(t)$ are the initial compression load and the compression load after time t during the stress relaxation, respectively. Here, $Y(t)=0$ means that the stress accumulated inside the compressed powder does not relax at all, while $Y(t)=1$ means that the stress is fully relaxed and dissipated. The $Y(t)$ can be measured by a stress relaxation test.¹⁸⁾ In this study,

Fig. 4. Evaluation of Capping Tendency Using E_c - E_p Diagram

Fig. 5. Effect of Decompression Time on Crushing Strength of Tablet

the stress relaxation test was conducted as follows: (1) powder was compressed by the tablet machine, (2) when the compression force reached the set-value, motion of the compression punch was stopped, and (3) temporal change in the load acting on the compression punch was monitored while the motion of the compression punch was stopped. F_0 and $F(t)$ in Eq. (2) were equivalent to the set-value of the compression force and the temporal change in the load acting on the lower punch, respectively. Finally, the stress relaxation parameter $Y(t)$ was calculated from the F_0 and $F(t)$.

Generally, with the progress of stress relaxation (*i.e.* with an increase in the stress relaxation parameter), strength of the interparticle bonding inside the compressed powder increased and the prepared tablet becomes more rigid.¹²⁾ Thus, a new interparticle bonding parameter $E_b(t)$ was proposed by taking into account the stress relaxation parameter. The $E_b(t)$ is

Fig. 6. Effects of Decompression Time on Plastic Deformation Energy (E_p) and Elastic Recovery Energy (E_e)

Fig. 7. Estimation Procedure of Interparticle Bonding Parameter $E_b(t)$

defined as a product of the E_p and $Y(t)$ as follows:

$$E_b(t) = E_p \cdot Y(t) \quad (3)$$

This equation means that the strength of the interparticle bonding (*i.e.*, $E_b(t)$) can be defined not only by how much the powder was compressed (*i.e.*, E_p) but also by how much the stress accumulated inside the powder was relaxed (*i.e.*, $Y(t)$). Figure 7 shows the estimation procedure of the $E_b(t)$. The procedure was as follows: (1) the stress relaxation test was preliminarily conducted before tableting under the same compression conditions used in the tableting, (2) a tablet was then prepared while monitoring the force-displacement curve and the decompression time, (3) the E_p were calculated from the force-displacement curve, (4) the decompression time in the tableting was considered as the relaxation time t in Eq. (2), and the $Y(t)$ was estimated from the result of the stress relaxation test, and (5) the $E_b(t)$ were estimated by Eq. (3). Although the $Y(t)$ strongly depends on the powder properties and the tableting conditions, the $Y(t)$ can be estimated at any powder samples and tableting conditions according to the above-mentioned procedure.

Figure 8 shows crushing strength of the tablets prepared under different stress relaxation conditions as a function of the interparticle bonding parameter. The tablets were prepared at the same conditions in Fig. 5. As can be seen in the result, crushing strengths of the tablets prepared under different stress relaxation conditions were well correlated by the proposed interparticle bonding parameter $E_b(t)$. This indicates that the proposed $E_b(t)$ can be used as an indicator of the

Fig. 8. Crushing Strength of Tablet as Function of Inter Particle Bonding Parameter $E_b(t)$

Fig. 9. Evaluation of Capping Tendency using E_e - $E_b(t)$ Diagram

interparticle bonding under various stress relaxation conditions.

To improve the capping discrimination ability, a corrected phase diagram consisting of the elastic recovery energy E_e and the interparticle bonding parameter $E_b(t)$ was proposed. Figure 9 shows the E_e - $E_b(t)$ diagram. It was found that the capping tendency was clearly discriminated by the E_e - $E_b(t)$ diagram. Overlapping of plots with and without capping was no longer observed. The result of HCA confirmed that the capping tendency was significantly discriminated between the two groups determined from the E_e and $E_b(t)$.

The powder samples (F) and (H) were the granules prepared with the powder samples (I) and (C), respectively. As can be seen in Fig. 9, the tablets of (F) and (H) were plotted in the higher $E_b(t)$ region than those of (I) and (C). This result well reflects improvement of compactibility of powders by the

fluidized bed granulation.

Conclusions

In this study, a novel in-die evaluation method of tablet capping tendency was proposed. The capping tendency of the tablets prepared by the double-compression with multi-component powder formulations were evaluated using the E_c-E_p diagram proposed in our previous study.⁹ It was found that the capping tendency could not be discriminated well using the E_c-E_p diagram in case of the double-compression and multi-component powder formulations, because the E_p was less sensitive to the stress relaxation. Therefore, a new phase diagram consisting of the E_c and the interparticle bonding parameter $E_b(t)$, named as the $E_c-E_b(t)$ diagram, was proposed. The $E_b(t)$ was proposed as a new parameter expressing strength of the interparticle bonding formed by the stress relaxation. The interparticle bonding parameter was defined as a product of the E_p and the stress relaxation parameter $Y(t)$. The E_p and $Y(t)$ were estimated from the force-displacement curve and the stress relaxation test. The results showed that the proposed $E_c-E_b(t)$ diagram could significantly discriminate the capping tendency of tablets prepared by the double compression with multi-component powder formulations.

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