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Research Paper

Characterization of Tableting using the OSDRC System

Kazuyuki Shimizu,[1,2] Masaki Ando,[1] and Yukiharu Nakayama[1]

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Purpose. We compared the compression properties and characteristics of tablets obtained using the OSDRC system (method (OSDRC)) and conventional compression methods including multi-layer compression with a pharmaceutical powder.
Materials and Methods. We prepared tablets using four methods of compression. The force profiles, ejection force, stress relaxation, pressure transmission ratio, and internal intensity of the tablets were measured as compression properties.
Results. Method (OSDRC) gave the highest value for the crushing strength of the tablets. Although the compression properties were similar regardless of the method of compression, the internal intensity of tablets compressed by method (OSDRC) was significantly larger than that of the tablets produced by the other methods.
Conclusions. In terms of crushing strength, the tablets compressed by method (OSDRC) were superior of those obtained by the conventional compression method. Therefore, it is possible to increase the crushing strength of tablets without changing the pharmaceutical formulation.

KEY WORDS: compression; conventional compression; crushing strength; OSDRC; tablet improvement.

INTRODUCTION

We previously reported a novel method, the One-Step Dry-Coated (OSDRC) method, of manufacturing dry-coated tablets (OSDRC tablets) using a unique punch and die (1,2). The OSDRC method does not require the preparation of a core tablet beforehand, allowing dry-coated tablets to be assembled in the single turn of a rotary tableting machine. The OSDRC system employs three compression processes; the first to form the lower-outer layer (the first layer), the second to make the core layer (the second layer) on the first layer, and the third (the final compression) to make the entire tablet including the upper-outer and side-outer layers (the third layer). With the OSDRC method it is possible to fill up the die with the pharmaceutical powder by three times. In general, two kinds of pharmaceutical powder are prepared for the OSDRC method to make a dry-coated tablet, one for the first and third layers and the other for the second layer. However, it is possible to add three kinds of pharmaceutical powder to the die or one pharmaceutical powder by three times. These tableting methods are similar to the multi-compression method which is useful for making bi-layer and triple-layer tablets for drug delivery systems (3,4).

Multiple compression is the basis of the well-known pre-compression process for manufacturing tablets. While powder compression is a widely studied area of research, a few reports are available on the effects of compressing the same tablet more than once (5) De Blaey et al. reported that the double compression techniques in an attempt to evaluate the degree of elastic deformation in a powder system (6). Although drug delivery systems using bi-layer and triple-layer tablets have been investigated, little is known of the compression properties of these tablets.

We reported that the compression properties of OSDRC tablets compared favorably with those of conventional dry-coated tablets, and the manufacturing process had no effect on the physical characteristics of the tablets. Furthermore, the internal structure of both OSDRC and conventional dry-coated tablets, in terms of density distribution, was similar. OSDRC tablets consist of a core and outer layer which comprise different pharmaceutical powders.

In this study, we investigated the compression properties obtained with the OSDRC system using the same pharmaceutical formulation for each layer and compared the characteristics of the tablets with those of conventional and multiple compressed tablets.

MATERIALS AND METHODS

Materials

The microcelac (Meggle, German) was used as a model powder. Lactose (Pharmatose 200M, D.M.V., Netherland), microcrystalline cellulose (MCC) (Asahi Chemical Co., Ltd., Japan), magnesium stearate (MgSt) (Taihei Chemical Co., Ltd., Japan), hydroxypropylcellulose (HPC-L, Nippon Soda Co., Ltd., Japan), phenacetin (Wako Chemical Co., Ltd.,

[1] Pharmaceutical Research & Technology Laboratory, Sanwa Kagaku Kenkyusho Co., Ltd., 363 Shiosaki Hokusei, Inabe Mie, 511-0406, Japan.
[2] To whom correspondence should be addressed. (e-mail:ka_shimizu@skk-net.com)

Japan), and Low-substituted hydroxypropylcellulose (L-HPC) (Shin-Etsu Chemical Co., Ltd., Japan) were also used.

The granulated sample (GS) was prepared with a fluidized bed granulator (FLO-5, Freund Sangyo Co., Ltd., Japan). The formulation of the GS is shown in Table I.

Compression

Microcelac was blended with 1% MgSt using a V blender (Tsutsui Rikagaku Instrument; microblender, Japan) for 1, 5, and 30 min. The GS was blended with or without phenacetin using the V blender for 3 min. The Autograph (AG-I 20 KNT; Shimadzu, Japan) was used to compress tablets at a fixed speed of 10 mm / min in all experiments. The OSDRC system consists of an upper-center punch, a lower center punch (diameter: 6 mm), an upper-outer punch, and a lower-outer punch (diameter: 8 mm), which are all circular and flat-faced.

The compression method, compression force, and volume are depicted in Fig. 1. Compression method (1–1) (Fig. 1a) was employed using die and punches of 8 mm. The pharmaceutical powder was added to the die all at once and compressed once. Compression method (1–3) (Fig. 1b) was employed using die and punches of 8 mm. The pharmaceutical powder was added to the die all at once and compressed three times. Compression method (3–3) (Fig. 1c) was employed using die and punches of 8 mm. The pharmaceutical powder was added to the die three times and compressed each time. Compression method (OSDRC) (Fig. 1d) was employed using die and punches of 8 mm and 6 mm. The pharmaceutical powder was added to a die of 6 mm two times and compressed each time as the first and second layers. Then, the powder was added to a die of 8 mm and compressed finally to give the third layer.

Tablet Analysis

The decrease ratio (DR 5 or DR 30) of the crushing strength was calculated as follows:

$$DR(5or30)(\%) = \{CS(5or30) - CS(1)\}/CS(1) \qquad (1)$$

where CS (5 or 30) is the crushing strength when microcelac was blended with MgSt for 5 or 30 min and CS (1) is the crushing strength when it was blended with MgSt for 1 min.

The height at the center of the tablet was measured with a thickness gauge (SM-528, Teclock, Japan), immediately after compression. The crushing strength was measured with a Portable checker PC-30 (Okada Seiko Co., Ltd., Japan), immediately after compression. Data are expressed as means ± standard deviation (n=3).

Table I. Formulation of the Granule (GS)

Ingredient	% (w / w)
Lactose	68.5
MCC	20
L-HPC LH21	8
HPC-L	3
MgSt	0.5

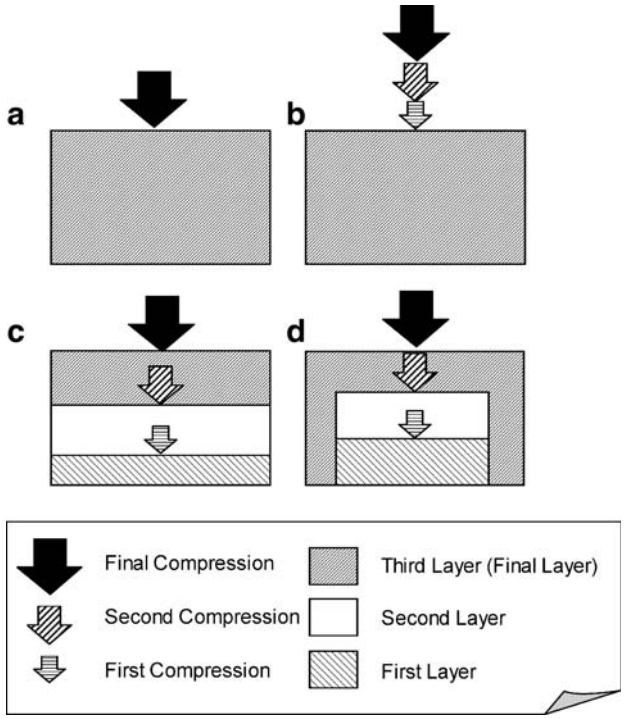

Fig. 1. Compression methods. **a** :Method (1-1), **b**: Method (1-3), **c**: Method (3-3), **d**: Method (OSDRC).

Compression Analysis

Microcelac was compressed at a fixed speed of 10 mm/min under 100 MPa by the Autograph. The force profiles, ejection force, stress relaxation, and punch displacements were recorded by use of software (TRAPEZIUM 2, Shimadzu, Japan). The Pressure transmission ratio (PTR) was calculated by dividing the lower punch pressure by the upper punch pressure when the upper pressure reached the maximal value. The tablets were ejected from the punch and die at 10 mm / min. Ejection force was measured by 20 KN load cells. The stress relaxation experiments to estimate constants "a" and "b" were obtained by the modification of Kawakita's equation (7,8). The percentage elastic recovery of each compression was determined as described in the previous paper (9).

Measurement of Internal Intensity of Tablets

The internal intensity of the tablets was measured using a constant load boring intensity tester (Nippon Denshi Kagaku, Spin Analyzer AS-100). The penetration of the drill tip (diameter: 0.8 mm) was measured continuously during the boring of the tablet. The drill rotation speed was 200 rpm and the load was 300 g. The drilling direction was horizontal to the direction of compression. The plot of drilling position versus time was represented by mean values of three experiments.

Table II. Parameter of the GS

Parameter		
Loose density (g/ml)		0.321
Tapped density (g/ml)		0.414
Angle of response (degrees)		47.9
Particle size distribution	< 500 μm	0.3
	< 250 μm	9
	< 150 μm	46.8
	< 75 μm	37.3
	75 μm pass	6.6

RESULTS AND DISCUSSION

Characteristic of Microcelac and the Granulated Sample (GS)

Table II shows the physical characteristics of the GS. The loose and tapped density of microcelac was 0.5 and 0.6 g/ml, respectively. The loose and tapped density of the GS was slightly smaller than that of microcelac. The angle of response of microcelac (34.8°) (10) was slightly smaller than that of GS (47.9°).

Influence of the Compression Methods on Crushing Strength

Figure 2 shows the influence of compression method and blend time using the microcelac with 1% MgSt. The crushing strength of the tablets blended for 1 min by methods (1–1), (1–3), and (3–3) did not differ significantly and was around 80 N. On the other hand, the crushing strength of the tablets blended for 1 min by method (OSDRC) was greater around 100 N. After 30 min of blending, the crushing strength of the tablet compressed by method (OSDRC) was around 80 N, compared of 60 N for the other methods. The DR (5) of methods (1–1), (1–3), (3–3), and (OSDRC) was 20.99, 19.26, 21.25, and 15.79, respectively. The DR (5) of method (OSDRC) was lowest. The DR (30) of methods (1–1), (1–3), (3–3), and (OSDRC) was 26.34, 36.23, 24.58, and 23.03, respectively. The DR (30) of method (OSDRC) was still slightly lower than that of the other methods. The crushing strength of tablets with MgSt was decreased by the blend time and did not depend on the compression method.

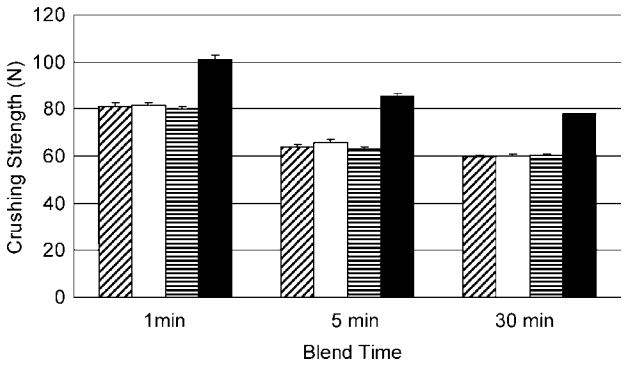

Fig. 2. Influence of compression method and blend time on crushing strength using microcelac tablets with MgSt. Each point represents the mean ± S.D. (n=3). ▨ :Method (1-1), □ : Method (1-3), ▤ : Method (3-3), ■ : Method (OSDRC).

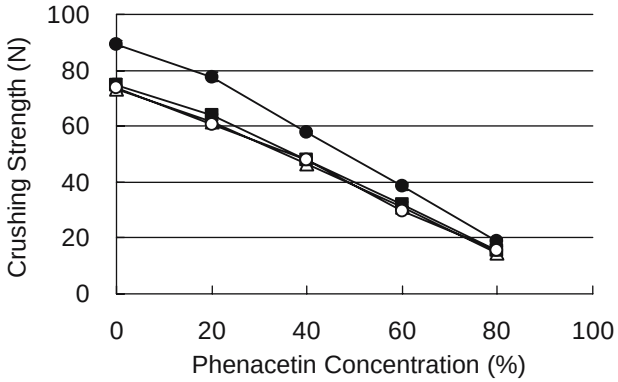

Fig. 3. Influence of phenacetin concentration on crushing strength using GS tablets. Each point represents the mean ± S.D. (n=3). △: Method (1-1), ■: Method (1-3), ○: Method (3-3), ●: Method (OSDRC).

However, the crushing strength of the tablet compressed by method (OSDRC) was less influenced by blend time than that of the tablets made by the other methods as shown by the DR values. In general, the crushing strength of the tablet of microcelac with MgSt was decreased by the blend time because of its weak binding force with other particles. (11,12) It may be that method (OSDRC) produces strong binding forces among the particles.

Figure 3 shows the influence of phenacetin concentration on the crushing strength of GS tablets. The phenacetin has less compressibility (13). The crushing strength of the tablets with phenacetin was decreased by the increase in the phenacetin concentration and did not depend on the method of compression. However, the crushing strength of the tablets compressed by method (OSDRC) was higher than that of tablets made by the other methods. As well as the result in Fig. 2, it was indicated that method (OSDRC) was more effective than the other methods in terms of the tablets' crushing strength. Furthermore, it was suggested that compression using method (OSDRC) was more useful to improve crushing strength without changing the formulation when the crushing strength of tablets made using a conventional compression machine was not enough.

Influence of Weight and Compression Pressure Using Method (OSDRC)

Figure 4 shows the influence of the weight of each layer on the crushing strength of tablets compressed by method (OSDRC). In this experiment, total tablet weight was a constant 200 mg and compression force of the first, second, and third layers was 3.5, 35.0, and 99.9 MPa, respectively. There was no clear relationship between the weight of the first layer and crushing strength (Fig. 4a), and between the second layer weight and the crushing strength (Fig. 4b). On the other hand, there was a clear relationship between the total weight of the first and second layers (weight 1+2) and crushing strength (Fig. 4c), and between the weight of the third layer and crushing strength (Fig. 4d). An increase of weight 1+2 increased the crushing strength and a decrease of the third layer's weight decreased the crushing strength. Figure 4 indicates that the individual weights of the first and second layers were not important factors, but the weight of

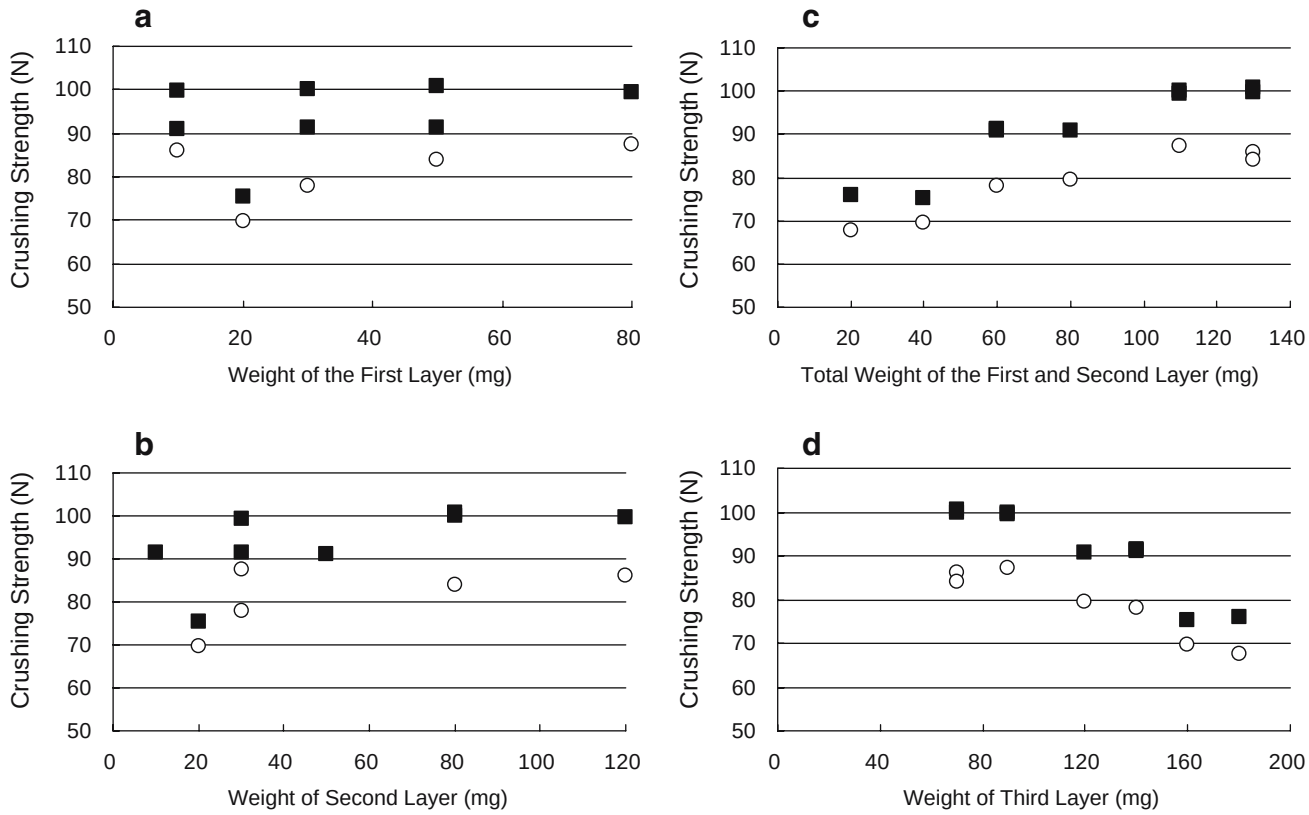

Fig. 4. Influence of the weight of each layer on the crushing strength of tablets compressed by method (OSDRC). **a**: First layer, **b**: Second layer, **c**: Total of first and second layer, **d**: Third layer. (■): Microcelac, (○): GS.

the third layer and weight 1+2 would be critical to the crushing strength of tablets compressed by method (OSDRC).

Figure 5 shows the relationship between compression force of the first or second layer and the crushing strength of tablets compressed by method (OSDRC). In this experiment, the compression force of the third layer was 99.9 MPa and the weight of the first layer, the second layer, and the third layer was 30, 80, and 90 mg, respectively. The compression force of the first layer of microcelac had no influence on the crushing strength of the tablets (Fig. 5a). The crushing strength might be slightly increased depending on the increase in compression force of the first layer in the case of the compression of the GS. The compression force of the second layer did influence crushing strength both with the GS and with microcelac. In the case of compression of the GS, the crushing strength of the tablet increased dependent on the increase in compression force of the second layer. On the other hand, in the case of microcelac, the crushing strength of the tablet increased with the increase in the compression force of the second layer between 3.5 and 70.8 MPa and the crushing strength was decreased depending on the increase in the compression force of the second layer over 106.2 MPa.

Dietrich et al. investigated the strength of adhesion between layers in complex two-layer tablets (14). They reported that a high compression force for the first layer had a negative effect on the adhesion of two-layer tablets while a high compression force for the second layer exerted a positive effect on adhesion. This report supports our result of the effect of the compression force of the second layer. Furthermore, they pointed out the influence of MgSt. A strongly negative influence on the adhesion strength of the two-layer tablet was exerted by the amount of MgSt in the second layer. Yang et al. investigated the compaction of triple-layer tablets and reported that compact lamination was only observed at both high punch velocity and high compaction force (15). These reports suggested that the adhesion of each layer was important to the crushing strength of the tablet. Additionally, Belda et al. pointed out the importance of component diffusion at the interface between the layers in the measurement of crushing strength (16). The component diffusion at the interface between the layers could play an important role in the adhesion of each layer (17). The interaction among each layer of microcelac decreased depending on the increase in compression force because each layer was sufficiently compressed at the low force. As a result, the adhesion strength of the layers of microcelac decreased with the increase in compression of the second layer, and then the crushing strength decreased when a high compression force was applied to the second layer. In fact, cross sections of each layer of microcelac, especially the second and third layers, were observed clearly after a crushing test at high compression force.

Although there was a difference between microcelac and the GS in the influence of compression force on the second layer, the crushing strength was strongly influenced by the total weight 1+2, but not the weight of just the first or at second layer, and also strongly influenced by the compression force at the second layer.

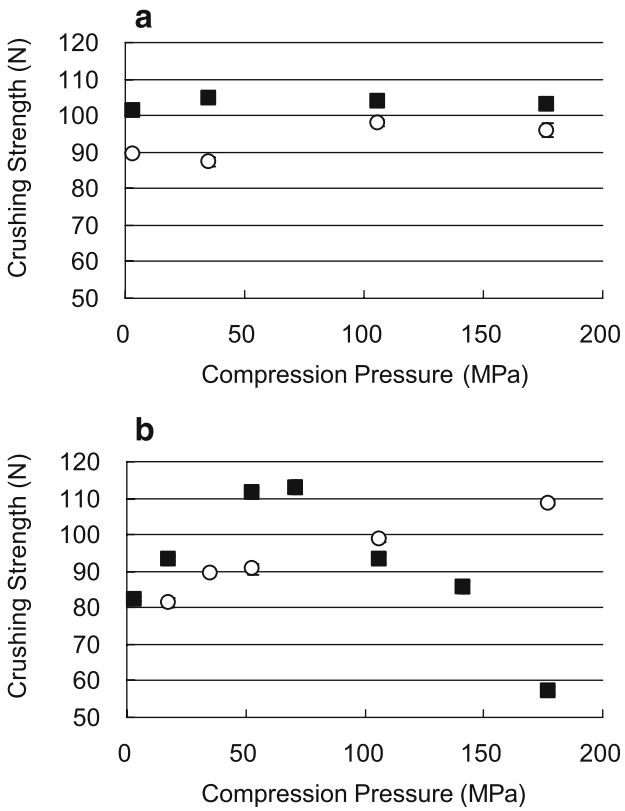

Fig. 5. Relationship between compression force of the first or second layer and crushing strength of tablets compressed by method (OSDRC). Each point represents the mean ± S.D. (n=3). **a**: First layer, **b**: Second layer. (■): Microcelac, (○): GS.

Evaluation of Compression Properties Using Microcelac

As the crushing strength of tablets compressed by method (OSDRC) was higher than that of tablets obtained by the other methods using the same pharmaceutical powders among each layer, the tablets compressed by method (OSDRC) are expected to have specific characteristics. Next, we evaluated compression properties.

Figure 6 shows the influence of compression method on tablet thickness. The thickness and diameter of the tablets did not differ significantly among the methods of compression. The diameter of the tablets used in this study was from 8.03 to 8.06 mm. It was suggested that the porosity of tablets ompressed by method (OSDRC) was almost the same as that of tablets obtained by the other methods. The relationship among compression force, porosity, and crushing strength has been widely investigated (18–21). An increase in porosity would tend to reduce crushing strength. Although the porosity of tablets compressed by method (OSDRC) was the same as when the other methods were used, the crushing strength was higher using method (OSDRC).

To investigate this characteristic of the tablets made using method (OSDRC), microcelac with 1% MgSt blended for 1 min was used.

Figure 7 shows PTR versus the distance between punches. The data are from three experiments. PTR is useful for evaluating, compression during tableting (22–25). PTR for method (1–1), (1–3), (3–3), and (OSDRC) was 96.8, 96.7, 96.8, and 96.7%, respectively. PTR for method (OSDRC) is consistent with the result of a previous study on the relationship between punch velocity and PTR for method (OSDRC) (26). These values indicated good compression property there and that there was no significant difference in PRT between the compression methods. For method (1–1), the data of PTR were spread at the beginning of the compression. This is probably because method (1–1) does not have a pre-compression step. In fact, the tablets prepared using method (1–3) were sufficiently compressed before the final compression, and there was no spread of data at the beginning of compression.

Figure 8 shows the effect of the method of compression on the ejection force of microcelac tablets. There was no significant difference in ejection force among the compression methods. Ejection force is a measure of the force required to overcome the residual radial die wall pressure resulting from the compression event and the friction between the die wall and the tablet in contact with it (27,28). Therefore, ejection force could represent the interaction between the die wall and tablet. Powder of ascorbic acid is sticky compound. Ejection force of ascorbic acid was about 12.4 MPa under the same compression pressure used in this study, which suggested that the interaction between the die wall surface and ascorbic acid was very strong (25). Ejection force of microcelac was smaller than that of ascorbic acid independent of the compression method indicating the weak interaction between the die wall and microcelac tablet. An increase in compression force tended to result on an increase in ejection force and crushing strength (24). Despite

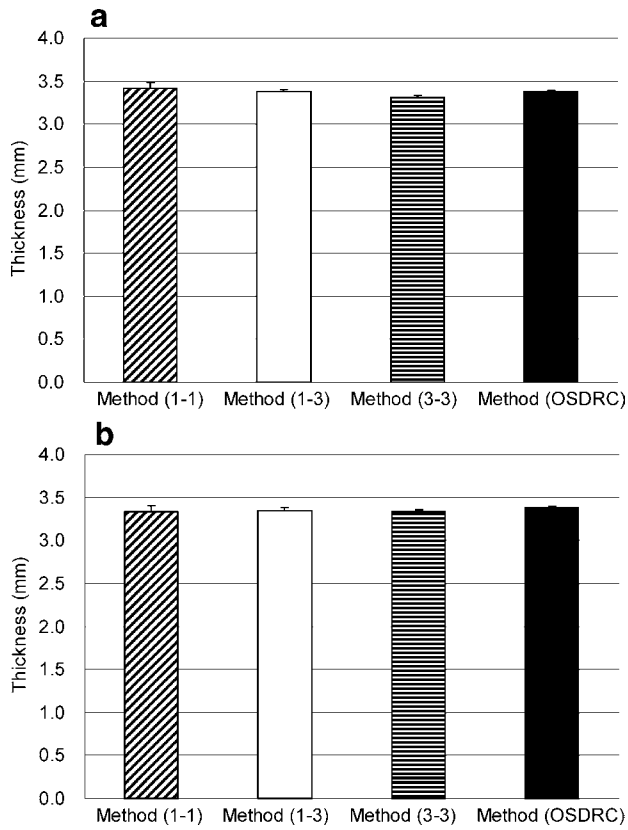

Fig. 6. Influence of compression method on tablet thickness. Each point represents the mean ± S.D. (n=3). **a** Microcelac, **b** GS.

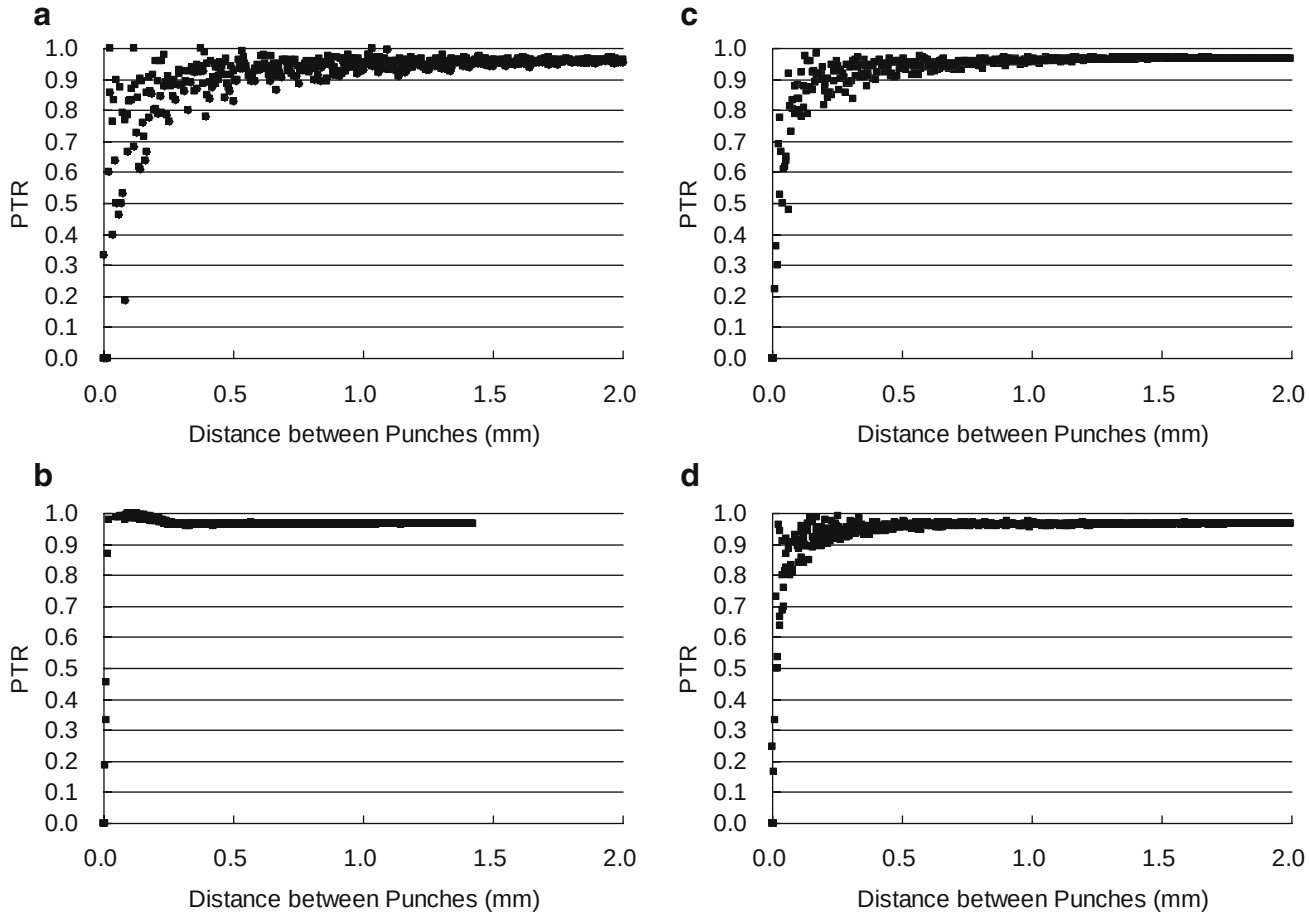

Fig. 7. PTR versus the distance between punches for each method at the final compression of microcelac tablets. **a** :Method (1-1), **b**: Method (1-3), **c**: Method (3-3), **d**: Method (OSDRC).

the high crushing strength of the tablets compressed by method (OSDRC), the interaction was weak the same as when the other methods were used.

Figure 9 shows the effect of the method of compression on the constant of the stress relaxation experiment. The plot of t/Y (t) versus t shows good linearity independent of the compression method. The correlation coefficient was 0.999 at each plot. There was no difference among the compression methods in the constant "a" or "b." The constant "a" shows the value of relaxation in infinite time and the constant "b" is an index showing relaxation speed (29). In this experiment, the stress relaxation was the same regardless of the method of compression because "a" was almost the same value. The constant "b" did not differ among the compression methods, indicating that relaxation occurred with almost the same speed. Stress relaxation is caused by the re-arrangement and crushing of the particles themselves (30). This result indicated that both the speed and extent of the re-arrangement in microcelac tablets was the same irrespective of the method of compression.

Figure 10 shows the effect of compression methods on elastic recovery. This parameter is associated with interparticulate friction or bonding (31). There was no significant difference in elastic recovery among the compression methods.

Consequently, the compression properties obtained using method (OSDRC) was the almost the same as those obtained with the other compression methods.

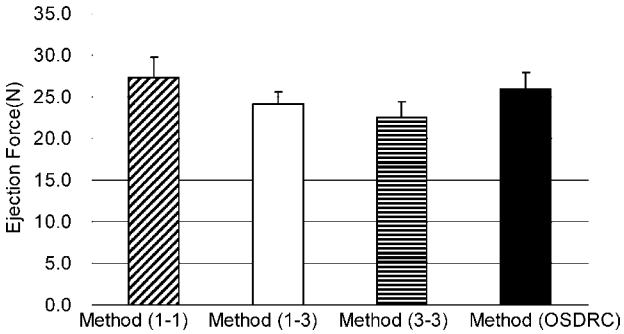

Fig. 8. Effect of compression method on ejection force of microcelac tablets. Each point represents the mean ± S.D. (n=3).

Evaluation of the Internal Intensity of the Tablet

The internal intensity of the tablet was evaluated using a constant load boring intensity analyzer. The intensity was indicated by the speed of the drill penetration (32).

Figure 11 shows the internal intensity of the tablets compressed by each method, the penetration speed indicated by the slope of the line. The slope for method (1–1) and (3–3) was constant from beginning to end, being 0.044–0.046 and 0.050–0.052, respectively. The drilling speed was higher for method (3–3) than method (1–1). The internal intensity of the tablet compressed by method (3–3) was slightly lower

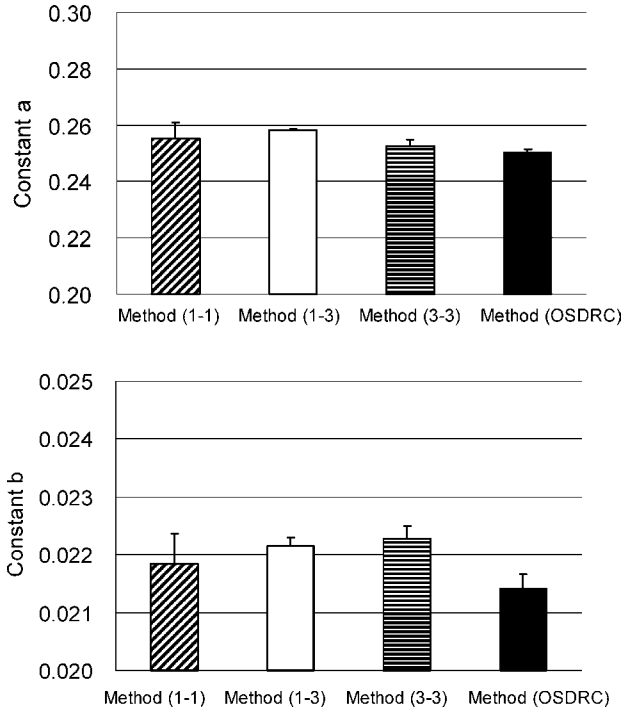

Fig. 9. Effect of compression method on the constants a and b in a stress relaxation experiment. Each point represents the mean ± S.D. (n=3).

than obtained used method (1–1). Although crushing strength was almost the same for method (1–3) and (3–3), internal intensity was slightly different. The slope of method (1–3) was bi-phasic. Early on, at a drilling position of 0.5–1.0 mm, the slope was 0.038±0.004. The slope at the end of the drilling, from 2.0 mm to 4.0 mm, was 0.051±0.002. The intensity was greater near the die wall than at the center of the tablet. The intensity at the center of the tablet compressed by method (1–3) was similar to that of the tablet produced by method (3–3). In contrast, the intensity near the die wall was higher for method (1–3) than method (1–1). The slope for method (OSDRC) was significantly different from that for the other methods. At the early stage of drilling, from 0 to 0.5 mm, the slope was 0.318±0.031, significantly larger than the slopes for the other methods. The slope after this early stage was significantly smaller, 0.039±0.003.

The slope of the early stage of tablet compressed by method (OSDRC) indicated that the intensity of the tablet's side was weaker than that of tablets compressed by the other

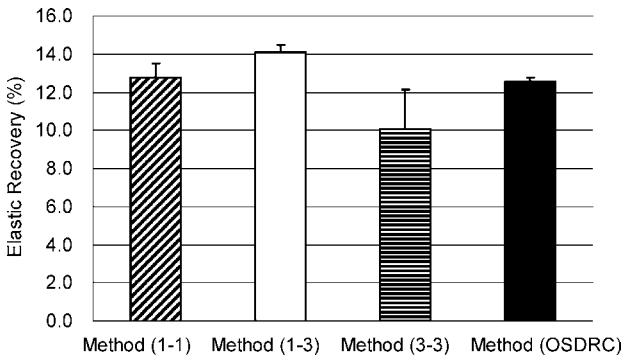

Fig. 10. Effect of compression method on elastic recovery. Each point represents the mean ± S.D. (n=3).

methods. Friability of tablets compressed by method (OSDRC) was the same as that for the other methods. The upper and lower surface of the tablet may be important in supporting the structural hardness of tablets compressed by method (OSDRC).

In general, crushing strength increases when a tablet is compressed under high compression force, resulting in an increase in ejection force (25,27,28). In this study, despite similar levels of ejection force and final compression force among the methods, crushing strength was increased by method (OSDRC) without change in the pharmaceutical formulation (Figs. 2 and 5). It could be that the crushing strength of the tablets compressed by method (OSDRC) was caused by a high internal intensity, and the low internal intensity near the die wall contributed to the low ejection force because ejection force strongly depended on the interaction between the die wall and the surface of the tablet (Figs. 11 and 10). This could be a useful characteristic for reducing die wall friction causing cracking and sticking.

The inflection point of the drilling position calculated from the intersection of the lines between 0 and 0.5 mm and between 1.0 and 3.0 mm was 0.79±0.10 mm. The first and second layers were pressed about 0.2 mm in the horizontal direction at the third layer against compression direction, because the initial thickness of the side of the tablet compressed by method (OSDRC) was 1.0 mm (Fig. 1). It was suggested that deformation of the first and second layers occurred after the final compression.

The importance of the compression force applied to the second layer and the adhesion of each layer was discussed (Fig. 5). A high compression force at the second layer might prevent deformation of the first and second layers at the final compression, decreasing the adhesion of each layer. Therefore, the compression force at the second layer would influence the crushing strength of the tablet.

Consequently, the characteristics of the tablets compressed by method (OSDRC) could be due to a unique internal intensity. Although the pharmaceutical formulation was investigated to improve crushing strength of tablets generally, it was possible to improve crushing strength without changing the pharmaceutical formulation.

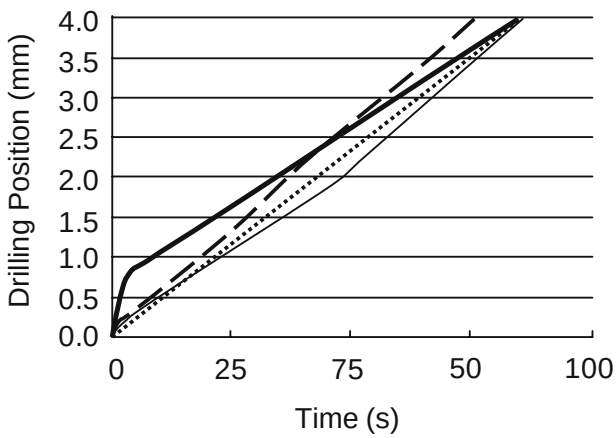

Fig. 11. Evaluation of the internal intensity of the tablets compressed by each method. Line represents the mean of three determinations. ····· :Method (1-1), ——— : Method (1-3), – – – : Method (3-3), ——— : Method (OSDRC).

Conclusion

The crushing strength of tablets compressed by method (OSDRC) was higher than that of the tablets obtained by the other methods with both the GS and microcelac as a pharmaceutical powder. In terms of crushing strength, method (OSDRC) was more effective than the conventional method of compression. The crushing strength was strongly influence on the total weight 1+2, which was not on the weight of the first layer or the second layer, and also strongly influence on the compression force of the second layer. The compression properties obtained with method (OSDRC) were almost the same as those obtained with the other methods. The intensity of the internal tablet was significantly different using method (OSDRC) than the other methods. It appeared that the characteristics of the tablet compressed by method (OSDRC) could be due to a unique internal intensity. These results suggested that compression using method (OSDRC) was useful at improving crushing strength without changing the formulation when the crushing strength of tablets produced with a conventional compression machine was not enough. Method (OSDRC) is more useful in terms of crushing strength than conventional or multiple compression.

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