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Evaluation of the compression characteristics and physical properties of the newly invented one-step dry-coated tablets

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Abstract

This study was conducted in order to clarify the compression characteristics, and to confirm the superiority of the physical properties, of the newly invented One-Step DRy-Coated tablets (OSDRC). We compared both the compression characteristics and the physical properties of OSDRC with those of physical-mixture tablets (PM) that were prepared with the same ingredients, quantity, and compression pressures. We selected potassium chloride (KCl) and acetaminophen (AAP) as the model drugs, since the former is known for its appropriate compression characteristics and the latter for its brittleness. The advantage of OSDRC is that they are capable of maintaining any kind of drug in their core, because the core is tightly surrounded by the outer layer, even when the drugs in the core have poor compression characteristics, which causes difficulties in forming a solid core tablet using conventional dry-coated tablet methods. The radial tensile strength of OSDRC was the same as, or superior to, that of PM containing of AAP. The results were in accordance with the compression process analysis performed according to Kawakita's equation. The friability of OSDRC was also superior to that of PM. These preferable characteristics were attributable to the high intensity of the OSDRC outer layer surface in comparison to that of PM. It was difficult to clarify the difference between OSDRC and PM in their physical properties when KCl was applied, since the tabletability of the whole tablet was high due to KCl's physical properties. The OSDRC containing AAP in their cores showed a controlled release pattern, though no other materials that have been known to influence drug release was present. It was considered that this controlled release pattern was caused by a reduced AAP particle surface area due to compression. It was confirmed with these experiments that the compression characteristics and the physical properties of AAP-OSDRC were superior to those of PM. These results indicated that it is possible to produce tablets that have materials with poor compression characteristics in the core portion, and high tabletability materials for the outer layers. In other words, it is possible to produce capsule-like tablets using the OSDRC compression method.

Keywords: One-step dry-coated tablets; Dry-coated tablets; Compression-coated tablets; OSDRC-system; Compression test; Stress relaxation; Tensile strength

1. Introduction

We previously reported on the One-Step DRy-Coated tablets (OSDRC) manufactured by a new process using a unique punch and die (Ozeki et al., 2001, 2002). The OSDRC manufacturing method (Fig. 1) does not require the preparation of core tablets beforehand, allowing dry-coated tablets to be assembled in a single turn of a rotary tabletting machine. With the OSDRC method, no technical problems are anticipated relating to the supply of the core, such as tablets which have no core or those with an off-center

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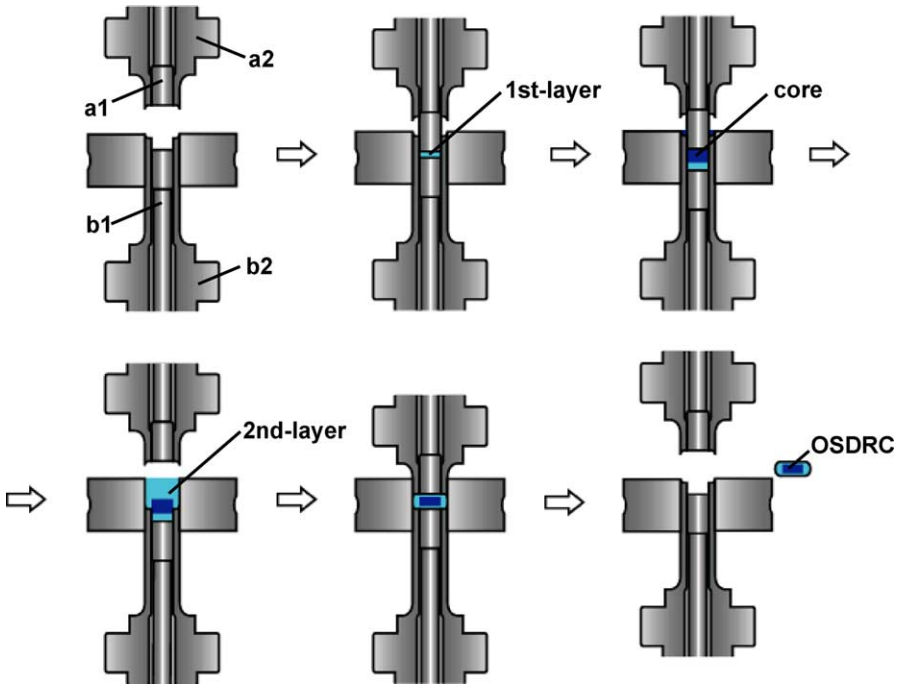

Fig. 1. Mechanism of OSDRC manufacturing method. Schematic sequence of OSDRC-system.

core, which are common problems with conventional dry-coated tablets (Lieberman and Lachman, 1980).

We reported that when comparing compression characteristics between OSDRC made by the new manufacturing method and conventional dry-coated tablets, there was no effect regarding the difference in the manufacturing method on the physical characteristics of the tablets. Furthermore, the internal structure in both types of tablets, as viewed from the distribution of densities, was similar (Ozeki et al., 2003). Further, OSDRC makes it possible to form tablets from ingredients with which it is usually difficult to do so by conventional tabletting methods due to their poor tabletability.

Formulators add diluents, including binders, or improve the drug properties by granulation to make a tablet of a drug with low tabletability. This is also the case for a conventional dry-coated tablet with a low tabletability drug in its core. The addition of diluents, however, causes a decrease in the drug content of a tablet. Granulation makes the manufacturing process complicated and increases manufacturing costs. As described above, OSDRC are new dry-coated tablets which can be applied to drugs with low tabletability, as well as to drugs with high tabletability without a time-consuming optimization process.

Acetaminophen (AAP) is a drug with low tabletability. It is difficult to make an AAP tablet with no diluents. To prepare a conventional dry-coated tablet of AAP, the formulator should add diluents with high tabletability in the AAP core. The increase in the ratio of diluents would improve the tabletability; however, this method could not be freely chosen due to the limitation of a drug content and tablet size.

Because a dry-coated tablet is prepared in one-step by the OSDRC method, it is expected that a low tabletability drug such as AAP could be formulated in the core with no diluents by using high tabletability ingredients for the outer-layer. To examine the usefulness of OSDRC, this study examined the applicability of OSDRC to drugs with different levels of tabletability.

In the present study, we selected potassium chloride (KCl) and AAP as the model drugs, as they have high and low tabletability, respectively. The radial tensile strength, friability, and internal intensity of

OSDRC were measured to compare them with those of physical-mixture tablets (PM) which were prepared with the same ingredients, quantity, and compression pressures. Furthermore, stress relaxation in the compression process was investigated. In conclusion, the radial tensile strength of OSDRC was the same as, or superior to, that of PM. The friability of OSDRC containing AAP was also superior to that of PM. The details are reported in subsequent paragraphs.

2. Materials and methods

2.1. Materials

Acetaminophen (Tyco Healthcare; SP, granule indicated as AAP) and potassium chloride (Sigma–Aldrich Japan; SP, Grade indicated as KCl) were selected as model drugs due to their brittleness or deformability. These model drugs were sieved into 180–300 μm fractions prior to the experiment. Commercially available lactose-cellulose spray dry granules (Meggle; Cellactose 80 mixture of lactose and cellulose at 3:1 in weight) were used as the excipient. The ingredients are shown in Table 1.

2.2. Preparation of the one-step dry-coated tablets (OSDRC)

The OSDRC were prepared by the method indicated below. The schematic sequence of the OSDRC manufacturing method is shown in Fig. 1. 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). The OSDRC system employs three compression processes; the first compression to form the lower-outer layer (indicated as the 1st-outer layer), the second compression to make the 1st-outer layer/core complex, and the third compression to make the whole tablet including the upper-outer and side-outer layers (indicated as the 2nd-outer layer).

Table 1
Ingredients of OSDRC and PM

Material (mg/tablet)	AAP–OSDRC[a]	KCl–OSDRC[a]	AAP–PM	KCl–PM
AAP	70	–	70	–
KCl	–	70	–	70
Cellactose	130	130	130	130
Total	200	200	200	200

[a] OSDRC core: 70 mg/tablet (AAP or KCl only).

In the first step to make the 1st-outer layer, the lower-center punch (b1) was slid down to fill the space made by the lower-center punch (b1) and the inside wall of the lower-outer punch (b2), with the powder for the 1st-outer layer (Cellactose), and then the powder was pre-compressed by the upper-center punch (a1). While the upper-center punch was pushing down the pre-compressed 1st-outer layer, the lower-center punch was slid down at the same time, the upper-center punch was pulled up to make a space which was to be filled with the powder for the core (AAP or KCl), and was then pre-compressed by the upper-center punch (a1). After sliding the lower-outer punch (b2) down, the space around the pre-compressed complex of the 1st-outer layer/core was filled with the remaining powder (Cellactose) to form the 2nd-outer layer. During the last compression, the remaining powder was compressed by the upper and lower punches with the pre-compressed complex. The final compression employed the simultaneous movement of the center and outer punches at a fixed speed of 1 mm/min under various pressures (100, 150 and 200 MPa), utilizing a universal tension and compression tester (Shimadzu; AG-I 20 kNT) to obtain an OSDRC weighing 200 mg (core weight 70 mg). The tips of center and outer punches were adjusted to create a flat face, like a normal punch. The quantity of powder for the 2nd-outer layer was adjusted to create the same thickness as the 1st-outer layer.

2.3. Preparation of physical-mixture tablets (PM)

The ingredients of the OSDRC were mixed with a V type blender (Tsutsui Rikagaku Instrument; micro blender). The mixture was compressed using 8 mm flat-face punches and dies at a fixed speed (1 mm/min) under various pressures (100, 150 and 200 MPa), utilizing the universal tension and compression tester.

2.4. Method for compression process analysis

2.4.1. Analysis by the modified Kawakita equation

The compression processes of the OSDRC and the PM were analyzed using the modified Kawakita

equation (Eq. (2)) (Danjo et al., 1996, 1998) that has a modified linear plot form of the Eq. (1) (Kawakita and Ludde, 1971).

$$-\frac{d\varepsilon}{dP} = K\varepsilon^2 \quad (1)$$

$$\frac{1}{\varepsilon} = \frac{1}{\varepsilon_0} + KP \quad (2)$$

where ε, P, and K are the porosity, compression pressure (MPa), and constant, respectively.

The plots were divided into three stages at the following refractions. The attributes of each stage K were calculated from each slope. K_1 ≒ (less than 2 MPa), K_2 ≒ (2–75 MPa), and K_3 ≒ (more than 75 MPa), were subjected to an analysis of their compression characteristics.

2.4.2. Stress relaxation test

The stress relaxation test was performed using the universal tension and compression tester. The decrease in force was recorded for 15 min after the compression pressure reached a predetermined value during the final compression at a fixed compression speed (1 mm/min) (Cutt et al., 1987; Kawashima et al., 1995; Imai et al., 2001). The stress relaxation value was adjusted by deducting the distortion value measured under the same conditions without powder.

The rate of relief, $Y(t)$, was calculated using the following equation (Peleg and Moreyra, 1979):

$$Y(t) = \frac{P_0 - P_t}{P_0} \quad (3)$$

where P_0 is the initial force, and P_t is the force after time t. The determined $Y(t)$ with t was fitted to Eq. (5), obtained by the modification of Kawakita's equation (Eq. (4)), to estimate constants a and b, which characterize stress relaxation (Danjo et al., 1998):

$$Y(t) = \frac{abt}{1+bt} \quad (4)$$

$$\frac{t}{Y(t)} = \frac{1}{ab} + \frac{t}{a} \quad (5)$$

2.5. Measurement of radial tensile strength

The model tablets were subjected to a diametral compression test using a tablet hardness tester (Toyama Kagaku; TH-203) after being left at room temperature for 24 h in a desiccator with silica gel. The test was performed by applying a diametrical load, measuring the maximum load H at the tablet fracture, and then calculated the radial tensile strength T using the following equation (Fell and Newton, 1970):

$$T = \frac{2H}{\pi dL} \quad (6)$$

where d is the tablet diameter and L is the tablet thickness.

2.6. Friability test

The tablets prepared by the above method were left at room temperature for 24 h in the desiccator with silica gel, and were then subjected to measurement with a friability tester (Electrolabo; EF-1W). Twenty polystyrene beads (Wako Pure Chemical; diameter of 6 mm) were put into a drum with the samples. After the drum rotation at a fixed number, the decrease in weight of each tablet was measured to calculate the friability.

2.7. Measurement of internal intensity

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 a drill tip (diameter: 1 mm) was measured continuously during the boring of the tablet. The drill rotation speed and the load were 200 rpm and 150 g, respectively. The relative intensity of the inside of the tablet was evaluated from the boring speed (Ishino et al., 1990; Hashimoto et al., 2002).

2.8. Release pattern of the model drugs

Evaluation of the drug release from the tablet was performed according to the 2nd method (paddle method) of the "Japanese Pharmacopoeia XIII". Purified water was used as the test solution (900 ml) and the paddle rotation speed was set at 50 rpm. Samples were taken at predetermined intervals, and the concentration of AAP dissolved in the medium was spectrophotometrically measured at a wave-length of 282 nm (Shimadzu; UV-1700).

3. Results and discussion

3.1. Relationship between the compression pressure and radial tensile strength of OSDRC and PM

The test results of the radial tensile strength of OSDRC and PM with AAP or KCl, prepared under various compression pressures, are shown in Fig. 2. The tensile strength of both tablets increased as the compression pressure increased. The radial tensile strength of OSDRC was the same as, or superior to, that of PM containing of AAP. On the other hand, the radial tensile strength of OSDRC with KCl was apparently higher than that of PM.

3.2. Analysis of the compression process

In order to clarify the difference in compression characteristics of both tablets, each compression process was analyzed according to the modified Kawakita's equation. The plots in Fig. 3 show the relationship between $1/\varepsilon$ and the compression pressure P of both tablets. The plots of both tablets indicated two refractions. Danjo et al. (1998) analyzed the dominant factors in the compression process by dividing each curve at the refractions.

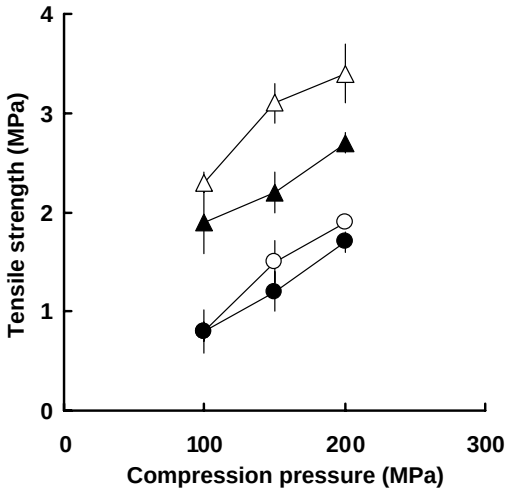

Fig. 2. Effect of compression pressure on the tensile strength of tablets consisting of AAP or KCl. (○, ●) AAP, (△, ▲) KCl. Tablets were prepared using the OSDRC method (open symbols) or physical-mixture method (closed symbols). Error bars indicate standard deviation ($n = 3$).

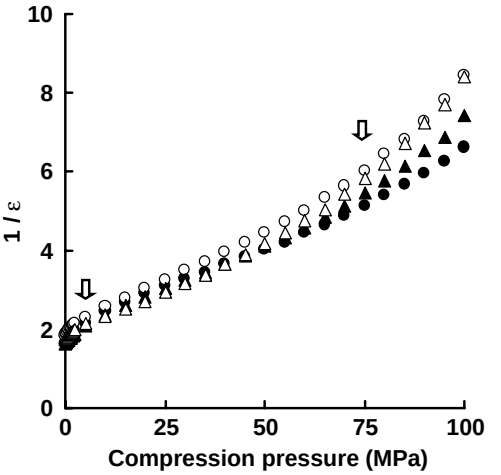

Fig. 3. Plots of the modified Kawakita's equation. (○, ●) AAP, (△, ▲) KCl. Compression pressure: 150 MPa. Tablets were prepared using the OSDRC method (open symbols) or physical-mixture method (closed symbols). Arrows indicate refractions.

The compression curve was divided into three stages. The refraction points were found at around 2 and 75 MPa on each curve. We analyzed the dominant factors in each stage (stages K_1 to K_3). The powder in stage K_1 was mainly influenced by the slide movement and re-arrangement of the particles, the powder in stage K_2 was influenced by plastic deformation and brittle breaking, and the powder in stage K_3 was influenced by the plastic deformation that took place due to reproduced particles by further brittleness. The results of the analysis, as attributes of each stage, are shown in Table 2. Both attributes of stage K_1 of OSDRC (which contained AAP or KCl) showed smaller values than those of PM. It was considered that this was due to the pre-compression process of the 1st-outer layer and the core (0.5 MPa) of OSDRC that brought about advanced particle slide and re-arrangement. On the contrary, the attributes

Table 2
Analysis of compression behavior

Sample	K_1 (1/MPa)	K_2 (1/MPa)	K_3 (1/MPa)
OSDRC–AAP	0.127	0.050	0.097
PM–AAP	0.144	0.042	0.059
OSDRC–KCl	0.105	0.047	0.105
PM–KCl	0.113	0.046	0.078

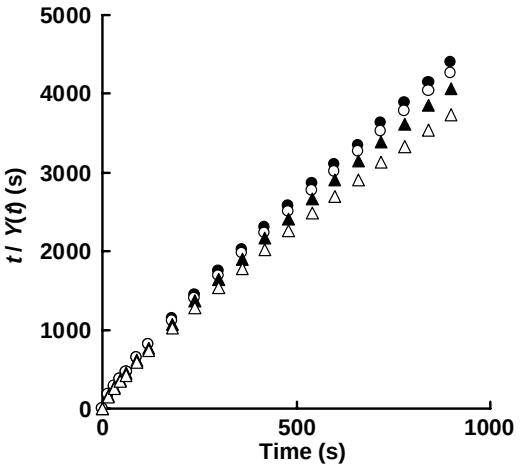

Fig. 4. Relationship between $t/Y(t)$ and t. (○, ●) AAP, (△, ▲) KCl. Compression pressure: 150 MPa. Tablets were prepared using the OSDRC method (open symbols) or the physical-mixture method (closed symbols).

of stage K_2 observed for OSDRC were equivalent or higher than those of PM for both AAP and KCl. Especially in AAP, since K_2 of OSDRC was higher than that of PM, it was thought that the plastic deformation and the brittle breaking progressed in OSDRC more than in PM. Larger attributes for K_3 than K_2 were noted in both tablets, which indicated that further compression occurred through the additional brittle breaking of particles. The attributes of K_3 for PM with AAP were obviously smaller than those of the other tablets. This phenomenon suggested that there was less compression progress.

3.3. Analysis of stress relaxation

In order to examine the compression characteristics in detail, the stress relaxation profile, as the index of plastic deformation and re-arrangement characteristics, was measured. The relaxation process was evaluated according to Eqs. (3) and (5), and the results are shown in Fig. 4. Clear linearity was obtained with all samples. The constants a and b were calculated from the slope of this straight line (Fig. 5). The constant a indicates the rate of relaxation in infinite time, a larger constant a means a bigger amount of stress relaxation. The amount of stress relaxation of OSDRC was larger than that of PM for both AAP and KCl. This would explain why particle re-arrangement, or plastic deformation, progressed more easily with OSDRC than with PM. Moreover, since KCl has a characteristic of plastic deformation, KCl showed a larger stress relaxation than AAP did.

Constant b is an index showing relaxation speed, and the relaxation speed is quick when the b value is large. The constant b of OSDRC was smaller than that of PM for both AAP and KCl. Many considerations have been made regarding Kawakita's constant b on

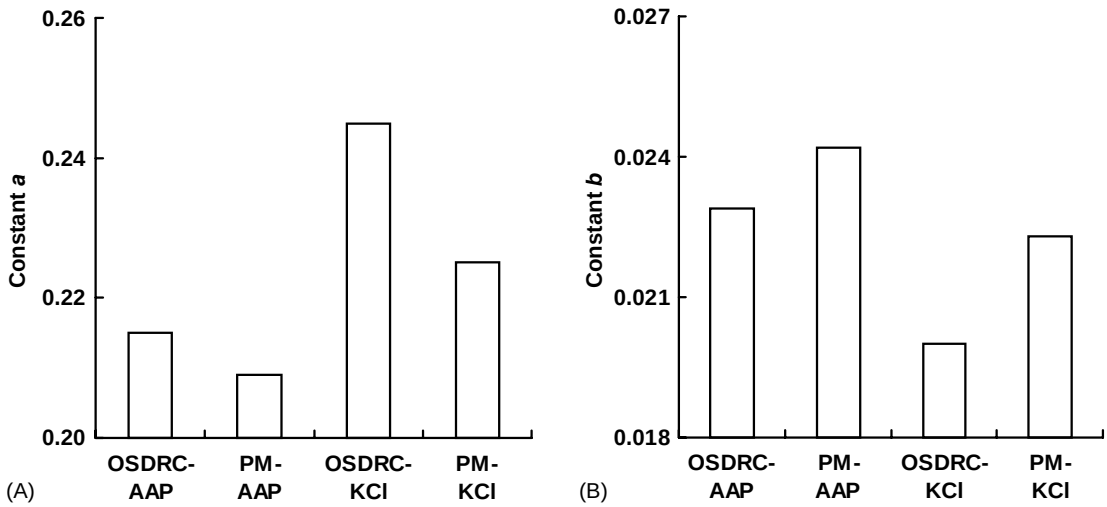

Fig. 5. Constant a and b of each sample. (A) Constant a. (B) Constant b.

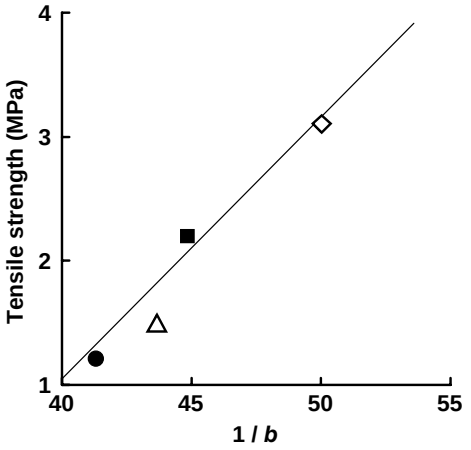

Fig. 6. Relationship between constant 1/*b* and tensile strength. (●) PM–AAP, (△) OSDRC–AAP, (■) PM–KCl, (◇) OSDRC–KCl. Compression pressure: 150 MPa. $y = -8.1216 + (-0.2251x)$ ($R^2 = 0.9549$); *y*: tensile strength; *x*: constant *b*.

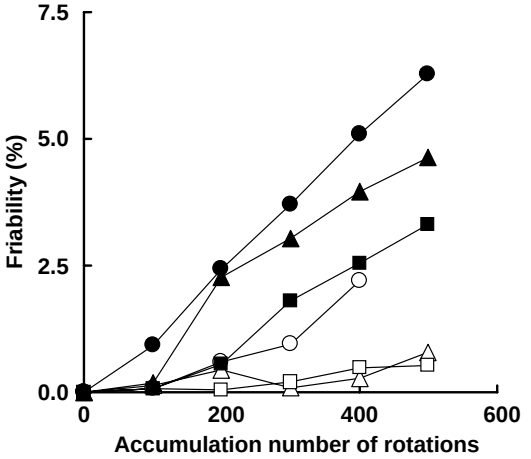

Fig. 7. Effect of compression pressure on the friability of tablets consisting of AAP. Compression pressure: (○) 100 MPa, (△) 150 MPa, (□) 200 MPa, (●) 100 MPa, (▲) 150 MPa, (■) 200 MPa. Tablets were prepared using the OSDRC method (open symbols) or the physical-mixture method (closed symbols).

the compression process in the past. Kawakita (1969) reported that 1/*b* has a positive correlation with an agglutination of particles. Yamada et al. also reported a positive correlation between the strength of the particles consisting of various materials and an increase in the 1/*b* value (Yamada and Hirosue, 1984; Yamada et al., 1987; Danjo et al., 1994). It can be interpreted that the compression of strong particles requires a longer time to be tightly compressed, that is granules under a high intensity will have a reduced compression speed. When this consideration is applied to the stress relaxation process, the stress relaxation speed would decrease as the tablet has a high intensity due to the progressing compression. Therefore, the slide movement and re-arrangement of particles would not progress, and the stress relaxation speed would decrease. The relationship between 1/*b* and the tensile strength is shown in Fig. 6. They were correlated well. Supposing that the conjecture on 1/*b* is valid, the particles of OSDRC would have stronger cohesion than those of PM. It is considered that the tensile strength of OSDRC rose in comparison with that of PM.

3.4. Relationship between the compression pressures and friability of OSDRC and PM

OSDRC and PM with AAP were subjected to a friability test under the various compression pressures. The results are shown in Fig. 7. The friability trends of both tablets differed greatly. The abrasion of OSDRC prepared at 150 and 200 MPa was small and independent of the accumulation number of drum rotations. On the other hand, the abrasion of PM increased as the accumulation number of drum rotations increased. The friability of PM decreased through the increase in compression pressure. However, for OSDRC, an

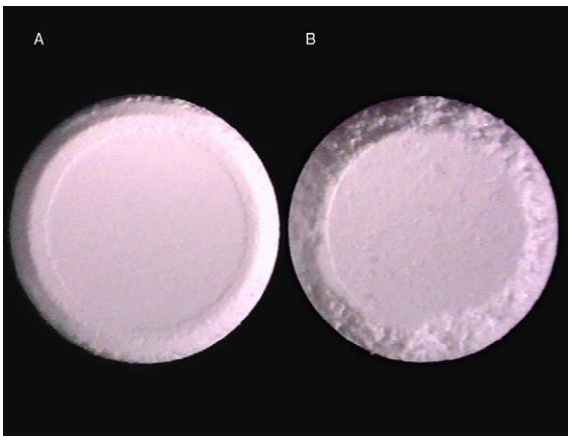

Fig. 8. The AAP tablets after the friability test. Accumulation number of rotations: 500. Compression pressure: 150 MPa. (A) The OSDRC method. (B) The physical-mixture method.

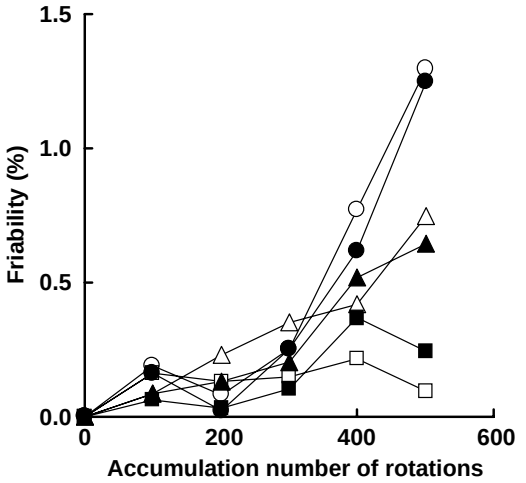

Fig. 9. Effect of compression pressure on the friability of tablets consisting of KCl. Compression pressure: (○) 100 MPa, (△) 150 MPa, (□) 200 MPa, (●) 100 MPa, (▲) 150 MPa, (■) 200 MPa. Tablets were prepared using the OSDRC method (open symbols) or the physical-mixture method (closed symbols).

almost constant friability was observed at every compression pressure, except at the low compression pressure, 100 MPa. OSDRC compressed at 100 MPa collapsed in the course of the test. The appearance of both tablets after the friability test is shown in Fig. 8. Remarkable differences at the edges of both tablets were recognized in particular. The same test was performed on tablets containing KCl. The results are shown in Fig. 9. Unlike AAP, the abrasion of both tablets slightly increased with an increase in the accumulation number of drum rotations. However, there was no difference of the friability between OSDRC and PM. The above experiments indicated that OSDRC had superior friability than PM because of its hard surface, even though both tablets were prepared under the same compression pressures with the same ingredients.

On the other hand, it was considered that no remarkable difference in friability would be seen with ingredients like KCl that have excellent plastic deformation characteristics, since the intensity of the whole tablet was high.

3.5. Evaluation of the inside intensity of both tablets

Distribution of the inside intensity of both tablets was evaluated using a constant load boring intensity analyzer. The distribution of the inside intensity of the tablet was indicated by the speed of the drill penetration. The drill penetrates rapidly into a tablet with a low intensity. The results of both OSDRC and PM, that contained AAP, are shown in Fig. 10. The penetration speed of the drill was slow at the early stage of boring for OSDRC, however the speed increased at the middle stage, an then returned to the same slow speed as the early stage at the end of the test. This indicated that there was a low-intensity portion at the center, and a high-intensity portion at the outer layer of OSDRC. Conversely, the boring speed of PM was almost constant from the early to the end stages.

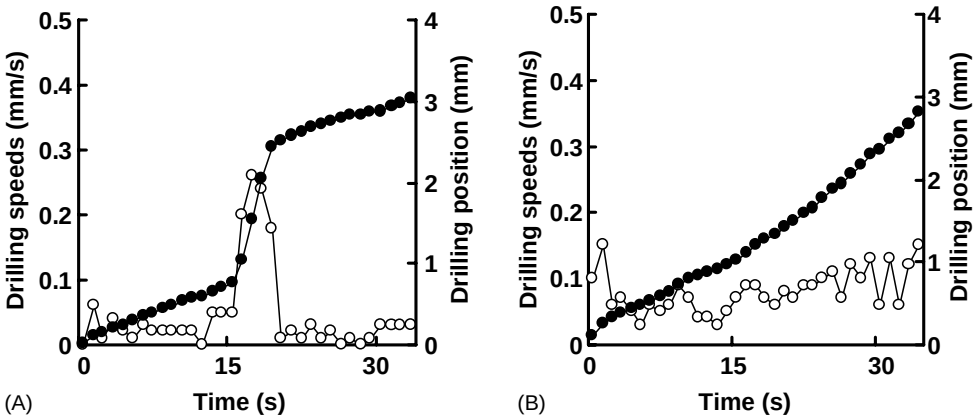

Fig. 10. Evaluation of the inside intensity of the AAP tablets with the spin analyzer. (A) The OSDRC method. (B) The PM method. (○) Drilling speeds, (●) drilling position. Compaction pressure: 150 MPa.

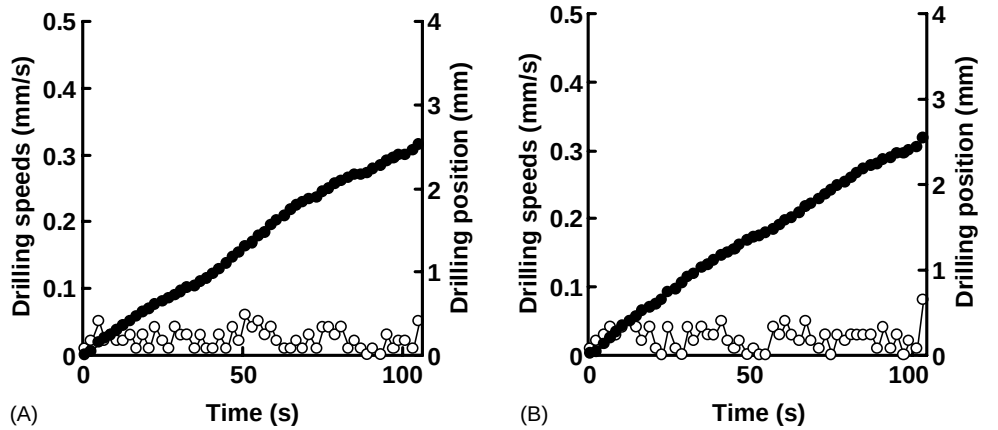

Fig. 11. Evaluation of the inside intensity of the KCl tablets with the spin analyzer. (A) The OSDRC method. (B) The PM method. (○) Drilling speeds, (●) drilling position. Compaction pressure: 150 MPa.

Furthermore, the boring speed was faster than that observed for the early stage of OSDRC. It meant that the surface intensity of PM was clearly lower than that of OSDRC.

The results for OSDRC or PM that containing KCl are shown in Fig. 11. Unlike the AAP, there was no difference between the tablets.

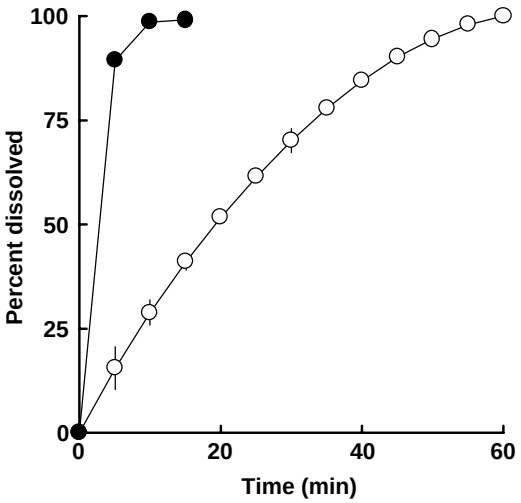

Fig. 12. Dissolution profiles of acetaminophen from OSDRC or PM in purified water. Compaction pressure: 150 MPa. Tablets were prepared using the OSDRC method (open symbols) or the physical-mixture method (closed symbols). Error bars indicate standard deviation ($n = 3$).

3.6. Evaluation of the release characteristics of the model drugs1111

The release pattern of AAP from both tablets was evaluated according to the dissolution test method. The results are shown in Fig. 12. Almost all the AAP was released from PM within a 10 min dissolution time course. On the contrary, the release of AAP from OSDRC was apparently controlled. The difference in the release pattern between OSDRC and PM was attributable to the fact that AAP was uniformly dispersed in the test solution due to a uniform distribution with an excipient in PM. This uniform distribution in PM increased the ratio surface area of AAP. On the contrary in OSDRC, since the particles were larger due to the compressed AAP particle itself, the surfaces of the AAP particles were decreased, and the release speed was lowered.

4. Conclusion

This study provided the following:

(1) The radial tensile strength of OSDRC was the same as, or superior to, that of PM. The analysis results of the compression characteristics according to Kawakita's equation also supported this feature.

(2) The friability of OSDRC containing AAP was superior to that of PM. The trend was remarkable with ingredients that had higher brittleness.
(3) The internal intensity of OSDRC containing AAP was high at its surface and low in the inside. OSDRC containing KCl, which has a superior plastic deformation ability, had a high internal intensity, and was thought to have no advantage with OSDRC that enabled it to arrange different ingredients in one tablet.
(4) OSDRC showed a controlled drug release pattern, even though it did not contain any material known for its influence on drug release. This was attributable to the decreased particle surface due to the compression of the AAP particles.
(5) The above suggests the possibility that conventional hard capsule like tablets can be produced by the OSDRC compression method, which arranges powder with low tabletability in the core, surrounded by an outer layer with a superior-compression-characteristic powder.

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