Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 336 (2007) 99–107
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Development and evaluation of a novel dry-coated tablet technology for pellets as a substitute for the conventional encapsulation technology

Masaki Ando[a,*], Sayaka Kojima[a], Yuichi Ozeki[a], Yukiharu Nakayama[a], Toshitaka Nabeshima[b]

[a] *Pharmaceutical Research & Technology Laboratory, Sanwa Kagaku Kenkysho Co. Ltd., 363 Shiosaki, Hokusei-cho, Inabe City, Mie 511-0406, Japan*
[b] *Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, 65, Tsuruma-cho, Showa-ku, Nagoya 466-8560, Japan*

Received 25 August 2006; received in revised form 13 November 2006; accepted 18 November 2006
Available online 26 November 2006

Abstract

Pellet formulations as represented by multiparticulate systems are often contained in hard capsules. We examined the use of a different approach to the making of compressed tablets containing pellets, OSDRC-technology. OSDRC-technology employs a double-structure punch (center punch and outer punch) allowing for dry-coated tablets to be assembled in a single run. We examined the effects of the thickness of the outer punch, formability of pellets, and diameter of tablets on pellet filling. The results revealed that thinner outer punches are not always better for filling small tablets with large amounts of pellets. We considered that this was because the core pellets spread in a cone shape within the formulating tablets at filling, requiring a thickness of the outer punch and a particle density of the diluents at which pellets would not exude from the formulating tablets. It was suggested that the formability of core pellets affects the maximum number of layers of pellets, and higher formability would yield better results. However, we found that pellets with poor formability (tensile strength of $\leqq 2$ kPa) could be used in tablets. For the tablets, the larger the diameter, the greater the maximum number of layers. We considered this to be due to the friction between the pellets and punch wall. We concluded that OSDRC-technology could be applied to capsule-like forms containing pellets $\geqq 50$ wt% through an unconventional approach.

Keywords: One-step dry-coated tablets; Dry-coated tablets; Compression-coated tablets; Capsule; Formulation

1. Introduction

Multiparticulate systems usually consist of coated pellets, pellets without a coating membrane, microcapsules, or microspheres, and have been receiving increasing attention as one of the technologies and methodologies of controlled release. Multiparticulate systems using pellets are thought to be more desirable than single unit dosage forms (Yao et al., 1997, 1998). Fekete et al. (1998) reported that the use of pellets prevented high local drug concentrations, since the pellets spread uniformly in the gastrointestinal tract, etc. Capsules are often employed as a dosage form to facilitate the oral administration of pellets as multiparticulate systems. It is expected that the pellets will be rapidly redispersed in the stomach with the disintegration of the capsules (Yao et al., 1997).

Capsules, however, do not satisfy all demands as a platform for the oral delivery of pellets, and a great deal of effort has been devoted to finding ways to incorporate pellets into compressed tablets (Bechard and Leroux, 1992; Maganti and Celik, 1994; Schwartz et al., 1994; Aulton et al., 1994). The demand for compressed tablets containing pellets is increasing compared with that for hard gelatin capsules. Torrado and Augsburger (1994) reported the advantages of tablets of be: (I) lower production costs; (II) reduced liability to tampering; (III) ease of swallowing. Haslam et al. (1998) showed the greatest advantage is what scored tablets-containing pellets can be prepared, easily offering dividable doses.

Though tablets have various advantages over capsules, it is difficult to apply conventional pharmaceutical technology to the preparation of tablets containing a lot of pellets. This is because pellets, in general, are not formable and are readily segregated from other diluents, and they are more likely to be destroyed in the compression process. For example, the segregation of the pellets from the blended powder is unavoidable as long as

---

[*] Corresponding author. Tel.: +81 594 72 6221; fax: +81 594 82 0070.
E-mail address: m_andoh@mb3.skk-net.com (M. Ando).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.11.042

a powder flow exists because of differences in size or density (Yubuta et al., 1995). Frequently, a blended powder with pellets for tableting segregates on the turntable of a rotary-tableting machine during the compression process due to vibration and centrifugal force (Edited by the Society of Powder Technology, Japan, 1998a). Tanino et al. (1995) reported that tableting using a segregated powder affected drug content and tablet weight.

For the reasons described above, it has been difficult until now to make tablets containing a lot of pellets and having good compression characteristics. We previously reported one-step dry-coated tablets (OSDRC®) manufactured by a new process using a unique punch and die (Ozeki et al., 2000, 2002, 2003a,b, 2004). Our own manufacturing technique, OSDRC-technology, does not require the preparation of core tablets beforehand, allowing for dry-coated tablets to be assembled in a single run with a rotary-type tableting machine. Further, OSDRC-technology makes it possible to form tablets with ingredients which are not suitable for conventional tableting due to their poor formability (Ozeki et al., 2003c). Furthermore, in the manufacture of OSDRC, since a blended powder of pellets and diluents is not used for the tableting, there are no conventional problems regarding the segregation of pellets and diluents. Thus, we tried to make dry-coated tablets containing only pellets in the core using our own manufacturing technique.

The objective of this study was to examine whether tablets containing large amounts of pellets can actually be prepared using OSDRC-technology. This study therefore focused on the pellet content and formability of the tablet. Another issue regarding pellet-containing formulations, damage to the pellets sustained during the compression process, will be discussed in another report. If preparations containing a large amount of pellets are to be made using the OSDRC-technology, a thinner outer punch equivalent thickness to the outer layer of the formulated tablets may be advantageous. Then, this study set as a target, pellet-containing preparations with an outer layer of 0.5 mm, which is absolutely impossible to prepare using the conventional dry-coated tablet manufacturing technique. The target filling volume was set at $\geqq$50 wt% at which pellet channels are more likely to be developed in conventional physically mixed tablets as shown by percolation theory.

2. Materials and methods

2.1. Materials

The pellets used as a model in this experiment were Harnal® 0.2 mg capsules (tamsulosin hydrochloride (JAN), a commercial product for hospital-use marketed by Yamanouchi Pharmaceutical Co., Japan (current Astellas Pharma Inc.)) which were available on the market. They were taken out of the capsule and used as a core for dry-coated tablets. Commercial lactose-crystal and cellulose-crystal spray dry granules (Microcelac 100; lactose and cellulose at a ratio of 3:1 in weight), a product of Meggle Co., Germany, were used as the ingredients for the outer layer. Magnesium stearate (MgSt) obtained from Taihei Chemical Co., Ltd., Japan, was used as a lubricant. Furthermore, food red No. 3 aluminum lake (Sankyo Chemical) was used as a colorant. Microcelac, MgSt, and aluminum lake were mixed at ratio of 99:1:0.01 in terms of weight, using a V type blender (Micro blender; Tsutsui Rikagaku Instrument Co., Japan) for 5 min. The mixture obtained was used as a powder for the outer layer.

2.2. Evaluation of the physical properties of model pellets

The mean particle diameter, particle density, and flowability of the pellets used for experiments were evaluated. The mean particle diameter was determined by the sieve method, and the particle density, bulk density, and tap density were determined with a powder tester (Hosokawa Micron Corporation). For the flowability, the angle of repose and compressibility were also measured using this tester.

2.3. Preparation of the one-step dry-coated tablets (OSDRC) containing pellets using a model punch and die

We have developed a rotary-type tableting machine to manufacture pellet-containing OSDRC (Fig. 1). For this study, however, we used a single set of punches and die for the preparation of OSDRC. The OSDRC were prepared by the method described below. The manufacturing process involved the use of an upper-center punch (5–9 mm in diameter), a lower-center punch, an upper-outer punch, and a lower-outer punch (7–11 mm in outer diameter).

This method of manufacturing employs three compression processes; the first compression is to form the bottom-outer layer (indicated as the first-outer layer), the second is to make the first-outer layer/core layer complex, and the third is to form the whole tablet consisting of the upper-outer and side-outer layers (the second-outer layer).

In the first step, the lower-center punch was slid down to fill the space made by the lower-center punch and the inside wall of the lower-outer punch, with the powder for the first-outer layer, and then the powder was pre-compressed by the upper-center punch. While the upper-center punch was pushing down on the pre-compressed first-outer layer, the lower-center punch was slid down. The upper-center punch was pulled up to make the space which was to be filled with the pellets for the core layer, and was then pre-compressed by the upper-center punch. The lower punch was slid down with a pre-compressed layer to fill the die with the powder for the second-outer layer. Then, the pre-compressed layer was pushed up into the die filled with the powder for the second-outer layer. During the final 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^{-1} under various compression pressures using a universal tension and compression tester (AG-I 20 kNT; Shimadzu Co., Japan). The tips of the center and outer punches were adjusted to create a flat face, like a normal punch. The tablets were left at room temperature for 24 h in a desiccator with silica gel, and then subjected to testing.

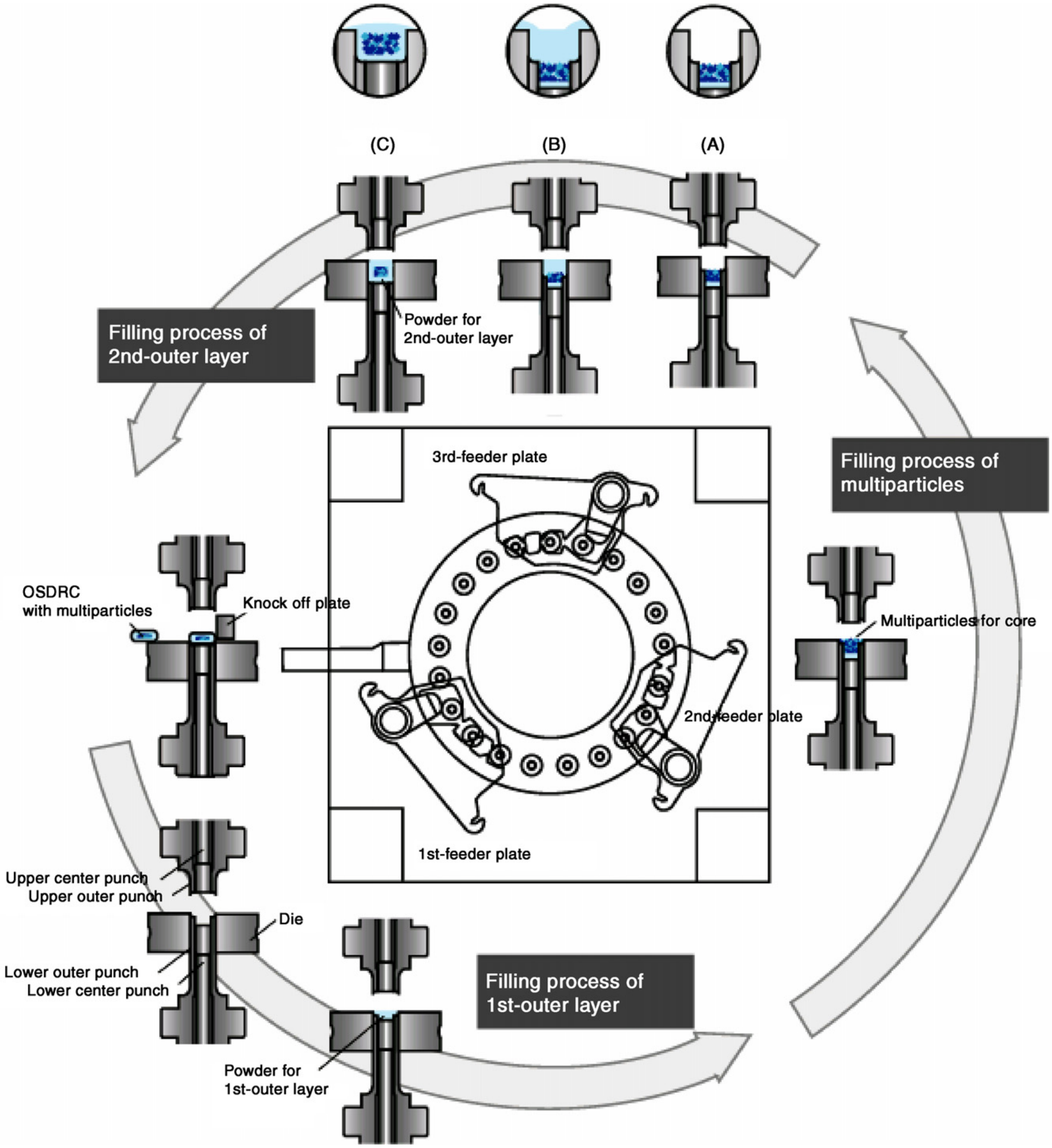

Fig. 1. Overhead view of the rotary tableting machine for OSDRC.

2.4. *Stress relaxation test*

The stress relaxation test was performed using the universal tension and compression tester. The decrease in force was recorded for 1200 s 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):

$$Y(t)=\frac{P_0-P_t}{P_0} \tag{1}$$

where P_0 is the initial force, and P_t is the force after time t. $Y(t)$ with t was fitted to Eq. (3), obtained by modifying Kawakita's equation, Eq. (2), to estimate constants a and b, which characterize stress relaxation (Danjo et al., 1998):

$$Y(t)=\frac{abt}{1+bt} \tag{2}$$

$$\frac{t}{Y(t)} = \frac{1}{ab} + \frac{t}{a} \tag{3}$$

2.5. Measurement of radial tensile strength

Given amounts of pellets were formed under various compression pressures. The pellets were subjected to a diametral compression test using a force gauge (Nihon Densan Shinpo; FGC-0.2B) 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 calculating the radial tensile strength T using the following equation (Fell and Newton, 1970):

$$T = \frac{2H}{\pi d L} \tag{4}$$

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

2.6. Measurement of elastic recovery rate

Given amounts of pellets were compressed under various pressures using a universal tension and compression tester, and then the height of the pellets formed under pressure was determined with a digital measure (Mitutoyo, HDS-20C) to calculate elastic recovery rates.

3. Technical view of the manufacturing process and the issue of segregation

The macroscopic segregation behavior of a powder is generated by its flow. Typical causes of segregation include (I) size, (II) density and (III) shape, etc. (Edited by the Society of Powder Technology, Japan, 1998b). Usually, segregation is generated by a combination of these causes. The segregation of a pharmaceutical powder is also frequently observed during the compression process. This is caused by the vibration and centrifugal force of the turntable of the rotary tableting machine. It should be realized that a powder often segregates when it is a physical mixture of pellets and diluents, which results in variation in the weight and formability of tablets.

Our manufacturing technique, OSDRC-technology, essentially prevents segregation during the preparation of pellet-containing tablets, since it does not use a physical mixture. Fig. 1 shows the turntable of the rotary-type tableting machine used to make the pellet-containing OSDRC. Three feeder plates were located on the turntable. The first, second, and third-feeder plates supplied the powder for the first-outer layer, the pellets for the core, and the powder for the second-outer layer, respectively. Therefore, there are no qualitative problems regarding the segregation of pellets and diluents using OSDRC-technology.

The new manufacturing technique has been designed to completely surround pellets having significantly poor compression characteristics, using diluents with good formability to form tablets. The motion of the punches is described briefly as follows.

The core being held by the lower-center punch and lower-outer punch and the pre-compressed first-outer layer are pulled down with the lower-punch (Fig. 1A) to make the space that is to be filled with the second-outer layer. Then, the powder for the second-outer layer is placed in the die (Fig. 1B). The pre-compressed layer is pushed up into the die filled with the powder (Fig. 1C). We therefore proved that the diluents as an outer layer can completely surround the pellets without segregation problems by using the manufacturing technique for pellet-containing OSDRC.

Furthermore, since the poor formability core is completely surrounded by the good formability ingredients of the outer layer, the tablets are superior in abrasiveness to conventional physically mixed tablets (Ozeki et al., 2003c).

4. Results and discussion

4.1. Evaluation of flowability and formability of model pellets

This study evaluated whether a formulation containing a large amount of pellets can actually be tableted. We chose model pellets with poor formability, which makes the tableting process difficult, and with high flowability, which makes them more likely to spread during the manufacturing process. This means that the model pellets would retain a nearly consistent low formability and high flowability even when tableted at increased compression pressure. Since we chose the pellets based on these requirements, we performed no evaluation of their destruction per se by compression.

The basic characteristics of the model pellets are presented in Table 1. The particle diameter for D_{50} was 562 μm, with a low angle of repose and compressibility, and the flowability determined from the Carr index was very good. The formability of pellets is described in the next section.

4.2. Prediction of the number of layers of model pellets

Evaluation of the filling volume of pellets by mass makes it difficult to compare formability due to changes in parameters such as tablet diameter. This means that even with the same mass of pellets, a monolayer is likely to be more advantageous in terms of formability than multiple layers. Then, this study set the criteria for evaluating filling volume as the number of layers the pellets formed in the compressed tablets. Assuming for convenience that the pellets formed the closest packed structure, a hexagonal structure, the number of layers was calculated using D_{50}. Fig. 2 illustrates the mass of pellets per layer for individual tablets.

Table 1
Characteristics of the model pellets

Average diameter (μm)	562
Angle of repose (°)	25
Bulk density ($\mathrm{g\,cm^{-3}}$)	0.886
Tap density ($\mathrm{g\,cm^{-3}}$)	0.993
Compressibilty (%)	5

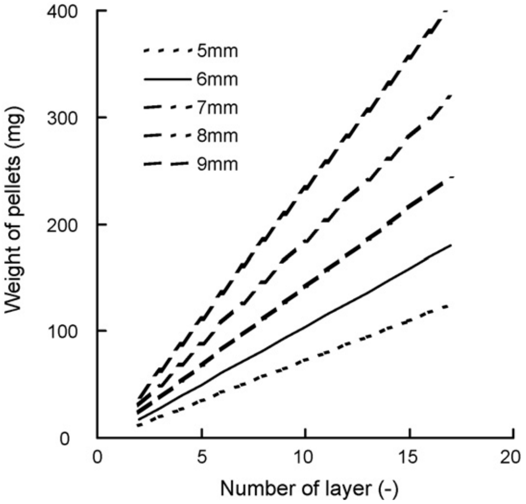

Fig. 2. Relationship between pellet mass and maximum number of layers. Each line indicates the diameter of the center punch.

4.3. *Effects of thickness of outer punch on pellet filling volume*

Since OSDRC are prepared by a double-punch system, the shape of the punches determines the shape of the final tablets. Theoretically, the diameter of the center punch is equivalent to the diameter of the core portion, and the outer diameter of the outer punch is equivalent to the diameter of the final tablets. In other words, the thickness of the outer punch is equivalent to one half of the difference between the diameter of the center punch and outer diameter of the outer punch.

Then we fixed the diameter of the center punch at 6 mm and evaluated the maximum number of layers using an outer punch with a thickness of 0.5, 1.0, or 2.0 mm. In this study, the number of cumulative layers (filling volume) on the destruction of compressed tablets or on exposure of the pellets at the surface of the tablets, was defined as the maximum number of layers. The results are shown in Fig. 3. An outer punch of 0.5 mm formed three layers, exhibiting a filling rate of just 35%, whereas one of 2.0 mm formed 40 layers or more, yielding a filling rate of 60% or more. This clarified that thicker outer punch results in increased filling volume and a greater number of layers. However, it was not clear whether the first target, a filling volume rate of 50% or more, could be achieved with an outer punch of 0.5 mm.

Here, we discuss the pellet filling system. The pellet compressing process when tableting OSDRC is performed by pushing up the pellets for the core into the die filled with the powder for the outer layer. As illustrated in Fig. 4, pellets with good flowability may be elevated through the powder in the die when pushed up. Since the pellets being pushed up are naturally pressed down by the powder in the die, they spread in a cone shape within the powder. Thus, thinner outer punches create less space for the pellets to spread in a cone shape. Fig. 5 presents a lateral picture of a tablet exceeding the maximum number of layers. The pellets exude from on the lower lateral surface of the tablet. The same trend was observed in all samples. This suggested that the pellets spread in a cone shape within the tablets.

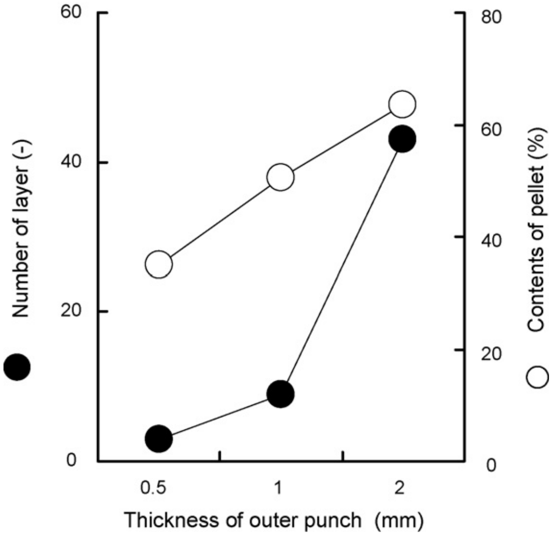

Fig. 3. Effects of thickness of the outer punch on maximum number of layers and maximum pellet filling volume. (○) Maximum pellet filling volume and (●) maximum number of layers. A center punch 6 mmφ and outer punch 7, 8, or 10 mmφ were used. Each sample was prepared with the pre-compression pressure set at 100 MPa and the final compression pressure set at 60 MPa for tableting.

When the pellets spread in a cone shape, the powder present in the outer punch is either transferred to another space or compressed toward the periphery of the outer punch. Since the same phenomenon was observed with 0.5 and 2.0 mm punches, the 2.0 mm punch may have created a denser of outer layer on the lateral surface than the 0.5 mm punch. As a result, at tableting, the pellets were transferred in the horizontal direction (toward the side of the tablets), but the increased density of the outer-layer powder with the 2.0 mm punch may have enabled 40 or more layers to form without the pellets being exposed from the side of the tablets.

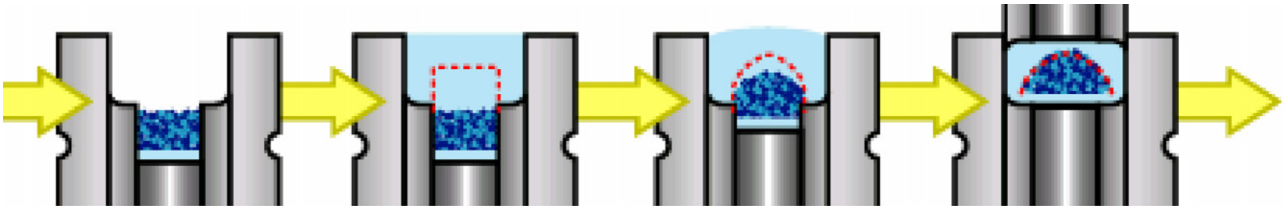

Fig. 4. Images of pellets spreading within a tablet in the core pellet compressing process.

Fig. 5. Sample tablets with pellets exuding from the side. The white on the side of the tablet is diluent, while the colored particles dotted on the lower surface are pellets.

4.4. Relationship between the thickness of the outer punch and of the outer layer of compressed tablets

If the pellets actually spread in a cone shape, the thickness of the outer layer of the compressed tablets should be less than that of the outer punch. Then, we measured the thickness of the outer layer on the lower side of samples prepared with the outer punches 0.5, 1.0, and 2.0 mm in thickness. The results are shown in Fig. 6. The thickness of the outer layer of the actual tablets was almost unchanged with the outer punch of 0.5 mm, whereas it was reduced about one half with the outer punches 1.0 and 2.0 mm in thickness. These results confirmed the consolidation of the outer layer is ingredients with the movement of the pellets and clarified that thinner outer punches yield less consolidation of the outer layer powder, whereas thicker outer punches promote consolidation of the outer layer powder. Such phenomena may not only prevent the pellets from exuding from the side of tablets but also positively affect the strength of tablets after tableting.

The actual tablet compressed by the outer punch 1 mm in thickness presented an outer layer 0.54 mm thick, with a pellet content of 50.5%, which met the first of our targets. It was suggested that upon the manufacture of tablets with a greater number of layers (higher content) using OSDRC technology, if the final product is to be 9 mm in diameter, setting the center punch (core diameter) at 7 mm rather than 8 mm results in tablets containing a larger amount of pellets.

4.5. Effect of differences in formability of pellets on filling volume

When the pellets are pushed up into the die during the manufacturing process, the cone-shape spread of pellets may be affected by: (1) the speed of the punch and (2) formability of the pellets. Since the speed with which the pellets are pushed up is kept constant in actual tableting, here we focused on formability for evaluation of the relationship between the formability and filling volume of pellets. In the manufacture of OSDRC, pre-compression is performed before the final compression on the core. We prepared core pellets with different formabilities by using various pressures for the pre-compression.

The radial tensile strength was measured in the core pellets prepared at various compression pressures. The results are shown in Fig. 7. With increased compression pressure, the radial tensile strength increased. This is because a larger compression pressure increases the contact area among the pellets due to rearrangement of the pellets, thereby increasing the inter-pellet frictional force. However, the tensile strength determined in this study was about 2 kPa at maximum, at which the pellets fall apart if they come into contact with any object, and cannot be handled at all.

Subsequently, we fixed the outer punch's thickness at 1 mm and the center punch's diameter at 6 mm and examined to what extent varying the compression pressure applied to the core pellets would change the maximum number of layers. Finally,

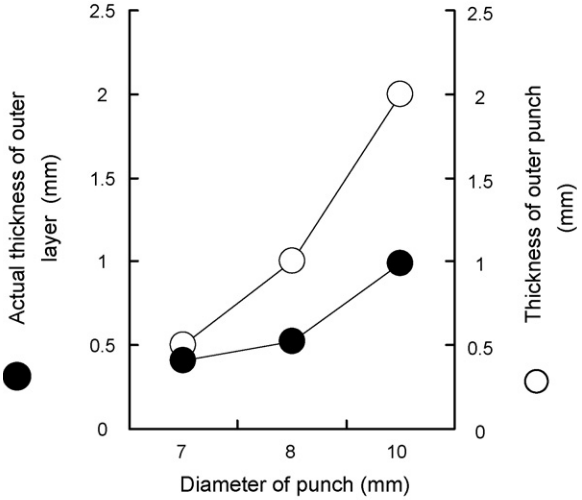

Fig. 6. Relationship between the thickness of outer punches and actual thickness of outer layer of tablets. (○) Thickness of outer punch; (●) thickness of outer layer of actual tablets.

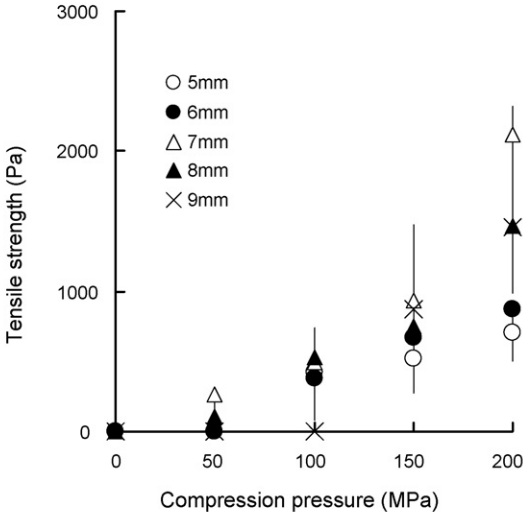

Fig. 7. Relationship between the core pellets and tensile strength at different pre-compression pressures. Center punch: (○) 5 mm, (●) 6 mm, (△) 7 mm, (▲) 8 mm and (×) 9 mm Data are expressed as the mean ± S.D. of three runs.

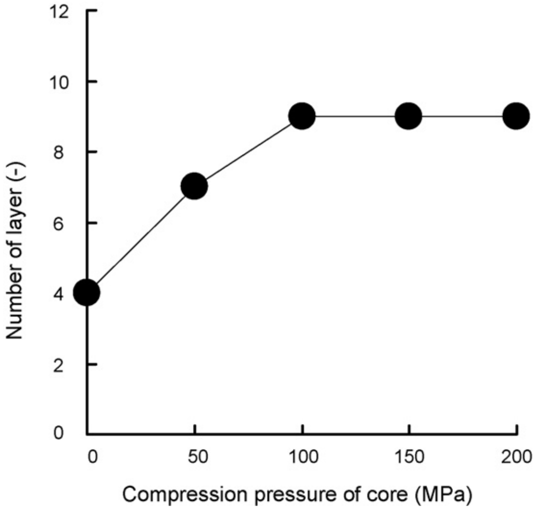

Fig. 8. Effect of pre-compression pressure on the maximum number of layers for the core pellets. A center punch 6 mmφ and outer punch 8 mmφ were used. Each sample was prepared with a pre-compression pressure of 0, 50, 100, 150, or 200 MPa and a final compression pressure set at 50 MPa for tableting.

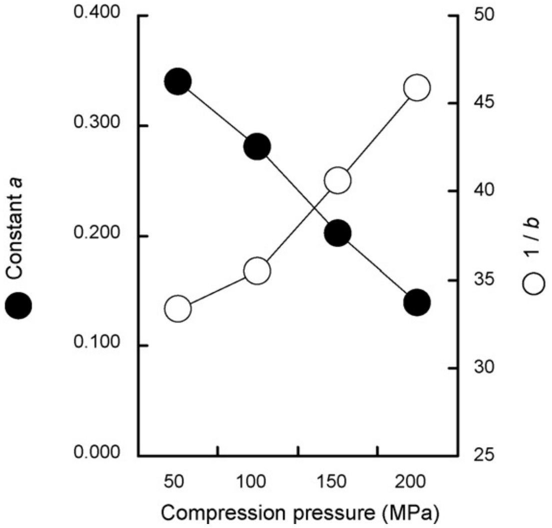

Fig. 9. Plastic deformation parameters of core pellets prepared at different pre-compression pressures. An amount equivalent to eight layers was used to perform a stress relaxation study for 1200 s after maximum stress. (○) 1/*b*; (●) Constant *a*.

the compression pressure to form tablets was determined to be 50 MPa. The results are shown in Fig. 8. At 0–100 MPa, the maximum number of layers increased together with the compression pressure. On the other hand, pressures exceeding 100 MPa all resulted in nine layers. Increasing the compression pressure increased the formability of pellets, thereby making the material less likely to exude. On the other hand, at ≧100 MPa, despite an increase in formability (see Fig. 7), the number of layers did not increase. The higher the compression pressure is, the more formability is increased, but at the same time, the elastic recovery of the pellets increased, which may make them more susceptible to destruction. Then, to investigate the effects of compression pressure on the physical properties of the pellets, we measured the stress relaxation and elastic recovery rate of the pellets. Fig. 9 shows constants *a* and *b* in the stress relaxation process under each compression pressure. In general, constant *a* represents stress relaxation for an infinite period of time.

As the compression pressure increased, constant *a* decreased. This suggested that when the core pellets are pressed tightly, plastic deformation takes place. On the other hand, constant *b* was evaluated as 1/*b*. Yamada and Hirosue (1984, 1987) have reported a good proportional relationship between 1/b and tensile strength. Also in this experiment, a good correlation was found between increases in 1/*b* and tensile strength, and the stress relaxation process also supported a relationship between compression pressure and formability of pellets.

Elastic recovery rates are given in Fig. 10. As compression pressure increased, the elastic recovery rate increased, and the pellets exhibited reversible elastic deformation. The results of the previous stress relaxation study suggested that increasing the compression pressure resulted in more frequent plastic deformation of the pellets, but taking the results shown in Fig. 10 into consideration, this may be due to filling and deformation attributable to the rearrangement of particles, which were within the elastic area. Therefore, the formability may have resulted from deformation due to rearrangement of the pellets and associated increases in the contact area and inter-pellet frictional force. Based on the above, as the compression pressure increased, the formability of the pellets increased, but at the same time, the elastic energy of the pellets increased, and as a result, the value for the maximum number of layers did not increase linearly due to the spread of pellets with pushing up and associated exuding from the side of tablets.

4.6. *Effects of tablet diameter on pellet filling volume*

In order to examine the effects of core diameter on pellet filling volume, using the outer punch 1 mm in thickness, we

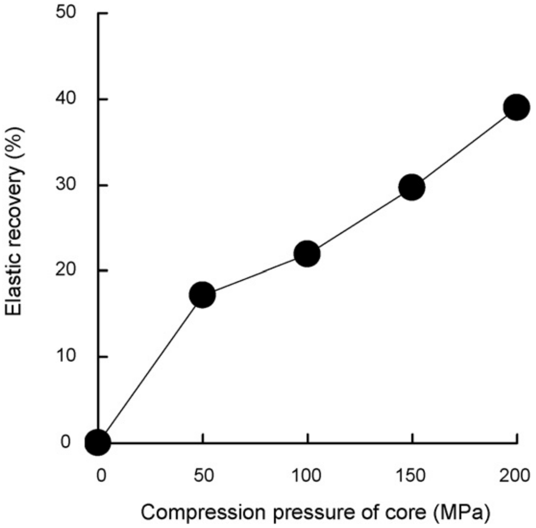

Fig. 10. Elastic recovery rates of core pellets prepared at different pre-compression pressures. A amount equivalent to eight layers was used and removed after compression at a certain pressure to measure the height of the core pellets.

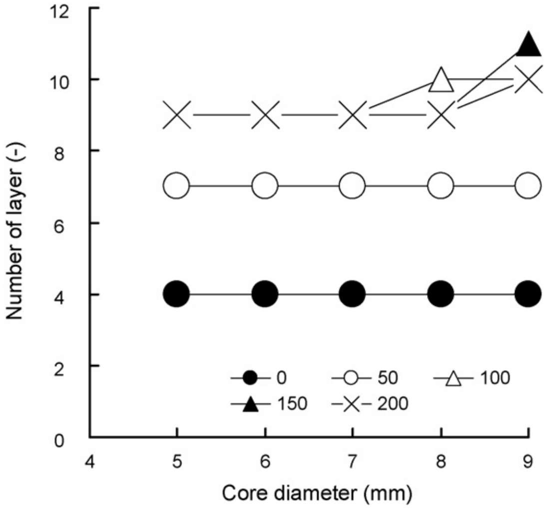

Fig. 11. Effects of tablet diameter on pellet filling volume. An outer punch 1 mm thick was used. Each sample was prepared with the pellet pre-compression set at: (●) 0 MPa, (○) 50 MPa, (△) 100 MPa, (▲) 150 MPa, (×) 200 MPa, and the final compression pressure set at 50 MPa for tableting.

evaluated the center punches 5–9 mm in diameter, i.e. for a tablet ranging in diameter from 7 to 11 mm. At the same time, we also evaluated different compression pressures on the core pellets equivalent to that of the pre-compression process.

The results are shown in Fig. 11. With a pre-compression pressure on the center core pellets of 0 and 50 MPa, no variation was found in the maximum number of layers according to the core diameter. On the other hand, at compression pressures of $\geqq$100 MPa, with the core punch of $\geqq$7 mm, there was a trend toward a increased maximum number of layers. This may be because of the effects of friction between the pellets and outer punch wall during in the manufacturing process as the pellets are pushed up into the die. The pressure on the wall of the powder layer can be explained by Janssen's equation, but the smaller center punch caused greater wall surface friction, thereby leading to the significant spread of pellets. In contrast, larger diameters may cause less friction, resulting in a larger number of layers. The reason why the pre-compression pressure of 0 and 50 MPa showed no such trend was that in the absence of or at low compression, the pellets were less likely to be affected by the outer punch wall's surface.

5. Conclusions

This study revealed the following findings:

(1) OSDRC technology enabled us to prepare capsule-like tablets containing pellets of 50 wt% or more.
(2) For filling tablets with large amounts of pellets, the sizes of the center punch and outer punch are important factors. For the manufacture of tablets with a greater number of layers, an outer punch with a thickness of >1.0 mm rather than 0.5 mm was suitable. We concluded that this was because the core pellets spread in a cone shape within the compressed tablets at filling, and a certain amount of physical space and particle density of diluents are required to prevent the pellets from exuding from the compressed tablets.
(3) The formability of core pellets affects the maximum number of layers of pellets, and greater formability is advantageous. However, it was clarified that pellets with very poor formability (tensile strength of $\leqq$2 kPa) could be tableted.
(4) The number of layer of pellets depends on both the thickness of the outer punch and center punch diameter. The outer punch needs to be at least 1.0 mm thick as mentioned above. With regard to the center punch diameter, a large diameter, such as $\geqq$7 mm, yielded a larger maximum number of layers. This may be because of the friction between the pellets and punch wall's surface.
(5) The results above suggested that tablets containing pellets could be prepared by an approach different from conventional ones. We will continue to examine those pellets damage to which may affect the dissolution profile such as coated pellets, but other pellets can probably be tableted using this technology.

Acknowledgement

We are grateful to Kikusui Seisakusho Co., Ltd. for supplying the model punches and die used for the experiments.

References

Aulton, M.E., Dyer, A.M., Khan, K.A., 1994. The strength and compaction of millispheres. The design of a controlled-release drug delivery system for ibuprofen in the form of a tablet comprising compacted polymer-coated millispheres. Drug Dev. Ind. Pharm. 20, 3068–3104.

Bechard, S.R., Leroux, J.C., 1992. Coated palletized dosage form: effect of compaction on drug release. Drug Dev. Ind. Pharm. 18, 1927–1944.

Cutt, T., Fell, J.T., Rue, P.J., Spring, M.S., 1987. Granulation and compaction of a model system. II. Stress relaxation. Int. J. Pharm. 39, 157–161.

Danjo, K., Hiramatsu, A., Otsuka, A., 1998. Effect of punch velocity on the compressibility and stress relaxation of particles and granules. J. Soc. Powder Technol. Jpn. 35, 662–670.

Fekete, R., Zelko, R., Marton, S., Racz, I., 1998. Effect of the formulation parameters on the characteristics of pellets. Drug Dev. Ind. Pharm. 24, 1073–1076.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 5, 688–691.

Haslam, J.L., Forbes, A.E., Rork, G.S., Pipkin, T.L., Slade, D.A., Khossravi, D., 1998. Tableting of controlled release multiparticulates, the effect of millisphere size and protective overcoating. Int. J. Pharm. 173, 233–242.

Imai, M., Kamiya, K., Hino, T., Yamamoto, H., Takeuchi, H., Kawashima, Y., 2001. Development of agglomerated crystals of ascorbic acid for direct tableting by spherical crystallization technique and evaluation of their compactibilities. J. Soc. Powder Technol. Jpn. 38, 160–168.

Kawashima, Y., Chi, F., Takeuchi, H., Niwa, T., Hino, T., Kiuchi, K., 1995. Improved static compression behaviors and tablettabilities of spherical crystallization technique with a two-solvent system. Pharm. Res. 12, 1040–1044.

Maganti, L., Celik, M., 1994. Compaction studies on pellets. II. Coated pellets. Drug Dev. Ind. Pharm. 103, 55–67.

Ozeki, Y., Kondo, Y., Watanabe, Y., 2000. Nucleated molded article, method of producing the same, and device for producing the same. PCT, WO01/98067, December 27.

Ozeki, Y., Kondo, Y., Watanabe, Y., Shimada, K., Harada, K., 2002. Rotary type compression molding machine. PCT, WO02/90098, November 14.

Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003a. Comparison of the compression characteristics between new one-step dry-coated tablets (OSDRC) and dry-coated tablets (DC). Int. J. Pharm. 259, 69–77.

Ozeki, Y., Kondo, Y., Watanabe, Y., 2003b. Multi-cored molded article, method of producing the same, and device for producing the same. PCT WO03/026560, April 3.

Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003c. Evaluation of the compression characteristics and physical properties of the newly invented one-step dry-coated tablets (OSDRC). Int. J. Pharm. 267, 69–78.

Ozeki, Y., Watanabe, Y., Okamoto, H., Danjo, K., 2004. Development of dividable one-step dry-coated tablets (dividable-OSDRC) and their evaluation as a new platform for controlled drug release. Pharm. Res. 21, 1177–1183.

Peleg, M., Moreyra, R., 1979. Effect of moisture on the stress relaxation pattern of compacted powders. Powder Technol. 23, 277–279.

Schwartz, J.B., Nguyen, N.H., Schnaare, R.L., 1994. Compaction studies on beads: compression and consolidation parameters. Drug Dev. Ind. Pharm. 20, 3105–3129.

Edited by the Society of Powder Technology, Japan, 1998a. Compression Molding Technology of Powder. Nikkan Kogyo Shimbun Ltd, pp. 47–50.

Edited by the Society of Powder Technology, Japan, 1998b. Compression Molding Technology of Powder. Nikkan Kogyo Shimbun, Ltd, pp. 279–280.

Tanino, T., Aoki, Y., Sato, K., Takeda, Y., Mizuta, T., 1995. Tablet weight variation in wet granule compression and a method to decrease variation. J. Pharm. Sci. Technol. Jpn. 55, 114–121.

Torrado, J.J., Augsburger, L.L., 1994. Effect of different excipients on the tableting of coated particles. Int. J. Pharm. 106, 149–155.

Yamada, N., Hirosue, H., 1984. The spray drying of slurries of fine particles and the strength of spray-dried particles. J. Soc. Powder. Technol. Jpn. 8, 22–29.

Yamada, N., Hirosue, H., ABE, E., 1987. The influence of relative humidity on the strength of spray-dried products. J. Soc. Powder. Technol. Jpn. 9, 14–19.

Yao, T., Yamada, M., Yamahara, H., Yoshida, M., 1997. Tableting of coated particles. I. Small particle size chitosan as an agent protecting coating membrane from mechanical damage of compression force. Chem. Pharm. Bull. 45, 1510–1514.

Yao, T., Yamada, M., Yamahara, H., Yoshida, M., 1998. Tableting of coated particles. II. Influence of particle size of pharmaceutical additives on protection of coating membrane from mechanical damage during compression process. Chem. Pharm. Bull. 46, 826–830.

Yubuta, K., Gotoh, K., Masuda, H., 1995. Size segregation of polydispersed particles caused by vertical tapping. J. Soc. Powder. Technol., Jpn. 32, 89–96.