Preparation of Antipyretic Analgesic by Direct Compression and Its Evaluation

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Direct compression is able to produce tablets at a lower cost than wet granulation and tableting method, due to a fewer items of process validation. In this study, acetaminophen was used as a medicine with various granular diameters to formulate tablets by direct compression, thus evaluating their physical properties. Consequently, direct compression was found effective in formulating tablets with excellent physical properties, with the granular diameter taken into account. It was confirmed that tablets produced by direct compression were similar in physical properties in tablets produced by wet granulation and tableting method. Further, it was suggested that use of a dry-type binder would make it possible to provide a tablet having higher content of the medicine with excellent physical properties.

Key words direct compression; acetaminophen; medicine content; antipyretic analgesic; tablet hardness

In Japan, most of tablets or pharmaceutical solid preparations are produced by wet granulation and tableting method, because this method offers an easier control over various properties such as compressibility, disintegration and solubility by changing granulation conditions.

On the other hand, direct compression is characterized by less complicated processes and the resultant fewer validation items, because it is an extremely simple processes made up with mixing and tableting. Reportedly, direct compression is advantageous over wet granulation and tableting method in time and energy consumption, thus making it possible to formulate tablets at a lower cost.[1)] However, direct compression is directly influenced by physical properties of powders to be used in the process such as fluidity, miscibility and compressibility, posing problem in making tablets. Nonetheless, in Western countries many tablets are made by direct compression, which should justify future adoption of direct compression making it possible to make tablets easily and less expensively in Japan as well. There are only a few reports available about direct compression in Japan.

Recent years have seen development of medicines and fillers excellent in fluidity and compressibility for direct compression. There are several reports about evaluation of tablet properties by using a filler for direct compression[2,3)] or about direct compression using medicines prepared by spray drying.[4)] There are, however, only a few reports available about evaluation of tablet properties using medicines with improved fluidity for direct compression.

In this study, an antipyretic analgesic was used as a model medicine to conduct basic research for direct compression. In the first place, an antipyretic analgesic with a different granular diameter was mixed with filler for direct compression to perform this process. Tablet hardness, friability, disintegration time, dissolution and content of a medicine were determined to evaluate the thus-formulated tablets. Tablets were also produced by wet granulation and tableting method to compared the results with those obtained by direct compression. Further, tablets were produced by direct compression, with a content of the medicine changed, to make discussion. We hereby report the results of the experiment as follows.

Experimental

Powder Samples and Experiment Methods. Samples and Formulation In this study, acetaminophen was used as a model medicine for antipyretic analgesic. Five different types of acetaminophen with an individually different diameter were used to determine their granular physical properties. The results were shown in Table 1. These 5 types of acetaminophen were all made by Mallinckrodt and called Size I to Size V respectively for convenience.

Size I was the largest in the particle diameter, and Size II was a type of acetaminophen relatively commonly made by direct compression in Western countries. Size III was obtained based on Size II by sieving the particles into those with the diameter less than 420 μm. Size IV was relatively small in the granular size and Size V was a powdery type of acetaminophen that has long been made by wet granulation and tableting method. These medicines were identical in their crystal structure.

As apparent from Table 1, Size I, II and III were all small in the repose angle and compressibility, and excellent in the fluidity. The determination results revealed that only Size I was larger in the apparent density than in the tapping density. Thus, in this study, the compressibility was expressed as 0. Size I was found super in fluidity to remaining medicines. Since Size IV and V were substantially higher in the repose angle and compressibility, it was also judged that these 2 medicines were lower in fluidity than the remaining 3 size.

Figure 1 showed an example of SEM observation results of the respective medicines. Size I, II and III had prismoidal rounded particles while Size IV had prismoidal particles to which smaller particles were attached. Size V made by wet granulation and tableting method had needle-like particles.

Table 2 showed the powders and formulation adopted in this study. The 5

Table 1. Mean Diameter and Properties of Acetaminophen

Properties	Size I	Size II	Size III	Size IV	Size V
Mean diameter sizr (μm)	787	473	309	150	40
Apparent density (kg/m^3)	828	784	787	496	291
Tapping density (kg/m^3)	806	840	841	908	619
Compressibility (%)	0	6.67	6.42	45.37	52.99
Angle of repose (deg.)	28	35	28	55	61

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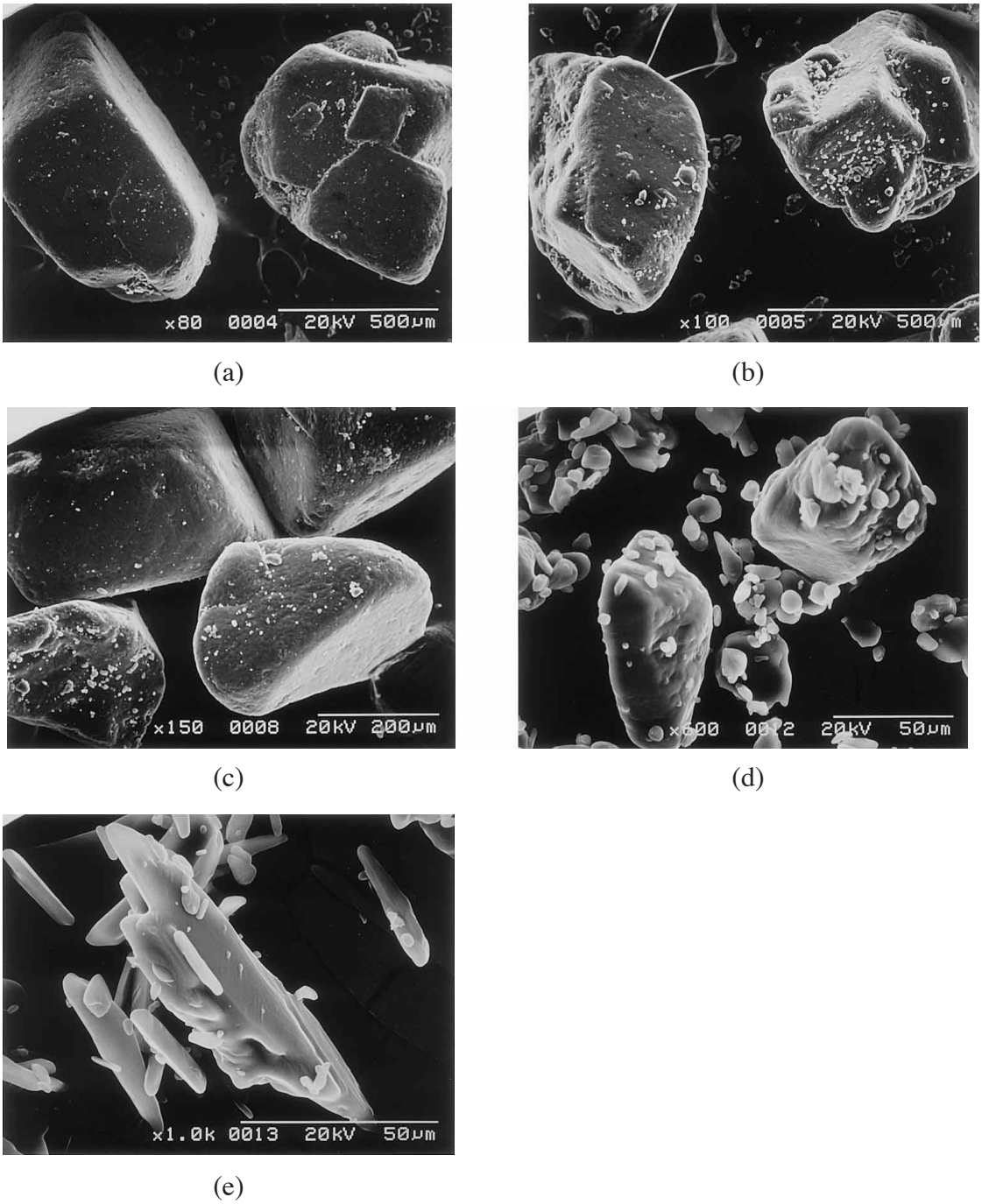

Fig. 1. SEM Photographs of Acetaminophen
(a) Size I; (b) Size II; (c) Size III; (d) Size IV; (e) Size V.

Table 2. Powders and Formulation

Materials	Company	Content ratio C (wt%)				
Acetaminophen	Mallinckrodt	10.0	20.0	30.0	50.0	70.0
d-Sorbitol	Merck Japan	51.7	45.9	40.2	28.7	17.2
Partly pregelatinized starch	Asahi Chemical Industry	20.3	18.1	15.8	11.3	6.8
Crystalline cellulose (Avicel PH-302)	Asahi Chemical Industry	18.0	16.0	14.0	10.0	6.9

types of acetaminophen were used to conduct compression at the medicine content ratio of C=30 wt%, making comparison of their tablet properties. The medicine content ratio was changed from 10 wt%, 20 wt%, 50 wt% and then 70 wt% to compare tablet properties, with attention given to a medicine having the highest tablet properties at the medicine content ratio of C=30 wt%. At higher medicine content ratios (C=50 wt%, 70 wt%), copolyvidone (Kollidon VA64 made by BASF) was used as a dry binder in place of crystalline cellulose for the purpose of improving tablet hardness.

Table 3 showed formulation for wet granulation and tableting method. Size V that has been so far commonly used for this purpose was adopted as a medicine in wet granulation and tableting method. This method was different from direct compression in that a binder (HPC-L) was added.

Tableting Method Powder, the formulation of which was shown in Table 2, was mixed by high-speed type agitator[5,6] (high-speed mixer FM-10J Model, made by Fukae Powtec) at the agitation rate of 3.33 rps for 300 s. Under this mixing condition, sampling was done at several spots in the mixer at every 60 s to determine lightness, thus calculating the mixing degree.[7] In the study adopted was such condition that the degree became smaller to give a better mixing state. Namely, the mixing condition was decided on the basis of the determination of the mixing degree.

Use of bovine grade magnesium stearate as a lubricant may pose problems such as bovine spongiform encephalopathy. Hence, vegetable grade magnesium stearate (Mallinckrodt) was used to conduct mixing at 0.5 wt% addition using the high-speed agitator for 10 s.

Tableting was done by rotary table machine (RT-F-9-2, by Kikusui) equipped with a 8mm-diamter 12R-faced punch to make tablets each weighing 200 mg. The powder was supplied by open-feed-shoe type. The tablet machine was designed to be equipped with 9 stations, but in this study the machine was equipped with one station to conduct tableting at the turntable rate of 0.167 rps. Further, since the tablet machine used in this study was not provided with precompression structure, it was liable to tablet impediment such as capping or sticking as compared with a tablet machine having the precompression structure. Further, an agitation-fluidized bed (MP-01 made by Powrex) was used to conduct tableting by wet granulation and tableting method.

Evaluation of Powder Properties and Tablet Properties Powder properties: A machine for determining powder properties (Powder Tester by Hosokawa Micron) was used to determine apparent density, tapping density and repose angle.

Compression Properties: A fully-automated testing system for compression characteristics and tensile strength of powder beds (Aggrobot by Hosokawa Micron) was used to evaluate the compression properties of powder for direct compression. Figure 2 showed a schematic diagram of the system. This was able to determine the tensile strength compressed at the tensile part (2), after powder was compressed at the compression part (1). In this experiment, a 15-mm across measurement cell was used to attain maximum compression stress up to 11.0 MPa at the compression rate of 0.1×10^{-2} m/s, thus evaluating the relationship between compression stress and compression displacement.

Tablet Hardness: A tableting breaking-strength measuring apparatus (TH-203RP by Toyama Sangyo) was used to determine the hardness. Load was given to 20 tablets in a diametric direction to determine an actual load when the tablet was broken. The result was expressed by the mean value.

Friability: Twenty tablets were charged into a friability tester and subjected to rotation at 0.42 rps for 240 s to obtain the friability by determining the weight before and after the test.

Disintegration Time: A disintegration tester (NT-1HM by Toyama Sangyo) was used to determine the time for 6 tablets in purified water having a temperature of 37.5 °C. The disintegration time was expressed by the result of the tablet, which disintegrated most slowly.

Dissolution Test: A dissolution tester (NTR-3000 by Toyama Sangyo) was used to evaluate dissolution of acetaminophen from the tablet in compliance with the procedures for dissolution test (paddle method) stipulated in the Japanese Pharmacopoeia 13th edition. A spectrophotometer (UV-1200 by Shimazu) was used to determine the absorbance at the wavelength of 285 nm to obtain the dissolution profile-time curve. Purified water was used as a test solution.

Content Ratio of Medicine: Ten tablets were used to determine the absorbance similarly as with the dissolution test, calculating the content ratio by referring to the previously prepared analytical curve.

This study was conducted to obtain desired physical properties such as tablet hardness $H\geqq40$ N, friability $F\leqq0.5\%$, disintegration time $t_D\leqq300$ s and 75% dissolution time of medicine $t_{75}\leqq300$ s. These physical properties would provide the tablet with less likelihood of breakage at handling and faster solubility of medicine. The validation guideline, established by Osaka Prefecture, describes Cm=100±15% as the upper and lower limit for the active ingredient content in the dosage form. While each drug product has its own acceptance criteria for the active ingredient content, the typical limit of from 93% through 107% is very likely to be employed. Because of things trending to such situation, the present studies have targeted on the active ingredient falling within a range of Cm=100±7%. Thus, we have set the more severe target, namely, content ratio of medicine Cm=100±7%.

Table 3. Formulation for Wet Granulation and Tableting Method

Materials	Company	Ratio (wt%)
Acetaminophen	Mallinckrodt	30.0
Lactose 200M	DMV	38.2
Corn Starch	Matsutani Chemical Industry	15.0
Crystalline cellulose (Avicel PH-302)	Asahi Chemical Industry	13.3
HPC-L[a)]	Nippon Soda	3.5

a) Hydroxypropylcellulose L. HPC-L is sprayed by 7% solution.

Results and Discussion

Powder Properties of Samples for Direct Compression

Table 4 showed the powder properties of samples for direct compression prepared by mixing 5 types of the size having a different diameter together with filler. The table also showed the powder properties of granules prepared by agitation fluidized bed granulation. The granules were mixtures all having 30 wt% medicine content (Table 2) and called Size.

As apparent from Table 4, all the samples for direct compression made with Size I, II and III were low in the repose angle and compressibility, and found favorable in the fluidity. The sample made with Size IV was low in the compressibility but relatively high in the repose angle, and found less fa-

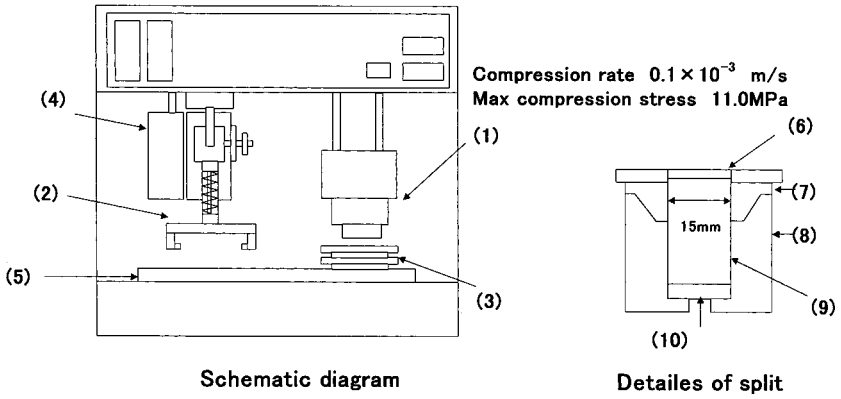

Fig. 2. Schematic Diagram of System (1) Compression Part, (2) Tensile Part, (3) Split Cell, (4) Laser Displacement Sensor, (5) Cell Table, (6) Upper Lid, (7) Upper Cell, (8) Lower Cell, (9) Powder, (10) Bottom Lid

Table 4. Properties of Powder for Tableting

Properties	Size I	Size II	Size III	Size IV	Size V	Granule
Apparent density (kg/m^3)	745	662	703	634	553	457
Tapping density (kg/m^3)	810	804	792	763	749	502
Compressibility (%)	8.02	17.66	11.24	16.91	26.17	8.96
Angle of repose (deg.)	32	35	35	42	50	40

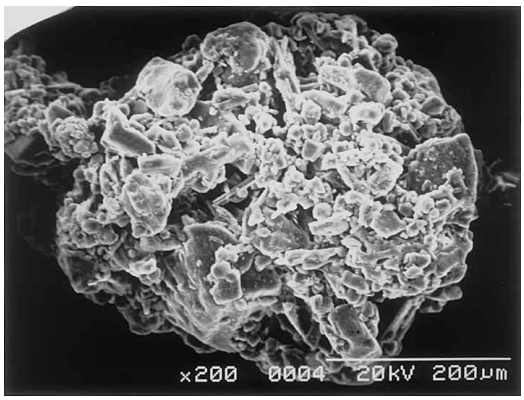

Fig. 3. SEM Photograph of Granule

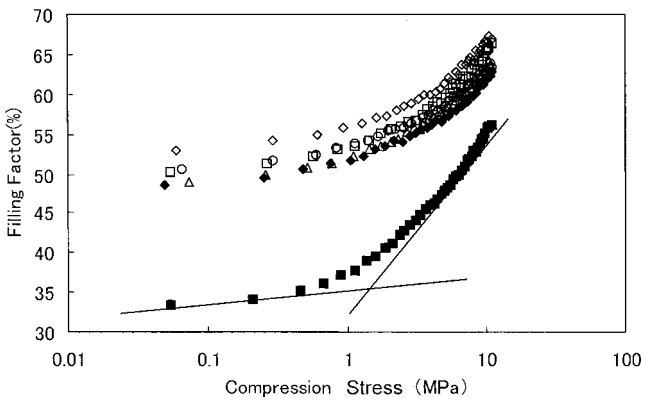

Fig. 4. Relationship between Filling Factor and Compression Stress
◇, Size I: □, Size II: △, Size III: ○, Size IV: ◆, Size V: ■, granule.

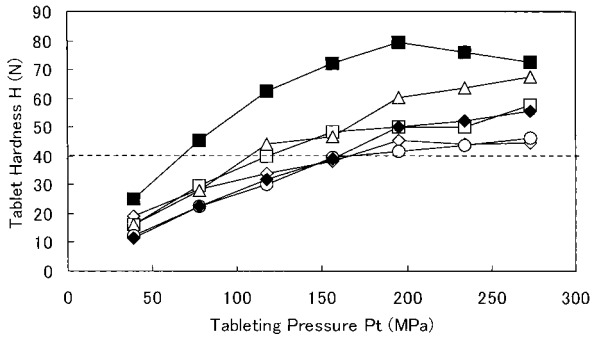

Fig. 5. Relationship between Tablet Hardness H and Tableting Pressure Pt
◇, Size I: □, Size II: △: Size III: ○, Size IV: ◆, Size V: ■, granule.

vorable in the fluidity. The sample made with Size V was high in the repose angle and compressibility, and found the worst in the fluidity among these 5 samples for direct compression. The granules were relatively low in the repose angle and compressibility, they were found favorable in the fluidity. Further, as apparent from Fig. 3, the granules were confirmed to be almost spherical and porous particles.

Figure 4 showed the relationship between filling factor and compression stress. This Figure also showed the results of the compression stress determined for the granules formulated by wet granulation and tableting method. The compression displacement and true density of the sample were calculated to obtain the filling factor. As shown in Fig. 4, all the samples for direct compression exhibited a remarkable increase in the filling factor around compression stress= 1.0 MPa. In general, when a powder is compressed, initially the particles undergo transformation and rearrangement to fill the space. However, no further transformation or rearrangement would result in compressive breakage of some particles. The broken particles underwent further rearrangement, thus leading to an increase in the filling factor. Namely, it was assumed that when more particles were broken more space could be filled rapidly to cause contact points between particles, thus resulting in a greater bonding strength. Therefore, a greater filling factor at compression stress≧1.0 MPa would result in a more densely packed powder to give a higher tablet hardness. The granule was found highest in the rate of increase in filling factor at the compression stress≧1.0 MPa, followed by the samples made with Size II, III and V.

Types of Size (Particle Diameter) and Tableting Properties. Tablet Hardness Figure 5 showed the results of tablet hardness measurement for the tablets formulated by direct compression of acetaminophen with different diameter (Table 2). This Figure also covered the results of tablet hardness measurements for the tablets formulated by wet granulation and tableting method (Table 3), the result of which was expressed as Granule. In the subsequent Figures and Tables, wet granulation and tableting method was expressed as Granule for convenience.

Figure 5 and thereafter showed the target hardness H≧40 N, but the powder samples made with Size II and III were actually subjected to direct compression at Pt≧117.1 MPa while those made with Size I, IV and V were actually subjected to direct compression at Pt≧195.1 MPa. Further, when acetaminophen with any particle diameter was subjected to direct compression at Pt≧195.1 MPa, the hardness was found to increase to a lesser extent. It was considered that the tableting pressure Pt≧195.1 MPa would give less compression fracture and rearrangement to particles, and no further load would less likely to obtain densely packed particles, rendering void fraction constant and resulting in a smaller increase in the tablet hardness.

On the other hand, the tablets were subjected to wet granulation and tableting method at Pt≧78.0 MPa to obtain the tablet hardness H≧40 N. A reason for attaining hardness≧ 40 N at tableting pressure, which was lower than that used in

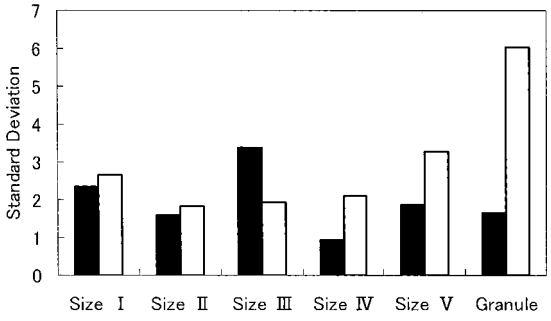

Fig. 6. Standard Deviation of Tablet Weight SDw and Tablet Hardness SDh at Tableting Pressure=195.1 MPa

■ SDw, □ SDh.

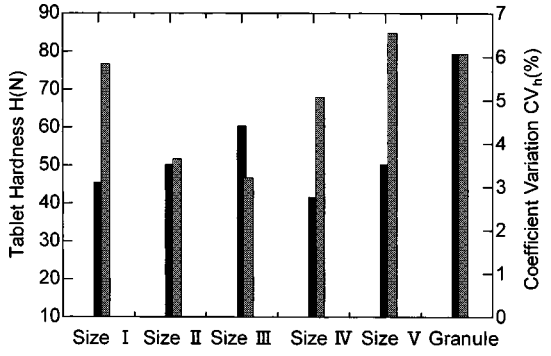

Fig. 7. Tablet Hardness H and Coefficient Variation CV_h at Tableting Pressure=195.1 MPa

■, tablet hardness H; ■, coefficient variation CV_h.

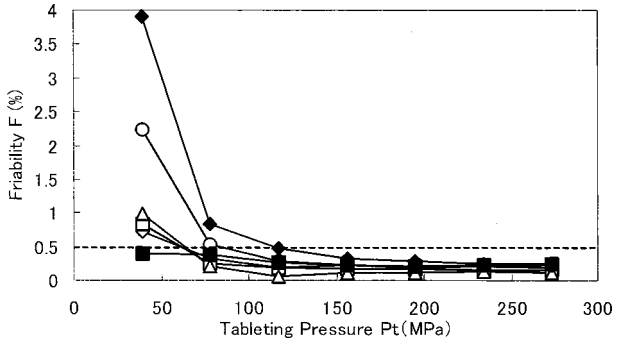

Fig. 8. Relationship between Friability F and Tableting Pressure Pt

◇, Size I: □, Size II: △, Size III: ○, Size IV: ◆, Size V: ■, granule.

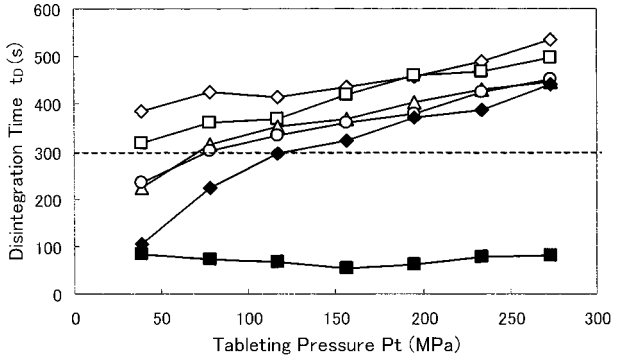

Fig. 9. Relationship between Disintegration Time t_D and Tableting Pressure Pt

◇, Size I: □, Size II: △, Size III: ○, Size IV: ◆, Size V: ■, granule.

direct compression was considered due to easy breakage of particles responsible for porous structure of the granule. Another reason was considered due to the use of hydroxypropylcellulose that was not used in direct compression. Macroscopic observation did not reveal any tablet impediment such as capping or sticking in the tableting experiment.

Figure 6 illustrates the standard deviation, SDw, in tablet weight, and the standard deviation, SDh, in tablet hardness. This result is from calculating the weight of 20 tablets. The tableting pressure applied was 195.1 MPa. As is indicated in Fig. 6 the result from the present experimentation can be interpreted as not always to support the effect that larger SDw is accompanied by larger SDh. Additionally, the reason for a large SDh for the granulate may probably be a large hardness value in itself.

Of the tablets made with Size I through Size V, we gave attention to that showing the tablet hardness $H \geqq 40$ N at which tableting pressure Pt=195.1 MPa was obtained, and examined the tablet hardness and the coefficient of variance, the results of which were shown in Fig. 7.

It was found that tablets made with direct compression were equal to or lower than those made with wet granulation and tableting method in the coefficient of variance CV_h for the tablet hardness. Shown below were reasons why the coefficient of variance for a tablet was slightly higher when the tablet was made with powder for tableting derived from Size I, Size IV or Size V.

Namely, in the case of Size I since it was larger in the granular diameter (Table 1), a slight variance in the number of medicine particles contained in a tablet could affect the tableting hardness. Further, in the case of Size IV or V, a poor fluidity of the mixed powder was assumed to be responsible for the higher coefficient of variance.

The results and discussion made so far revealed that the use of Size III provided a higher tableting hardness in direct compression. It was also confirmed that Size III was lower in the coefficient of variance for tablet hardness.

Friability of Tablet Figure 8 showed the relationship between friability and tableting pressure. Friability rapidly decreased at tableting pressure Pt$\leqq$78.0 MPa, when any size was used, whereas exhibiting an almost constant value at the level exceeding the said tableting pressure. It was also found that target friability $F \leqq 0.5\%$ was obtained at tableting pressure Pt$\geqq$117.1 MPa, when any size was used. This result confirmed that tableting pressure Pt$\geqq$117.1 MPa could provide tablets, which were not easily broken during transportation or at handling. No substantial difference in friability was found at the tableting pressure of Pt$\geqq$117.1 MPa between the tablets produced by wet granulation and tableting method and those by direct compression.

Disintegration Time Figure 9 showed the relationship between disintegration time and tableting pressure. The target disintegration time of $t_D \leqq 300$ s was obtained when the tablet prepared by Size V at Pt$\leqq$117.1 MPa and when prepared by Size III and IV at Pt=39.0 MPa. However, a longer disintegration time than the target was obtained when prepared by Size I or II at any tableting pressure. On the other hand, when the tablet was prepared by wet granulation and tableting method, the target disintegration time of $t_D \leqq 300$ s was obtained at any tableting pressure.

In direct compression, a higher tableting pressure resulted in a longer disintegration time. Since disintegration was observed to occur gradually around the tablet, it was considered that a greater bonding strength between particles led to a longer disintegration time of the tablet.

Dissolution Test Figure 10 showed the results. In this dissolution test were used tablets attaining the target hardness of $H \geqq 40$ N (tableting pressure Pt=195.1 MPa constant). A tablet attaining 75% dissolution time of medicine $t_{75} \leqq 300$ s was obtained in the powders of tableting made with Size II, III, IV and V. This result indicates Size II, III, IV and V were rapid released. Size I exhibited a longer 75% dissolution time t_{75}, because a larger diameter of the medicine resulted in a narrower surface area and also narrower contact area with test solution. In wet granulation and tableting method, the 75% dissolution time of the medicine was $t_{75} \leqq 120$ s and slightly shorter than direct compression. However, this difference would not result in great difference in the solubility between wet granulation and tableting method and direct compression.

Content of Medicine It is extremely important to attain a uniform content of medicine in validation of solid pharmaceuticals. Hence, tablets produced by direct compression were used to evaluate the mean content of medicine and variance coefficient CVc, the results of which were shown in Table 5. This Table also covered the results obtained by wet granulation and tableting method.

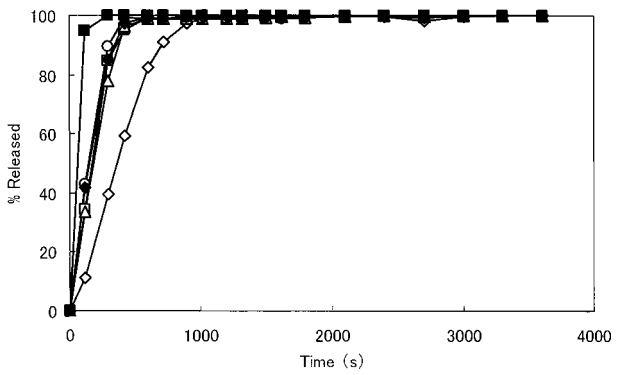

Fig. 10. Dissolution Profiles of Acetaminophen from Tablets Prepared at Tableting Pressure=195.1 MPa

◇, Size I: □, Size II: △, Size III: ○, Size IV: ◆, Size V: ■, granule.

Table 5. Content of Medicine and Coefficient of Variation CVc

	Average content of medicine (%)	CVc (%)
Size I	102.6	4.976
Size II	97.7	2.774
Size III	101.3	0.892
Size IV	102.5	0.885
Size V	99.8	2.127
Granule	102.8	1.325

As apparent in the table, the tablets produced by direct compression exhibited content of medicine Cm=100±7% regardless of size used. The use of Size 3 and Size 4 in manufacturing by direct compression has been demonstrated to provide the tablets excellent in content uniformity, with a small coefficient of variation, CVc. This variation coefficient was found to surpass that obtained by tableting according to the wet granulation method. This indicates that the content uniformity through the direct compression method is not always inferior to tableting by the wet granulation method.

Overall Evaluation Table 6 showed the overall evaluation of physical properties of the tablets so far made.

The tablets produced by wet granulation and tableting method met all target physical properties and evaluated to be excellent. As apparent in Table 6, since direct compression provided a better fluidity when Size III having mean particle diameter=300 μm was used, tablets with excellent physical properties were obtained. Further, no great difference in the physical properties was found between the tablets made with Size III by direct compression and those by wet granulation and tableting method. Namely, it was confirmed that direct compression could provide tablets with excellent physical properties.

Content Ratio of Medicine and Tablet Properties Direct compression was conducted to change the content ratio of medicine, with attention given to Size III which successfully provided tablets with excellent physical properties at content ratio of medicine C=30 wt%. The physical properties of tablets in which content ratio of medicine was changed were evaluated by referring to the tablets produced at tableting pressure, Pt=195.1 MPa, which were evaluated in all the items including dissolution test and uniformity of content of medicine at medicine content C=30 wt%.

Table 7 showed the relationship between the physical properties and content ratio of medicine. Macroscopic observation revealed no tablet impediments such as capping and sticking at any content ratio of medicine.

As apparent from Table 7, the tablet hardness decreased with increasing in the content ratio of medicine and the target hardness $H=40$ N was obtained at the content ratio of medicine C≧50 wt%. This was considered due to the fact that an increased content ratio of medicine led to decreased ratio of the filler having greater bonding strength, thus resulting in weaker bonding strength between particles.

Hence, copolyvidone, a dry binder, was used in place of crystalline cellulose to make tablets in order to improve the

Table 6. Overall Evaluation of Physical Properties of the Tablets

Tablet property	Size I	Size II	Size III	Size IV	Size V	Granule
Fluidity of powder for tableting	○	○	○	△	△	○
Tablet hardness	△	○	○	△	○	◎
Disintegration time	×	×	△	△	△	◎
Friability	○	○	○	○	○	○
Dissolution rate	×	○	○	○	○	○
Content of medicine	×	×	◎	◎	×	○

◎ Excellent, ○ good, △ normal, × bad.

Table 7. Properties of Tablet Changing Content Ratio of Acetaminophen at Tableting Pressure=195.1 MPa

Content ratio of acetaminophen (%)	Tablet hardness H (N)	Friability F (%)	Disintegration time t_D (s)
30	91	0.022	476
20	71.2	0.074	462
30	44	0.12	404
50	23.1	0.438	367
70	13	9.608	146
	Contained copolyvidone		
50	47.9	0.175	703
70	20.5	1.016	360

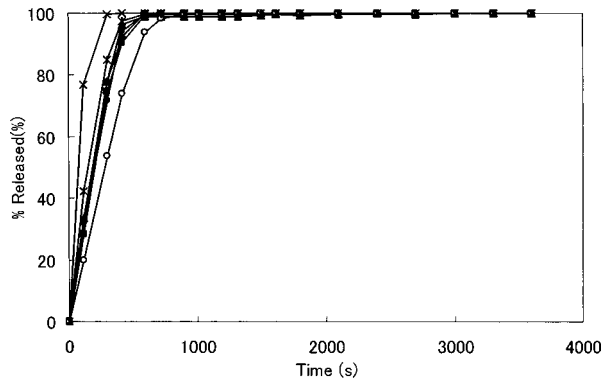

Fig. 11. Dissolution Profiles of Acetaminophen from Tablet in Various Content Ratio of Medicine at Tableting Pressure=195.1 MPa

◆, 10%: ■, 20%: ●, 30%: ▲, 50%: ×, 70%: △, 50% (contained copolyvidone): ∗, 70% (contained copolyvidone).

bonding strength even at a lower ratio of the filler. Table 7 covered the results as well. At content ratio of medicine C=50 wt%, the tablet hardness was $H \geqq 40$ N, or about 2.1 times higher than that for the tablet in which crystalline cellulose was used as a filler (H=23.1 N). However, at content ratio of medicine C=70 wt%, the tablet hardness exhibited a slightly higher hardness but failed to attain the target hardness (H=40 N).

Table 7 also showed that a larger friability was obtained as content ratio of medicine was increased. Tablets with friability$\leqq$0.5% were obtained at content ratio of medicine C$\leqq$ 50 wt%. A higher friability at the content ratio of medicine= 70 wt% was due to breakage of tablets by friability test. Tablets having friability $F \leqq 0.5$% were obtained only at the content ratio of medicine C$\leqq$50 wt% when copolyvidone was adopted. However, the friability at the content ratio of medicine C=70 wt% was relatively lower than the ratio obtained when crystalline cellulose was used (friability F= 9.61%).

As also apparent from Table 7, the disintegration time decreased with increasing the content ratio of medicine, but the target disintegration time $t_D \leqq 300$ s was obtained only at the content ratio C=70 wt%, which showed a lower tablet hardness. Use of copolyvidone in place of crystalline cellulose provided 1.9 to 2.5 time-longer disintegration time.

Figure 11 showed the dissolution profiles obtained from various content ratio of medicine. It was found that tablets produced at content ratio of medicine C=70 wt% exhibited 75% dissolution time of medicine $t_{75} \leqq 120$ s, showing faster

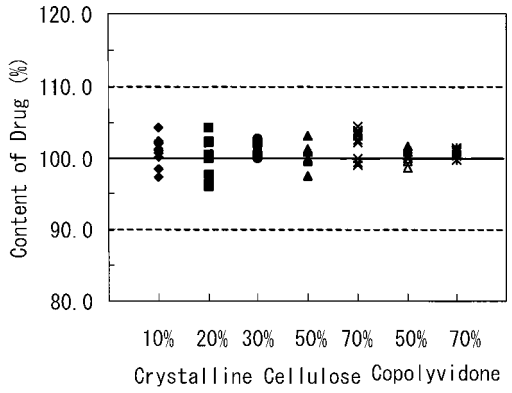

Fig. 12. Effect of Content of Medicine on Content Ratio of Acetaminophen at Tableting Pressure=195.1 MPa

◆, 10%: ■, 20%: ●, 30%: ▲, 50%: ×, 70%: △, 50% (contained Copolyvidone): ∗, 70% (contained copolyvidone).

solubility, whereas tablets produced at C=10, 20 or 50 wt% exhibited 75% dissolution time of medicine $t_{75} \leqq 420$ s, which was slightly longer than the target of 300 s. However, since not less than 70% of the medicine was dissolved at 300 s, the solubility content was more or less similar to other size. It was also found that use of copolyvidone in place of crystalline cellulose slightly slowed the dissolution time.

Figure 12 showed the results of content of medicine obtained by changing content ratio of medicine. Tablets produced at any content ratio of medicine fell into the content of medicine Cm=100±7% and were considered excellent in uniformity of content of medicine. Tablets in which copolyvidone was added as filler also fell into the content of medicine Cm=100±7%, showing the uniformity of content of medicine was kept.

Conclusion

We adopted acetaminophen, an antipyretic analgesic, to conduct some basic experiments on direct compression, finding the followings through the study.

(1) For the purpose of evaluating powder properties of medicines suitable for direct compression, five types of the size having a different particle diameter were used to make tablets and compare the physical properties determined. Consequently, it was found that use of acetaminophen having a particle diameter of about 300 μm (Size III) excellent in fluidity would provide tablets with the tablet hardness and friability less liable to breakage at handling. Further, such tablet was also found excellent in the solubility and uniformity of content of medicine.

(2) It was further found that direct compression of Size III successfully provided tablets similar in tablet hardness, friability and solubility to those produced by wet granulation and tableting method. Therefore, we confirmed that use of a medicine suitable for direct compression could produce tablets excellent in tablet properties even when produced by direct compression.

(3) Direct compression was employed to make tablets at various content ratios of medicines, with attention given to Size III. As the result, it was found that the tablet hardness decreased with increasing content ratio of medicine, and tablets with a greater friability was obtained. However, use of a dry binder provided tablets excellent in physical properties

at content ratio of medicine＝50 wt% by direct compression. In other words, it has been suggested that direct compression can provide tablets excellent in tablet properties even at a higher content ratio of medicine if formulation is properly managed.

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