Development of Agglomerated Crystals of Ascorbic Acid by the Spherical Crystallization Technique for Direct Tableting, and Evaluation of Their Compactibilities\textsuperscript{†}

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Abstract

Spherically agglomerated crystals of ascorbic acid for direct tableting were successfully prepared by the spherical crystallization technique. This agglomeration dramatically improved the micromeritic and compaction properties of the original ascorbic acid crystals. The dominating mechanisms that improved compaction properties of the spherically agglomerated crystals depended on their fragmentation and plastic deformation during compaction. Support for this mechanism existed because the compacted agglomerated crystals had higher stress relaxation and lower elastic recovery than the original crystals. Spherically agglomerated crystals were tableted directly without capping by using a single-punch tableting machine under dynamic compaction, although the tensile strength of tablets with spherically agglomerated crystals decreased when the compression speed increased.

1. Introduction

Tablets are the most frequently used form of pharmaceuticals. The main tableting method in Japan used to involve first making granules, and then compressing them into tablets by way of indirect (granule) tableting, but the need in recent years for process validation, GMP, and automation of production processes has focused renewal attention on the direct tableting method, which involves few steps.

Because direct tableting necessitates an active ingredient powder that excels in flowability, bindability, mechanical strength, and other qualities more than the materials for indirect tableting, there are currently limited pharmaceutical tablets on commercial production that can be made by direct tableting. For that reason development of the design method of active ingredient crystals that can be directly tableted has been waited. As the model drug in our research ascorbic acid, which is difficult to tablet directly, was used to develop directly compactable crystals without a binder for direct tableting. The compactibility of resultant crystals were evaluated.

Our design method involved using a process called spherical crystallization developed originally by us [1], which allowed us to manufacture agglomerated crystals with two different internal structures that were suited to our purpose. After assessing the crystals’ flowability and packability to ascertain their adequacy as the powder for direct tableting, we conducted static and dynamic compression tests. We analyzed the static compression process and determined the factors related to improving the granulated crystals’ compactibility. Further, anticipating the commercial production of tablets, we determined the effect of compression speed on compactibility.

2. Materials and Methods

2.1 Materials

Ascorbic acid was chosen as a model drug because of its brittleness and its strong cohesive properties. As a control for assessing powder physical properties such as flowability and packability fine crystals (100 mesh product, average particle diameter of 18.8 \(\mu\)m, made by Takeda Chemical Industries, Ltd.) was used, and for assessing compactibility it was coarse crystals with excellent flowability (FG product, average parti-
particle diameter of 425 µm, made by Takeda Chemical Industries, Ltd.). A control for both assessments was commercially available granulated ascorbic acid for direct tableting (hereinafter, “C97 granules,” average particle diameter of 422 µm, made by Takeda Chemical Industries, Ltd.). C97 granules are produced in a fluidized bed with 3% starch added as a binder. As the model drug for plastic deformability we used potassium chloride (Japanese Pharmacopoeia, hereinafter written “KCl,” average particle diameter of 650 µm, produced by Yamazen Corporation).

2.2 Preparation of Ascorbic Acid Agglomerated Crystals for Direct Tableting

Ascorbic acid was dissolved in 50°C purified water (a good solvent) to prepare a 0.4 g/ml saturated solution. A pipette was used to quickly drop a prescribed amount of the solution into a 500 ml cylindrical agitator tank containing 300 ml of ethyl acetate (a poor solvent, maintained at 5°C) while stirring with a four-bladed propeller-type agitator at either 300 or 800 rpm. By choosing a water-to-ethyl acetate volumetric ratio of either 1:100 or 4:150, we prepared spherical agglomerated crystals of ascorbic acid by two different crystal agglomeration mechanisms: spherical agglomeration (SA), and emulsion solvent diffusion (ESD). We inserted baffles in the agitator tank to promote granulation with SA, but with ESD we let granulation occur without using baffles so as to prevent the breakdown of emulsion droplets. After stirring for 20 min the crystal agglomerates obtained were suction filtered, washed with a small amount of methanol, and dried under reduced pressure for at least 24 h. We used the agglomerate fraction in the 125 to 500 µm range, obtained by classifying with a screen to bring them into line with the C97 granule particle size range. This fraction’s yield was good at 70 to 80%.

2.3 Measuring Physical Properties of Agglomerated Crystals

A scanning electron microscope (JTM-T330A, JEOL., Ltd.) was used to observe the particle form of the original crystals (100 mesh product), coarse crystals (FG product), and C97 granules, and the surface property and cross sections of the two types of spherically agglomerated crystals (SA and ESD products).

Sample flowability was measured and assessed by using the pouring method to make them pile, then measuring their angle of repose. Sample packability was assessed by analysis of the tapping process with the Kawakita [2] (Eq. 1) and Kuno [3] (Eq. 2) methods, and using the parameters

\[ \frac{n}{C} = (1/a) + \frac{n}{a}, \frac{C}{V_0 - V_n}/V_0 = \frac{p_f - p_n}{p_f - p_0} \exp (-kn) \]  

Where:

- a is the degree of volume reduction when the tap number is infinity,
- b and k are constants for the apparent packing rate,
- \( V_0 \) and \( V_n \) are the volume in the initial loosely packed and the nth tapped state, and
- \( p_0, p_n, \) and \( p_f \) are the apparent density in the initial state, the nth tapped state, and the most densely packed state.

2.4 Tablet Preparation

A screen was used to classify the test samples into a 125 to 500 µm fraction. We placed 150 mg of each sample into a die with diameter of 8 mm, and used an AUTOGRAPH (Instron type press) (AG5000D, Shimadzu Corporation) to tablet the samples at a constant rate of 10 mm min\(^{-1}\) and at various compression pressures between 50 and 300 MPa\(^{5}\). Assuming commercial production, we mixed 1% magnesium stearate into each sample and used the universal tensile compression tester and a single-punch tableting machine (TabA11, Okada Seiko Co., Ltd.) to produce tablets under a constant compression pressure of 200 MPa\(^{5}\) and at various compression speeds. The compression speed of single-punch tableting machine was calculated from the displacement rate of upper punch when compressing.

2.5 Compression Behavior Analysis

2.5.1 Heckel Analysis [4, 5]

We used Heckel’s equation (Eq. 3) to analyze the compression process of agglomerated crystals, and assessed their compactibility.

\[ \ln \left[ \frac{1}{1 - D} \right] = K \rho_p + A \]  

Where:

- \( D \) is the relative density of the tablets under compression pressure \( P \) (MPa; the ratio of tablet density to the powder’s true density),
- \( K \) is the slope of the straight portion of the Heckel plot, and
- the reciprocal of \( K \) is the mean yield pressure (\( P_y \)).

Eq. 4 gives the intercept obtained by extrapolating the straight portion of the plots.

\[ A = \ln \left[ \frac{1}{1 - D_0} \right] + B \]  

Where:
Eqs. 5 and 6 give the relative densities corresponding to A and B.

\[ D_A = 1 - e^{-A} \]  
\[ D_B = D_A - D_0 \]  

2.5.2 Stress Relaxation Test

We put 150 mg of each sample in a die with 8 mm diameter the surface of which was coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed of 10 mm min\(^{-1}\). After the pressure attained 200 MPa, the upper punch was held in the same position for 20 min, during which time we measured the reduction amount of the stress applied on the upper punch. \[6\] The result was corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions. We used Eq. 8 to find the relationship between relaxation ratio \(Y(t)\) and time \(t\), calculated the parameters \(A_s\) and \(B_s\), and assessed relaxation behavior. \[7, 8\]

\[ Y(t) = \frac{(P_0 - P_t)}{P_0} \]  

Where:
\(P_0\) is the maximum compression pressure, and \(P_t\) is the pressure at time \(t\).

\[ t/Y(t) = 1/A_sB_s + t/A_s \]  

2.5.3 Tablet Elastic Recovery Test

We placed 150 mg of each sample in a die with 8 mm diameter and used the universal tensile compression tester to compress them up to 200 MPa at the constant speed of 10 mm min\(^{-1}\). We measured the thickness of each tablet under maximum pressure \((H_c)\) and at about 24 h after tablet ejection \((H_e)\). Eq. 9 was used to calculate the elastic recovery ratio \((ER)\). \[9\]

\[ ER = \left[ \frac{(H_e - H_c)}{H_c} \right] \times 100 \]  

About 24 h after the tablet was ejected, its weight, diameter, and thickness was measured, and its apparent density \((\rho_a)\) calculated. Eq. 10 was used to calculate internal tablet porosity \((\varepsilon)\) from true density \((\rho_t)\), which was measured with an air comparison pycnometer (Model 930, Beckman-Toshiba, Ltd.).

\[ \varepsilon = 1 - \frac{\rho_a}{\rho_t} \]  

2.6 Tablet Tensile Strength Test

Tablets were kept in a desiccator (silica gel) for about 24 h, and then a hardness tester (GRANO, Okada Seiko Co., Ltd.) was used to measure a load across the diameter of each tablet at a compression speed of 100 \(\mu m\) s\(^{-1}\) to find the hardness \(F\) when crushing. Eq. 11 was then used to calculate the tensile strength \(T\). \[10\]

\[ T = 2F/\pi dL \]  

Where:
\(d\) and \(L\) are a tablet's diameter (m) and thickness (m).

We crushed the tablets made by compressing the two types of spherically agglomerated crystals, and observed the fracture planes with a scanning electron microscope.

3. Results and Discussion

3.1 Spherical Crystallization Mechanism and Physical Properties of Agglomerated Crystals

It was found that crystal agglomeration was possible with two different types of mechanisms depended on the amount of drug solution added to the system (poor solvent). When both solvents were mixed at a small water-to-ethyl acetate volumetric ratio (1:100), a W/O emulsion formed at first. Then as the emulsion drops cooled and the water and ethyl acetate counter-diffused, solubility in the emulsion drops decreased, and crystals precipitated on the surfaces of drops. Spherical agglomerates were obtained when crystallization completed. This agglomeration mechanism is called emulsion solvent diffusion, or ESD. On the other hand, when the water-to-ethyl acetate volumetric ratio was large (4:150) and the solvents did not mix, crystals precipitated in the same way after an emulsion formed. At this system a small amount of water that was liberated from the ethyl acetate phase acted as a liquid bridging agent (forming a liquid bridge), which caused particles to randomly agglomerate, and then become spherical under the shearing force of stirring, after first passing through funicular and capillary forms. This agglomeration mechanism is called spherical agglomeration, or SA. Fig. 1 illustrates the SA and ESD mechanisms, and Fig. 2 presents electron photomicrographs of the surfaces and cross sections of the two types of ascorbic acid agglomerated crystals. Both types of agglomerated crystals were spherical.

As one can see from the agglomeration mechanism...
in Fig. 1, while in the SA method the primary crystals randomly agglomerated, crystals in the ESD method grow toward the center. Owing to this difference in the agglomeration mechanism, the two methods yield two types of agglomerated crystals with different internal structures.

The physical properties of the agglomerated crystals are shown in Table 1.

The angle of repose of agglomerated crystals was clearly lower than that of the original crystals, and about the same as that of commercially available C97 granules. We used the equations of Kawakita and Kuno to analyze the tapping process. The value a in Kawakita’s equation was lower than that of the original crystals, while b in Kawakita’s equation and k in Kuno’s equation were both higher. Both of the agglomerated crystals obtained had excellent flowability and packability, and in terms of handling properties such as feeding into die, the agglomerated crystals were useful for direct tableting.

3.2 Compression Behavior Analysis

To determine the compression characteristics of the agglomerated crystals, Heckel’s equation [4, 5] was used to analyze the compression behavior of agglomerated crystals (Fig. 3).

Except for KCl, none of the agglomerated crystal types exhibited a linear relationship at low compression pressures, while they did at high pressures. This shows that at low compression pressures the rearrangement and crushing of agglomerated crystals proceeds simultaneously, and that at high pressures crystal particles are cohered and bonded with one another while undergoing plastic deformation. The initial portions of Heckel plot curves are a general indication of the tendency for particle fracturing. Doelker used the values for $D_a$, $D_0$, and $D_B$ calculated from Heckel plots, respectively, as an indicator of compaction by the densest packing of rearranged and fractured particles into a die; an indicator of compaction by initial packing; and an indicator of fracturing characteristics (compaction of a powder bed by the rearrangement of primary particles and fractured particles). The higher the value of $D_a$, the better the

<table>
<thead>
<tr>
<th>Sample</th>
<th>Angle of repose (°)</th>
<th>a</th>
<th>b</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>56.1 ± 2.3</td>
<td>0.508</td>
<td>0.066</td>
<td>0.021</td>
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<tr>
<td>C97</td>
<td>33.7 ± 1.0</td>
<td>0.079</td>
<td>0.151</td>
<td>0.045</td>
</tr>
<tr>
<td>SA</td>
<td>33.8 ± 2.6</td>
<td>0.224</td>
<td>0.176</td>
<td>0.065</td>
</tr>
<tr>
<td>ESD</td>
<td>33.0 ± 1.6</td>
<td>0.133</td>
<td>0.155</td>
<td>0.063</td>
</tr>
</tbody>
</table>

1) Parameters in Kawakita’s equation: $(n/C) = (1/ab) + (n/a)$ and $C = (V_0 - V_n)/V_0$, where n is the tap number and $V_0$ and $V_n$ are the powder volumes at the initial and nth tapped state, respectively.

2) Parameter in Kuno’s equation: $p_1 - p_0 = (p_1 - p_0) \exp(-kn)$, where $p_0$, $p_1$, and $p_0$ are the apparent densities at equilibrium, the nth tapped, and initial state, respectively.
Fig. 2  Scanning electron photomicrographs of external appearance and cross-section of original ascorbic acid crystals, a C97 granule, potassium chloride crystals, and SA and ESD agglomerated crystals of ascorbic acid
initial packability in a die, while the higher the value of \( D_B \), the greater the fracturing tendency exhibited by a powder. [11] Analysis results indicated that the original coarse crystals and KCl had high \( D_0 \) values, which is probably because the surfaces of these crystals were comparatively smooth (Fig. 2), which made them easy to pack into a die. Because SA agglomerated crystals had the highest \( D_B \) value, it was evident that considerable fracture occurred during compression (Table 2).

Plastic flow of the particles during compression occurred mainly after rearrangement and fracture. Plastic deformability is generally evaluated according to mean yield pressure (\( P_Y \)), which was calculated from the slope of the linear portion of plots. \( P_Y \) values in descending order were SA crystals, ESD crystals, C97 granules, and the original coarse crystals (Table 2). All these values are higher than that of KCl, a substance that tends to undergo plastic deformation, and they are about the same with regard to plastic deformability. They had lower elastic recovery values than the original coarse crystals.

![Fig. 3](https://example.com/figure3.png)

**Fig. 3** Heckel’s plot for ascorbic acid and potassium chloride crystals at a compression speed of 10 mm min\(^{-1}\). Straight lines were obtained by a linear regression analysis of data between 50 and 150 MPa. (a) Original coarse crystals, (b) C97 granules, (c) SA agglomerated crystals, (d) ESD agglomerated crystals, and (e) KCl crystals
To investigate compactibility in more detail, we measured stress relaxation, which is an indicator of plastic deformability (Table 2). Fig. 4 shows the results obtained by interpreting the relaxation process with Eq. 8. Good linear correlations were obtained with all samples, and constants \( A_S \) and \( B_S \) were determined from their slopes (Table 3).

\( A_S \) indicates the relaxation ratio at infinity time; the higher the value, the greater the stress relaxation. \( 1/B_S \) indicates the time until the relaxation ratio attains \( A_S/2 \), and means that the larger the \( B_S \) value, the faster the relaxation rate. Spherically agglomerated crystals had larger stress relaxation than other crystals, with that of SA crystals larger than that of ESD crystals. And because the \( A_S \) and \( B_S \) values were large, Table 3 shows that stress relaxation under static pressure was large, and that the relaxation rate was rapid. Stress relaxation occurred because of particle fracturing and rearrangement caused by packing, and because of the plastic deformation of the particles themselves. [12] It is thought that because spherically agglomerated crystals were easily fractured during compression, their particle sizes became smaller, and their stress relaxation increased due to rearrangement. By contrast, the original coarse crystals and C97 granules had small relaxation values. This is likely because, as one can estimate from the values for \( D_0 \) and \( D_B \) calculated from the Heckel plots, the initial packing rate in the die was high, and little rearrangement was caused by fracturing during compression. KCl had small stress relaxation. The small \( A_S \) value shows that stress relaxation under static pressure decreased owing to the adequate stress relaxation afforded by the strong plastic flow during compression (Fig. 3). Further, the low \( B_S \) value means that the relaxation rate under static pressure was extremely slow.

### 3.3 Improving the Compactibility of Spherically Agglomerated Crystals

We assessed the compactibility of agglomerated crystals samples according to the tensile strength of tablets (Fig. 5). [10]
Capping of the original coarse crystals occurred at compression pressures of 200 MPa and above. Owing to the small $D_B$ value of the original crystals, there was less fracturing than agglomerated crystals and elastic recovery was high (Table 2), thereby allowing capping. When ascorbic acid was made into crystal agglomerates by crystal agglomeration, tableting was possible without the occurrence of capping. What is more, the tensile strength of the resulting tablets improved dramatically; it was significantly better even than C97 granules, and displayed superior compactibility. The reasons for this are likely that as the $D_B$ value of spherically agglomerated crystals was significantly high (Table 2), making the crystals fracture easily under compression, this increased the points of contact among particles; the large stress relaxation (Table 2) facilitated plastic flow, thereby increasing the contact area; and new high-energy surfaces appeared because of fracturing, which strongly bonded the particles. [13]

### 3.4 Effect of Compression Speed on the Compactibility of Spherically Agglomerated Crystals

It was found that spherically agglomerated crystals exhibited an excellent capacity for compactibility under static compression. Nevertheless, powder beds are compressed rapidly in the commercial production of tablets. For that reason we mixed a lubricant (magnesium stearate) into the samples, and used a single-punch tableting machine as well as universal tensile compression tester to investigate the effect of compression speed on tensile strength. Fig. 6 shows the relationship between compression speed and tensile strength.

When the universal tensile compression tester was used to compress the original coarse crystals, the tablets exhibited low tensile strength, but there was a tendency for tensile strength to increase somewhat as the compression speed increased. Although the commercially available C97 granules had a value higher than that of the original coarse crystals, the tendency was the same. KCl, which tends to undergo plastic deformation, had a tendency for tensile strength to decrease as the compression speed increased. While spherically agglomerated crystals displayed the same tendency as KCl, under compression with the compression tester its tensile strength increased at a compression speed of 300 mm min$^{-1}$. But when compressing with the single-punch tableting machine, all samples had about the same tensile strength, no matter what the compression speed. When compression was performed with both the universal tensile comp-

![Fig. 5](image_url) **Fig. 5** Relationship between tensile strength of ascorbic acid tablets and compaction pressure
Sample: 150 mg
Compostion speed: 10 mm min$^{-1}$
(□) Original coarse crystals, (□) C97 granules, (□) SA agglomerated crystals, and (□) ESD agglomerated crystals
†: Some tablets are capped during compaction. The results are expressed as the mean ± S.D. of four runs. There was a significant difference with the value for C97 granules at p<0.001 (□), p<0.01 (□) and p<0.5 (□).

![Fig. 6](image_url) **Fig. 6** Relationship between tensile strength of ascorbic acid tablets and compression speed
Sample: 150 mg
Compaction pressure: 200 MPa
(□, □) Original coarse crystals, (□, □) C97 granules, (□, □) SA agglomerated crystals, (□, □) ESD agglomerated crystals, and (□, □) KCl crystals
Tablets were prepared using an Instron-type hydraulic press (closed symbols) or single-punch tableting machine (open symbols) at a 200 MPa compaction pressure. The results are expressed as the mean ± S.D. of four runs.
pression tester and the tableting machine at the same compression speed, tablets made with the compression tester had the higher tensile strength. We assume this is due to a characteristic of the compression imposed by the tester, which is static compression at a constant speed that places uniform stress on the powder. By contrast, compression applied by the tableting machine initially has a high speed, then gradually slows. It is therefore characterized as dynamic compression in which changes in the powder bed's internal stress are non-equilibrium. Thus, it is likely that tablet tensile strength was low because the compression energy was not effectively applied for powder compaction and formation.

Fig. 7 shows the relationship between tablet porosity and compression speed.

![Fig. 7 Relationship between porosity of ascorbic acid tablets and compression speed](image)

Tablets made from the original coarse crystals with the single-punch tableting machine had lower porosity than those made with the universal tensile compression tester. This is probably because when the compression speed was high, the powder was subjected to a bigger impact, and brittle original crystals was fragmented, rearranged, and compacted by compression. With respect to spherically agglomerated crystals, although no clear difference in ESD crystals was found, when making SA crystals at the same compression speed with the universal tensile compression tester and the single-punch tableting machine, the tablets made with the compression tester had lower porosity. This correlates to the above-noted fact that tablets made with the compression tester have a higher tensile strength. To investigate the packed state of crystals in tablets made with the compression tester we used a scanning electron microscope to examine tablet cross sections (Fig. 8).

At a low compression speed, solid bridges formed between crystals in both types of agglomerated crystals, but when the compression speed was high there was no fusion between crystals, and the cross sections were very similar to those of agglomerated crystals prior to compression. We assume this is because when compression time is long, crystals undergo considerable plastic deformation. [6] In our examination of tablets obtained from SA agglomerated crystals we observed only the primary crystals that made up the agglomerated crystals, suggesting that compression fractured the agglomerated crystals back down to their primary crystals, which is the reason for the large D₀ value. On the other hand, examination of tablets obtained from ESD agglomerated crystals revealed that the internal structure of agglomerated crystals in the tablets was partially retained, suggesting that compression fractured only the outside surface of the agglomerated crystals. Because the internal structures of agglomerated crystals differed according to the mechanism by which spherically agglomerated crystals were made, the agglomerates also differed with respect to the extent of fracturing during compression and the arrangement of crystals in tablets, which is likely the reason for their different plastic deformability (Table 2).

4. Conclusion

By applying spherical crystallization methods to ascorbic acid with strong cohesive and brittle properties, we were able to make agglomerated crystals with excellent flowability and packability, and with better compactibility than commercially available granulated particles for direct tableting, thereby determining that these agglomerated crystals are useful as particles for direct tableting. In consideration of the drying conditions for this method, it is believed that the ethyl acetate remaining in the agglomerated crystals is under the 5,000 ppm standard of the residual solvent guideline. [14] We found that major reasons for the superior compactibility of spherically...
agglomerated crystals are the increased fragmentation of granulated crystals and plastic deformability (flowability) of fractured particles under compression, and the low elastic recovery. An increase in the speed of compression on spherically agglomerated crystals reduces the tensile strength of tablets, but our study showed that even direct tableting can be done at high speed. Spherical crystallization can be used for any drug as long as an appropriate solvent is chosen. This is a useful granulating technology that can solve the problems of poor powder physical properties and compactibility that make other drugs hard to tablet, and that can make them into powder that is responsive to direct tableting.

Acknowledgements

We wish to thank Takeda Chemical Industries, Ltd. for supplying the samples used in this research.

Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tr>
<td>A</td>
<td>total densification of powder bed due to die filling and particle rearrangement</td>
</tr>
<tr>
<td>A_S</td>
<td>constant</td>
</tr>
<tr>
<td>a</td>
<td>constant</td>
</tr>
<tr>
<td>B</td>
<td>densification of powder bed due to particle fragmentation</td>
</tr>
<tr>
<td>B_S</td>
<td>constant</td>
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<td>b</td>
<td>constant</td>
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<td>C</td>
<td>constant</td>
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<tr>
<td>D</td>
<td>relative density of powder at applied pressure</td>
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<td>D_0</td>
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<tr>
<td>d</td>
<td>tablet diameter (m)</td>
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<tr>
<td>ER</td>
<td>elastic recovery ratio (%)</td>
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<td>F</td>
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<td>tablet thickness at maximum pressure (m)</td>
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<td>H_e</td>
<td>tablet thickness at 24 h after ejection (m)</td>
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<tr>
<td>K</td>
<td>slope of straight line by Heckel plot (1/Pa)</td>
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Fig. 8  Scanning electron photomicrographs of cross section of ascorbic acid tablets prepared by static compression
References


Author’s short biography

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Dr. Yoshiaki Kawashima is Professor of Laboratory of Pharmaceutical Engineering at Gifu Pharmaceutical University. He received B.S. (1964) degree from Nagoya City University and M.S. (1966) and Ph.D. degree (1969) from Kyoto University. He joined Gifu Pharmaceutical University as a faculty member in 1969. Since 1991, he becomes a visiting professor of Shen-Yang Pharmaceutical University. He received FIP Colocon award and AAPS fellow ship in 1995 and 1996. He is chairman of the society of Powder Technology, Japan since 1999. He developed spherical crystallization techniques and his research interests are in the development and application of spherical crystallization for drug delivery system with nanoparticulate carriers.
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