Preparation of Rapidly Disintegrating Tablet Using New Types of Microcrystalline Cellulose (PH-M Series) and Low Substituted-Hydroxypropylcellulose or Spherical Sugar Granules by Direct Compression Method

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To decrease the sensation of roughness when a tablet, which is rapidly disintegrated by saliva (rapidly disintegrating tablet), is orally taken, we prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M series), a new type of pharmaceutical excipient that is spherical and has a very small particle size (particle size, 7–32 μm), instead of conventional microcrystalline cellulose (PH-102) used in the formulation of tablets containing acetaminophen or ascorbic acid as model drugs for tableting study. Tablets (200 mg) prepared using spherical microcrystalline cellulose, PH-M-06, with the smallest particle size (mean value, 7 μm) had sufficient crushing tolerance (approximately, 8 kg) and were very rapidly disintegrated (within 15 s) when the mixing ratio of PH-M-06 to low-substituted hydroxypropylcellulose (L-HPC) was 9:1. Sensory evaluation by volunteers showed that PH-M-06 was superior to PH-102 in terms of the feeling of roughness in the mouth. Consequently, it was found that particle size is an important factor for tablet preparation using microcrystalline cellulose. It is possible to prepare tablets such as acetaminophen and aspirin (concentration of approximately 50%) in the tablet form using PH-M-06 in combination with L-HPC as a good disintegrant at a low compression force (1–6 kN). To solve the problem of poor fluidity in the preparation of these tablets, we investigated the use of spherical sugar granules (Nonpareil®, NP-101 (sucrose and starch, composition ratio of 7:3), NP-103 (purified sucrose), NP-107 (purified lactose) and NP-108 (purified D-mannitol)). Rapidly disintegrating tablets can be prepared by the direct compression method when suitable excipients such as fine microcrystalline cellulose (PH-M-06) and spherical sugar granules (NP) are used.

Key words rapidly disintegrating tablet; fine microcrystalline cellulose; low-substituted hydroxypropylcellulose; spherical sugar granule; direct compression method

Recently, the clinical usefulness of tablets that are rapidly disintegrated by saliva (rapidly disintegrating tablet), an attractive dosage form for patient-oriented pharmaceutical preparations, has been reported.2) Previously, we formulated rapidly disintegrating tablets containing meclizine hydrochloride, an antihistaminic agent, using microcrystalline cellulose (Avicel PH-102®: mean particle size, 100 μm), a conventional pharmaceutical excipient, and low-substituted hydroxypropylcellulose (L-HPC: mean particle size, 50 μm), a good disintegrant, by the direct compression method at a low compression force (1–6 kN).3) Bi et al.4) also reported the preparation of compressed tablets that can rapidly disintegrate in the mouth, using Avicel PH-102 and L-HPC with ethenamide and aspirin as model drugs. However, patients often complain of a feeling of roughness in their mouths after taking these tablets, due to the surface texture and the large particle size. Generally, the rough texture of particles with size below 15 μm is not felt in the mouth.5–7) Therefore, in this study we attempted to formulate a new type of rapidly disintegrating tablet with good texture using excipients with particle size smaller than that of PH-102 by the direct compression method. Although the most suitable disintegration time is not confirmed, we set the desirable disintegration time at 15 s based on information on the disintegration time of commercially available preparations with the characteristic of rapid disintegration.8) The microcrystalline cellulose PH-M series is a new type of pharmaceutical excipient that is spherical and has a very small particle size, and is used as an ingredient in cosmetics. To decrease the sensation of roughness in the mouth, we prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M-06®) with a small particle size (mean particle size, 7 μm) instead of PH-102 in the formulation of tablets containing acetaminophen or aspirin as the model drug for tableting study. Furthermore, to improve the fluidity of excipients in the tabletting process, we investigated the usability of spherical sugar granules9) instead of L-HPC in combination with PH-M-06.

Experimental

Materials

Acetaminophen (JP XIII) and ascorbic acid (JP XIII) were purchased from Maruishi Seiyaku Co. (Osaka, Japan). Microcrystalline cellulose (Avicel® PH-102, PH-M-06, PH-M-15, PH-M-25, JP XIII) and L-HPC (LH-11®, JP XIII) were kindly supplied by Asahi Chemical Industry Co., Tokyo, Japan and Shin-etsu Chemical Co., Tokyo, Japan, respectively. Spherical sugar granules (water-soluble sugar granule, Nonpareil®, hereafter abbreviated as NP), sucrose starch spheres (NP-101), purified sucrose spheres (NP-103), purified lactose spheres (NP-107) and purified D-mannitol spheres (NP-108) were kindly supplied by Freund Industry Co., Tokyo, Japan. All other reagents were of analytical grade.

Physical Characteristics of Crystalline Cellulose

The particle size distribution of crystalline cellulose was measured using a centrifugal particle size analyzer (SA-C2® Shimadzu, Co., Kyoto, Japan), and the angle of repose, using an ABD powder tester4) (MIWA Type, Tsutsui Scientific Instruments Co., Tokyo, Japan). Loose bulk density and packed bulk density were measured using a tapping density analyzer (KYT-100® Seishin Enterprise, Co., Tokyo, Japan) at a tapping number of 200 (100 taps/min). Compressibility was calculated as follows:

\[
\text{Compressibility} \%= (P_L/P) \times 100
\]

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where \( P \) is the packed bulk density and \( L \) is the loose bulk density. The true density was measured using a multivolume pycnometer (Accupyc 1330®, Shimadzu, Kyoto, Japan). The data obtained are listed in Table 1.

**Preparation of Tablets** Rapidly disintegrating tablets were prepared according to the following procedure. Firstly, microcrystalline cellulose and L-HPC or spherical sugar granules at various weight ratios were mixed using a V-shaped mixer (3 l, 50 rpm (Mixwell®, Tokuju Kosakusho, Kanagawa, Japan)) for 15 min. Subsequently, acetaminophen or ascorbic acid was mixed well with the mixture of crystalline cellulose and L-HPC or spherical sugar granules, and then, magnesium stearate (1%) was mixed using the V-shaped mixer (total amount, 0.5 kg) for 15 min. To prepare 200 mg tablets, the above-mentioned mixtures of each type of crystalline cellulose and other excipients at various weight ratios, and magnesium stearate were compressed at various forces (1—10 kN). A tablet-hitting pressure displacement system (Stratt Press®, model N-20E, Okada Seiko, Tokyo, Japan) equipped with flat-faced punches (diameter 8 mm) was employed as the single-punch tabling machine (press speed, 15 tablets/min).

**Evaluation of Tablets** The crushing tolerance of tablets (force required to break the tablet) by diametrical compression was measured with a digital crushing tolerance measuring machine (TS-50N®, Okada Seiko, Tokyo, Japan). The absolute density (\( \rho \)) of ten tablets was measured using a multivolume pycnometer (Accupyc 1330®, Shimadzu, Kyoto, Japan) and the mean value of porosity (\( E \)) for these ten tablets was calculated as follows:

\[
E(\%) = (1 - \frac{\rho_d}{\rho}) \times 100
\]

where \( \rho_{ap} \) is the apparent density calculated using the mean weight, diameter and thickness.

Determination of the disintegration time in the mouth and sensory evaluation of roughness were carried out according to the method of Kimura et al., with slight modification. Six healthy volunteers, from whom informed consent was first obtained, randomly took one prepared tablet and the time required for complete disintegration of the tablet in the mouth, without biting and without drinking water, was recorded. The degree of roughness and irritation was scored as follows: 0 = not rough, 1 = slightly rough, and 2 = markedly rough. Immediately after the in vivo disintegration test, volunteers rinsed their mouths without ingesting the disintegrated materials.

**Results**

1. **Effect of Particle Size of Microcrystalline Cellulose on Crushing Tolerance and Disintegration Time of Tablets** Previously, we reported the preparation of rapidly disintegrating tablets by the direct compression method using microcrystalline cellulose PH-102 and L-HPC as excipients. These tablets had a crushing tolerance that exceeded 5 kg and disintegrated in the mouth within 30 s. In the present study, we intended to prepare tablets with a shorter disintegration time (within 15 s). Generally, the crushing tolerance of tablets to be of practical use should be at least 3—5 kg.

Therefore, we required that the minimum level of crushing tolerance of the tablets be 3 kg in this investigation. The particle size of microcrystalline cellulose used in the preparation of rapidly disintegrating tablets (mixing ratio by weight, PH-102 : L-HPC=8 : 2) may affect the relationship between crushing tolerance of the tablets and disintegration time in the mouth.

We prepared rapidly disintegrating tablets using a mixture of PH-102 with various particle sizes (<75 μm, 75—150 μm, 150—300 μm), determined using appropriate sieve sizes, and L-HPC (mean value of particle size; 50 μm) at a mixing ratio of 8 : 2. As shown in Fig. 1(A), the crushing tolerance of tablets prepared using microcrystalline cellulose with a small particle size (less than 75 μm) was larger than that of tablets prepared using microcrystalline cellulose with a large size (exceeding 150 μm). On the other hand, the disintegration time in the mouth was significantly shorter when PH-102 with small particle size (<75 μm) was used (Fig. 1(B)). Figure 1(C) shows the relationship between crushing tolerance and disintegration time in the mouth. Disintegration time increased with increasing crushing tolerance. The shaded area in Fig. 1(C) indicates the required value in this study. It was found that fine microcrystalline cellulose with small particle size is suitable for the preparation of rapidly disintegrating tablets.

In the subsequent study, a new type of fine microcrystalline cellulose (PH-M series) with very small particle size was chosen instead of PH-102 for the preparation of tablets. The physicochemical properties of the PH-M series are summarized in Table 1. To our knowledge, little experimental data on the preparation of tablets using the PH-M series have been reported.

![Figure 1](image-url)
been reported thus far. Therefore, we investigated the effect of the type of PH-M used on the relationship between crushing tolerance of tablets and the disintegration time. Tablets prepared using spherical microcrystalline cellulose, PH-M-06, which has the smallest particle size, had sufficient crushing tolerance (approximately 8 kg) and were very rapidly disintegrated in the mouth (within 15 s, Fig. 2(A)).

2. Effect of Mixing Ratio (PH-M-06 and L-HPC) and Drug Concentration on Crushing Tolerance and Disintegration Time of Tablets

To examine the most suitable mixing ratio of PH-M-06 to L-HPC, tablets were prepared using mixtures of the above two materials at various weight ratios. As shown in Fig. 2(B), tablets with sufficient crushing tolerance (>3 kg), and short disintegration time (within 15 s) could be prepared when the mixing ratio of PH-M-06 to L-HPC was 9 : 1.

Figure 3 illustrates the relationship between crushing tolerance of tablets and disintegration time in the mouth when tablets containing acetaminophen or ascorbic acid (concentration 10, 25 and 50%) were prepared in combination with PH-M-06 and L-HPC at a mixing ratio of 9 : 1. Using this formulation, consolidation tended to decrease due to the decrease in PH-M-06 and L-HPC concentration. Therefore, the compression force should be increased to prepare the tablets. Consequently, rapidly disintegrating tablets with a drug concentration of 50% could be prepared.

3. Physical Characteristics of Rapidly Disintegrating Tablets Using Sugar Granules

The powder mixture of PH-M-06 and L-HPC (weight ratio=9 : 1) had a characteristic of poor fluidity (angle of repose 54°) due to a high angle of repose of PH-M-06 with small particle diameter. It was unsuitable to use conventional sugar powder in combination with microcrystalline cellulose due to its low fluidity and adhesivity. Generally, the angle of repose should be approximately 25—45° for tableting by direct compression. Therefore, spherical sugar granules with good fluidity were chosen instead of L-HPC.

Recently, spherical sugar granules such as sucrose-starch spheres (NP-101) and purified sucrose spheres (NP-103) have been used in pharmaceutical manufacturing.9) NP is classified according to material (kind of sugar) and size, as summarized in Table 2. For instance, NP-103, which is pure sucrose spherical granules (concentration 100%) with uniform size distribution, is applied as the core of controlled-release pills. It has a low angle of repose (approximately 30°).

To improve the fluidity of tableting materials, NP is chosen

![Table 2. Physicochemical Properties of Nonpareil](https://example.com/table2.png)

<table>
<thead>
<tr>
<th>NP-101</th>
<th>NP-103</th>
<th>NP-107</th>
<th>NP-108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Sucrose</td>
<td>Sucrose</td>
<td>Lactose</td>
</tr>
<tr>
<td>Particle size (µm)</td>
<td>589</td>
<td>589</td>
<td>610</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Granule tolerance (g/mm²)</td>
<td>647</td>
<td>1217</td>
<td>1097</td>
</tr>
</tbody>
</table>

Each value is expressed as the mean.
in the preparation of tablets with sufficient crushing tolerance (3 kg) and short disintegration time (within 15 s). Although many kinds of spherical sugar granules are commercially available, we used the following four types: NP-101, NP-103, NP-107 and NP-108.

Figure 4 shows the relationship between crushing tolerance of the tablet and disintegration time in the mouth when the mixing ratio of PH-M-06 to NP was changed. The crushing tolerance tended to increase with increasing compression force and decreasing mixing ratio of NP in the tableting materials. Furthermore, it was found that crushing tolerance was not increased by the use of NP-101 and NP-103, in comparison with NP-107 and NP-108. The angles of repose of mixtures of PH-M-06 and NP at various ratio are summarized in Table 3. It was found that the mixing ratio of NP of 30—50% is suitable for tableting. The disintegration time corresponded to the increase in the compression force of tablets using PH-M-06 and NP at various ratio summarized in Table 3. It was found that the mixing ratio of NP of 30—50% is suitable for tableting. The disintegration time corresponded to the increase in the compression force of tablets using PH-M-06 and NP-101 or NP-103, and was prolonged when compression force was increased. In the case of tablets prepared with PH-M-06 and NP-107 or NP-108, the disintegration time remained short (within 15 s) when crushing tolerance was increased (exceed 3 kg). Therefore, NP-107 and NP-108 are preferred for the preparation of rapidly disintegrating tablets.

4. Effect of Particle Size in Tablets on the Sensation of Roughness after Disintegration in the Mouth

To elucidate the effect of particle size on the feeling of roughness when prepared tablets were taken orally, a sensory evaluation of tablets containing PH-M-06 and L-HPC at a mixing ratio of 9:1 was performed using a paired test. PH-102 was used as reference material. The results of evaluation by volunteers are presented in Table 4. These indicate that PH-M-06 was superior to PH-102 in terms of texture. It was found that particle size is an important factor to consider in choosing the microcrystalline cellulose to be used for tablet preparation. On the other hand, although particles of NP, a spherical sugar granule, are large, it does not give a feeling of roughness in the mouth after disintegration of the tablets prepared with PH-M-06 and NP-108.

Discussion

Certain factors in the compaction process of powdered materials significantly influence the disintegration of tablets. The rapid disintegration of tablets with high porosity is thought to be due to rapid water absorption. Heckel proposed an equation that can be used to evaluate the compaction process for tableting, taking into account compression force and tablet porosity. The compaction of powders has been analyzed as a two-stage process in terms of the expression:

\[ \ln(1/(1 - D^2)) = KP + \ln(1/(1 - D_0)) \]  

where \( D_0 \) is the relative apparent density of the powder and \( P \) is the compression force. The replacement of the term \( \ln(1/(1 - D_0)) \) with a constant, \( A \), and \( 1/(1 - D) \) reworded porosity, \( E \), gives the expression:

\[ \ln(1/E) = KP + A \]  

In the compaction process, the first stage involves filling of the die; the degree of densification is indicated by \( D_0 \), the relative apparent density of the powder. \( D_0 \) is a function of the geometry of powder particles. The second stage is characterized by individual particle movement and rearrangement at low pressures before interparticle bonding occurs. Density–pressure curves may be described by two parameters. It is postulated that one is related to low-pressure densification by interparticle motion and the other is a measure of the ability of the powder to compress after appreciable interparticle bonding has taken place. The compression process of the tablet was analyzed using Heckel’s equation. Figure 5 shows
the Heckel plot of the tablets containing acetylaminophen or ascorbic acid. The value of 1/E increased linearly with increasing compression force, suggesting that the material undergoes plastic deformation without fragmentation. However, despite the same conditions for preparation using PH-M-06 and L-HPC, differences in the slope of the lines were observed between acetylaminophen and ascorbic acid formulations (Fig. 5 (A)). On the other hand, this difference was not observed in the compaction process when NP-108 was used with PH-M-06 (Fig. 5 (B)). It is presumed that the compaction process is not influenced by the use of the formulation containing PH-M-06 and NP-108.

Usually, as the applied compression force (or pressure) used to prepare tablets increases, the disintegration time increases. In this study, we also observed a good relationship between compression force and disintegration time for rapidly disintegrating tablets prepared using crystalline cellulose (PH-102 or PH-M-06) and L-HPC or spherical sugar granules (NP). In contrast, the effects of hardness (crushing tolerance) of tablet on the disintegration time for conventional tablets were observed. For instance, a good correlation between hardness (crushing tolerance) and disintegration time was obtained by Kitazawa and co-workers for conventional uncoated tablets containing caffeine. For rapidly disintegrating tablets, the same good relationship between crushing tolerance and disintegration time was obtained. These two parameters increased with increasing particle size of PH-102 and PH-M-06 (Figs. 1(C) and 2(A)). This indicates that the particle size of crystalline cellulose plays an important role in the disintegration mechanism. Generally, the concentration of a disintegrating agent influences the relationship between the applied compression force and the disintegration time. Furthermore, the disintegration time tends to increase with increasing crushing tolerance. Prepared tablets containing lower concentrations (10—20%) of L-HPC showed rapid disintegration time and high crushing tolerance. On the other hand, disintegration time increased with decreasing crushing tolerance when higher concentrations (40—50%) of L-HPC were used. In the case of tablets with high concentrations of L-HPC, L-HPC swelled significantly, that is, the maximum swelling rate of L-HPC was approximately ten-fold that of microcrystalline cellulose. However, the high concentration of L-HPC in tablets interferes with the rapid disintegration function (increasing disintegration time) due to the decrease in the degree of wetting (increasing wetting time). We previously reported that the disintegration time of tablets prepared with PH-102 and L-HPC significantly decreased (25→5 s) with increasing tablet porosity (approximately, 25→45%). Similar results were obtained in the case of tablets prepared with PH-M-06 and L-HPC. The rapid disintegration of tablets with high porosity is thought to be due to rapid water absorption. The disintegration occurs via capillary action rather than swelling; disintegrating materials such as PH-M-06 and L-HPC increase the porosity of tablets, thus promoting capillary action. Sugars, such as lactose, sucrose and mannitol, are often used as soluble filler-binders in tableting by direct compression. In case of tablets prepared with PH-M-06 and NPs that are used to improve fluidity, it is presumed that spherical shape of NP is destroyed during the compaction process in tableting, based on observations of tableting with NP alone. Thus, sugar in the tablets prepared with NP alone is dissolved well by water that is absorbed by the tablets, thus accelerating disintegration by microcrystalline cellulose.

Consequently, rapidly disintegrating tablets could be obtained by the use of NP. PH-M-06 is better than PH-102 in terms of reducing the feeling of roughness in the mouth. To improve the taste of rapidly disintegrating tablets, Bi and co-workers reported a formulation using erythritol in combination with conventional crystalline cellulose, PH-102, and L-HPC. They observed that the taste of tablets was further improved by the addition of large amounts of erythritol. On the other hand, none of the volunteers complained about the taste of rapidly disintegrating tablets prepared using PH-M-06 with small particle size. Generally, particle size less than 15—20 µm is recommended to avoid the feeling of roughness in the field of food science. Therefore, PH-M-06 with small particle size (<10 µm) is preferable to PH-102 (approximately 100 µm) for the preparation of rapidly disintegrating tablets. Fortunately, the rough texture after disintegration in the mouth was less detectable when tablets were prepared using PH-M-06 in combination with sugars such as NP-108. This is probably related to the dissolution properties of the crushed spherical sugar granules.

In conclusion, tablets with sufficient crushing tolerance (exceeding 3 kg) and short disintegration time (within 15 s) in the mouth can be prepared using L-HPC and fine spherical microcrystalline cellulose (PH-M-06) at a low compression force. It is possible to prepare drugs (concentration of approximately 50%) in the tablet form using PH-M-06 in combination with L-HPC as a good disintegrant. Rapidly disintegrating tablets can be prepared by the conventional direct compression method when suitable excipients such as fine spherical microcrystalline cellulose (PH-M-series) are used. Poor fluidity of excipients is improved by the use of spherical sugar granules during the manufacture of rapidly disintegrating tablets. Furthermore, spherical sugar granules are superior to L-HPC to decrease the rough texture. This is probably related to the dissolution properties of the crushed spherical sugar granules. Fortunately, the rough texture after disintegration in the mouth was less detectable when tablets were prepared using PH-M-06 in combination with NP.

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References and Notes


