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Further improvement of orally disintegrating tablets using micronized ethylcellulose

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ABSTRACT

The aim of this study is to design a new orally disintegrating tablet (ODT) containing micronized ethylcellulose (MEC). The new ODT was prepared by physical mixing of rapidly disintegrating granules (RDGs) with MEC. To obtain RDGs, mannitol was spray-coated with a suspension of corn starch and crospovidone (9:1, w/w ratio) using a fluidized-bed granulator (suspension spray-coating method). The new ODTs were evaluated for their hardness, friability, thickness, internal structure (X-ray-CT scanning), in vivo disintegration time, and water absorption rate. Since MEC increases tablet hardness by increasing the contact frequency between the granules, the new ODTs could obtain high hardness (>50 N) and low friability (<0.5%) with relatively low compression force. In addition, fine capillary channels formed in ODTs facilitated the wicking action and enabled rapid disintegration in vivo (<30 s). On the other hand, since MEC has low hygroscopicity, the tablet hardness of ODTs containing MEC remained high for 1 month in high-humidity conditions.

In conclusion, the new ODTs containing MEC developed in this study possessed superior properties for clinical use and are expected to be applied for a wide range of functionally released drugs for bitter taste masking, sustained release, and controlled release (pH-dependent film coating, matrix, and microcapsule).

1. Introduction

Older people, children, and bedridden patients sometimes have difficulties in swallowing conventional tablets or capsules. In these patients, medication compliance and therapeutic effect could be improved by taking orally disintegrating tablets (ODTs) that can rapidly and easily disintegrate in the oral cavity without water (CDER, 1992; William and Tapash, 2005; FDA, Rockville, MD, 2008). In addition, ODTs are applicable to active working people who have no access to water.

Recently, ODTs have become increasingly popular around the world. On the basis of requests from patients to enhance their quality of life (QOL), new types of ODTs have been developed and then released globally by many pharmaceutical companies. In addition, numerous reports have been published regarding the technologies for preparation of ODTs (Watanabe et al., 1995; Y.X. Bi et al., 1999; Y. Bi et al., 1999; Chang et al., 2000; Ishikawa et al., 2001; Sugimoto et al., 2001, 2005, 2006a,b; Schiermeier and Schmidt, 2002; Mizumoto, 2005).

However, most ODTs are difficult for pharmacists and patients to handle in the hospital and at home because of their extremely brittle character. In addition, special equipment, such as a freeze-dryer for wet mass filled into PTP packaging, a tabletting machine for wet mass methods, and drying and wetting chambers for the crystalline transition of amorphous sucrose, is required to manufacture these ODTs. In addition, ODTs prepared by direct compression methods were reported to show incomplete dissolution and swelling of contained additives that resulted in a rough feeling on the tongue and delayed disintegration in the mouth (Bi et al., 1996; Ishikawa et al., 2001).

To overcome all of these problems for ODTs, we have developed a new ODT with high hardness of tablet, high disintegration rate, and better mouth feeling (Okuda et al., 2009). This new ODT has already been commercialized under the trade name RACTAB®. RACTAB® was prepared by a suspension spray-coating method (SUSPM), in which saccharides were spray-coated with a suspension of corn starch and crospovidone using a fluidized-bed granulator. Among all RDGs prepared by SUSPM, mannitol spray-coating with a suspension of corn starch and crospovidone (2.5:1, w/w ratio) showed the most appropriate properties for ODTs: short in vivo oral disintegration time and high tablet hardness.

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Table 1
Mean particle size (D_{50}) of materials and formulation of orally disintegrating tablets (180 mg/tab.).

Material	(Conditions)	Particle size D_{50}(μm)	Formula No.				
			F-0	F-1	F-2	F-3	F-4
RDG1[a]		67.8[c]	98.9				
RDG2[b]		64.3[c]		98.9	96.4	93.9	91.4
Micronized ethyl cellulose	(Extra.)	5 - 10[d]	0	0	2.5	5	7.5
Light Anhydrous Silicic Acid	(Extra.)	3.2[d]	←	←	0.3	→	→
Magnesium Stearate	(Extra.)	6.9[d]	←	←	0.8	→	→
Total (%)			←	←	100	→	→

[a]RDG1; mannitol:corn starch:crospovidone (9:2.5:1).
[b]RDG2; mannitol:corn starch:crospovidone (26:9:1).
[c]Measured by laser particle counter (LA-920, HORIBA).
[d]Cited from production catalogues.

However, it was found that, during storage in high-humidity conditions (40 °C, 75% RH), this ODT developed decreased tablet hardness because crospovidone has hygroscopicity. In addition, it was difficult to prepare the ODT with taste-masking granules for bitter-tasting drugs or with controlled-release granules using insoluble polymers because the coating membrane was often broken at high compression force.

Ethylcellulose (EC) is an inert, hydrophobic polymer and is essentially tasteless, odorless, colorless, calorie-free, and physiologically inert. EC has been extensively utilized as a pharmaceutical device (filler) in a number of oral dosage forms. A well-known drug-release technology using EC was developed using film coating, microcapsule, microsphere, and matrix for sustained-release systems and colon-specific drug delivery systems (Siew et al., 2000; Takishima et al., 2002; Rehman et al., 2006; Das and Rao, 2006). EC can be dissolved or dispersed in different solvents in the process of coating or granulating. On the other hand, micronized ethylcellulose (MEC) is provided as solid dispersion to use for water-based coating systems (Keshikawa and Nakagami, 1994; Heng et al., 2003). Furthermore, several reports have addressed the use of EC as a directly compressible excipient in a controlled-release matrix or immediate-release tablet (Upadrashta et al., 1993; Katikaneni et al., 1995; Desai et al., 2001). However, the effect of MEC on the physical properties of ODTs has not been reported.

In this study, a new ODT, which possesses high resistance against humidity and high physical strength (clinically handling, friability, etc.) at low compression force, was designed by applying an appropriate composition of micronized ethylcellulose (MEC). This new ODT is composed of RDGs and MEC added as a physical mixture. Its physical properties, such as compressibility (tablet hardness), friability, tablet thickness, oral disintegration time, and capability of disintegration, were evaluated.

2. Materials and methods

2.1. Materials

As a saccharide, D-mannitol (Merck Co., Ltd., Japan) was used. As disintegrants, corn starch (Nippon Shokuhin Kako Co., Ltd., Japan) and crospovidone (ISP Co., Ltd., Japan) were used. As functional additive, micronized ethylcellulose (Dow Chemical Co., Ltd., USA) was used. All other materials used in this study were of Japanese Pharmacopoeia (JP) grade.

2.2. Methods

2.2.1. Preparation of the orally disintegrating tablets (ODTs)

Fig. 2 shows the manufacturing process for ODTs tested in this study. At first, rapidly disintegrating granules (RDGs) were prepared by suspension spray-coating method using a fluidized-bed granulator (MP-01, Powrex, Japan) at 500 g size scale. The granules were blended with micronized ethylcellulose, and were with light anhydrous silicic acid and magnesium stearate by shaking by hand in a plastic bag. After the blending, the granules were compressed using a rotary tabletting machine (VIRG, Kikusui seisakusho, Japan) to obtain tablets of 180 mg in weight.

In this study, to investigate the effect of the preparation method on the physicochemical properties of ODTs, various tablets were prepared according to the formulas and methods presented in Table 1.

2.3. Evaluation of granules and tablets

2.3.1. Particle size

The mean particle size (D_{50}) of the granules was measured using a laser particle counter (LA-920, HORIBA Corporation, Japan).

2.3.2. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) of the granules was performed using a scanning electron microscope (VE-7800S; KEYENCE, Japan).

2.3.3. X-ray inspection tomograms (CT-scanning)

X-ray inspection tomograms (CT-scanning) of the tablets were obtained using an X-ray CT-scan analyzer (SMX-100CT; Shimadzu, Japan).

2.3.4. Moisture adsorption and desorption

The moisture adsorption and desorption of the granules were measured using a moisture sorption analyzer (IGAsorp; HIDEN Corporation, USA). The sample was loaded into the IGAsorp in a stainless steel mesh bucket. It was then dried at 25 °C for 5 hours.

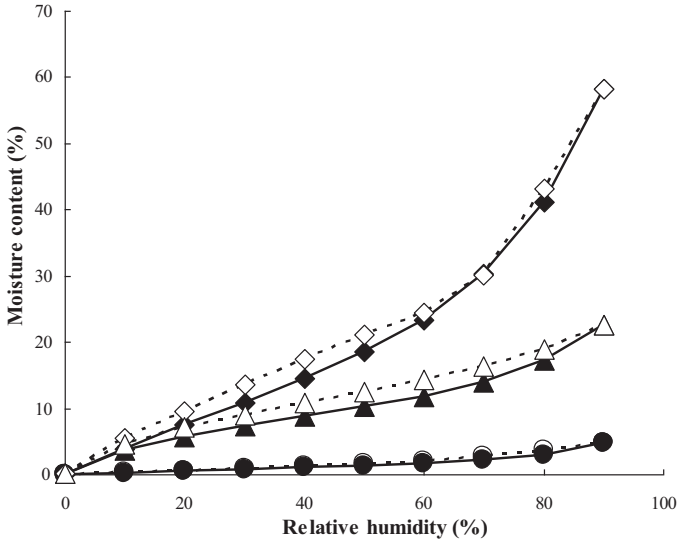

Fig. 1. Relationship between relative humidity and moisture content for materials: micronized ethylcellulose (absorption/desorption) (●/○), corn starch (absorption/desorption) (▲/△), and crospovidone (absorption/desorption) (♦/◊).

The 8-step isotherm from 0 to 90% RH was performed with RH steps of 10% RH.

2.3.5. Liquid absorption process for tablets

The liquid absorption capacity of the tablets was measured using a dynamic contact angle measuring device and tensiometer (DCAT21; Dataphysics Corporation, USA). The tablet was placed on a piece of paper filter inside a glass tube with glass filter. The water was then passively drawn into the tablet from a water vessel at room temperature. The absorbed water volume per cross section of tablet (g/cm^2) was calculated.

2.3.6. Tablet hardness

The tablet hardness was determined using 5 random tablets using a tablet hardness tester (TBH450 WTD IC, ERWEKA Corporation, Germany) for each test formulation.

2.3.7. Tablet friability

The tablet friability was measured as the percentage of weight loss of 36 tablets tumbled in a friabilator (TFF-03, TSUTSUI Scientific Instruments Corporation, Japan). After 4 min of rotation at 25 rpm, dust of tablets was removed and the percentage weight loss was calculated.

2.3.8. Disintegration time in oral cavity

The complete disintegration time of the tablets in oral cavity was evaluated in five healthy volunteers. The endpoint for the disintegration in the mouth was the time when the tablet placed on the tongue had disintegrated until no lumps were remaining. The volunteers rinsed out their mouths with water before the test. The protocol and experimental design for all disintegration tests in the oral cavity were approved by the Ethical Committee of TOWA Pharmaceutical Co., Ltd.

3. Results

3.1. New formulations of orally disintegrating tablets tested in this study

Fig. 1 shows the profile of moisture adsorption and desorption for crospovidone, corn starch, and micronized ethylcellulose (MEC).

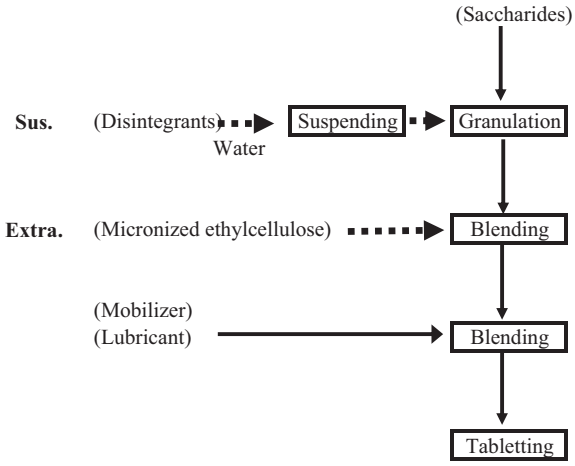

Fig. 2. Manufacturing process for orally disintegrating tablets using fluidized-bed granulator. Rapidly disintegrating granules (RDGs) were prepared by suspension spray-coating method.

Among these 3 compounds, crospovidone was most hygroscopic and showed hysteresis in the moisture adsorption and desorption profile. Corn starch showed less hygroscopicity but had almost the same profile as crospovidone. In contrast, the moisture adsorption of MEC was about 1/20 of that of crospovidone at conditions of 25 °C and 60% RH, indicating its low hygroscopicity. Rapidly disintegrating granules (RDGs) used for RACTAB® in our previous study were prepared by spray-coating of mannitol with a suspension of corn starch and crospovidone (2.5:1, w/w ratio). Therefore, tablet hardness may decrease during storage in high-humidity conditions (40 °C, 75% RH) because crospovidone is swollen by a small amount of water, which results in decrease in the binding force between RDGs.

In this study, to improve the hygroscopicity of ODTs, MEC was added by physical mixing with RDGs. RDGs were prepared by a suspension spray-coating method (SUSPM). As shown in Table 1, since the mean particle size of MEC is small (5–10 μm), MEC is expected to function as a dry-binder to improve the physical properties of ODTs.

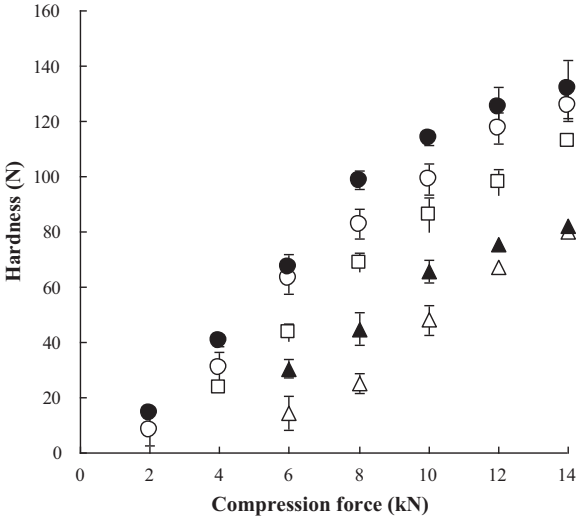

Fig. 3. Relationship between compression force and tablet hardness for ODTs. RDG1 (corn starch and crospovidone; 2.5:1, w/w ratio) was used with F-0. RDG2 (corn starch and crospovidone; 9:1, w/w ratio) was used with F-1, F-2, F-3, and F-4. F-0 (without MEC: 0 mg/tablet) (▲), F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

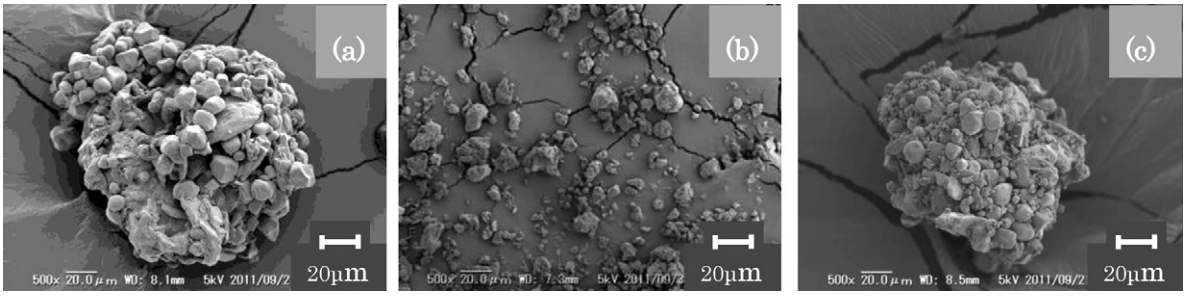

Fig. 4. Scanning electron micrographs of (a) rapidly disintegrating particle (RDG), (b) micronized ethylcellulose (MEC) and (c) RDG containing MEC.

In order to evaluate the effect of MEC on the physical properties of ODTs, five different ODTs were prepared (formulations F-0 to F-4 in Table 1 and Fig. 2). F-0 is a formulation consisting of RDG1 that was prepared in a previous study and MEC was not included. Formulations F-1 to F-4 consist of RDG2 in which the ratio of crospovidone to RDG1 is reduced (the ratio of corn starch:crospovidone is 2.5:1, w/w for RDG1 and 9:1, w/w for RDG2). These RDGs were tabletted at compression forces of 2–14 kN. F-1 dose not include MEC. In the case of formulations F-2, F-3, and F-4, MEC was added at 4.5 mg, 9 mg, and 13.5 mg/tablet (2.5, 5.0, and 7.5, w/w% of total weight) to RDG2, respectively. As shown in Fig. 4, the scanning electron micrographs (SEM) of RDG, MEC, and RDG containing MEC.

3.2. Hardness of orally disintegrating tablets

The relationship between the compression force and hardness of five ODTs is shown in Fig. 3. The hardness of ODTs was increased by the addition of MEC in an amount-dependent manner, suggesting that MEC acted as a dry-binding agent. The internal structure of these ODTs (F-1 to F-3) at appropriate compression force (6 kN) was observed using an X-ray-CT scan analyzer (SMX-100CT) (Fig. 5). F-1 showed apparently vacant space (low density) in the center of the tablet. Vacant space was decreased by the addition of MEC (in F-2) and was not observed in F-3. These findings indicated that MEC increased the contact frequency between granules in the tablet that led to higher hardness with relatively low compression force.

3.3. Physical property of orally disintegrating tablets prepared with micronized ethylcellulose

As the next step, the influence of MEC on the tablet friability of these ODTs was evaluated. In Fig. 6a, the relationship between the compression force and friability is shown. The friability of ODTs was decreased by the addition of MEC and by the increase in the compression force. This relationship was significantly dependent on the amount of MEC added to the formulation. On the other hand, all formulations showed almost the same relationship between hardness and friability (Fig. 6b). When hardness increased to 50 N, friability of all ODTs became less than 0.5%. Consequently, ODTs containing 9–12.5 mg/tablet of MEC (corresponding to 5–7.5, w/w% of total weight) could achieve appropriate properties for clinical handling, namely, friability less than 0.5% and hardness more than 50 N, at the compression force of 6 kN that is usually used for tabletting.

The relationship between the compression force and thickness of four ODTs is shown in Fig. 7a. Fig. 7b also shows the relationship between the hardness of tablets compressed with varying forces and thickness. The thickness of ODTs was decreased by the addition of MEC but not in an amount-dependent manner. However, at the same hardness, tablet thickness was greatest when 7.5, w/w% of MEC (high dose) was added as a dry binder followed by >5, w/w% of MEC > 2.5, w/w% of MEC > without MEC. It was suggested that MEC enhanced the magnitude of contact frequency between the RDGs at relatively low compression force.

3.4. Evaluation of water absorption capability for disintegration of orally disintegrating tablets

"Liquid transfer" properties of ODTs were studied with Bristow-type equipment where a paper strip is moved over the liquid sourcing slit (Bristow, 1967). The volume of absorbed liquid (V) is as follows:

$$V = \mathrm{Vr} + \mathrm{Ka}\ \ (T - \mathrm{Tw})^{1/2},$$

where Vr is the volume of filled up liquid in the surfaces of glass membrane filter and paper filter, Ka is the rate of liquid absorption, T is the contact time of liquid, and Tw is the lag time of liquid absorption. To evaluate the liquid absorption capacity, which is the major factor for disintegration of ODTs, dynamic contact angle measurement was performed for ODTs (F-1 to F-4). The relationship between the contact time and absorbed (transferred) liquid volume per cross section of tablet (g/cm^2) is shown in Fig. 8a. The liquid-absorption profiles for all ODTs were separated into four different steps (lag time was not observed). The first step (S1) was initiated by uptake of liquid from glass membrane filter at a contact time of 0–0.2 s. Then, the second step (S2) was started by uptake of liquid from the paper filter at a contact time of 0.2–1 s. At the third step, liquid was absorbed into the tablet and the absorption rate was accelerated (S3, 1–10 s), and saturated at the fourth step (S4, 10–60 s). Water absorption capacity of ODTs was unaffected by steps S1 and S2 because the speed of uptake of liquid was very high in these steps. In Fig. 8b, a Bristow plot, the relationship between the square root of the contact time up to 10 s and the absorbed liquid volume per cross section of tablet (g/cm^2) is shown for ODTs with the compression force of 6 kN. From 3 to 10 s of contact time (T_{3-10}), good correlations between the square root of contact time and the absorbed liquid volume were observed in all ODTs. From each linear correlation line, a slope (Ka) was calculated by the curve fitting method that corresponds to the absorption rate constant in the unit of cross section of tablet. As shown in Fig. 8c, Ka increased with increasing amount of MEC in the tablets.

The relationship between the tablet hardness and Ka value is shown in Fig. 9a. In the case of ODTs without MEC, Ka value increased with increasing hardness at compression forces of 6–14 kN. On the other hand, in the case of ODTs containing MEC, Ka value was kept constant regardless of the tablet hardness at various compression forces. In addition, the amount of MEC did not affect Ka values significantly.

The relationship between the tablet thickness and Ka value is shown in Fig. 9b. In the case of ODTs without MEC, Ka value increased when the thickness of the tablet decreased at compression forces of 6–14 kN. However, in the case of ODTs containing MEC, Ka values were not affected by the tablet thickness.

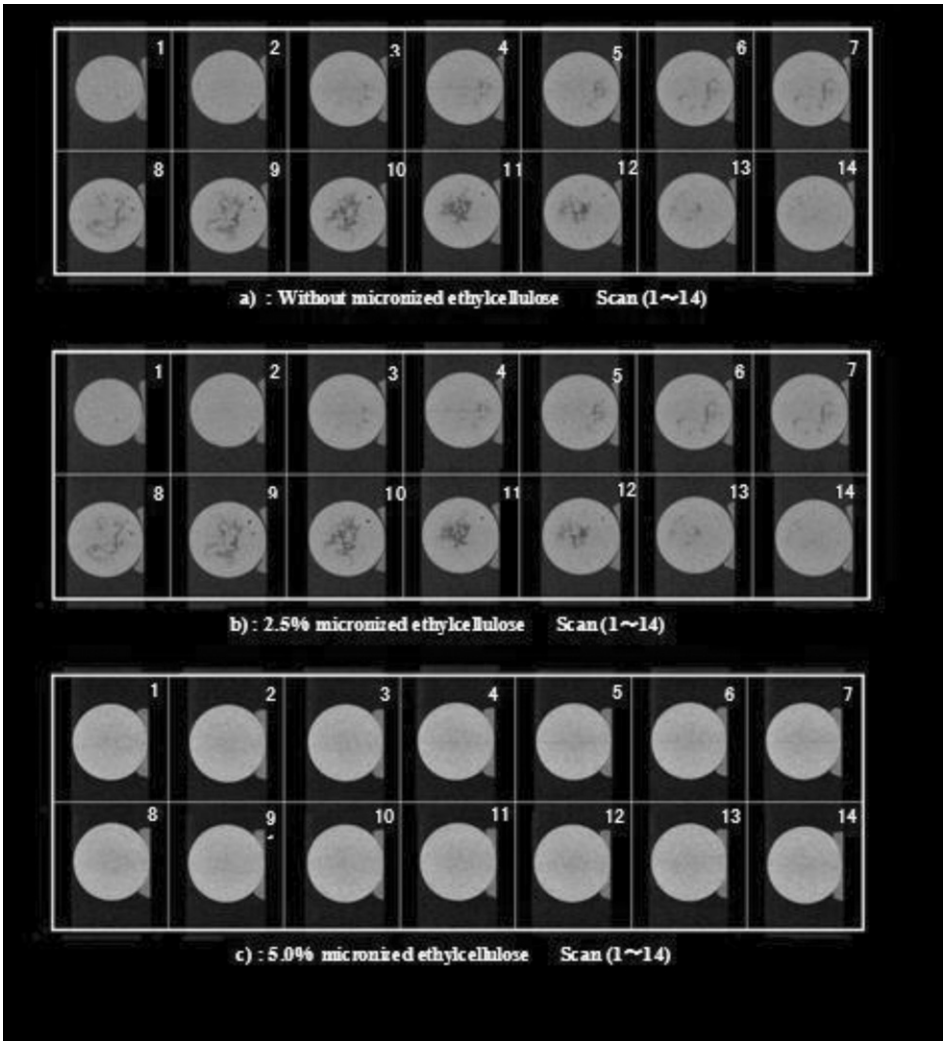

Fig. 5. X-ray inspection tomograms of rapidly disintegrating tablets containing various amounts of micronized ethylcellulose: (a) without MEC: 0 mg/tablet, (b) 2.5% MEC: 4.5 mg/tablet, and (c) 5.0% MEC: 9 mg/tablet.

3.5. Practical utility of orally disintegrating tablets

Fig. 10 shows the relationship between the hardness of tablets compressed with varying forces and their disintegration time in the oral cavity (oral disintegration time). The oral disintegration time of ODT prepared from RDG1 was significantly longer than that of other ODTs at all ranges of hardness. In ODTs prepared from RDG2, oral disintegration time was short and almost constant

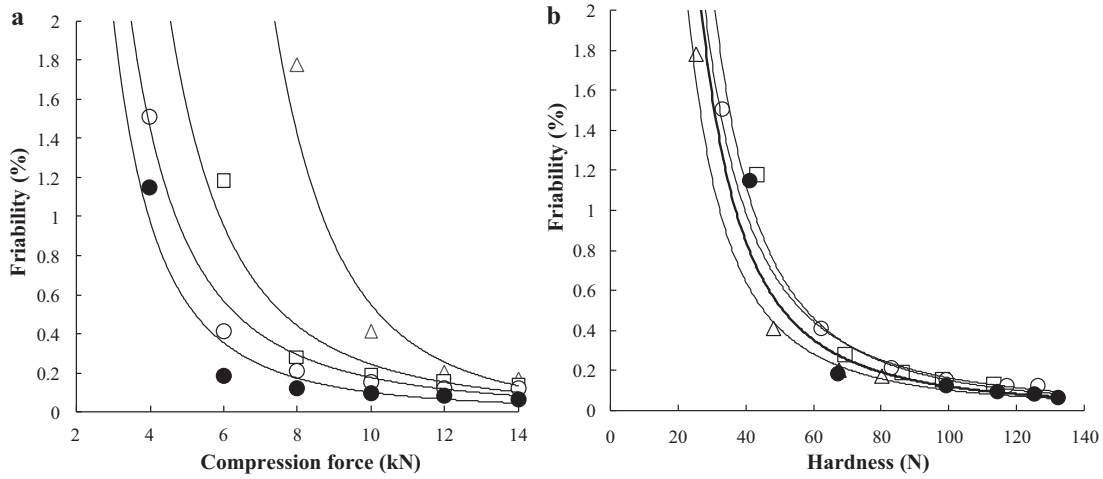

Fig. 6. (a) Relationship between compression force and tablet friability for ODTs. (b) Relationship between tablet hardness and tablet friability for F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

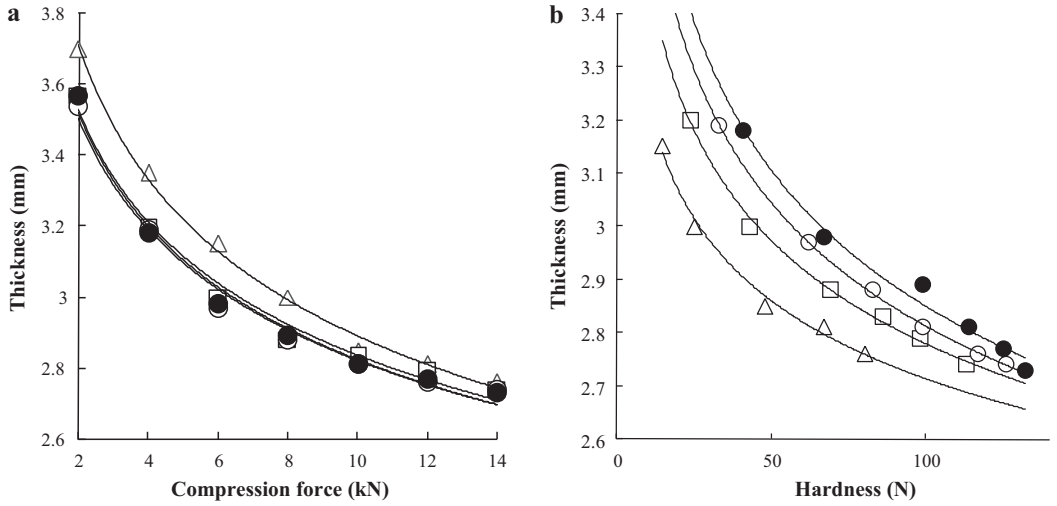

Fig. 7. (a) Relationship between compression force and tablet thickness for ODTs. (b) Relationship between tablet hardness and tablet thickness for ODTs. F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

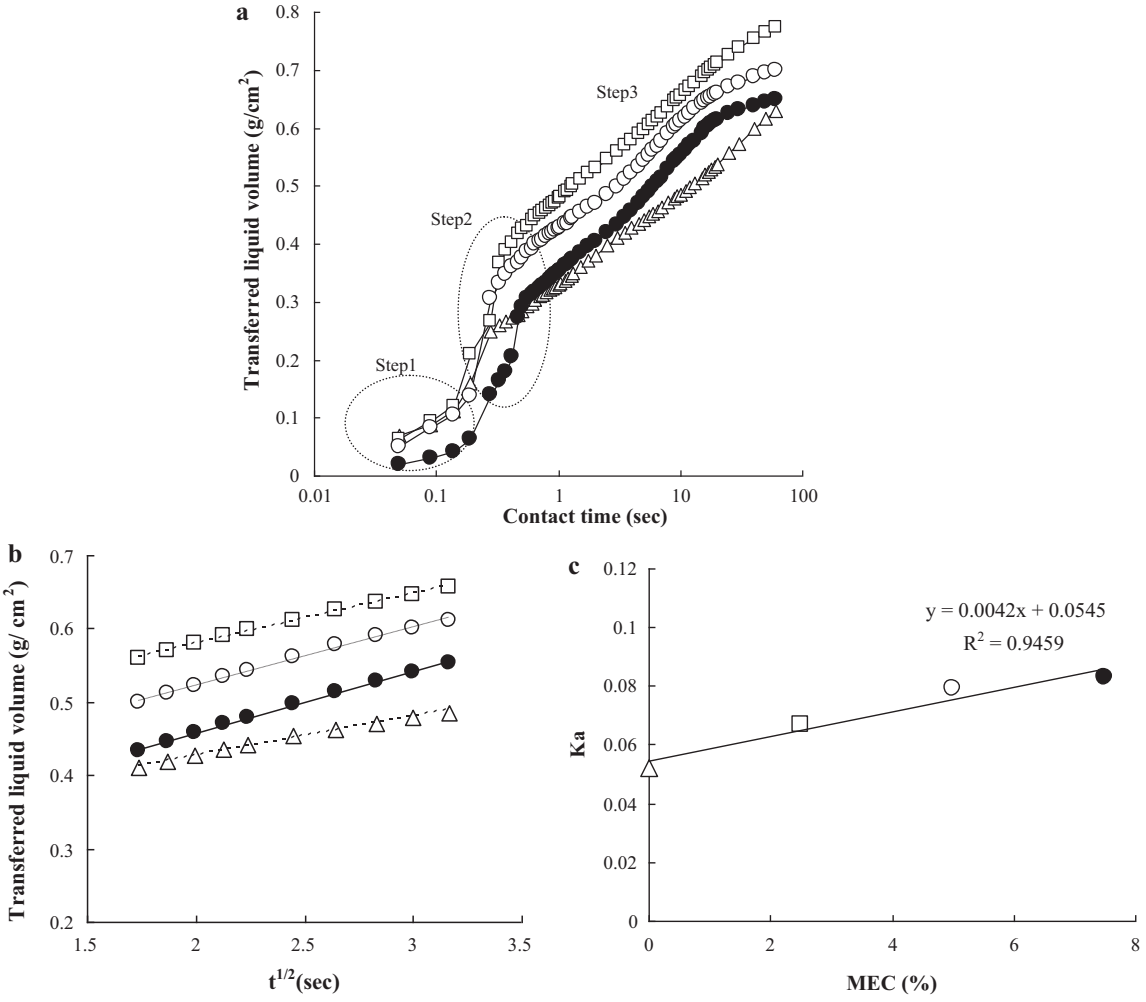

Fig. 8. (a) Relationship between contact time and transferred liquid volume per cross section of tablet. F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●). (b) Bristow plot: relationship between square root of the contact time up to 10 s and transferred liquid volume per cross section of tablet at low compression force (6 kN). F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●). (c) Relationship between various amounts of MEC and water absorption rate per cross section of tablet (Ka) at low compression force (6 kN). F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

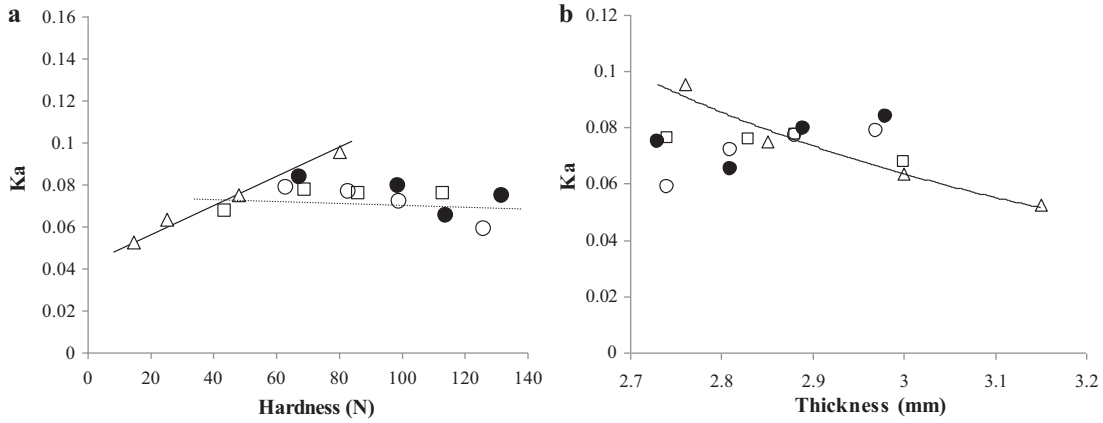

Fig. 9. (a) Relationship between tablet hardness and water absorption rate per cross section of tablet at various compression forces (6–14 kN). (b) Relationship between tablet thickness and water absorption rate per cross section of tablet at various compression forces (6–14 kN). F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

(10–15 s) in the range of 20–100 N of hardness. The addition of MEC to ODTs prepared from RDG2 did not affect the relationship between oral disintegration time and hardness. From each linear correlation line, a slope and an intercept were calculated by the curve fitting method. The slope (D/H value) indicates the oral disintegration time in the unit of tablet hardness. The intercept (D/H_0 value) represents the oral disintegration time when tablet hardness becomes zero, meaning an intrinsic potency of granules for disintegration (disintegratability). Since ODTs with small D/H and D/H_0 values could disintegrate immediately in the oral cavity regardless of the tablet hardness, these values are considered to be key parameters to select better ODTs (Okuda et al., 2009). In Fig. 10, at the high-hardness range (over 100 N), the tablet might cause plastic deformation and show longer disintegration time; therefore, the D/H value was calculated at hardnesses under 100 N. As shown in Table 2, the D/H value was almost constant (around 0.05) and did not depend on the amount of MEC. Since ODTs with MEC showed the lowest D/H value up to about 100 N, it was suggested that the plasticity of the tablets with MEC was very small.

Finally, the stability of hardness of ODTs containing MEC under accelerated stability test conditions (40 °C, 75% RH, one month for ICH) was compared with that of other ODTs without MEC. Fig. 11 shows the change in the hardness of all ODTs. The tablet hardness of new ODT containing MEC (5, w/w%) decreased only slightly during 1 month but was always over 50 N, while that of ODT without MEC remarkably decreased at high-humidity conditions if the initial hardness was set high. Hence, it was suggested that MEC added to ODTs worked to prevent moisture absorption and maintain high hardness of the tablet at high-humidity conditions.

Table 2
D/H value of ODTs with various concentrations of micronized ethylcellulose and compression forces.

Formula	Rapidly disintegrating granules	Micronized ethylcellulose (%)	D/H value (slope)
F-0	RDG1[a]	Without	0.157
F-1	RDG2[b]	Without	0.027
F-2	RDG2[b]	2.5	0.051
F-3	RDG2[b]	5	0.049
F-4	RDG2[b]	7.5	0.046

[a] Corn starch:crospovidone (9:1).
[b] Corn starch:crospovidone (2.5:1).

4. Discussion

In our previous study, a new ODT with high tablet hardness and high oral disintegration rate was developed using a new preparation method (Okuda et al., 2009). This newly developed ODT is composed of rapidly disintegrating granules (RDGs). These RDGs

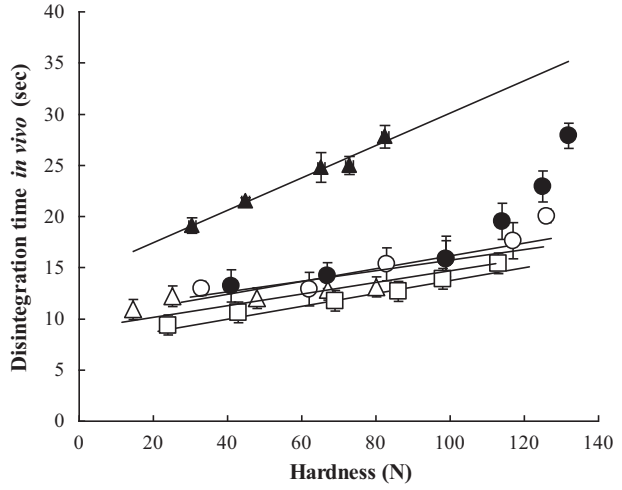

Fig. 10. Relationship between tablet hardness and disintegration time in the oral cavity for ODTs (without/with micronized ethylcellulose) when tabletted using various compression forces (2–14 kN). F-0 (without MEC: 0 mg/tablet) (▲), F-1 (without MEC: 0 mg/tablet) (△), F-2 (2.5% MEC: 4.5 mg/tablet) (□), F-3 (5.0% MEC: 9 mg/tablet) (○), and F-4 (7.5% MEC: 12.5 mg/tablet) (●).

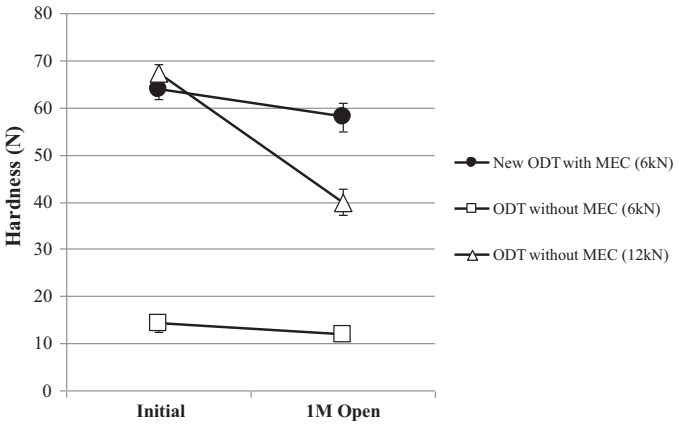

Fig. 11. Stability of tablet hardness under accelerated conditions (40 °C, 75% RH) for ODTs (without/with micronized ethylcellulose).

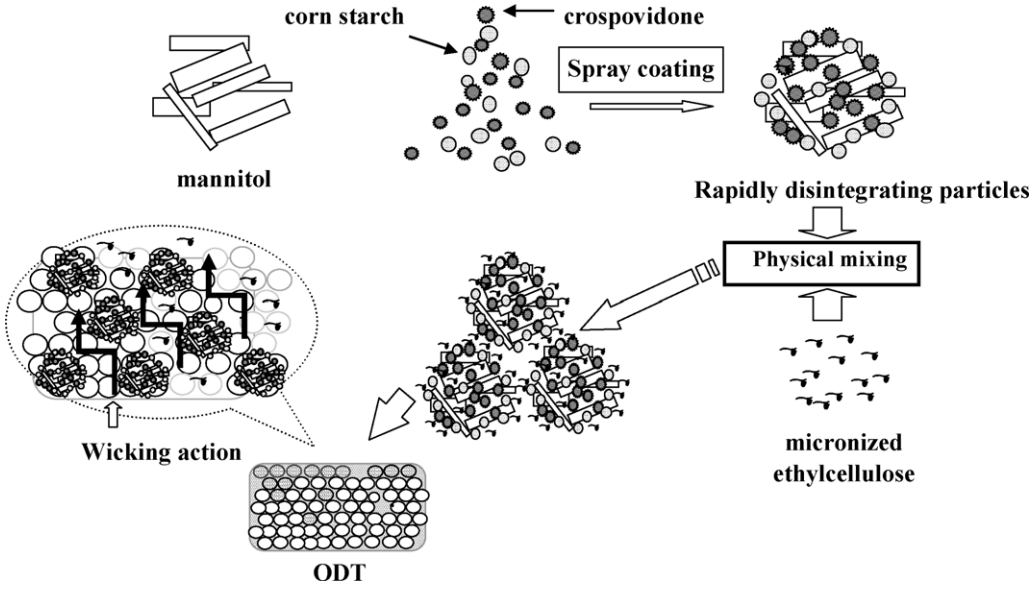

Fig. 12. Schematic representations of the structure of rapidly disintegrating particles containing micronized ethylcellulose and disintegration by capillary action.

consist of mannitol, the surface of which is completely coated by corn starch and crospovidone particles. Surface coating of mannitol is performed by the suspension spray-coating method (SUSPM). The RDGs possess extremely large surface areas, narrow particle size distribution, and numerous micro-pores. When these RDGs were tabletted at appropriately high compression force (over 10 kN), the tablet hardness increased by decreasing plastic deformation and increasing the contact frequency between granules. However, by this method, it was difficult to prepare the ODT with taste-masking granules or controlled-release granules using insoluble polymers because the coating membrane was often broken at relatively high compression force. In addition, for practical use, this ODT caused a decrease in tablet hardness during storage in high-humidity conditions (40 °C, 75% RH) because crospovidone has high hygroscopicity (Fig. 1) and causes swelling.

To overcome these problems, a new ODT, which possesses high resistance against high humidity and high physical strength at low compression force, was designed by applying an appropriate amount of micronized ethylcellulose (MEC). MEC is known to form a matrix in the tablet during the compression process. Crowley et al. (2004) reported that the release of active ingredients from a tablet having an ethylcellulose matrix depended on the particle size of ethylcellulose and the compression force. For these reasons, MEC is often included in sustained-release formulations. In this study, MEC was selected as an appropriate dry-binder agent to increase resistance against humidity and physical strength for ODTs. Furthermore, since MEC might affect the disintegration of the tablet, the effect of MEC on the oral disintegration time was evaluated.

Since crospovidone has high hygroscopicity (Fig. 1), in this study, ODTs were prepared with RDGs containing a small amount of crospovidone. As shown in Fig. 11, when tabletted with high compression force (12 kN), the ODT having a small amount of crospovidone initially showed high hardness, but after 1 month of storage, it markedly decreased. Furthermore, with low compression force (6 kN), the hardness was low and not sufficient for clinical use.

In contrast, in the case of ODTs with MEC, the hardness of tablet became higher even at low compression force, and remained high enough for clinical use for 1 month. This result might be related to the magnitude of contact frequency between the RDGs. Fig. 4 shows scanning electron micrographs (SEM) of RDG, micronized ethylcellulose (MEC), and RDG containing MEC. From these pictures, it was revealed that MEC adhered to the surface of RDGs by physical mixing and was filled between the RDGs during the tabletting because the particle size of MEC (5–10 μm) is small enough compared with the particle size of RDGs (Table 1). The vacant spaces were not observed in ODTs with MEC by X-ray-CT scanning tomography (Fig. 5), indicating that the internal structure of ODTs was closely packed because MEC uniformity was distributed between the RDGs. Therefore, it was suggested that the compression force between the RDGs was transmitted completely. In other words, MEC worked as a dry-binder agent for ODTs.

In order to clarify the effect on compatability of MEC for these ODTs, properties of ODTs were investigated. At the same compression force, the friability of ODTs was lowest for MEC 7.5, w/w% followed by 5.0, w/w% > 2.5, w/w% > 0, w/w% (Fig. 6a), and also the thickness of ODTs decreased by addition of MEC. These results correspond with the study of X-ray-CT scanning (Fig. 6). Consequently, the physical strength (hardness, friability) for ODTs was improved by the addition of MEC and ODTs with appropriate amounts of MEC, which resulted in sufficient physical strength for clinical use with relatively low compression force.

On the other hand, at the same hardness, the thickness of ODTs with MEC was dependent on the amount of MEC. The thickness was greatest for MEC 7.5, w/w% followed by 5.0, w/w% > 2.5, w/w% > 0, w/w% (Fig. 7b). This rank order could be related to the magnitude of the binding force of MEC, which correlates with the transmission of compression force. Generally, the thickness of tablet depends on the compression force and the hardness because particles cause the plastic deformation during the tabletting process. However, the thickness of ODTs with MEC might be related to the magnitude of matrix formation between RDGs. Therefore, the compression force between the RDGs was transmitted completely at low compression force because MEC worked as a dry-binder for ODTs. These findings suggest that new ODTs can include various functional particles because ODTs containing MEC were prepared at low compression force.

MEC is a water-insoluble polymer and is often used in controlled-release dosage forms. Therefore, MEC might delay the oral disintegration time of ODTs. However, as seen in Fig. 10, all ODTs containing MEC showed short in vivo oral disintegration time (<30 s) at tablet hardness over 50 N. In order to clarify the reason for the fast disintegration of these ODTs, liquid transfer profiles were investigated. The Ka value increased with increasing amount

of MEC at a compression force of 6 kN (Figs. 8 and 9). In addition, in the case of ODTs with MEC, Ka values were constant regardless of tablet hardness and thickness. These results clearly suggested that the matrix was formed by the cross-linked binding among MEC and RDGs in the ODTs and acted as capillary channels. RDGs with MEC were packed instantly by tabletting and increased contact frequency between granules. These findings indicated that the wicking action enables the fast disintegration of ODTs containing MEC. The wicking action occurs with the following three phases:

Phase 1: water absorption by capillary channels
Phase 2: decreasing of binding force between RDGs
Phase 3: increasing of porosity by dissolved mannitol

Fig. 12 illustrates the structure of ODTs containing MEC and their disintegration by the wicking action. This disintegration process occurs rapidly after the tablets contact water (Fig. 8). Water is pulled into pores for ODTs, and the physical binding force between RDGs composed of MEC is reduced. The water transfer rate between RDGs is higher than the swelling rate of individual RDGs.

However, when tabletted at a high compression force over 10 kN (tablet hardness: >110 N), the oral disintegration rate of ODTs containing a high amount of MEC (7.5, w/w%) became low, suggesting that capillary channels in ODTs were partially broken by the high compression force because the porosity between the RDGs was closely matched by the excess amount of MEC. From these results, it was considered that MEC has a compressibility property (matrix-forming ability) and that the most appropriate amount of MEC in our ODTs is 5% (w/w).

5. Conclusion

This study successfully indicated that appropriate ODTs with high tablet hardness, low friability, high resistance against humidity, and rapid disintegration in the oral cavity could be prepared by tabletting the physical mixture of RDGs and MEC at low compression force. With this method, it is possible to prepare ODTs that contain functional releasable drugs such as for bitter taste masking, sustained release, and controlled release (pH-dependent film coating, matrix, and microcapsule). The combination of RDGs and MEC, therefore, can facilitate future application and formulation design for ODTs. The new ODTs developed in this study are expected to improve the quality of life of patients and the handling convenience in clinical sites.

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