Preparation and Evaluation of Orally Disintegrating Tablets Containing Vitamin E as a Model Fat-Soluble Drug

Yasuyuki Ikematsu,a,b Shinya Uchida,a and Noriyuki Namiki*a,
bDepartment of Pharmacy Practice & Science, School of Pharmaceutical Sciences, University of Shizuoka; Yada, Suruga-ku, Shizuoka 422–8526, Japan; and bGlobal Formulation Research Japan, Pharmaceutical Science and Technology Core Function Unit, Eisai Product Creation Systems, Eisai Co., Ltd.; 1 Kawashimatakehaya-machi, Kakamigahara, Gifu 501–6195, Japan.
Received August 19, 2014; accepted December 22, 2014

The purpose of the present study was to develop orally disintegrating tablets (ODTs) containing fat-soluble drugs that disintegrate rapidly while having appropriate tablet strength. We chose vitamin E (VE) as a model drug; d-a-tocopheryl acetate, as the oily VE (VE-OI), and d-a-tocopheryl acid succinate, as the powder VE (VE-PO), were used. The oily VE was added directly to ODTs (VE-OI ODTs) and also used for the preparation of two types of VE granule, i.e., granules prepared using adsorption to calcium silicate (VE-FL granules) and granules prepared using spray-drying with gelatin (VE-SD granules); each type of granule was added to ODTs (VE-FL ODTs and VE-SD ODTs). Powder VE was added directly to ODTs (VE-PO ODTs). Various VE ODTs were prepared using these four additional methods with varying amounts of VE per tablet and were evaluated with respect to their manufacturability, physicochemical characteristics, and stability. It was demonstrated that a tablet porosity of 30% to 35% and tensile strength of 7kg/cm² or greater are required to provide VE ODTs with rapid disintegration and appropriate tablet strength, and that VE-SD granules and powder VE are suitable forms of VE to be added. When stability tests of VE-SD ODTs and VE-PO ODTs were performed, VE-PO ODTs exhibited prolongation of disintegration time and increased tensile strength, whereas VE-SD ODTs showed none of these changes. These changes were thought to be attributable to a decrease in the pore size of VE-PO ODTs resulting from the softening and migration of powder VE under hot storage conditions.

Key words orally disintegrating tablet; fat-soluble drug; vitamin E; disintegration; tensile strength; porosity

Most pharmaceutical dosage forms for oral administration are developed for drug delivery after swallowing. In particular, tablets and capsules are the most common oral solid dosage forms, because they are convenient to carry, the duration of action of the contained drugs can be controlled, and their taste or smell can be improved.

However, many geriatric and pediatric patients often have difficulties swallowing conventional tablets or capsules. It is estimated that 50% of the population experiences this problem, which results in a high prevalence of non-compliance and ineffective therapy. To overcome this issue, a variety of pharmaceutical substances have been conducted to develop new dosage forms. Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet (ODT) is one of the most widely employed in commercial products. Numerous studies have therefore been performed on the various compositions of and manufacturing methods for ODTs. For example, ODTs can be prepared by several manufacturing methods, e.g., lyophilization, granulation, the cotton candy process, and phase transition of sugar alcohols by direct compression.

The oily type of fat-soluble drugs have generally been produced and marketed commercially in soft capsule form, though some prescription and over-the-counter drugs, e.g., tablets and granules as therapeutic agents for gastric ulcer, have already been marketed. A tablet preparation of oily drugs can be expected to improve the compliance and utility of the medicine for patients. In particular, from the viewpoint of many geriatric and pediatric patients who may have difficulty swallowing, the use of ODTs to deliver fat-soluble drugs is favorable among the various dosage forms. However, during the preparation of tablets containing fat-soluble drugs, there is often adhesion to manufacturing equipment due to heat generation in the manufacturing process; therefore, advanced formulation development is required for tablet preparation. As such, there are very few reports on the preparation of solids or tablets containing fat-soluble drugs, with previous studies being limited to the particle design of tabletting granules using the spherical crystallization technique or porous excipients and studies on prevention of sticking during the tableting process. To our knowledge, there has been no report on the preparation of ODTs containing fat-soluble drugs.

The purpose of the present study was to develop ODTs containing fat-soluble drugs that disintegrate rapidly while providing appropriate tablet strength. We chose vitamin E (VE) as a model drug. VE is widely used in drugs and foods and is marketed mainly in a soft capsule form. VE has many derivatives, which are present as oils and powders. In the present study, d-a-tocopheryl acetate, as an example of oily VE, and d-a-tocopheryl acid succinate, as an example of powder VE, were used. Various VE ODTs were prepared using wet powder tableting with varying the method of VE incorporation and the amount of VE per tablet. Oily VE was added directly to ODTs (VE-OI ODT) and was also used for the preparation of 2 kinds of VE granules, i.e., granules prepared using adsorption to calcium silicate (Florite® RE) (VE-FL granules) and granules prepared using spray-drying with gelatin (VE-SD granules), and each type of VE granule was added to ODTs.
(VE-FL ODT and VE-SD ODT). Powder VE was added directly to ODTs (VE-PO ODT).

Here, we report the physicochemical characteristics of various VE ODTs and the physical properties of 2 kinds of VE granules obtained by powdering oily VE, as well as the manufacturability and stability of VE ODTs.

**Experimental**

**Materials**  As model drugs, 2 types of vitamin E (VE) with different physical properties were chosen. First, d-α-tocopheryl acetate (99.8% purity, Tama Biochemical Co., Ltd., Japan) was chosen as a model drug for oily VE (VE-OI) and d-α-tocopheryl acid succinate (99.6% purity, Eisai Food Chemical Co., Ltd., Japan) was chosen as a model drug for powder VE (VE-PO). The melting point, density, and particle size in mean diameter were 75°C, 0.35 g/cm³, and 32 μm, respectively.

Calcium silicate (Florite® RE, Eisai Food Chemical Co., Ltd.) was used as an adsorbing carrier for oily VE, and corn starch (Nihon Shokuhin Kakou, Co., Ltd., Japan) was employed as a binder and a disintegrant in the preparation of VE granules (VE-FL granules).

Hydrolyzed gelatin (Gelatin TAZ, Nippi Incorporated, Japan) was used as a support agent for oily VE to prepare spray-dried VE granules, and hydrated silicon dioxide (Sylysia® 350, Fuji Silysia Chemical Co., Ltd., Japan) was used as a binder and a disintegrant in the preparation of VE granules (VE-SD granules).

Table 1. Formulations of Test Tablets (VE ODTs)

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>ODT</th>
<th>VE preparation</th>
<th>VE-OI ODT</th>
<th>VE-FL Granule</th>
<th>VE-SD Granule</th>
<th>VE-PO ODT</th>
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<tr>
<td><strong>Abbreviation</strong></td>
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<tr>
<td>d-α-Tocopheryl acetate (Oily VE)</td>
<td></td>
<td></td>
<td>7</td>
<td>14</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>d-α-Tocopheryl acid succinate (Powder VE)</td>
<td></td>
<td></td>
<td>7</td>
<td>14</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>Calcium silicate (Florite® RE)</td>
<td></td>
<td></td>
<td>3.5</td>
<td>7</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Corn starch</td>
<td></td>
<td></td>
<td>1.2</td>
<td>2.4</td>
<td>4.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Hydrolyzed gelatin (Gelatin TAZ)</td>
<td></td>
<td></td>
<td>6.87</td>
<td>13.74</td>
<td>27.48</td>
<td>54.96</td>
</tr>
<tr>
<td>Hydrated silicon dioxide (Sylysia® 350)</td>
<td></td>
<td></td>
<td>0.13</td>
<td>0.26</td>
<td>0.52</td>
<td>1.04</td>
</tr>
<tr>
<td>d-Mannitol (Mannit® P)</td>
<td></td>
<td></td>
<td>270.2</td>
<td>263.2</td>
<td>249.2</td>
<td>221.2</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP K-30)</td>
<td></td>
<td></td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Polystyrene beads were suspended in a stream of air and dispersed through a 1.0 mm mesh. Preparation of VE-SD Granules Containing Oily VE Hydrolyzed gelatin (687 g) was dissolved in purified water (700 g) and added to oily VE (700 g) that had been pre-heated to 60°C. The mixture was agitated at 60°C with a homomixer (T.K. homomixer, Tokushu Kika Kogyo, Co., Ltd., Japan) at 10000 rpm for 10 min. After adding Sylysia® 350 (13 g) and purified water (800 g), agitation was continued for another 15 min under the same conditions.

The wet granules were dried in a tray dryer at 60°C, while the outlet temperature was about 200°C, and the feeding rate was 1.5 mL/min. Evaluation of VE-FL and VE-SD Granules The mean particle size (D₅₀) of the VE-FL and VE-SD granules was measured using a laser particle counter (LA-910, Horiba, Co., Ltd., Japan). For the bulk density (g/cm³) measurements, each type of granule was poured into a 30 mL cylinder and the mass of the powder sample within the cylinder was then measured. Scanning electron microscopy (SEM) images of the surfaces of the VE-FL and VE-SD granules were obtained (Real Surface View VE-7800, Keyence Co., Ltd., Japan).

Preparation of VE ODTs The formulations of the VE ODTs employed in this study are summarized in Table 1. The test tablets involved in the evaluation of the physicochemical properties were prepared with a range of 7 mg to 56 mg VE content and employed the same VE-FL and VE-SD granules. The diameter of the VE ODTs was 9.5 mm (flat tablets). The VE ODTs were manufactured using the procedure developed by Morita et al.²⁰ d-Mannitol and VE-OI, VE-FL granules, VE-SD granules or VE-PO were mixed using a high-speed mixer (Mechanomil MM-10, Okada Seiko Co., Ltd., Japan).
Polyvinylpyrrolidone (PVP) K-30 was dissolved in a solvent composed of 50% (w/w) ethanol/water. The amount of solvent used was 13% (w/w) to the tablet weight. The wet powder was kneaded and moistened with the binder solution in order to achieve uniform moisture. Subsequently the wet powder was compressed at 20 kg per tablet by a novel molding tabletting system, which consisted of a molding tabletting machine (EMT-18) and a belt dryer (ETD-18, at 35°C), developed by Eisai Co., Ltd. (Japan) and Sankyo Seisakusho Co., Ltd. (Japan). Following drying with the belt dryer, the VE ODTs were dried in a tray dryer at 35°C (DAE-20, Sanwa Kaki Kogyo Co., Ltd., Japan) for 15 h in order to reduce the loss on drying of the tablets to <0.5% (w/w) on a wet weight basis.

Properties of VE ODTs

Measurement of Tensile Strength  The tablet crushing load, which is the force required to break a tablet by compression in a radial direction, was measured using a tablet hardness tester (KHT-20, Fujiwara Factory Co., Ltd., Japan). The test was performed on 10 tablets and the average was calculated. Tensile strength for crushing ($\sigma$, kg/cm$^2$) was calculated using the following equation:

$$\sigma = \frac{2L}{\pi DT}$$

where $L$ (kg) is the tablet crushing load, and $D$ (cm) and $T$ (cm) denote the diameter and the thickness of the tablet. The diameter and thickness of each tablet were determined by a micrometer (Mitsutoyo digimatic indicator IDF-1030E, Mitsutoyo, Co., Ltd., Japan).

Measurement of Tablet Friability  The tablet friability was measured as the percentage weight loss of 20 tablets tumbled in a Roche type friabilator (TFF-03, Tsutsui Scientific Instruments Co., Ltd., Japan). Twenty tablets were carefully dedusted before the test. The tablets were accurately weighed, loaded into the drums, and then subjected to the friability test. After 4 min of rotation at 25 rpm, the tablet dust was removed and the percentage weight loss was calculated. The test was performed 3 times and the average was calculated.

Measurement of Disintegration Time  Disintegration time was measured with a JP disintegration tester (TFF-03, Tsutsui Scientific Instruments Co., Ltd., Japan) involving 6 tablets in a basket equipped with an automatic end point detector (Distopper ®, Toyama Sangyo Co., Ltd.). End point determination with the naked eye is not possible.

Results and Discussion

Physical Properties of VE-FL and VE-SD Granules

The particle size distribution and the SEM image of the VE-SD granules are shown in Figs. 1a and b. Oily VE was included in gelatin by spray-drying and VE-SD granules were prepared. The mean particle size of these granules was 50 $\mu$m with a bulk density of 0.58 g/cm$^3$. The particle size distribution and the SEM image of the VE-FL granules are shown in Figs. 1c and d. Oily VE was adsorbed to porous Florite® RE, and VE-FL granules were prepared by wet granulation using corn starch. The mean particle size of these granules was 500 $\mu$m with a bulk density of 0.38 g/cm$^3$.

Preparation of VE ODTs with Various Amount of VE

All VE ODTs prepared by wet powder tableting with the EMT-18, except VE-OI ODTs, could contain a maximum of 56 mg VE per tablet. VE-OI ODTs could contain a maximum of 28 mg VE. In the preparation of VE-OI ODTs containing 56 mg of VE, VE exudations from ODTs and marked adhesion of wet granules to the polymer film of the EMT-18 were observed during compression, making it impossible to prepare the VE ODTs.

Physicochemical Properties of VE ODTs with Various Amounts of VE

Effect of the Amount of VE on the Tensile Strength and Friability of VE ODTs  The relationship between the amount of VE and the tensile strength and friability of various VE ODTs was investigated. Figure 2a illustrates the relationship between the amount of VE and tensile strength and Fig. 2b illustrates the relationship between the amount of VE and friability.

VE-OI ODTs showed an increase in tensile strength from 8.7 kg/cm$^2$ to 11.6 kg/cm$^2$ with increasing amounts of VE. Simultaneously, friability decreased and became almost 0% when the amount of VE was 14 mg. This was likely attributable to the caking of oily VE adsorbed to the excipient after the drying process. VE-FL ODTs, VE-SD ODTs, and VE-PO ODTs showed a decrease in tensile strength and an increase in friability with increasing amounts of VE. The magnitude of the changes was in the descending order of VE-FL ODTs>VE-PO ODTs>VE-SD ODTs. VE-FL ODTs showed relatively larger changes than the other 2 VE ODTs; tensile strength decreased from 9.2 kg/cm$^2$ to 2.9 kg/cm$^2$ and friability was increased from 0.9% to 2.0%.

In the preparation of VE-PO ODTs by wet powder tableting
with the EMT-18, the caking of powder VE was not observed. This was likely attributable to mild drying conditions with a belt dryer (ETD-18, at 35°C) and a tray dryer (DAE-20, at 35°C for 15 h) after wet powder tableting. Therefore, it was assumed that the powder VE had been maintained as a powder in the tablets. It is generally recognized that tablet strength decreases by decreasing the bonding surface area of the inter-particle, which results in decrease in formation of solid bridging with PVP K-30 between D-mannitol particles in a tablet during drying process after wet powder tableting. This might have decreased the tensile strength and increased the friability.

In the preparation of VE-SD ODTs and VE-FL ODTs by wet powder tableting with the EMT-18, oily VE exudations from VE-SD granules and VE-FL granules in addition to caking of oily VE were not observed. They were likely attributable not only because oily VE was covered in gelatin and well

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Fig. 1. (a) Particle Size Distribution of Vitamin E (VE) Granules Spray-Dried Using Hydrolyzed Gelatin (VE-SD Granules); (b) Scanning Electron Microscopy (SEM) Images of VE-SD Granules; (c) Particle Size Distribution of VE Granules Adsorbed to Florite® RE (VE-FL Granules); (d) SEM Images of VE-FL Granules

Fig. 2. (a) Effect of the Amount of Vitamin E (VE) on the Tensile Strength of VE Orally Disintegrating Tablets (ODTs); (b) Effect of the Amount of VE on the Friability of VE ODTs

(a) Each point represents the mean ± standard deviation (S.D.) n=10. (b) Each point represents the mean ± S.D., n=3. ▲, oily VE (VE-OI); ■, VE granules adsorbed to Florite® RE (VE-FL); ●, VE granules spray-dried using hydrolyzed gelatin (VE-SD); and ●, powder VE (VE-PO).
adsorbed to porous Florite® RE, respectively, but also because all wet powder to prepare VE ODTs were compressed at a low pressure condition, i.e., at 20 kg per tablet. Therefore, it was assumed that VE-SD granules and VE-FL granules had been maintained these shapes in the tablets, which result in a decrease in formation of solid bridging with PVP K-30 between β-mannitol particles in a tablet during drying process after wet powder tableting. However, VE-SD granules were prepared using gelatin that has hydrophilicity. Therefore, it was assumed that only minimal part of moistened gelatin might have slightly contributed to formation of solid bridging with PVP K-30 between β-mannitol particles, leading to the smaller decrease in tensile strength and smaller increase in friability observed in the VE-SD ODTs as compared with the VE-PO ODTs. In addition, the physical property of VE-FL granules is bulky and large particle sizes, as shown in Fig. 1. Therefore, it was assumed that the formation of solid bridging with PVP K-30 between β-mannitol particles in the tablet during drying process after wet powder tableting dramatically decreased, leading to the marked decrease in tensile strength and increase in friability observed in the VE-FL ODTs as compared with the VE-PO ODTs and the VE-SD ODTs.

Effect of the Amount of VE on the Disintegration Time and Porosity of VE ODTs The relationship between the amount of VE and disintegration time was investigated in various VE ODTs, the results of which are illustrated in Fig. 3a. VE-OI ODTs and VE-PO ODTs showed prolongation of disintegration time with increasing amounts of VE. The disintegration time of VE-PO ODTs increased from 22 to 30 s, while that of VE-OI ODTs increased up to about 60 s. In contrast, the disintegration times of VE-FL ODTs and VE-SD ODTs slightly decreased from 16 to 10 s and from 21 to 17 s, respectively, with increasing amounts of VE granules. According to the Guidance on ODTs issued by the Food and Drug Administration (FDA), U.S.A., the recommended disintegration time of ODTs was within 30 s. Therefore, the VE ODTs, with the exception of the VE-OI ODTs, have been found to disintegrate rapidly. Rapid penetration of water into the tablet can be a mechanism of disintegration in rapidly disintegrating tablets. The fact that VE is a fat-soluble drug suggests that the prolongation of disintegration time seen with VE-OI ODTs and VE-PO ODTs is attributable to decreased hydrophilicity of the tablet surface. In contrast, VE-FL ODTs and VE-SD ODTs did not show prolongation of disintegration time, which was thought to be attributable to the increased hydrophilicity of the tablet surface owing to the particle design of oily VE.

The differences in disintegration time among the VE ODTs may also be attributable to differences in tablet porosity. The relationship between the amount of VE and tablet porosity was thus investigated in the various VE ODTs, the results of which are shown in Fig. 3b. The porosity of VE-OI ODTs decreased from 27% to 22% with increasing amounts of VE. It was assumed that the pores of VE-OI ODTs were filled because of the caking of oily VE adsorbed to the excipient after the drying process with increasing amounts of VE. The VE-PO ODTs and VE-SD ODTs showed only minor changes in porosity; porosity remained at about 33% for VE-PO ODTs and increased from 32% to 34% for VE-SD ODTs. The VE-PO ODTs showed prolongation of disintegration time by about 10 s as a result of decreased hydrophilicity of the tablet surface because of powder VE. However, the disintegration time was not markedly prolonged, likely because the change in porosity was small. Regarding VE-SD ODTs, it was assumed that the penetration of water into the tablet was facilitated by cover of the gelatin on the surface of VE-SD granules, while porosity was slightly increased, thus shortening disintegration time. With respect to the VE-FL ODTs, porosity increased from 34% to 41% in association with an increase in the amount of VE-FL granules. VE-FL granules are bulky as shown in Fig. 1, leading to the bulkiness of wet powder of VE-FL ODTs. In the preparation of VE-FL ODTs by wet powder tableting with the EMT-18, the filling amount of wet powder into die cavity, that corresponds to tablet weight, gradually decreased in association with an increase in the amount of VE-FL granules. In contrast, the significant changes of tablet volume and true density were not observed in VE-FL ODTs, regardless of the amount of VE-FL granules. Therefore, the increased tablet porosity was thought to be attributable to the decreased filling amount of wet powder of VE-FL ODTs. VE-FL granules are prepared by wet granulation using corn starch. In general, the presence of a highly swellable disintegrant inhibits the penetration of water into the tablet because of the high water retention of the disintegrant. Corn starch, on the other hand, absorbs water rapidly but has low swellability, being a dis-

Fig. 3. (a) Effect of the Amount of Vitamin E (VE) on the Disintegration Time of VE Orally Disintegrating Tablets (ODTs); (b) Effect of the Amount of VE on the Porosity of VE ODTs

(a) Each point represents the mean±standard deviation (S.D.), n=6. (b) Each point represents the mean±S.D., n=10. ▲, oily VE (VE-OI); ■, VE granules adsorbed to Florite® RE (VE-FL); ○, VE granules spray-dried using hydrolyzed gelatin (VE-SD); ●, powder VE (VE-PO).
integrant with good water-conducting ability. Therefore, the shortened disintegration time was thought to be attributable to the increased water-conducting ability of the tablets, not only because of increased porosity but also because of the use of corn starch for the preparation of the VE-FL granules.

Effect of the Tensile Strength and Porosity of Various VE ODTs on the Friability and Disintegration Time  The effects of tensile strength and porosity on the friability and disintegration time of various VE ODTs were evaluated. In addition, the VE ODT characteristics required to provide tablet strength equivalent to that of conventional tablets and to enable rapid disintegration were evaluated.

The relationship between tensile strength and friability was evaluated based on the results shown in Figs. 2a and b. Figure 4a illustrates the relationship between tensile strength and friability. Friability decreased with increasing tensile strength. A significant negative correlation was observed between the tensile strength and friability of VE ODTs \( (r=0.75, p<0.001) \). Friability is one of the important physical properties in the handling of tablets. The ICH Q4B Annex \(^{27}\) recommends tablet friability to be 1.0% or less. The results in Fig. 4a indicate that friability would be 1.0% or less if the tensile strength was 7 kg/cm\(^2\) or greater. A tensile strength of 7 kg/cm\(^2\) is equivalent to about 4 kg on the basis of VE ODTs hardness. It has been reported that a hardness of at least 3 kg or more is required for tablets to tolerate the stress of packaging during the manufacturing process and transportation\(^{28,29}\) and at least 4 kg or more to tolerate the mechanical stress during dispensing using an automatic tablet packaging machine.\(^{30}\) Therefore, it was assumed that, if the tensile strength of VE ODTs was 7 kg/cm\(^2\) or more, they could tolerate these stresses.

The relationships between porosity and disintegration time and friability were evaluated based on the results in Figs. 3a and b. Figure 4b illustrates the relationship between porosity and disintegration time and Fig. 4c illustrates the relationship between porosity and friability. With increasing porosity, disintegration time was shortened and friability was increased; the porosity of VE ODTs correlated significantly with disintegration time and friability \( (r=0.83, p<0.001, \text{Fig. 4b and } r=0.78, p<0.001, \text{Fig. 4c}) \). It has been demonstrated that a porosity of 30% to 35% is required to achieve a disintegration time within 30 s and friability of 1.0% or less. Sugimoto \textit{et al.} have shown that, for the preparation of ODTs by crystal transformation of sugar alcohols and water-soluble excipients, a tablet porosity of 30% to 40% is required for disintegration within 15 s while providing an appropriate tablet strength.\(^{25}\) Tsushima has demonstrated that, in the preparation of ODTs by wet powder tableting using n-mannitol, a tablet porosity of 32% to 38% is required for disintegration within about 20 s while providing an appropriate tablet strength, irrespective of

![Fig. 4. (a) Relationship between the Tensile Strength of Various Vitamin E (VE) Orally Disintegrating Tablets (ODTs) and Friability; (b) Relationship between the Tablet Porosity of Various VE ODTs and Disintegration Time; (c) Relationship between the Tablet Porosity of Various VE ODTs and Friability](image-url)
variation in the amount of water-soluble excipient and tabletting pressure. The optimal porosity of VE ODTs is slightly lower than in these studies but has been shown to be 30% or more from the viewpoint of rapid disintegration and 35% or less from the viewpoint of friability. Therefore, ODT characteristics are impaired in VE-OI ODTs from the viewpoint of disintegration and in VE-FL ODTs from the viewpoint of friability. It has been demonstrated that adding VE-SD granules of small particle size (VE-SD ODTs) and the addition of powder VE (VE-PO ODTs) are preferable strategies for preparing VE ODTs.

Effect of Storage Period on the Disintegration Time and Tensile Strength of VE-SD ODTs and VE-PO ODTs Containing 14 mg and 56 mg of VE. The stability study of VE-SD ODTs and VE-PO ODTs containing 14 mg and 56 mg of VE per tablet was performed at 45°C for 3 months. Figure 5a illustrates the effect of storage period on disintegration time and Fig. 5b illustrates the effect of storage period on tensile strength. It has been demonstrated for 2 VE-PO ODTs that the initial disintegration time of 25 s and 29 s were prolonged to 60 s and 62 s after storage for 1 month or longer, namely the property of rapid disintegration was impaired. In association with this prolongation of disintegration time, tensile strength was increased from 11.5 kg/cm² to 20 kg/cm² and from 7.3 kg/cm² to 22 kg/cm², respectively. In contrast, these changes were not observed with 2 VE-SD ODTs, regardless of the amount of VE and the duration of the storage period.

In order to clarify the cause of the changes in disintegration time and tensile strength of 2 VE ODTs, the pore size distributions of the VE ODTs were investigated. In the investigation, VE-SD ODTs and VE-PO ODTs containing 14 mg of VE per tablet were employed because the changes in disintegration time and tensile strength showed the same tendency, regardless of the amount of VE. Figure 6 illustrates pore size distributions before and after storage of VE-PO ODTs and VE-SD ODTs. The median pore size of VE-PO ODTs, as shown in Fig. 6a, was decreased from 4.6 μm to 3.2 μm after 3 month’s storage. In contrast, the median pore size of VE-SD

**Fig. 5.** (a) Effect of Storage Period on the Disintegration Time of Vitamin E (VE) Orally Disintegrating Tablets (ODTs) Containing 14 mg and 56 mg of VE; (b) Effect of Storage Period on the Tensile Strength of VE ODTs Containing 14 mg and 56 mg of VE.

(a) Each point represents the mean±standard deviation (S.D.), n=6. (b) Each point represents the mean±S.D., n=10. ◦, VE granules spray-dried using hydrolyzed gelatin (VE-SD) ODTs containing 14 mg of VE; ○, VE-SD ODTs containing 56 mg of VE; ●, powder VE (VE-PO) ODTs containing 14 mg of VE; □, VE-PO ODTs containing 56 mg of VE.

**Fig. 6.** Effect of Storage Period on the Pore Size Distributions of Vitamin E (VE) Orally Disintegrating Tablets (ODTs) Containing 14 mg of VE

(a) powder VE (VE-PO) ODTs, (b) VE granules spray-dried using hydrolyzed gelatin (VE-SD) ODTs. ◦, before storage; ○, after storage at 45°C for 3 months in a closed glass bottle.
ODTs, as shown in Fig. 6b, was 5.7 μm both before and after storage. The decrease in median pore size in VE-PO ODTs was thought to be attributable to softening and migration of powder VE under hot storage conditions. With respect to disintegration of the tablets according to the Washburn’s equation, it is generally recognized that the water penetration rate into a powder bed is proportional to the pore size. Therefore, it was assumed that the slight decrease in pore size in a tablet might have led to the observed prolongation of disintegration time of VE-PO ODTs. In addition, it is also well known that tablet strength increases by increasing the bonding surface area of the inter-particle. Therefore, it was assumed that hot storage conditions caused softening and migration of VE and caking occurred when the temperature was restored to room temperature, which resulted in increase in the bonding surface area of the inter-particle and tensile strength. On the other hand, with respect to VE-SD ODTs, oily VE was covered and maintained in gelatin by spray-drying. Therefore, it was assumed that hot storage conditions did not cause VE exudations from VE-SD granules in addition to softening and migration of VE-SD granules, which resulted in no change in physical properties of VE-SD ODTs.

Overall, it has been demonstrated that, during the development of formulations for VE ODTs, it is important to account for changes in tablet quality under hot storage conditions.

**Conclusion**

VE that is available in oil and powder forms was selected as a fat-soluble drug, and VE ODTs were prepared using wet powder tableting with varying additional methods for incorporating VE and the amount of VE per tablet; physicochemical properties, including manufacturability and stability, were evaluated. In the case of VE ODTs, with the exception of VE-OI ODT, each tablet contained a maximum of 56 mg of VE. The physicochemical properties of various VE ODTs were evaluated. The results indicate that a tablet porosity of 30% to 35% and tensile strength of 7 kg/cm² or greater are required for VE ODTs to rapidly disintegrate and have sufficient strength. It has also been demonstrated that, for the addition of VE, VE-SD granules of small particle size and powder VE are the most suitable. In the stability study of VE-SD ODTs and VE-PO ODTs performed under hot storage at 45°C, prolongation of disintegration time and increase in tensile strength were observed only for VE-PO ODTs. The reason for this was thought to lie in the decrease in the pore size of VE-PO ODTs because of softening and migration of VE-PO under hot storage conditions. These results have demonstrated that, in the development of formulations for VE ODTs, it is important to account for changes in tablet quality under hot storage conditions.

**Acknowledgment**

The authors thank Ms. Kazumi Nanbu for her excellent technical assistance in the experimental work.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**