Potential Use of 2-Hydroxypropyl-β-cyclodextrin for Preparation of Orally Disintegrating Tablets Containing *dl*-α-Tocopheryl Acetate, an Oily Drug

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To expand the application of a drug in orally disintegrating tablets, the potential use of β-cyclodextrin (β-CyD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) as excipients for the tablets containing *dl*-α-tocopheryl acetate (VE), an oily drug, was evaluated. HP-β-CyD, not β-CyD, solubilized VE in water through the formation of higher order of complexes at the molar ratio of 1 : 2 (VE : HP-β-CyD). When prepared under the optimal preparation conditions, the VE tablets containing lactose and 5% (w/w) of HP-β-CyD, not β-CyD, had high hardness more than 4 kg and rapid disintegration within 100 s both *in vitro* and *in vivo*. In addition, VE tablets containing lactose and 5% (w/w) of HP-β-CyD, not β-CyD, maintained the high hardness and rapid disintegration under the accelerated stability test using different conditions for 4 weeks. Therefore, these results suggest the potential use of HP-β-CyD, not β-CyD, as an excipient for orally disintegrating tablets containing VE, an oily drug, in the molding method.

Key words cyclodextrin; orally disintegrating tablet; *dl*-α-tocopheryl acetate; molding method; hardness; disintegration time

As an average human life span increases, drug administration for elderly patients has become more important, because a great number of elderly patients hardly take medicine in the currently used dosage forms, such as conventional tablets, capsules and powders, due to a decrease in swallowing ability with age.[1,2] A Silver Science Researching Group of Ministry of Health, Labour and Welfare reported that among the currently used dosage forms, the most favorite dosage form is a tablet, followed by capsule, powder and fine granule.[3] So far, a number of rapidly disintegrating tablets such as Zydis™, Lyoc®, FlashTab®, WOWTAB-WET® and WOWTAB-DRY® have been developed to easily take tablets in elderly patients.[4—10] Recently, orally disintegrating tablets with a taste masking ability have been studied.[11,12] However, applications of these rapidly disintegrating tablets without water for elderly are sometimes not sufficient to improve their quality of life (QOL), if the other medicines need water to take them. Therefore, much more rapidly disintegrating tablets have been expected to apply for many kinds of drugs, especially oily and viscous drugs.

dl-α-Tocopheryl acetate (VE, Fig. 1) is used in prevention or treatment of improvement of peripheral circulation or pregnant function, and is also used in supplementary for VE deficiency. VE is a high fat-soluble and syrupy liquid.[13] Therefore, attention should be given to the importance of application of VE as an oily drug, to orally disintegrating tablets. Actually, the preparation of orally disintegrating tablets using a molding method is thought to be difficult, because oily drugs would not be well-dispersed in aqueous solution, probably followed by low hardness and slow disintegration of the tablets.

Cyclodextrins (CyDs) and their hydrophilic derivatives form inclusion complexes with hydrophobic molecules. CyDs can improve the solubility, dissolution rate and bioavailability of the drugs, and so the widespread use of CyDs is well known in the pharmaceutical field.[14,15] Recently, high functional and bioadaptability of CyD derivatives have been developed to accommodate various applications.[16—18] Regarding the application of CyDs to oily drugs, conventional tablets containing CyD complexes with prostaglandin or nitroglycerin are known.[19] Therefore, in the present study, we prepared orally disintegrating tablets containing VE, lactose and β-CyDs as additives, and examined the potential use of β-CyD and 2-hydroxypropyl-β-CyD (HP-β-CyD) as excipients of orally disintegrating tablets containing VE.

Experimental

Materials *dl*-α-Tocophorol acetate (VE) having a melting point of *ca.* 3 °C was donated by Nisshin Seifun (Tokyo, Japan). β-CyD was kindly donated from Nihon Shokuhin Kako (Tokyo, Japan). HP-β-CyD, with the degree of substitution of 4.8, was gifted from Shiseido (Tokyo, Japan). Press through package (PTP) sheets were kindly donated by Astellas Pharma (Tokyo, Japan). The chemical structures of β-CyDs and the abbreviations used in this study are summarized in Table 1. All other chemicals and solvents were of analytical reagent grade, and deionized double-distilled water was used throughout the study.

Phase Solubility Diagram The solubility of VE with β-CyDs in water at 25 °C was measured using the method of Higuchi and Connors.[20] The screw-capped vials containing VE in excess amounts (5 mg) in aqueous β-CyDs solutions (1.0 ml) at various concentrations were shaken at 25 °C for 2

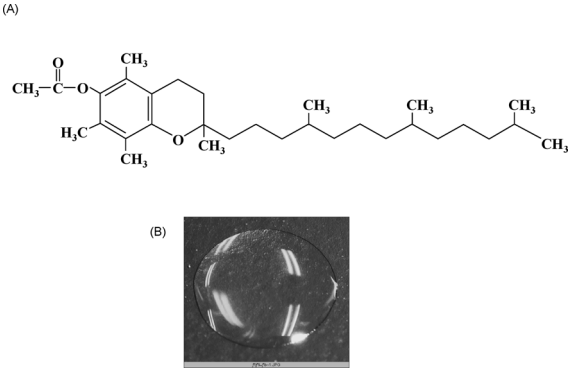

Fig. 1. Chemical Structure (A) and Appearance (B) of *dl*-α-Tocopheryl Acetate (VE)

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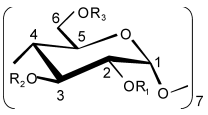
Table 1. Chemical Structures of β-CyDs Used in This Study



Compound	Abbreviation	R_1	R_2	R_3	D.S.[a]
β-Cyclodextrin	β-CyD	–H	–H	–H	—
2-Hydroxypropyl-β-cyclodextrin	HP-β-CyD	–H or $-CH_2CH(OH)CH_3$			4.8

a) Average degree of substitution.

weeks, the solutions were centrifuged at 3000 rpm for 5 min, and the supernatant was filtered through a membrane filter (ADVANTEC DISMIC-13CP, Toyo-Roshi, Tokyo, Japan), then analyzed for VE by using a high-performance liquid chromatography (HPLC) under the following conditions: GL packed column LiChrosorb RP-18 (4.6 mm×150 mm, Tokyo, Japan), mobile phase of methanol/water (49/1 v/v), a flow rate of 1.0 ml/min, and detection at 284 nm. The stability constants of higher order complexes ($K_{1:n}$) were calculated by the optimization technique reported by Higuchi and Kristiansen.[21]

Solid-State NMR Spectroscopy The complex of VE with β-CyD was prepared by a kneading method.[22] Solid-state ^{13}C-NMR spectra were taken on a JEOL JNM EX-270 spectrometer with a cross polarization/magic angle spinning (CP/MAS) accessory (Tokyo, Japan), operating at 270 MHz (^{1}H) at 25 °C. The CP radio frequency field strength was about 56 kHz, the constant time was 5 ms, the repetition time of accumulation was 6 s, and the MAS was 6.2—6.4 kHz. The ^{13}C chemical shifts were measured in ppm with respect to the hexamethyl benzene as an external reference.

Hygroscopicity of β-CyDs Hygroscopicity of β-CyDs was estimated by water content after drying under reduced pressure overnight. Five hundred milligrams of β-CyDs left in desiccators at the indicated relative humidity (R.H.) prepared by saturated salt solutions, and then the water content in 100 mg of β-CyDs was detected by the volumetric Karl Fischer method using a commercially prepared Karl Fischer Reagent (Karl Fischer Reagent SS Mitsubishi, Mitsubishi Kasei, Tokyo, Japan).

Surface Tension and Viscosity of β-CyDs Solutions The aqueous solutions containing lactose or β-CyDs in the concentration range of 20—90% (w/v) were prepared. Viscosity and surface tension of lactose or β-CyDs solutions were measured by Couette viscometer Low Shear 30 (Contraves AG, Zurich, Switzerland) and Du Noüy Surface & Interfacial Tensionmeter (Shimadzu, Kyoto, Japan), respectively. The experiments were performed at 25 °C.

Preparation and Evaluation of Orally Disintegrating Tablets VE, lactose and/or β-CyDs were dispersed in water by vigorous agitation without an emulsification procedure, and 250 μl of mixture was poured into PTP sheets. The total weights of VE, lactose and β-CyDs were 170 mg per a tablet. The diameter and thickness of tablets were 8 mm and 4 mm, respectively. The contents of VE were used in the range of 0—25 mg per a tablet, and the content of VE in tablets used after optimization study was 12.5 mg. As the results of several studies described below, the tablets were prepared under the following experimental conditions: dispersion and filling at 4 °C and drying at 4 °C/25 °C/40 °C (1 step/1 day). Hardness of tablets was measured by a Monsant sclerometer. Disintegration time of tablets in water at 37 °C was measured using a JPXV disintegrating apparatus. A tablet was put into the mouth of healthy three male adult volunteers without water and the oral disintegration time was recorded until the volunteer felt that the tablet had disappeared in their mouths. As an index of wettability, water uptake into tablets was measured by the apparatus reported by Wang *et al*.[23]

Water Content in Tablets The amount of water content in tablets was measured by the volumetric Karl Fischer method using a commercially prepared Karl Fischer Reagent (Karl Fischer Reagent SS Mitsubishi, Mitsubishi Kasei, Tokyo, Japan). Tablets were crushed using mortar and pestle, and the portion was rapidly weighed and introduced into the titration chamber. Water content values (in percent by weight) are indicated as the mean of three trials.

Scanning Electron Microscopy (SEM) Tablets were sputtered with gold (5 min, 6—8 mA) by Ion Coater IB-3 (Eiko Engineering, Ibaraki, Japan) and observed in a Hitachi S-2150 SEM (Tokyo, Japan) at an accelerating voltage of 8—15 kV.

Statistical Analysis Data are given as the mean±S.E.M. Statistical significance of means for the studies was determined by analysis of variance followed by Scheffe's test. *p*-Values for significance were set at 0.05.

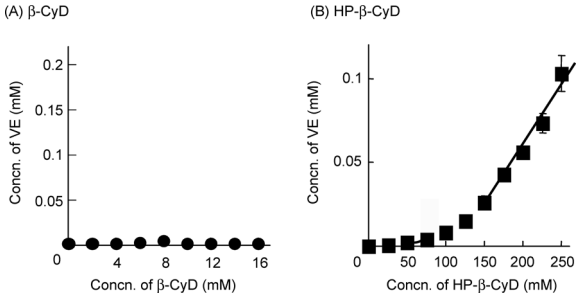


Fig. 2. Phase Solubility Diagrams of VE/β-CyD (A) and VE/HP-β-CyD (B) Systems in Water at 25 °C

Each point represents the mean±S.E.M. of three experiments.

Results and Discussion

Interaction between VE and β-CyDs in Water The solubility method is useful for studying inclusion complexation of poorly soluble drugs with β-CyDs in water, because it gives not only the solubilizing ability but also the stability constant of the complexes by analyzing the solubility curves.[20] Figure 2 shows the results of phase solubility diagrams of the VE/β-CyDs systems in water at 25 °C. β-CyD was found to solubilize VE only very slightly owing to the low solubility of β-CyD in water (Fig. 2A). The extremely low solubility of VE (1.07×10^{-7} M in water at 25 °C) was increased by adding HP-β-CyD in a concentration dependent manner and the VE/HP-β-CyD system showed the A_P type solubility curve,[20] suggesting that HP-β-CyD interacts with VE in a formation of higher-ordered complexes in water (Fig. 2B). Then, this upward curvature was analyzed according to the optimization technique to obtain the stability constants of higher-order complexes.[21] Stability constants of $K_{1:1}$ and $K_{1:2}$ for VE/HP-β-CyD complexes at the molar ratios of 1 : 1 and 1 : 2 (VE : HP-β-CyD) were 1.8 ± 1.3 M^{-1} and 12785 ± 767 M^{-1}, respectively. These results suggest that HP-β-CyD potentially solubilized VE through the formation of 1 : 2 (VE : HP-β-CyD) complex in water.

Interaction between VE and β-CyDs in a Solid State It is difficult to evaluate the interaction between VE and β-CyDs by a thermoanalytical method and powder X-ray analysis because VE is an oily drug. Thereby, the interaction in a solid state was evaluated by ^{13}C CP/MAS NMR spectroscopy using a kneading product of VE with β-CyD. Here we could not evaluate the interaction of VE with HP-β-CyD using this spectroscopy, because the NMR spectra of HP-β-CyD are very complicated and broad owing to its multicomponent

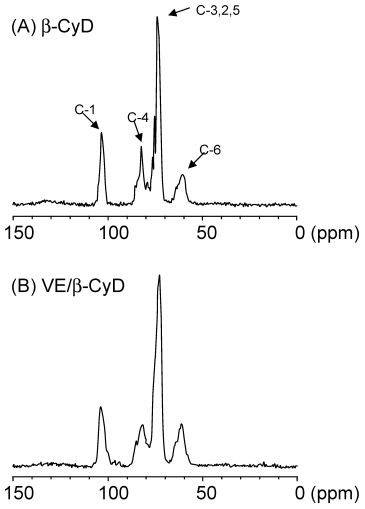


Fig. 3. ^{13}C CP/MAS NMR Spectra of β-CyD (A) and VE/β-CyD Complex (B) at a Molar Ratio of 1 : 1

mixture. The peaks of C-3,2,5 of β-CyD were converged (Fig. 3A) and that of C-6 was sharpened by a kneading of VE with β-CyD (Fig. 3B). These changes could be attributed to an increase in a symmetry of the cavity of β-CyD and a fixation of hydroxyl groups of β-CyD toward an outer side of the cavity, consistent with the result in the flurbiprofen/permethylated β-CyD complex.[24] Considering this result, it is possible that HP-β-CyD may interact with VE in a solid state, since HP-β-CyD interacts with VE much stronger than β-CyD in water as shown in Fig. 2. Therefore, these results suggest that VE may form the complexes with β-CyDs in solution and in a solid state.

Hygroscopicity of β-CyDs β-CyDs have been found to change the pharmaceutical properties of drugs, depending on the physicochemical properties of CyD itself. Therefore, we firstly investigated the moisture adsorption of β-CyDs and lactose at the indicated R.H. at 25 °C. As shown in Fig. 4, water contents of lactose and β-CyD were almost constant from 20 to 90% R.H., whereas that of HP-β-CyD below 75% R.H. was lower than those of β-CyD and lactose, and that of HP-β-CyD extremely increased at 90% R.H., reflecting highly water-soluble property of HP-β-CyD.

Viscosity and Surface Tension of β-CyDs Solutions Figures 4B—D show the viscosity curves of aqueous solutions containing lactose, β-CyD or HP-β-CyD. The curves provided the three different curves of viscosity: the curve corresponding to lactose solution had a linear ascent portion (Fig. 4B), that of β-CyD solution had an initial ascending portion followed by a plateau region (Fig. 4C), and that of HP-β-CyD solution had an upward curvature (Fig. 4D), indicating that HP-β-CyD solution was viscous compared to the other solutions and the viscosity of HP-β-CyD solution increased in a concentration dependent manner. Figure 4E shows surface tension of β-CyDs solutions. The surface tension of β-CyD solution did not change up to the concentration of 1% (w/v), while that of HP-β-CyD solution strikingly lowered (Fig. 4E), because of surface active property of HP-β-CyD.[25] Collectively, these results suggest that the addition of small amount of HP-β-CyD to tablets should increase the wettability and the water penetration into the pore of a tablet, because HP-β-CyD is highly water-soluble and surface active. Hereafter, additional studies should be, however, required to further clarify the relationship between the physicochemical properties of powders in the presence of VE and those of the tablets, because these results may not be directly associated with the physicochemical properties of the tablets owing to the lack of VE.

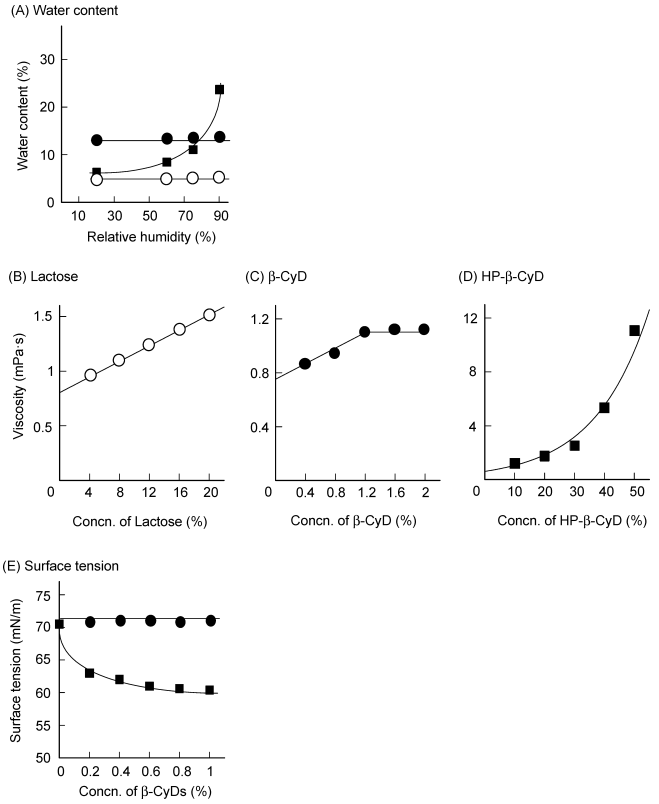


Fig. 4. Moisture Adsorption Curves of β-CyDs (A) and Viscosities (B, C, D) and Surface Tensions (E) of β-CyDs Solutions

(A) Water contents of lactose and β-CyDs were determined by the Karl Fischer method at 25 °C. Viscosity (B, C, D) and surface tension (E) of β-CyDs solutions were measured by Couette viscometer Low Shear 30 and Du Noüy Surface & Interfacial Tensionmeter, respectively. The symbols of open circle, closed circle and closed square stand for lactose, β-CyD and HP-β-CyD, respectively. Each point represents the mean of three experiments.

Evaluation of Preparation Condition of Orally Disintegrating Tablets Orally disintegrating tablets are generally prepared by the molding method or the compression method, and the former is classified into two methods according to whether the presence or absence of a freeze-dry process. In the present study, we used the molding method without freeze-dry,[7] because it is simple and available in our laboratory. Firstly, we examined the effects of temperature on formulation and the properties of lactose tablets. As shown in Table 2, we found that the best temperature in dispersion and filling processes was 4 °C, because tablets prepared at 25 °C and 40 °C in the dispersion and filling processes showed a cracking and chipping, possibly due to the lack of recrystallization of lactose in the tablets. In the following experiments, dispersion and filling processes were performed at 4 °C. Next, the effects of drying temperature on physicochemical properties of the tablets were examined. When PTP sheets filled with the lactose suspension were dried at 40 °C, the tablets could not be formed. When PTP sheets filled with the lactose suspension were stored at 25 °C or 40 °C for a day followed by drying at 40 °C, a half of samples did not still

Table 2. Various Conditions for Preparation of Lactose Tablets and Their Physicochemical Properties

No.	Temperature (°C)		Formability	Hardness (kg)	Disintegration time (s)	Water uptake (μl)
	PTP and water	Drying				
1	40	4(1)[a]—25(1)—40(1)	5/10[b]	—[c]	—	—
2	25	4(1)—25(1)—40(1)	0/10	1.13	93	48
3	4	4(1)—25(1)—40(1)	0/10	1.25	86	44
4	4	40(1)	10/10	—	—	—
5	4	25(1)—40(1)	5/10	—	—	—
6	4	4(1)—40(1)	6/10	—	—	—
7	4	4(1)—25(1)—25(1)	0/10	0.73	95	51
8	4	4(1)—25(1)—60(1)	0/10	0.86	92	50

a) The number in a parenthesis indicates a day period. *b*) Incidence of trouble such as cracking and chipping. *c*) Not determined.

form the tablets. Meanwhile, when prepared at 4 °C in both the filling and drying processes, the sufficient tablets were found to be capable of preparing, especially the tablets had the highest hardness and the fastest disintegration, when dried at 25 °C for a day, and then further at 40 °C for 1 day. As a result, of various temperature conditions, dispersion and filling at 4 °C and drying at 4 °C/25 °C/40 °C (1 step/1 day) were found to be the optimal condition, judging from the results of formability and physicochemical properties of the tablets (Table 2). Therefore, in the following studies we prepared the orally disintegrating tablets under the optimal conditions.

Effects of VE Content on Appearance, Hardness and Disintegration Time of Tablets It is well known that drug content markedly affects the various properties of tablets. So, the effects of VE content on appearance, hardness and disintegration time were evaluated. Here the maximal content of VE was set to 25 mg, considering its therapeutic dose. Figure 5A shows the formula of the tablets in this experiment. The appearance of tablets became rough as the VE content increased (Fig. 5B). Appearance of VE/lactose tablets showed oily on the surface of the upper side of tablets. This phase separation of VE in tablets could be ascribed to the lack of an emulsification procedure. Hereafter, further studies regarding the homogeneity of VE content in the tablets should be necessary. Meanwhile, hardness of tablets was approximately 1 kg in spite of the VE content, possibly due to the insufficient liquid bridge between VE (Fig. 5C). In addition, disintegration time of tablets tended to prolong as the VE content in tablets increased, in particular the time showed approximately 180 s with a large deviation at the VE content of 25 mg, which could be attributed to the decrease in wettability of the surface of tablets (Fig. 5D). Considering these results, we prepared the tablets containing VE of 12.5 mg/tablet in the following studies.

Effects of β-CyDs on Appearance, Hardness and Disintegration Time of Tablets Orally disintegrating tablets require not only high hardness (at least more than 2 kg) to resist strength to push them out from PTP sheet, but also rapid disintegration ability in oral cavity. As already shown in Fig. 5, the hardness of tablets containing only 12.5 mg of VE and 157.5 mg of lactose was quite low (about 1 kg). To improve the physicochemical properties of the tablets, tablets containing VE, lactose and 1.5% (w/w) of polyvinylpyrrolidone (PVP) or 1.5% (w/w) of hydroxypropylcellulose (HPC) to total weights of VE, lactose and a binder were prepared.

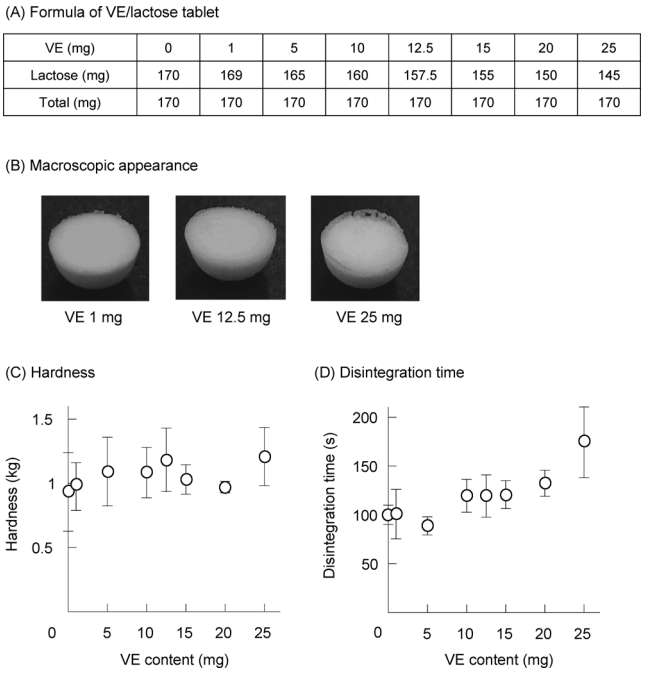


Fig. 5. (A) Formula of VE/lactose Tablets and Effects of VE Content on Macroscopic Appearance (B), Hardness (C), Disintegration Time (D) of VE/Lactose Tablets

(C) Hardness of tablets was measured by Monsant sclerometer. (D) Measurement of disintegration time was performed using a JPXV disintegrating apparatus, using distilled water at 37 °C. Each point represents the mean±S.E.M. of three experiments.

Compared to tables containing only VE and lactose, the hardness of tablet containing PVP or HPC was increased and disintegration time was shortened to less than 100 s, but the appearance of tablets was very rough and asperous (data not shown). To further improve the physicochemical properties of the tablets, we examined the effects of β-CyDs on these physicochemical properties of VE tablets. At first, we examined the effects of the concentrations of β-CyDs on them. Here the formula of the tablet was shown in Fig. 6A. Appearance of VE/lactose tablets containing 5% (w/w) of β-CyD (VE/lactose/β-$CyD_{5\%}$) was grainy and glossy (Fig. 6B) and hardness of the VE/lactose/β-$CyD_{5\%}$ tablets was less than 2 kg up to 40% (w/w) of β-CyD in tablets (Fig. 6C). Moreover, disintegration time of VE/lactose/β-CyD tablets decreased as the content of β-CyD increased. Therefore, these results suggest that the VE/lactose/β-CyD tablets have insufficient appearance, hardness and disintegration time.

Appearance of VE/lactose tablets containing 5% (w/w) of HP-β-CyD (VE/lactose/HP-β-$CyD_{5\%}$) was grainy and glossy, and markedly improved the phase separation of VE observed in the VE/lactose tablets (Fig. 6B). However, appearance of VE/lactose/HP-β-$CyD_{40\%}$ shows very rough (Fig. 6B). Meanwhile, the hardness of VE/lactose/HP-β-$CyD_{5\%}$ tablets was approximately 5 kg, and that increased up to 20% (w/w) of HP-β-CyD, and then decreased in 30% (w/w) and 40% (w/w) of HP-β-CyD in tablets (Fig. 6C). Meanwhile, disintegration time of tablets VE/lactose/HP-β-CyD prolonged as the content of HP-β-CyD increased (Fig. 6D). Fortunately, the VE/lactose/HP-β-$CyD_{5\%}$ tablets disintegrated within 90 s (Fig. 6D) having a high hardness (Fig. 6C). These results suggest that the addition of 5% (w/w) HP-β-CyD in VE-containing tablets gave the favorable properties with fine appearance, relatively high hardness and rapid disintegration. Next, we evaluated the disintegration time *in vivo*. As shown in Fig. 6E, tablets containing VE and lactose without β-CyDs and VE/lactose/HP-β-$CyD_{5\%}$ tablets disintegrated at approximately 20—30 s, but the disintegration time of VE/lactose/HP-β-CyD tablet prolonged as the content of HP-β-CyD in tablets increased, *e.g.*, VE/lactose/HP-β-$CyD_{20\%}$ tablets disintegrated at approximately 100 s, reflecting the results of the *in-vitro* disintegrating test. Hereafter, further study which more than ten volunteers participate in the *in vivo* test should be required to increase the power of the test, because only three volunteers received the tablets in the present study. Thus, these results suggest that the appearance, hardness and disintegration time of VE/lactose/HP-β-$CyD_{5\%}$ tablets are more adequate to those of VE/lactose/β-CyD tablets and VE/lactose/HP-β-$CyD_{40\%}$ tablets.

(A) Formula of VE/lactose tablet

CyD content (%)	0	5	10	20	30	40
VE (mg)	12.5	12.5	12.5	12.5	12.5	12.5
β-CyDs (mg)	0	8.5	17	34	51	68
Lactose (mg)	157.5	149	140.5	123.5	106.5	89.5
Total (mg)	170	170	170	170	170	170

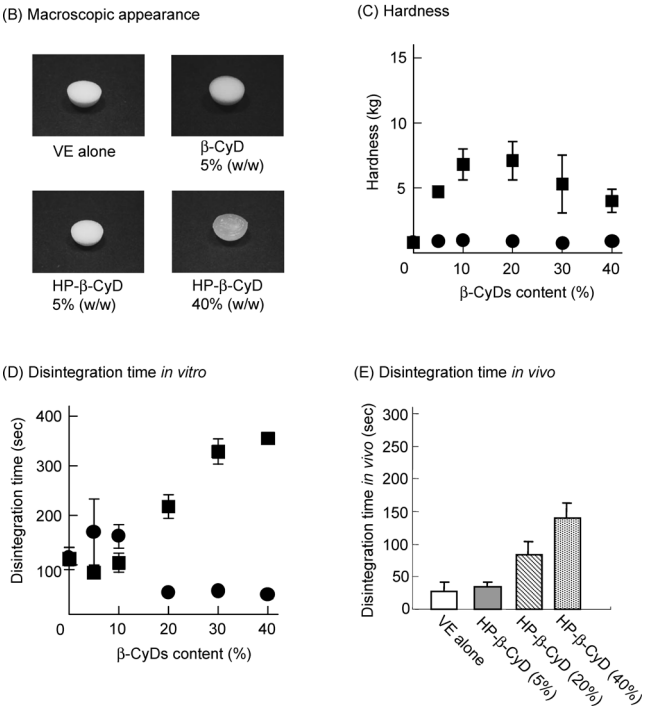


Fig. 6. (A) Formula of VE/lactose/β-CyDs Tablets and Effects of β-CyDs Content on Macroscopic Appearance (B), Hardness (C), Disintegration Time *in Vitro* (D), Disintegration Time *in Vivo* (E) of VE/lactose/β-CyDs Tablets

(C) Hardness of tablets was measured by Monsant sclerometer. (D) Measurement of disintegration time was performed using a JPXV disintegrating apparatus, using distilled water at 37 °C. (E) The time required for complete disintegration in the oral cavity was collected from three healthy volunteers per formulation. The symbols of circle and square stand for β-CyD and HP-β-CyD, respectively. Each point represents the mean±S.E.M. of three experiments.

Then, we performed the stability study of VE/lactose/HP-β-$CyD_{5\%}$ tablets under the various conditions such as 4 °C, 40 °C, 60 °C and 40 °C with 75% R.H. for 4 weeks (Table 3). VE/lactose/HP-β-$CyD_{5\%}$ tablets maintained high hardness more than 4 kg and rapid disintegration ability less than 100 s under various storage conditions. In addition, a significant difference in weight, water content and water uptake of VE/lactose/HP-β-$CyD_{5\%}$ for 4 weeks were not also observed. Therefore, VE/lactose/HP-β-$CyD_{5\%}$ tablets may be stable at various temperatures and 75% R.H. under the accelerated test conditions. Recently, there are some reports that HP-β-CyD and methyl-β-CyD improved photo stability and antiradical activity of Trolox, a derivative of VE, through the formation of complexation.[26—28] Therefore, it is possible that the photo stability of VE in the tablets containing HP-β-CyD prepared by a molding method may be increased. Hereafter, further investigation for chemical and photo stability of VE in the tablets should be required.

Mechanism of High Hardness and Rapid Disintegration of VE Tablets Containing 5% (w/w) of HP-β-CyD

To gain insight into the mechanism for high hardness and rapid disintegration ability of VE/lactose/HP-β-$CyD_{5\%}$ tablets, at first, we examined the microscopic appearance of tablets containing various concentrations of HP-β-CyD. In this experiment the formula of the tablets was shown in Fig. 7A. From microscopic analysis by SEM, control (VE/lactose) tablets showed much of large pores (*ca.* 150 μm) between lactose particles on the surface (Fig. 7B), but VE/lactose/HP-β-$CyD_{5\%}$ tablets showed much of small pores (*ca.* 110 μm)

Table 3. Stability Tests of VE Tablets Containing 5% (w/w) of HP-β-CyD

Time (week)	Weight (%)			Hardness (kg)			Disintegration time (s)			Water content (%)			Water uptake (μl)		
	0	2	4	0	2	4	0	2	4	0	2	4	0	2	4
4 °C	100.0	99.9	101.5	6.2	5.5	5.6	82	82	78	7.0	7.1	7.8	3.7	3.8	3.9
40 °C	100.0	99.9	100.7	6.2	6.2	4.7	82	88	94	7.0	7.3	7.7	3.7	3.7	3.5
60 °C	100.0	99.8	101.2	6.2	4.5	4.8	82	91	95	7.0	7.4	8.0	3.7	3.6	3.8
40 °C, 75%R.H.	100.0	100.8	101.3	6.2	6.7	6.2	82	102	84	7.0	7.5	8.0	3.7	4.2	3.7

Each value represents the mean of three experiments.

(A) Formula of VE/lactose/β-CyDs tablet

CyD content (%)	0	5	20	40
VE (mg)	12.5	12.5	12.5	12.5
β-CyDs (mg)	0	8.5	34	68
Lactose (mg)	157.5	149	123.5	89.5
Total (mg)	170	170	170	170

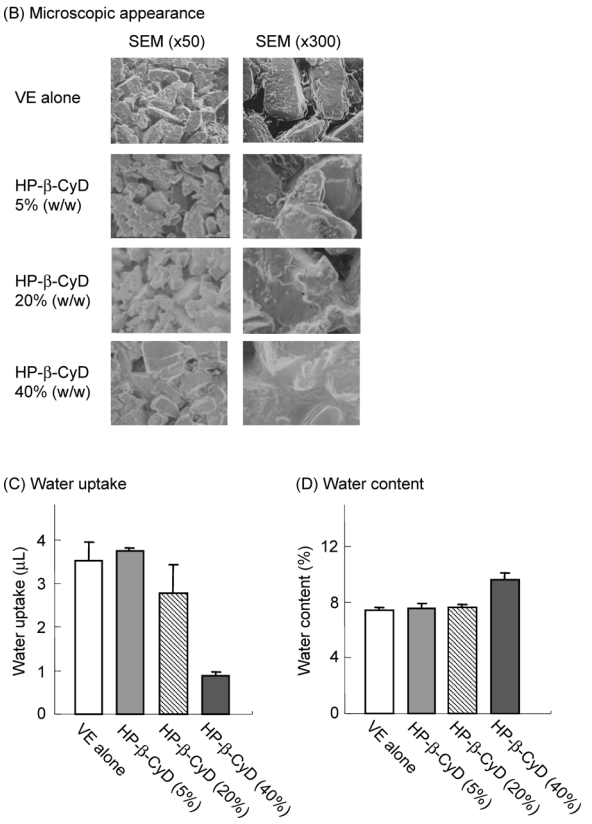


Fig. 7. (A) Formula of VE/lactose/HP-β-CyD Tablets and Microscopic Appearance (B), Water Uptake (C), Water Content (D) of VE/Lactose/HP-β-CyD Tablets

(B) Microscopic analysis was performed by S.E.M. at 50- and 300-fold magnification. These figures show representative data for three experiments. (D) Water uptake rate into tablets was measured using an apparatus as reported by Wang. (E) Water contents in tablets were determined by the Karl Fischer method at 25 °C. Each value represents the mean±S.E.M. of three experiments.

with much of solid bridges between lactose particles, suggesting higher porosity in tablets. This solid bridge is known to be the product of lactose crystal formed by recrystallization during a drying process, depending on the solubility of lactose in suspension.[29] However, the number of the pores and the pore space between particles decreased as the content of HP-β-CyD increased (Fig. 7B). Therefore, the addition of small amount of HP-β-CyD may increase the solubility of lactose, resulting in the formation of solid bridge in the tablets, possibly resulting in high hardness. Collectively, these results suggest that solid bridge is associated with an increase in the total number of coordination and adherent force between lactose particles, leading to the high hardness of VE/lactose/HP-β-$CyD_{5\%}$.

Finally, we examined the water uptake into tablets to estimate the wettability of the tablets (Fig. 7C). Control (VE/lactose) tablets and VE/lactose/HP-β-$CyD_{5\%}$ tablets could uptake more water, compared to VE/lactose/HP-β-$CyD_{20\%}$ and VE/lactose/HP-β-$CyD_{40\%}$ tablets, suggesting the high extent of porosity, possibly due to increase in the number of pores and/or pore space in the tablets. In addition, we examined water content in tablets by the Karl Fischer method (Fig. 7D). There is no significant change in water content between control, VE/lactose/HP-β-$CyD_{5\%}$ and VE/lactose/HP-β-$CyD_{20\%}$ tablets. Meanwhile, VE/lactose/HP-β-$CyD_{40\%}$ tablets showed higher water content, compared to control and VE/lactose/HP-β-$CyD_{5\%}$ tablets. This high water content in VE/lactose/HP-β-$CyD_{40\%}$ tablets may result in long disintegration time over 350 s (Fig. 6D), because this higher water content in VE/lactose/HP-β-$CyD_{40\%}$ tablets increased the amount of HP-β-CyD dissolved in the water, leading to highly viscous properties. Taken together, these results suggest that VE/lactose/HP-β-$CyD_{5\%}$ tablets may uptake much water into tablets and dissolve rapidly, possibly due to high wettability and high porosity in tablets.

The existing state of the complex of VE with β-CyDs in the tablets is not still unknown. Based on the data regarding the phase solubility study and the physicochemical properties of the tablets, it is possible that HP-β-CyD formed the complex with VE to some extent in the tablets, although the molar ratio of VE to HP-β-CyD was 4.4 in the VE/lactose/HP-β-$CyD_{5\%}$ tablets, *i.e.*, 26.4 μmol of VE and 6.0 μmol of HP-β-CyD existed in the tablets. However, it is difficult to determine the extent of the complex in the tablets. Hereafter, elaborate studies using a magnetic resonance imaging are further required to reveal the existing state of the complex of VE with β-CyDs.

In conclusion, we revealed that VE tablets containing 5% (w/w) of HP-β-CyD, not β-CyD, prepared by the molding method possessed high hardness and rapid disintegration ability both *in vitro* and *in vivo* with a fine appearance, when prepared under the optimal conditions, through the formation of much of small porosity and solid bridge between lactose particles in the tablets. These results suggest the potential use of HP-β-CyD as an excipient for orally disintegrating tablets containing VE, an oily drug.

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