Formulation Variation and *in Vitro–in Vivo* Correlation for a Rapidly Swellable Three-Layered Tablet of Tamsulosin HCl

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In order to develop a preferable once-a-day oral tablet formulation, various formulations of three-layered tablets containing tamsulosin HCl as a hydrophilic model drug were evaluated and compared with a commercial reference, tamsulosin OCAS®. When the test tablet was exposed to a release medium, the medium quickly permeated to the mid-layer and the two barrier layers swelled surrounding the mid-layer rapidly. Volume expansion showed faster and enough swelling of the three-layered tablet up to 2 h. Larger amount of barrier layers caused reduced release kinetics and a high molecular weight polymer showed more resistance against agitation force. A formulation with water-soluble mid-layer showed fast erosion decreasing its volume significantly. On the pharmacokinetic study, the mean ratio of area under the curve (*AUC*) and C_{max} for the test formulation to the reference was 0.69 and 0.84, respectively, showing that the absorption of the drug was less complete than the reference. Plasma concentration at 24 h of the test formulation was higher than the reference. The Wagner–Nelson method showed that decreased initial dissolution rate might be the cause of the less complete absorption. On considering *in vitro–in vivo* correlation (IVIVC), level A, the reference (R^2=0.981) showed more linear relationship than the test (R^2=0.918) due to the decreased dissolution and absorption rate of the formulation. This result suggests that the *in vitro* dissolution profiles and release kinetics might be useful in correlating absorption kinetics as well as overall plasma drug concentration–time profiles for formulation studies.

Key words tamsulosin; controlled-release; three-layered tablet; swelling; *in vitro–in vivo* correlation; beagle dog

A novel three-layered tablet technology consisting of an inner immediate release layer and two extended release barrier layers with swellable polymers has been suggested and investigated as once-a-day tablet formulations.[1] In that formulation, dissolution medium quickly permeates to the inner layer of water-soluble excipients, and the two barrier layers swell to surround the inner layer rapidly, controlling drug release from the inner layer. After oral administration, the tablet might become fully hydrated quickly and reach the colon where little water is available. The hydrated state of the tablet might induce continuous drug release even in the colon.

As an extended study on the technology and to investigate the feasibility as a once-a-day tablet formulation, a hydrophilic model drug (tamsulosin HCl) was selected and various three-layered tablet formulations were evaluated together with their properties. These formulations were also compared with a commercial product, tamsulosin OCAS®, to achieve more consistent plasma drug concentrations. Additionally, a pharmacokinetic study of the three-layered tablets using beagle dogs was performed in comparison with the results of the reference tablet.

Tamsulosin HCl, (−)-(*R*)-5-[2-[[2-(*o*-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide monohydrochloride (Fig. 1), is a third-generation α1-adrenoceptor (AR) antagonist and has been developed for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH).[2] Among the currently available α1-AR antagonists, tamsulosin is the most frequently prescribed pharmacological therapy due to its favorable selectivity for human prostatic tissue, which is probably related to the $\alpha 1_A$ and $\alpha 1_D$-AR subtypes.[3,4]

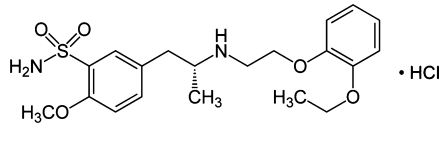

Fig. 1. Structural Formula of Tamsulosin HCl

Tamsulosin HCl modified-release (MR) capsules are developed by Astellas Pharma Inc., and marketed under the trade names Harnal, Flomax, Flomaxtra, and Urimax. On the other hand, generic non-modified release capsules are still approved and marketed in many countries such as Canada and the U.S. The tamsulosin MR capsule formulations, however, have some limitations such as food dependent absorption.[3] The labeling information recommends that the capsule needs to be taken after breakfast or after the first meal of the day. Lack of compliance with this dosing recommendation may cause increased exposure to the drug, leading to a higher risk of vasodilatation-related adverse effects like dizziness, headache, orthostatic hypotension, and syncope.[5]

To reduce the occurrence of the adverse effects, new oral controlled absorption systems have been developed and used to overcome the low absorption properties even from the colon.[6] The OCAS® formulation is a controlled release system of a gel matrix type, with gel-forming and gel-enhancing components. Polyethylene glycol (PEG), a gel-enhancing agent, is a hydrophilic agent that facilitates water uptake into the tablets. It may ensure very rapid and nearly complete gelation/hydration of a hydrophilic gel-forming agent (*i.e.*, polyethylene oxide (PEO)) in the upper part of the gastrointestinal (GI) tract, stomach, and small intestine. The gel matrix then has gel strength to allow drug release in the colon, where release medium is limited, producing consistent release throughout the GI tract. It also improved pharmacokinetic profiles.[7,8] Even though the overall design concept of

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Table 1. Formulation Compositions of the Three-Layered Tablets

		F1	F2	F3	F4
Barrier layers (upper and lower)	Polyox WSR 303	100.0	100.0	120.0	100.0
	Polyethylene glycol	—	50.0	—	—
Mid-layer	Tamsulosin HCl	0.4	0.4	0.4	0.4
	Mannitol	30.0	30.0	30.0	—
	Polyethylene glycol	20.0	20.0	20.0	—
	NaCl	9.6	9.6	9.6	—
	Dextrate	—	—	—	92.3
	Mg. strearate	0.3	0.3	0.3	0.3
Total weight (mg)		260.3	360.3	300.3	293.0

the formulations could be to achieve constant drug release throughout the GI tract and in the colon,[8,9] the new tablet formulation has different geometrical configuration.[1] The present study was undertaken to investigate the effect of three layered tablets with various layer formulations on *in vitro* dissolution profiles and tablet properties together with *in vitro–in vivo* correlations.

Experimental

Materials Tamsulosin HCl (molecular weight 449.98) was purchased from Cadila Healthcare (Gujarat, India), and is sparingly soluble in water. Polyox WSR (water-soluble resin) 303 (average molecular weight 7×10^6, Dow Chemical, Midland, MI, U.S.A.) was used as a main excipient. Polyethylene glycol (PEG) 6000 was purchased from Sanyo Chemical Industries (Ibaraki, Japan). Dextrate and magnesium stearate were obtained from JRS Pharma (Patterson, NY, U.S.A.) and Faci Asia (Jurong Island, Singapore), respectively.

For the analysis of plasma drug concentration, terazosin internal standard (IS) was obtained from Sigma-Aldrich (St. Louis, MO, U.S.A.). Acetonitrile and methanol (HPLC grade) were from J.T. Baker (Philipsburg, NJ, U.S.A.). Water was purified using the Milli-Q purification system (Millipore Corp., Bedford, MA, U.S.A.). All other reagents were of analytical or HPLC grade.

Preparation of Three-Layered Tablets Table 1 shows the formulations to prepare three-layered tablets. All materials were passed through a sieve (#20 mesh) before mixing or granulation to remove aggregates. For the preparation of the mid-layer, a general wet granulation with water using a planetary mixer (Model KSM 90, KitchenAid, St. Joseph, MI, U.S.A.) was applied. The weighed ingredients were placed into a granulation bowl, and then dry mixed for 1 min. After turning on the planetary mixer, the water was added to the granulation bowl and mixed for 30 s. The wet mass was sieved using U.S. sieve #8. The collected wet granules were spread evenly on trays and then placed on a drying oven set at 45 °C for 6 h. Ingredients of the barrier layers were dry-mixed, if necessary. Exact amount of each layer was loaded one by one into a die and compressed on a hydraulic laboratory press using place-face punches with a diameter of 9.0 mm. The final compression force was kept constant at 6.0 MPa.

Tablet Evaluation: Degree of Swelling, Erosion, and Layer Separation The degree of swelling (water uptake) was calculated using a gravimetric analysis after immersion of test tablets in 900 ml of dissolution medium (pH 6.8, 50 mM phosphate buffer) and stirring for 6 h. The tablets were removed from the medium, blotted with absorbent tissue to remove any excess medium on the surface, and weighed ($n=3$). The degree of water uptake was calculated as:

$$\%\ \text{water uptake} = \left(\frac{W_2 - W_1}{W_1}\right)\times 100 \quad (1)$$

where W_1 is the initial weight of the dry tablet and W_2 is the weight of the hydrated and swollen tablet. Erosion values were calculated using the same tablets. After weighing, the hydrated tablets were dried in a vacuum-drying oven at 60 °C for 24 h, and the remaining dry weight, W_3, was subtracted from W_1, the initial weight of the dry tablet, to give percent (%) erosion:

$$\%\ \text{erosion} = \left(\frac{W_1 - W_3}{W_1}\right)\times 100 \quad (2)$$

Additionally, the degree of volume expansion was calculated as:

$$\%\ \text{volume expansion} = \left(\frac{V_2 - V_1}{V_1}\right)\times 100 \quad (3)$$

where V_1 is the initial volume of the dry tablet and V_2 is the volume of the hydrated and swollen tablet. For the tablet layer separation, the tablets were visually observed for the separation between the layers as introduced in the water uptake.

***In Vitro* Drug Release Test** Drug release tests were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (VK 7000, Varian Inc., Edison, NJ, U.S.A.) with 900 ml dissolution medium maintained at 37±0.5 °C and mixed at 100 rpm. Since the permeation of the hydrogel PEO (polyethylene oxide) based matrices is not sensitive to pH of the medium,[10] simulated intestinal fluid (SIF) (pH 6.8, 50 mM phosphate buffer) without any enzymes was selected as the dissolution medium otherwise indicated. Samples were withdrawn at predetermined time intervals and analyzed for drug content using a HPLC system (Agilent 1100 Series, Agilent Technologies, Waldbronn, Germany) at a wavelength of 225 nm. Samples were filtered with 30 μm PE filters, and then 20 μl of the sample ($n=4$) was injected into a CapcellPak® C_{18} 5 μm column (4.6×150 mm) (Shiseido, Tokyo, Japan). The mobile phase contained a mixture of aqueous buffer (35 mM KH_2PO_4) and acetonitrile in a volume ratio of 70 : 30.

Comparison of *in Vitro* Dissolution Profiles Dissolution profiles *in vitro* can be compared by using factors such as a difference factor (f_1) and a similarity factor (f_2).[11,12] The difference factor measures the percent error between two profiles as in the following equation.

$$f_1 = \left(\sum_{j=1}^{n}\left|R_j - T_j\right| \Big/ \sum_{j=1}^{n} R_j\right)\times 100 \quad (4)$$

where n is the sampling number, and R and T are the cumulative percentage dissolved amounts of the reference and test products at each time point j. The similarity factor (f_2) can also be calculated by:

$$f_2 = 50\times\log\left\{\left[1+(1/n)\sum_{i=1}^{n}(u_{ti}-u_{ri})^2\right]^{-1/2}\times 100\right\} \quad (5)$$

The similarity factor (f_2) is a function of the reciprocal of the mean square-root transform of the sum of square distances between the test profiles u_{ti} and the reference profiles u_{ri} over all time points (from $i=1$ to n). f_2 values should be close to 100 if the two drug release profiles would be identical. The higher the f_2 value, but the lower the f_1 value, the more similarity between the two drug release profiles. In general, f_1 values lower than 15 and f_2 values higher than 50 show the similarity of the dissolution profiles within 10% of the difference.[11]

Pharmacokinetic Study in Beagle Dogs This was a single-dose, open-label, randomized, two-period crossover study in dogs. The experiments for the evaluation of the pharmacokinetic study in dogs were approved by the Ethics Committee for Animal Experimentation of Haeeun Primate Research Center (Seongnam, Gyeonggi, Korea). Beagle dogs ($n=6$, 12±2 kg) were deprived of food, with *ad libitum* access to water, from 16 h before the experiment to 4 h after the experiment. Beagle dogs received 0.4 mg of tamsulosin formulations: (a) three-layered tablet; (b) OCAS® tablet. Tamsulosin formulation was given with a 1-week interval ("washout period") in a crossover design. Blood samples were obtained periodically, centrifuged immediately, and kept at −70 °C until further analysis.

Calibration Standard and Quality Control Samples A stock solution of tamsulosin was prepared in 100% methanol at 1000 μg/ml. This stock solution was further diluted with 100% methanol to obtain tamsulosin calibration standard solutions with the concentration of 1, 2, 5, 10, 50, and 100 ng/ml. Plasma calibration at concentrations of 0.1, 0.2, 0.5, 1, 5, and 10 ng/ml were obtained by adding 30 μl of stock solution into 270 μl of blank beagle plasma (LOQ=0.1 ng/ml, r^2=0.9997). Quality control (QC) samples (1, 5, 10 ng/ml) were also prepared by the same procedure of plasma calibration. To prepare stock solutions (1000 μg/ml) of IS, 10 mg of terazosin was dissolved in 10 ml of 100% methanol, and diluted further to the final concentration of 5 μg/ml.

Instrumentation and Chromatographic Conditions A Waters 2795 HPLC system and a Waters Micromass Quattro API triple quadruple mass spectrometer equipped with a *z*-spray interface in positive ionization mode (Waters Ltd., Watford, U.K.) were used for the LC-MS/MS analysis. Two channels of a positive ion MRM mode were used to detect tamsulosin and IS. The most abundant product ions of the compounds were at *m*/*z* 228.20 from the precursor ion *m*/*z* 409.20 of tamsulosin and at *m*/*z* 388.13 from the *m*/*z* 290.11 of IS. Data acquisition was performed using Micromass Masslynx 4.0 and data processing was conducted using a Quanlynx data analysis program.

The analytical column used was a Luna hilic C_{18} (5×2.0 mm i.d. 5 μm, Phenomenex, Torrance, CA, U.S.A.). The mobile phase consisted of 95% methanol and 5% 50 mM ammonium acetate buffer (pH 4.5), and was filtered through a 0.2 μm filter and degassed before use. A flow rate of 0.2 ml/min was used for sample analysis. The temperatures of the autosampler and column oven were 4 °C and 40 °C, respectively.

Sample Preparation After thawing the samples at room temperature, an aliquot of each sample (300 μl) was pipetted into an eppendorf tube and 20 μl of IS working solution (1 μg/ml) was added. After vortexing briefly, 1.4 ml of the organic solvent (dichloromethane) was added to each sample, shaken for 10 min, and then centrifuged for 10 min at 8500 rpm. The upper aqueous layer was then removed, and 1 ml of the organic layer was evaporated to dryness using a nitrogen flow in a TurboVap LV (Caliper Life Sciences, Mountain View, CA, U.S.A.) evaporation system at 45 °C. The residue obtained was dissolved in 100 μl of 95% methanol and vortexed for 10 min. After centrifugation (3000 rpm for 10 min), samples were transferred to autosampler vials and 15 μl aliquots were injected into the HPLC system.

Pharmacokinetic Analysis and *in Vitro–in Vivo* Correlation The pharmacokinetic parameters were determined from the experimental drug concentration–time data by using the non-compartment method. The maximum observed concentration (C_{max}), time at which C_{max} occurred (T_{max}), and area under the plasma concentration–time curve (*AUC*) were calculated using the linear trapezoidal rule from time zero to 24 h ($AUC_{0—24}$).

The fraction-absorbed calculations employed the Wagner–Nelson Method.[13] The percentages absorbed vs. time were calculated by:

$$\% \text{ absorbed} = \left(\frac{C(t)/Ke + AUC_{0—t}}{AUC_{0—\infty}} \right) \times 100 \quad (6)$$

where $C(t)$ is the plasma concentration at time t, Ke is the elimination rate constant, $AUC_{0—t}$ and $AUC_{0—\infty}$ are the area under the plasma concentration–time curve from zero to time t and infinity, respectively.

An attempt was made to perform *in vitro–in vivo* correlation (IVIVC), level A, which shows that the *in vivo* drug absorption rate of the dosage form has a direct relationship with the *in vitro* drug release rate of formulation.[14] The relation between the *in vitro* dissolution and *in vivo* pharmacokinetic data was examined by plotting the percent drug dissolved *in vitro* after 1, 2, 4, 6, 8, 12, and 24 h *vs.* percent absorbed *in vivo* at equivalent time intervals.

Results and Discussion

Effects of the Amount of Polymer in Swellable Layers on Dissolution Profiles Compared to F1, F3 contains larger amount of the swellable polymer (Polyox WSR 303) in the barrier layers (Table 1), and it showed reduced drug release kinetics (Fig. 2). Moreover, to make the dissolution medium penetrate easily through a swellable layer and reach the polymer,[8] 50% of PEG compared to the amount of PEO was incorporated and then the resulting tablets were evaluated (Table 1). Similarity factor (f_2 values) can be used to compare the dissolution profiles. The value can range from 0 to 100 and the higher values indicate more similarity between the two profiles. Taking F1 as a reference, the f_2 value of F2 was 44.6. However, taking F2 as a reference, the f_2 value of F3 was 84.4. Therefore, F2 showed decreased dissolution rate compared to F1 and similar rate to F3 (Fig. 2).

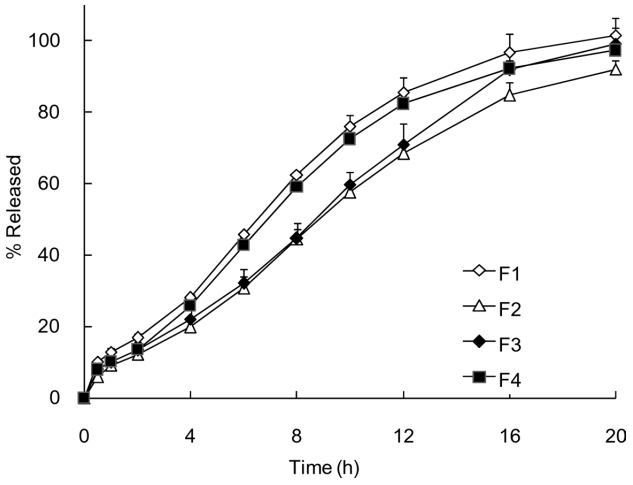

Fig. 2. *In Vitro* Drug Release Profiles in Buffer at pH 6.8 Showing the Influence of Polymer Amounts and Addition of PEG in the Barrier Layers on the Dissolution Profiles and the Three-Layered Tablets with Different Excipients in the Mid-Layer: Barrier Layers Are Composed of 100% Polyox WSR-303 (m.w. 7×10^6)

Each point represents the mean±S.D. (n=4).

Although the barrier layers are designed to allow the dissolution medium to penetrate easily, the total amount of the layers may affect the overall dissolution rates. Due to the additional amount of PEG, it causes elongated diffusion path length for the dissolution medium and drug molecules during swelling. In this case, the larger amount of barrier layers might affect the overall dissolution rate together with the layers' intrinsic properties. Therefore, it will be important to consider the amount and properties of swellable layers for controlling drug release kinetics.

Effects of Soluble Excipients in the Mid-Layer on Dissolution Profiles To evaluate the effects of excipients in the mid-layer on dissolution profiles, tablets with the same amount but different compositions in the mid-layer were investigated as F1 and F4 (Table 1). 100% Polyox WSR 303 (m.w. 7×10^6) was used as a gelling polymer in barrier layers. Among the excipients, mannitol (water solubility 1 in 5.5) and NaCl (water solubility 1 in 2.8) have less solubility than dextrate (water solubility 1 in 1). However, the two formulations did not exhibit significant difference in dissolution profiles (Fig. 2). Taking F1 as a reference, the f_2 value of F4 was 74.9. It might be due to the minimal effect of the mid-layer on the overall drug release kinetics when water-soluble excipients are incorporated.[15] Polyox WSR 303 in the barrier layer might dominate in generating drug release characteristics, and the other excipients in the mid-layer give relatively less significant effects on the drug delivery modulation.[16] On the other hand, based on the excipient screening, as the solubility of the excipients in the mid layer decreased, the probability of layer-separation became higher during the dissolution test.[1]

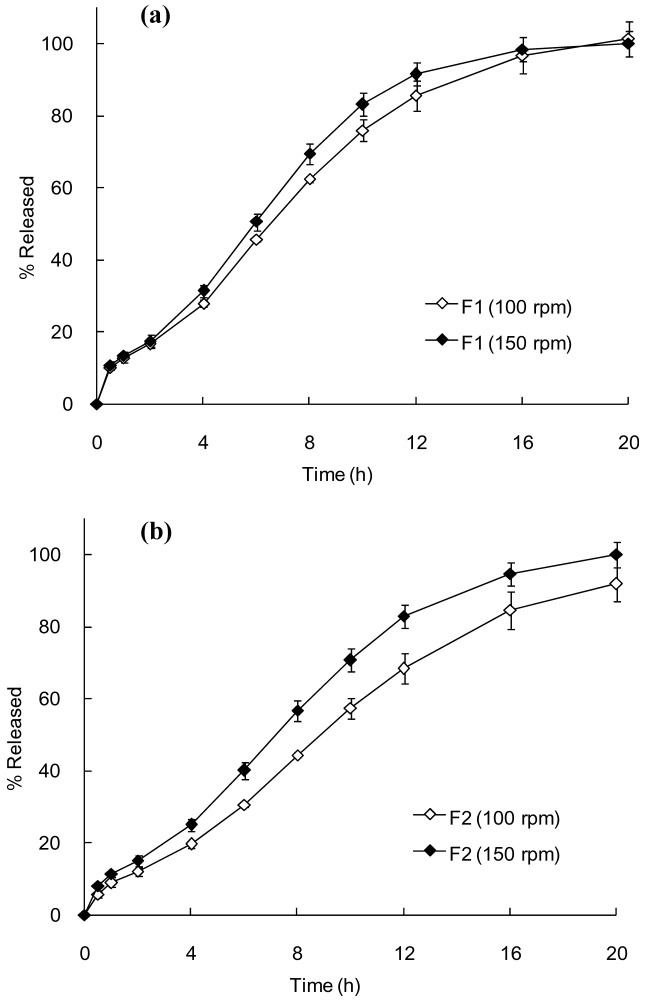

Fig. 3. Influence of Agitation Force (Paddle Speed 100 rpm and 150 rpm) on the *in Vitro* Dissolution Profiles of the Three-Layered Tablets in Buffer at pH 6.8: (a) F1; (b) F2

Each point represents the mean±S.D. (n=4).

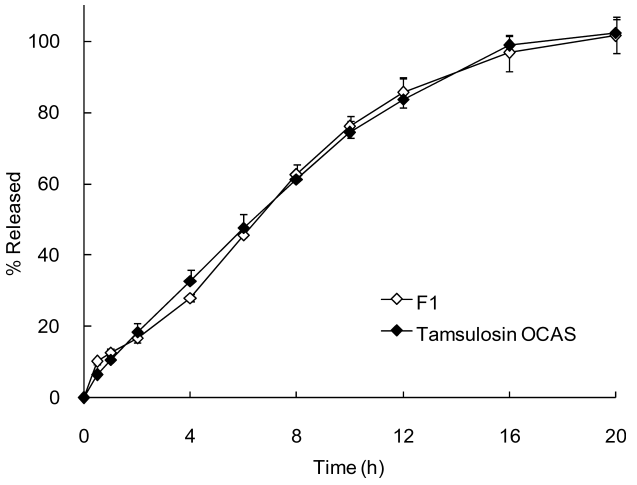

Fig. 4. *In Vitro* Drug Release Profiles Comparing the Dissolution between the Three-Layered Tablets (F1) and the Reference (Tamsulosin OCAS®) Tablets in pH 6.8 at 100 rpm

Each point represents the mean±S.D. (n=4).

Effect of Various Hydrodynamic Conditions and Ionic Strength Since extended-release preparations need to release drugs for a longer period of time in the GI tract, it is desirable for the preparations to maintain consistent release rate as exposed to various *in vivo* environments. If well-controlled, *in vitro* dissolution test might be used as a surrogate for *in vivo* studies. Variations in hydrodynamic conditions recommended by specified stirring speed, namely 50 rpm, 100 rpm, and/or 150 rpm for the paddle method may provide valuable insight into system performance.[17] In some cases, low hydrodynamic intensity have shown to mimic *in vivo* situation more closely.[18,19] Changes in paddle speed or agitation intensity during the *in vitro* dissolution study might be a simple indicator of the environmental effect on the release rate. It may not represent the *in vivo* environment, but may give an idea how to modify formulations.

Figure 3 shows the dissolution profiles by varying the paddle speed of dissolution test from 100 to 150 rpm with the formulations of F1 and F2. F1 is observed to be more stable against the effect of agitation force compared to F2. It might be due to the higher mechanical strength of the higher molecular weight Polyox WSR 303 when swollen compared to the PEG–PEO mixture. However, as the difference and the similarity factors for F1 and F2 were considered, f_1 (5.53, 14.44, respectively)<15 and f_2 (65.8, 51.4, respectively)>50, the effect of paddle speed may not so significant. It indicated that two preparations passed FDA's similarity criterion of less than 10%. Separately, Fig. 4 shows the dissolution profiles of F1 and the OCAS® tablets and reference OCAS® tablets showed f_1=8.09 and f_2=63.8, which was very similar to F1.

Additional dissolution test was conducted to examine the effect of ionic strength on the drug release profiles (n=4). The release media was divided into three categories including low, medium, and high ionic strength, whose ionic strength was 0.074, 0.108 and 0.142, respectively. Low ionic strength solution was prepared by not adding sodium chloride to the SIF. Medium and high ionic strengths were prepared by adding additional amount of sodium chloride to the SIF. pH of the solutions did not change with the addition of sodium chloride (pH 6.8). Taking the low ionic strength as a reference, f_2 values of the reference (OCAS) and test (F1) tablets in medium ionic strength were 71.8 and 73.8, respectively. Moreover, f_2 values of high ionic strength were 73.8 and 63.9, respectively. Based on the results, it might be hard to tell that the ionic strength affects the dissolution profiles of the reference and the test tablets.

Comparison of Water Uptake and Erosion of Three-Layered Tablets One of the main aims of this study is to develop once-a-day extended-release tablet formulations by designing them to induce "self-dissolution" as the tablet transits down the lower GI tract, where the dissolution medium is limited. The major strategy would be to develop tablet formulations that absorb release medium with a different manner fast enough in the upper GI tract, where the amount of dissolution medium is abundant.

The water uptake test was performed to compare the swelling properties of the three-layered tablets. This test evaluated how much the tablets could absorb the medium (Fig. 5a). After 4 h of absorption, the three-layered tablets had more than triple of its initial weight (300%). Water uptake of F1 and F4 formulations showed similar swelling properties.

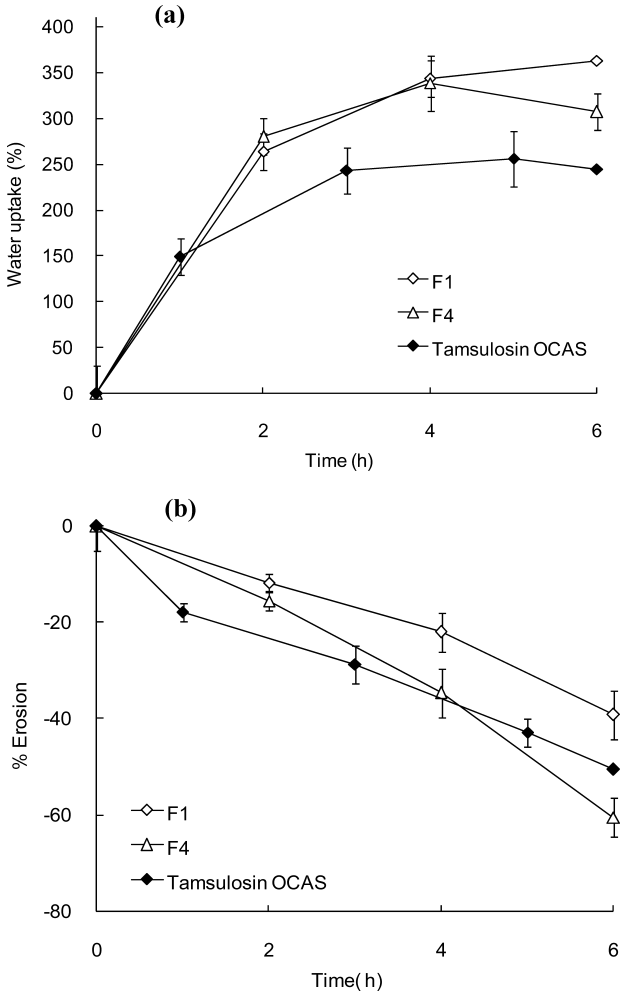

Fig. 5. Comparison of (a) Degree of Swelling (Water Uptake) and (b) % Erosion between the Three-Layered and Reference Tablets

Each point represents the mean±S.D. (n=3).

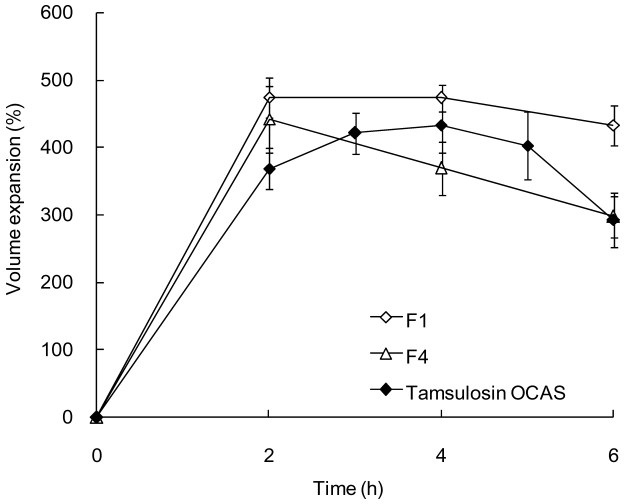

Fig. 6. Comparison of Volume Expansion between the Three-Layered and Reference Tablets

Each point represents the mean±S.D. (n=3).

Therefore, it can be said that the swellable polymer has a significant effect on the swelling properties. It was alsio confirmed that the reference tablets were able to absorb the medium more than two and a half fold (250%) of its initial weight. The addition of water-soluble excipients to both the barrier layers and the mid-layer is known to enhance water penetration into the matrix.[20] However, the extent of the swelling will be dependent on many factors such as ratio among the excipients, geometrics of the tablet, compression pressure, and so on. Moreover, soluble or insoluble drugs may influence water penetration into the matrix and the also polymer swelling process.[21,22]

In the case of tablet erosion (Fig. 5b), F4's erosion kinetics was the fastest, whose mid-layer had the higher solubility. While the three-layered tablet progressed with constant kinetics, the reference tablet showed the similar behavior only after the early fast erosion. It was already suggested that the highly water-soluble excipients dissolve to enhance water penetration into the preparation increasing erosion ratio.[20] Moreover, in the case of monolithic matrix tablets, the gelation index increased when the tablets contain highly water-soluble ingredients.[9] Therefore, the water solubility of the excipients might affect tablet erosion properties and excipients' solubility in the mid-layer might be one of the significant factors to be considered carefully.

Volume expansion test (Fig. 6) showed faster and enough swelling of the three-layered tablet up to 2 h compared to the reference. The volume of F4 which showed the fastest erosion had decreased. It might be due to the effect of the soluble excipient. All the formulations in this test did not show any separation during the separation study.

Pharmacokinetic Analysis and IVIVC The reference tablet was already confirmed that the drug could be absorbed even in the large intestine.[7] By comparing pharmacokinetic profiles between the reference and the three-layered tablet, it may present the tablet' absorption properties in the lower GI tract and hence feasibility of the formulation for once-a-day drug administration. Therefore, *in vivo* pharmacokinetic study using beagle dogs were carried out together with F1. Before the *in vivo* study, the dissolution similarity of F1 was evaluated in several dissolution media (water, pH 4.0, and pH 6.8) and different paddle speeds (50, 100, 150 rpm). In the case of dissolution media, the f_2 values were 81.8, 59.8, and 55.1, respectively. Moreover, in the case of paddle speeds the f_2 values were 55.1, 58.3, and 65.2, respectively. The values clearly showed that the similarity of the dissolution profiles within 10% of the difference.[11]

The statistical summary for pharmacokinetic data and mean plasma drug concentration profiles were presented in Table 2 and Fig. 7. Mean plasma concentrations throughout 24 h for the test and reference followed a similar trend with comparable plasma levels over the entire time. The half-life and T_{max} of F1 are 10.11 h and 4.8 h, respectively. It showed that three-layered tablet extended the absorption of the model drug much longer compared to those of immediate release formulation; half-life 1.27—1.68 h and T_{max} 0.13—0.5 h,[23] and OCAS® tablet; half-life 7.1 h and T_{max} 5.7 h. Therefore, the extended release tablets might improve the efficiency of the therapeutics. The mean ratio of *AUCs* and C_{max} for F1 *vs.* the reference tablet was 0.69 and 0.84, respectively, which suggests that the absorption of tamsulosin from the three-layered tablet was less complete than the reference tablet. Al-

Table 2. Pharmacokinetic Parameters of the Three-Layered Tablet Formulations and the Reference Tablets in Beagle Dogs

	$AUC_{0—24}$ [a)] (ng h/ml)	C_{max} [a)] (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Tamsulosin IR[b)]	—	—	0.13—0.50	1.27—1.68
F1	4.804±4.585	0.912±1.328	4.8±6.2	10.11[c)]
Reference	6.987±4.247	1.087±0.926	5.7±3.1	7.10[c)]
Test/ref. point estimate	0.69	0.84	0.68	1.42

a) Geometric mean values. *b*) Matsushima *et al.*, 1998.[23] *c*) Calculated from mean plasma concentrations.

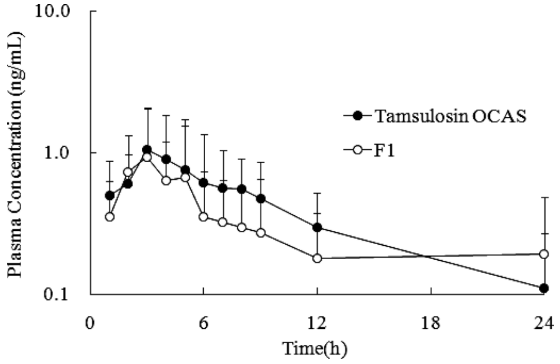

Fig. 7. Pharmacokinetic Profiles of Tamsulosin in Beagle Dogs (n=12): F1 and Reference (Tamsulosin OCAS®) Tablet

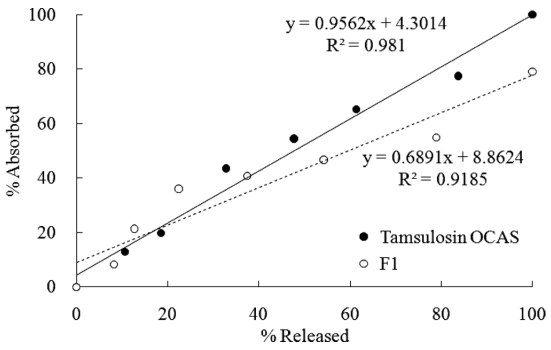

Fig. 9. *In Vivo–in Vitro* Correlations, Level A, for F1 and the Reference Tablet

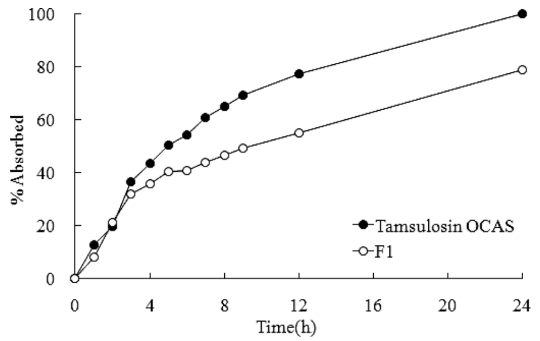

Fig. 8. Absorption Profiles *in Vivo* for F1 and the Reference Tablet after Deconvolution of Plasma Concentration–Time Profiles According to the Wagner–Nelson Method

though the dissolution similarity between F1 and the reference tablet was within 10% in all *in vitro* conditions, F1 showed slower dissolution for the entire time in all dissolution tests. Despite the less complete absorption compared to the reference, the plasma concentration at 24 h of F1 was higher than that of the reference, which might suggest that F1 possibly obtains a more favorable trough level to maintain the therapeutic plasma concentration range for once-a-day administration. Further work is ongoing for the formulation development.

To evaluate the cause of the lower absorption of the three-layered tablet compared to the reference, the absorption rate *in vivo* was calculated by using the Wagner–Nelson equation and deconvolution of mean plasma concentration data (Fig. 8). The total extent of absorption from the three-layered tablet was substituted with that of the reference to consider less complete absorption. Figure 8 shows that an initial rapid absorption, about 40% of the total absorption at 4 h, was followed by a prolonged absorption. After similar absorption rates of the two formulations were obtained until 2 h, the gap of absorption rate started to widen from 3 h to about 8 h. Then the gap was maintained until 24 h. This absorption pattern could also be found in the dissolution profiles of the pH 6.8 buffer. In other words, the decreased dissolution rate from 2 to 8 h might be the cause of the less complete absorption of the three-layered tablet.

The attempt to perform a level A, IVIVC showed that the *in vivo* drug absorption rate of the dosage form has a high correlation with the *in vitro* drug release rate of the formulation (Fig. 9). The reference tablet (R^2=0.981) showed a more linear relationship than the three-layered tablet (R^2=0.918) because of the decreased dissolution and absorption rate from 2 to 8 h of the test formulation. This result suggested that the *in vitro* dissolution profiles and release kinetics to be useful in predicting absorption kinetics as well as overall plasma drug concentration–time profiles for tamsulosin formulation studies.

Conclusion

Three-layered tablet formulations containing tamsulosin were investigated with their various properties and also compared with those of a commercial product. F1 was stable against the effect of agitation force and absorbed the medium to more than triple of its tablet weight (300%). Volume expansion showed faster and enough swelling of the three-layered tablet up to 2 h. Although the barrier layers are designed to allow the dissolution medium to penetrate easily, the amounts of swellable layer controlled the kinetics of the drug release profiles. The pharmacokinetic study found that the decreased dissolution rate of the three-layered tablet might cause the less complete absorption and less linear relationship between absorption and dissolution than the reference tablet through the Wagner–Nelson method and IVIVC, level A. This result suggests that the *in vitro* dissolution profiles

and release kinetics might be useful in correlating absorption kinetics as well as overall plasma drug concentration–time profiles for formulation studies.

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