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Evaluating tamsulosin hydrochloride-released microparticles prepared using single-step matrix coating

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ABSTRACT

The objective of the present study was to determine the optimum composition for sustained-release of tamsulosin hydrochloride from microparticles intended for orally disintegrating tablets. Microparticles were prepared from an aqueous ethylcellulose dispersion (Aquacoat®), and an aqueous copolymer based on ethyl acrylate and methyl methacrylate dispersion (Eudragit® NE30D), with microcrystalline cellulose as core particles with a fluidized bed coating process. Prepared microparticles were about 200 μm diameter and spherical. The microparticles were evaluated for *in vitro* drug release and *in vivo* absorption to assess bioequivalence in a commercial product, Harnal® pellets. The optimum ratio of Aquacoat® and Eudragit® NE30D in the matrix was 9:1. We observed similar drug release profiles in microparticles and Harnal® pellets. Higuchi model analysis of the *in vitro* drug release from microparticles was linear up to 80% release, typical of Fickian diffusion sustained-release profile. The *in vivo* absorption properties from microparticles were comparable to Harnal® pellets, and there was a linear relationship between *in vitro* drug release and *in vivo* drug release. In conclusion, this development produces microparticles in single-step coating, that provided a sustained-release of tamsulosin hydrochloride comparable to Harnal® pellets.

1. Introduction

Alpha-1-adrenoreceptor antagonists are used in clinical practice to treat transient orthostatic disorders. Tamsulosin hydrochloride is a highly selective α1-adrenoreceptor antagonist and has been used for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) (O'Leary, 2001; Takenaka et al., 1995). The use of conventional α1-adrenoreceptor antagonists can be limited by adverse effects related to the cardiovascular system, such as asthenia, dizziness and orthostatic hypotension (Carruthers, 1994; Djavan et al., 2004). A capsule containing a sustained-release formulation for tamsulosin hydrochloride (Harnal®) was originally developed to reduce occurrence and severity of adverse effects (Tsunoo et al., 1990, 1991). Other formulations have been reported for the preparation of tamsulosin hydrochloride controlled-release pellets (Kim et al., 2005a,b, 2006, 2007; Zhang et al., 2009). Patients on tamsulosin hydrochloride treatment with LUTS/BPH are men aged in their mid-sixties, and the drug is rarely prescribed for patients under the age of 50 years (Michel et al., 1998). About half of the patients found it difficult to take medications, and considered tablets were easier than capsules or powders (Honda and Nakano, 1998).

A better formulation for use by the elderly would be easy to swallow and handle. To meet these requirements, attempts have been made to develop an orally disintegrating tablet (Chang et al., 2000). Elderly patients find orally disintegrating tablets easier to take as the tablets break down in a small amount of water in the mouth. An orally disintegrating tablet containing sustained-release microparticles for tamsulosin hydrochloride was later launched in response to high demand among elderly patients ingesting therapeutic agents for LUTS/BPH. Mizumoto (2008) reported microparticles under 200 μm diameter produced a pleasant sensation in the mouth but Harnal® sustained-release pellets are about 500 μm diameter.

The microparticles are composed of a core particle of microcrystalline cellulose, a layer of media containing the drug, surrounded by a sustained-release membrane of water-soluble and water-insoluble polymers, and an enteric layer coating over the sustained-release membrane.

The sustained-release membranes control the dissolution of the microparticles. Several coating processes have been developed to manufacture these microparticles with different membrane char-

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acteristics. Ichikawa et al. (1997, 2001) and Miyamoto et al. (1997) reported drug release over 10 h from particles coated by a process using a multilayered, water-insoluble membrane surrounding the drug layer. For the lansoprazole fast-disintegrating tablet, multiple-layered enteric microgranules were manufactured using a fluidized bed coating process (Shimizu et al., 2003a,b,c). These microgranules reduce damage during a compression process, improve drug stability and mask the unpleasant bitter taste.

For similar reasons, microcapsules were prepared with water-insoluble polymer matrix using an emulsion method. This formulation provided a sustained drug release system, controlled first order kinetics (Farhana et al., 2009; Swamy et al., 2008) and was pH-sensitive (Maghsoodi, 2009; Mastiholimath et al., 2007; Nilkumhang et al., 2009). The existing production processes require several steps, and there is opportunity to improve the cost effectiveness microparticle production methods.

The objective of this study was to determine an optimum composition for sustained-release microparticles, about 200 μm in diameter, containing tamsulosin hydrochloride for orally disintegrating tablet. Microparticles were prepared in single-step matrix coating using Aquacoat® and Eudragit® NE30D as coating materials. The release of tamsulosin hydrochloride from microparticles and bioequivalence with Harnal® pellets was evaluated.

2. Materials and methods

2.1. Materials

Tamsulosin hydrochloride was synthesized and Harnal® pellets were obtained at Astellas Pharma Inc. (Yaizu, Japan); microcrystalline cellulose (Celphere® CP-102) and ethylcellulose aqueous dispersion (Aquacoat®) (Asahi Chemical Industry Co., Ltd., Tokyo, Japan); methacrylic acid copolymer dispersion (Eudragit® L30D-55) and ethyl acrylate–methyl methacrylate copolymer dispersion (Eudragit® NE30D) (Evonik Degussa Japan Co., Ltd., Tokyo, Japan); acetylated monoglyceride (Myvacet™) (Eastman Chemical Japan, Inc., Tokyo, Japan) and polyoxyethylene hydrogenated castor oil 60 (Nikkol HCO-60) (Nikko Chemicals Co., Ltd., Tokyo, Japan). All other excipients are specified in *Japanese Pharmaceutical Excipients*.

2.2. Preparation of enteric film-coated microparticles

Tamsulosin hydrochloride was dissolved in deionized water and the solution mixed with Aquacoat® and Eudragit® NE30D. The mixture was coated onto Celphere® CP-102 or 150 μm sieved CP-102, by side-spraying in a fluidized-bed granulator (FLO-1, Freund, Tokyo, Japan). After overnight incubation in a drying oven at 80 °C, the microparticles were coated with a mixture of Eudragit® L30D-55 and triacetin by side-spraying in the fluidized-bed granulator. Coating conditions were: total charge amount, 350–450 g; inlet air temperature, 40–50 °C; product temperature, 30–35 °C; atomizing air pressure, 3 kg/cm^2; spray rate: 8 g/min.

2.3. Particle size distribution

Five grams of modified-release microparticles were weighed, and the particle size distribution of samples measured with an Automated Sonic Sieving Particle Size Analyzer (Robot Sifter RPS-105, Seishin Enterprise Co., Ltd., Tokyo, Japan).

2.4. Particle observation by scanning electron microscopy

The morphology of microparticle surfaces was observed by scanning electron microscope (JSM-5000 Jeol Ltd., Tokyo, Japan).

2.5. Dissolution tests

Drug dissolution was tested with formulations containing 10 mg of tamsulosin hydrochloride and an automatic 6-series dissolution-testing device (Toyama Sangyo Co., Ltd., Osaka, Japan) with an ultraviolet–visible spectrophotometer (Shimadzu Co., Kyoto, Japan). The tests were performed in accordance with the dissolution test method 2 (paddle method, *The Japanese Pharmacopeia* 15th ed.). The test fluid was phosphate buffer at pH 7.2 (phosphate buffer, disintegration test, *The Japanese Pharmacopeia*, 15th ed.). The test fluid volume was 500 mL, paddle rotation speed was 100 rpm, at wavelengths 254 and 400 nm.

2.6. Bioavailability studies in dogs

After 20 h of fasting, 0.4 mg of tamsulosin hydrochloride containing modified-release microparticles was orally administered to healthy male beagle dogs with 20 mL of water under fasted conditions. 1 mg/kg of famotidine was injected intramuscularly 1.5 and 0.5 h before dosing and 2, 4, 6, 8, and 10 h after dosing with tamsulosin hydrochloride. The study was carried out in a crossover fashion. Venous blood samples (5 mL) were collected 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 h after dosing and immediately centrifuged. Plasma samples were kept frozen at −20 °C until assay. Tamsulosin in the plasma was determined using liquid chromatography–tandem mass spectrometry (LC–MS/MS). All animal experiments were performed in compliance with the regulations of the Institutional Animal Care and Use Committee of Astellas Pharma Inc. (Yaizu, Japan).

2.7. LC–MS/MS analysis

One milliliter of plasma sample was mixed with 0.1 mL of 0.05 N hydrochloric acid solution containing internal standard (tamsulosin derivative), 1 mL of saturated sodium bicarbonate solution, and 5 mL of diethyl ether, shaken for 15 min and centrifuged at 2000 rpm for 5 min. The supernatant was concentrated to dryness using low heat (40–45 °C). The residue was dissolved in 0.2 mL of 50 mM acetic acid/ammonium acetate buffer solution (pH 4.0):methanol (60:40) mixture, 80 μL of which was injected into LC–MS/MS (TSQ7000, Thermo Fisher Scientific K.K., Yokohama, Japan).

Total plasma concentration of tamsulosin was determined using a reversed-phase LC–MS/MS assay (J'sphere ODS-H80 column, 4.6 mm × 75 mm; YMC Co., Ltd., Kyoto, Japan). Buffer (50 mM acetic acid/ammonium acetate buffer solution [pH 4.0]:methanol [50:50]) was used as the mobile phase. The samples were calibrated against a standard curve in dog plasma at five concentration levels (0.05–20 ng/mL).

3. Results and discussion

3.1. Effect of core particle size on in vitro drug release

Here, we prepared sustained-release of tamsulosin hydrochloride from microparticles by matrix diffusion, using microcrystalline cellulose particles about 130 or 180 μm in diameter as core particles, and examined the effect of core particle size on *in vitro* release properties.

Formulations of microparticles are described in Table 1, and release of tamsulosin hydrochloride from microparticles in phosphate buffer at pH 7.2 is shown in Fig. 1. Drug release from Formulation 2 (F2) (core particles about 130 μm in diameter) was faster than other formulations; approximately 80% of loaded drug was released within 30 min of administration. In contrast, drug release from F1 (core particles about 180 μm in diameter) was

Table 1
Formulations of microparticles for evaluating effects of core particle diameter and matrix components on *in vitro* drug release (CP-102: 180 μm; sieved CP-102: 130 μm).

Formulation no.	1	2	3	4
Core				
CP-102 (mg)	13.3	–	13.3	–
Sieved CP-102 (mg)	–	13.3	–	13.3
Matrix				
Tamsulosin hydrochloride (mg)	0.2	0.2	0.2	0.2
HCO60 (mg)	0.3	0.3	0.3	–
Aquacoat (mg)	6.0	6.0	6.0	6.0
Eudragit NE30D (mg)	0.6	0.6	–	2.6
Myvacet (mg)	–	–	2.0	–
Pure water (mL)	6.7	6.7	6.7	20.0
Mean particle size (μm)	215	N.T.[a]	N.T.[a]	203

[a] N.T.: not tested.

slower than other formulations. Given that the only difference between Formulations 1 and 2 was core particle size, the results suggest that core particle size has a significant effect on drug release rate. We infer that as microparticle surface area relative to drug load increases with decreasing core particle size, drug release accelerates in the smaller particle size formulations.

3.2. Effect of matrix components on in vitro drug release

The effect of two matrix components and core particle size on drug release from microparticles was evaluated. F3 consisted of Aquacoat® and a plasticizing agent (Myvacet™) as a matrix and a core particle size of about 180 μm diameter.

F4 consisted of a mixture of Aquacoat® and Eudragit® NE30D, without surfactant, as a matrix, and a core particle size of about 130 μm diameter. Tamsulosin hydrochloride is a crystalline powder, with low wetting characteristics and is only slightly soluble in water. Surfactant was removed from the formulation by increasing the water content (Table 1).

The releases profiles of tamsulosin hydrochloride from microparticles and commercial product (Harnal® pellets) are shown in Fig. 1. F1, 2 and 3contain a surfactant; core particle size for Formulations 1 and 3 was larger than for 2 and 4.

The drug release profile for F3 was prolonged and slightly faster than F1. The initial release rate in F4 was slower than F2. Further, a comparison of Formulations 1 and 3, and Formulations 2 and 4 suggest that drug release from microparticles with a core particle diameter of about 130 μm was affected by the presence of surfactant (Fig. 1).

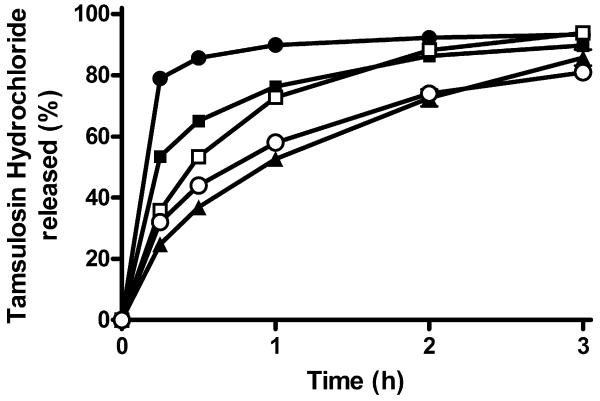

Fig. 1. *In vitro* release profiles of tamsulosin hydrochloride from microparticles in phosphate buffer at pH 7.2 for evaluating effects of core particle diameter and matrix components on *in vitro* drug release (mean ± SD, $n = 3$). ○: Formulation 1, ●: Formulation 2, □: Formulation 3, ■: Formulation 4, and ▲: Harnal® pellets.

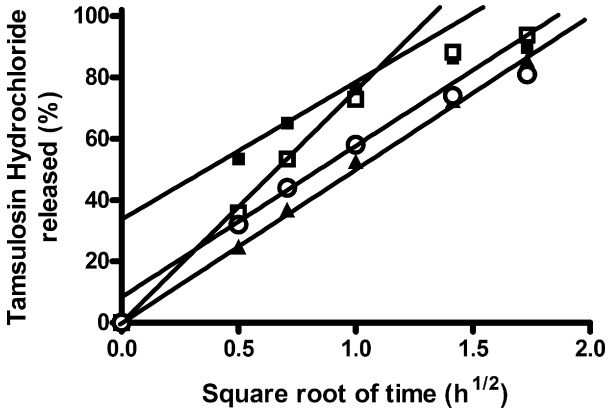

Fig. 2. Higuchi-type plot for evaluating effects of core particle diameter and matrix components on *in vitro* drug release. ○: Formulation 1, □: Formulation 3, ■: Formulation 4, and ▲: Harnal® pellets.

A preliminary analysis of tamsulosin hydrochloride release from Harnal® pellets corresponded with Higuchi model (Kim et al., 2007). Similarly, the drug release profiles from microparticles were analyzed, following Eq. (1) (Higuchi, 1963; Kim et al., 2007).

$$Mt = k \times t^{0.5} + C \quad (1)$$

where Mt is the rate of drug released up to time t, k is the kinetic constant, C is constant. The optimum values for the parameters presented in Higuchi model were determined by nonlinear regression using GraphPad Prism® 5 software (GraphPad Software, Inc., La Jolla, CA, USA). With the exception of F2, the release of tamsulosin hydrochloride from microparticles was plotted against the square root of time (Fig. 2). The coefficient of determination (R^2) of F1, F3, F4 and Harnal® pellets were 0.9922, 0.9950, 0.9881 and 0.9980, respectively, indicating the *in vitro* release of tamsulosin hydrochloride from microparticles fitted the Higuchi model up to 80% release. Accordingly, drug release from microparticles conformed to Fickian diffusion model (Costa, P. and Sousa Lobo, J.M., 2001). The kinetic constants of F1, F3 and F4 were 45.5, 73.5 and 45.2, respectively. The kinetic constant of F1 and F4 were nearly identical to that (50.2) of Harnal® pellets. This suggests the diffusion mechanism of F1 and F4 is comparable to Harnal® pellets (Table 4).

In other words, F1 (core diameter about 180 μm, particle diameter about 215 μm) releases drug at the desired rate, but is larger than the target size. The matrix content of F4 (core diameter about 130 μm, particle diameter 203 μm) should be modified to suppress initial burst, so that microparticles of 200 μm diameter have drug release property comparable to Harnal® pellets.

3.3. Effect of matrix content on in vitro drug release

To evaluate the effect of matrix content on drug release with core particle diameters of about 130 μm, microparticles were prepared by alternating the matrix content (Aquacoat®: Eudragit® NE30D) between 7:3, 8:2 and 9:1. In addition, the amount of matrix was increased in order to increase particle diameter and suppress the initial drug release burst. Formulations 5 through 7 are shown in Table 2, and the release of tamsulosin hydrochloride for each formulation in Fig. 3. The matrix contents of Formulations 5 and 6, were Aquacoat®:Eudragit® NE30D = 7:3 and 8:2, and exhibited drug release profiles identical to that of F4, which had a matrix content of Aquacoat®:Eudragit® NE30D = 7:3.

Although the matrix amount F5 and F6 was larger than F4, there was no change in the speed of initial drug release. Drug release from F7 (Aquacoat®:Eudragit® NE30D = 9:1) was successfully controlled.

Table 2
Formulations of microparticles for evaluating effects of matrix content on *in vitro* drug release.

Formulation no. (Aquacoat:Eudragit NE30D)	5 (7:3)	6 (8:2)	7 (9:1)
Core			
Sieved CP-102 (mg)	13.3	13.3	13.3
Matrix			
Tamsulosin hydrochloride (mg)	0.2	0.2	0.2
Aquacoat (mg)	12.6	12.6	12.6
Eudragit NE30D (mg)	5.4	3.2	1.4
Pure water (mL)	20.0	20.0	20.0
Mean particle size (μm)	210	206	202

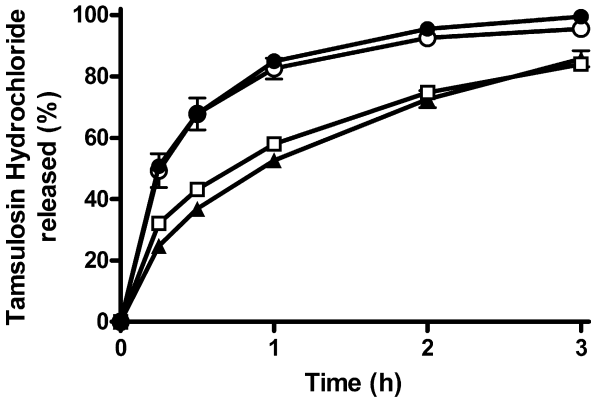

Fig. 3. *In vitro* release profiles of tamsulosin hydrochloride from microparticles and Harnal® pellets in phosphate buffer at pH 7.2 for evaluating effects of matrix content on *in vitro* drug release (mean ± SD, $n = 3$). ○: Formulation 5, ●: Formulation 6, □: Formulation 7, and ▲: Harnal® pellets.

Dissolution profiles of microparticles and Harnal® pellets were compared by calculating the similarity factor ($f2$) (Costa and Sousa Lobo, 2001):

$$f2 = 50 \times \log\left\{\left[1 + \frac{1}{n} \times \sum_{t=1}^{n} (Rt - Tt)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the number of dissolution sample times and Rt and Tt are the mean percent dissolved at each time point (t) for Harnal® pellets and microparticles, respectively.

The $f2$ for F5 and 6 was <50, but the $f2$ for F7 and Harnal® pellets was 68.0, indicating F7 and Harnal® pellets have similar drug release profiles. Kucera et al. (2008) tested the effect of ethylcellulose on the thermal properties of Eudragit® NE30D sprayed films and reported the two polymers were substantially immiscible. The third miscible phase was 85% ethylcellulose and 15% acrylic polymer and occupied only a small fraction of total film. F5 and F6 contained more than 20% acrylic polymers, which produced an immiscible matrix, leading rapid initial drug release.

Scanning electron microscopic observation of surface morphology of F7 and microcrystalline cellulose core particles are shown in Fig. 4. Microparticles were nearly spherical and almost all the same size. Some irregular shaped microparticles were observed and surface condition was slightly textured. The morphology of microcrystalline cellulose also contained irregular textured particles. We attribute the irregular shape of microparticles to the initial shape of microcrystalline cellulose. The mean diameter of microparticles in F7 was about 200 μm.Taken together, these results suggest that sustained-release of tamsulosin hydrochloride from microparticles with desirable particle size for orally disintegrating tablet can be successfully prepared using a single-step of fluidized bed coating.

Table 3
Formulation of enteric film-coated microparticles (Formulation 8).

Formulation no.	8
Core	
Sieved CP-102 (mg)	13.3
Matrix	
Tamsulosin hydrochloride (mg)	0.2
Aquacoat (mg)	12.6
Eudragit NE30D (mg)	1.4
Pure water (mL)	20.0
Enteric film	
Eudragit L30D-55 (mg)	6.9
Triacetin (mg)	1.4

3.4. Influence of enteric film coating on in vitro drug release

Harnal® pellets exhibit pH-dependent drug release profiles due to enteric coating. The effect of the coating process of enteric film on *in vitro* drug release from microparticles in F7 was evaluated. A mixture of Eudragit® L30D-55 and plasticizer was chosen as general enteric film (Bodmeiyer and Paeratakul, 1997) and was coated on microparticles using a fluidized bed coating process.

The formulation of enteric film-coated Formulation 7 (F8) is shown in Table 3, and Fig. 5 shows the release of tamsulosin hydrochloride from F8 and Harnal® pellets in phosphate buffer at pH 7.2. The calculated $f2$ values between Formulations 7 and 8 and between F8 and Harnal® pellets were 55.3 and 62.0. No significant difference was noted between the drug release profile of F8, F7 and Harnal® pellets. The release of tamsulosin hydrochloride from microparticles from F8 was plotted against the square root of time (Fig. 6). Coefficient of determination (R^2) and the kinetic constant of F8 were 0.9929 and 44.8 up to 80% release, indicating the *in vitro* drug release from F8 conformed to Fickian diffusion (Table 4).

These findings suggest that drug release using this formulation was not affected by the enteric film coating process. We note that drug release under acidic condition was not compared to Harnal® pellets as the enteric film was used. Future work should investigate the effect of enteric film composition on drug release.

3.5. Absorption studies in dogs

The release profile of Harnal® pellets is pH-dependent and declines in acidic conditions. This characteristic avoids a sudden build up of drug in blood plasma following dissolution in the stomach (Tsunoo et al., 1990, 1991). As development of the enteric film of F8 was not complete, test dogs were given famotidine to pro-

Table 4
The statistics of microparticles and Harnal® pellets obtained from Higuchi model.

Formulation no.	1	3	4	5	6	7	8	Harnal
Statistics[a]								
R^2	0.9922	0.9950	0.9881	0.9738	0.9906	0.9955	0.9929	0.9980
k	45.5	73.5	45.2	65.5	68.0	46.5	44.8	50.2
S.E.	2.28	5.19	4.96	10.8	6.61	2.22	1.89	1.11

[a] R^2, coefficient of determination; S.E., standard error of the kinetic constant, k.

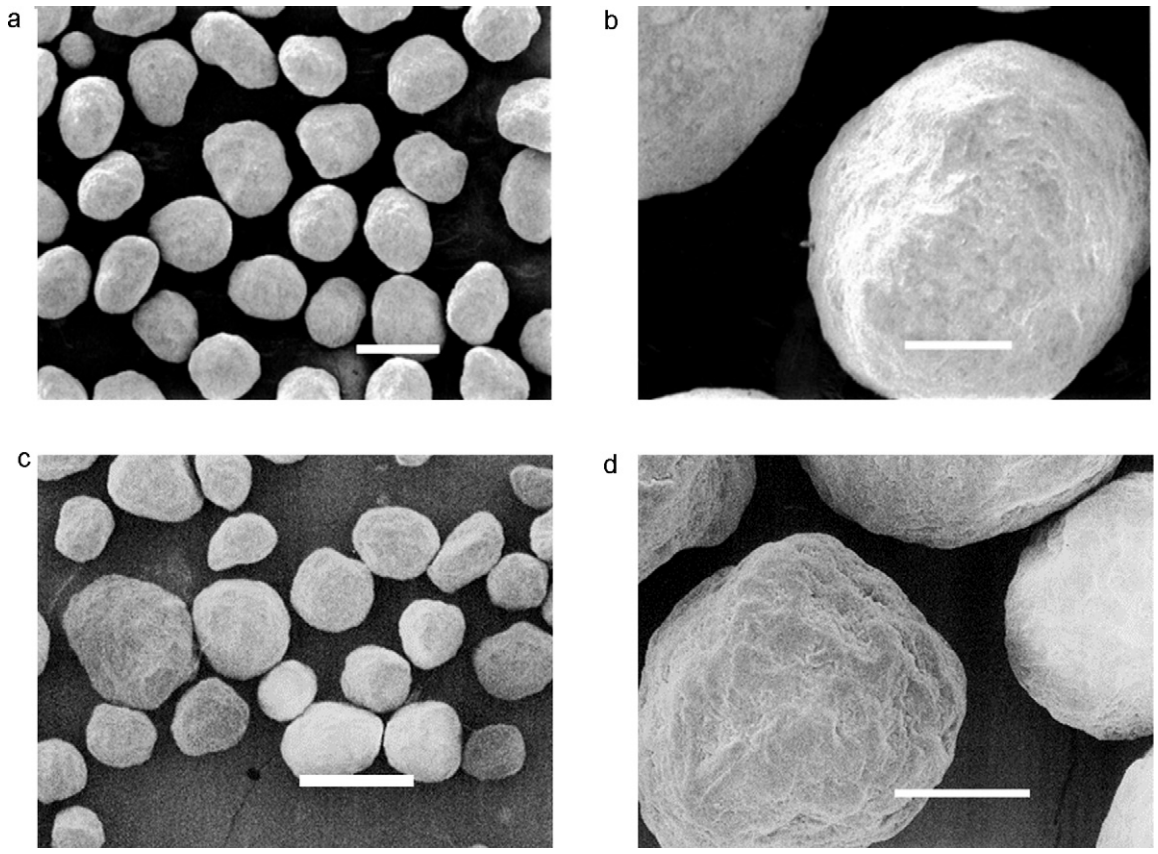

Fig. 4. Scanning electron microscopic photographs of Formulation 7 and CP-102. (a) Formulation 7; bar length 200 μm, (b) Formulation 7; bar length 50 μm, (c) CP-102; bar length 200 μm, and (d) CP-102; bar length 50 μm.

duce neutral stomach conditions, prior to *in vivo* administration of F8 and Harnal® pellets. The changes in plasma mean drug concentration after single oral administration of F8 and Harnal® pellets are shown in Fig. 7, and pharmacokinetic parameters are listed in Table 5. Mean plasma concentration curves were nearly identical for F8 and Harnal® pellets.

All pharmacokinetic variables were calculated via non-compartment methods. C_{max} and T_{max} values were read directly from the data, and AUC values were calculated using the trapezoidal method (Yamaoka et al., 1981). Respective mean values for C_{max}, T_{max}, and $AUC_{0-24\,h}$ after oral administration of Harnal® pellets were 15.1 ng/mL, 2.83 h, and 79.7 ngh/mL, while those after F8 administration were 16.2 ng/mL, 3.50 h, and 80.1 ngh/mL. We concluded there was little difference C_{max} and $AUC_{0-24\,h}$ in F8 or Harnal® pellets. Results from paired *t*-test at 5% bilateral significance showed no significant difference between the two groups for all parameters. Taken together, these results suggest that the *in vivo*

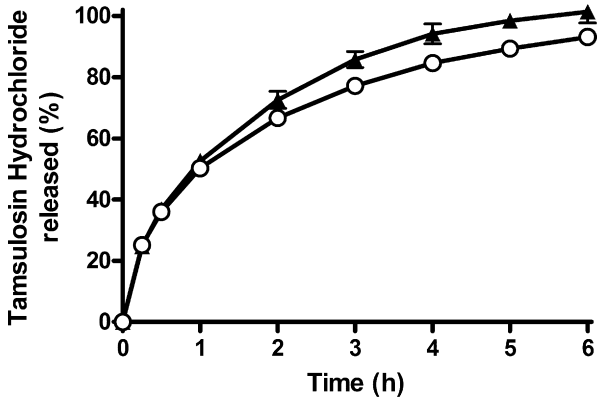

Fig. 5. *In vitro* release profiles of tamsulosin hydrochloride from Formulation 8 and Harnal® pellets in phosphate buffer at pH 7.2 for evaluating influence of enteric film coating process on *in vitro* drug release (mean ± SD, $n = 3$). ○: Formulation 8, and ▲: Harnal® pellets.

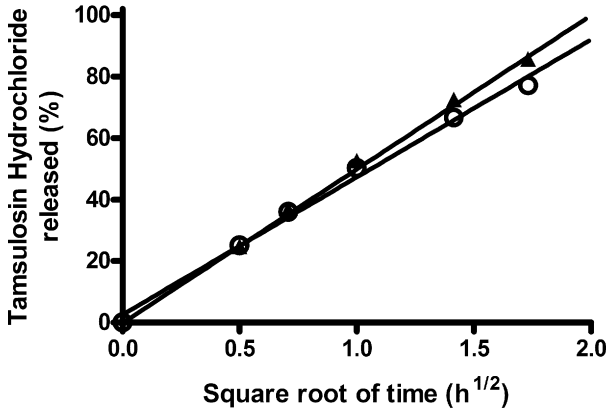

Fig. 6. Higuchi-type plot for *in vitro* release profiles of tamsulosin hydrochloride from Formulation 8 and Harnal® pellets. ○: Formulation 8, and ▲: Harnal® pellets.

Table 5
Pharmacokinetic parameters after oral administration of Formulation 8 and Harnal® pellets at 0.4 mg/animal to non-fasted dogs with famotidine (mean ± SD, $n = 6$).

Formulation	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ngh/mL)
Harnal pellets	15.1 ± 4.0	2.8 ± 1.1	79.7 ± 17.5
Formulation 8	16.2 ± 3.4	3.5 ± 0.9	80.1 ± 13.0

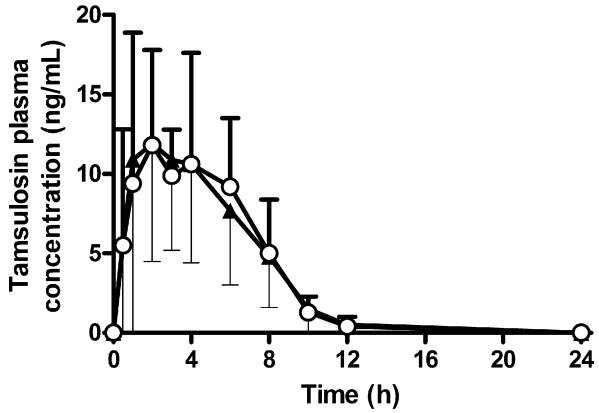

Fig. 7. Mean plasma concentration curves after oral administration of Formulation 8 and Harnal® pellets at 0.4 mg/animal to non-fasting dogs with famotidine (mean ± SD, $n = 6$). ○: Formulation 8, and ▲: Harnal® pellets.

absorption properties of F8 and Harnal® pellets are comparable.

Absorption kinetics after oral administration of F8 were evaluated using the deconvolution trapezoidal method (Chan et al., 1987):

$$It = \frac{Rt}{Wt} \tag{3}$$

where *It* is the input function (*in vivo* dissolution), *Rt* is the response function (plasma levels for the investigated microparticles), and *Wt* is the weighing function (plasma levels for aqueous solution). Since the weighing function was obtained from intravenous administration of 0.1 mg/kg of tamsulosin hydrochloride saline solution, the input function was an estimate of the *in vivo* absorption profile.

The *in vitro*/*in vivo* correlation for tamsulosin hydrochloride sustained-release microparticles was explored by comparing the *in vitro* drug release with *in vivo* drug absorption obtained from deconvolution. The absolute bioavailability after oral administration of F8 was calculated to be 29.7%, which was in close agreement with previously reported values of 29.7–42.0% in dogs (Matsushima et al., 1998). As the absolute bioavailability in human was approximately 100% (Hoogdalem et al., 1997), the *in vitro*/*in vivo* correlation was evaluated by considering 30% absolute bioavailability in dogs as 100% *in vivo* drug release. The result in Fig. 8 demonstrated linear correlation between *in vitro* drug release and *in vivo* drug release with coefficient of determination (R^2) of 0.9878. A slope of 1.16 with *x*-intercept of 29.0 up to 85% of *in vitro* drug release indicated near 1:1 relationship. Although a linear relationship between *in vitro* drug release and *in vivo* drug release was obtained, the *x*-intercept value differs from zero which suggests delayed *in vivo* initial absorption. This was attributed to gastric emptying time under fasted condition about 40–90 min (Sagara et al., 1992; Sagawa et al., 2009; Tsukamoto et al., 1999).

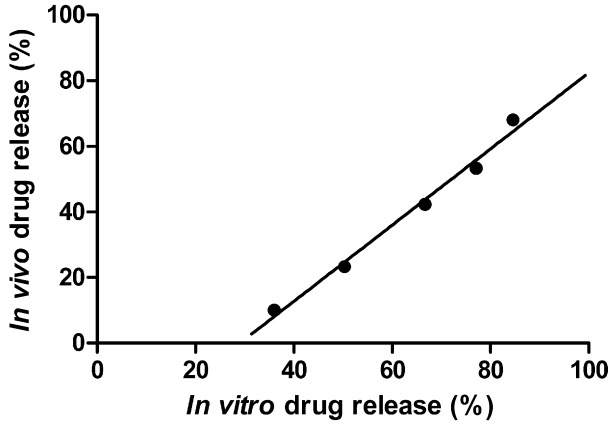

Fig. 8. Correlation between *in vitro* drug release and *in vivo* drug release profile of tamsulosin after oral administration of Formulation 8 calculated via the deconvolution method.

The enteric film used in this study was not optimized to acidic conditions. Future studies should examine correlation between *in vitro* drug release profiles and *in vivo* absorption profiles under acidic conditions. In addition compression force during tableting may also affect drug release profiles from microparticles in orally disintegrating tablets.

4. Conclusion

We prepared microparticles containing tamsulosin hydrochloride, and optimized composition for sustained-release, in single-step matrix coating process. The microparticles provided Fickian diffusion sustained-release of tamsulosin hydrochloride. Drug release profiles of microparticles and Harnal® pellets were similar. To produce a target diameter 200 μm, an optimum ratio of Aquacoat® and Eudragit® NE30D in the matrix was 9:1. The *in vivo* absorption properties from microparticles were comparable to Harnal® pellets, and there was a linear relationship between *in vitro* drug release and *in vivo* drug release. Further investigation of the effect of enteric film on response of microparticles and Harnal® pellets under acidic condition is required. The application of microparticle production methods to orally disintegrating tablets will require further optimization studies in the future.

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