Original Research Paper

Design and evaluation of an extended-release matrix tablet formulation; the combination of hypromellose acetate succinate and hydroxypropylcellulose

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ABSTRACT

The purpose of this study was to develop an extended-release (ER) matrix tablet that shows robust dissolution properties able to account for the variability of pH and mechanical stress in the GI tract using a combination of enteric polymer and hydrophilic polymer. Hypromellose acetate succinate (HPMCAS) and hydroxypropylcellulose (HPC) were selected as ER polymers for the ER matrix tablet (HPMCAS/HPC ER matrix tablet). Oxycodone hydrochloride was employed as a model drug. Dissolution properties of the HPMCAS/HPC ER matrix tablets were evaluated and were not affected by the pH of the test medium or paddle rotating speed. In a USP apparatus 3 (bio-relevant dissolution method), dissolution profiles of the HPMCAS/HPC ER matrix tablets containing oxycodone hydrochloride were similar to that of the reference product (OxyContin). Moreover, *in vivo* performance after oral administration of the HPMCAS/HPC ER matrix tablets to humans was simulated by GastroPlus based on dissolution profiles from the USP apparatus 3. The plasma concentration-time profile simulated was similar to that of the reference product. These results suggest that the combination of HPMCAS and HPC shows a robust dissolution profile against pH and paddle rotating speed and indicates the appropriate extended-release profile in humans.

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1.   Introduction

Extended-release (ER) dosage forms undergo transit in the gastrointestinal (GI) tract after oral administration and the drug is dissolved by degrees. The drug dissolution rate of oral ER dosage form is sometimes affected by composition of GI fluids (pH and bile salts) and the hydrodynamic conditions in the GI tract [1,2]. For oral ER dosage forms, the effects of agitation intensity and mechanical impact force expected in the GI tract, such as contraction or peristalsis, have been investigated [3,4]. Also, it is well known that both physical pH and motility in the GI tract are highly variable among individuals [5–7]. Therefore, the drug release of oral ER dosage forms is required to show robustness accounting for the variability of pH and mechanical stress in the GI tract [8]. It is also important to avoid dose dumping after oral administration of ER dosage forms, especially for drugs which possess the characteristics of a higher solubility, higher dose or a fatal side effect [9,10]. Furthermore, an alcohol-induced dose dumping effect in oral ER dosage forms has gained increased attention in recent years [11,12]. Therefore, the understanding of *in vitro* drug release properties is of great importance to the development of oral ER dosage forms when considering the *in vivo* performance.

Recently, several attempts have been made to develop an ER matrix tablet that shows robust dissolution properties [9,10]. For example, the AcroContin delivery system, which is applied to OxyContin (oxycodone hydrochloride ER matrix tablet), is a single unit system basically consisting of two hydrophobic polymers (ammonio methacrylate copolymers) and shows robust dissolution properties for pH in the GI tract [13,14]. In some articles evaluating ER matrix tablets, a single polymer or a combination of several polymers was used to not only control the drug release but also avoid the effects of mechanical stress [15]. In this study we have focused attention on the characteristics of an enteric polymer and how its pH dependent solubility may overcome mechanical stress in the stomach (acidic condition) by maintenance of the tablet shape of the ER matrix tablet.

Hypromellose acetate succinate (HPMCAS), the enteric polymer, is essentially insoluble in medium under pH 5 due to the presence of a relatively hydrophobic methyl and acetate group. HPMCAS is usually employed as an enteric coating material for sustained release formulations and applied with a solid dispersion technology [16]. There are some studies in which HPMCAS has been applied to ER matrix tablets [17,18]. However, these studies have not focused on robust dissolution properties in the GI tract of humans.

In this study, HPMCAS and HPC (a hydrophilic polymer) were selected as ER polymers for an ER matrix tablet. ER matrix tablets with a combination of HPMCAS and HPC were prepared (HPMCAS/HPC ER matrix tablet), and the characterization of dissolution properties in several test conditions was evaluated, including an estimation indicating robust dissolution properties and dose-dumping accounting for the variability of pH, mechanical stress in the GI tract, and alcohol-induced effect. Moreover, *in vivo* performance after oral administration of the HPMCAS/HPC ER matrix tablets to humans was simulated by GastroPlus based on dissolution profiles using the USP apparatus 3.

2.   Materials and methods

2.1.   Materials

Oxycodone hydrochloride, a water soluble drug, was obtained from Daiichi Sankyo Propharma Co., Ltd. (Japan). Hydroxypropylcellulose (HPC-H; fine particle grade, 1000 mPas to 4000 mPas, HPC-SL; 150 mPas to 400 mPas) was purchased from Nippon Soda Co., Ltd. (Japan). Hypromellose acetate succinate (Shin-Etsu AQOAT; LF) was purchased from Shin-Etsu Chemical Co., Ltd. (Japan). D-Mannitol was purchased from Merck Millipore Corporation (Germany). Magnesium stearate (Hyqual, vegetable source) was purchased from Mallinckrodt Pharmaceuticals (USA). All other chemicals and solvents were of reagent grade. The reference product, OxyContin, was purchased from Japanese market purchasing (Shionogi & Co., Ltd., Japan).

2.2.   Methods

2.2.1.   Preparation of the ER matrix tablets
ER matrix tablets (Rp.1 to Rp. 7 in Table 1) were manufactured as follows. The respective powders were mixed thoroughly with a pestle and mortar. Then the mixtures were weighed and compressed using a single-punch tableting machine (hydraulic pump, Riken power model P-1B, Riken Seiki Co. Ltd., Japan) equipped with a punch and die (diameter of 6 or 7 mm) and operated at a compression force of 1 kN.

2.2.2.   In vitro dissolution test (USP apparatus 2)
In vitro dissolution studies were carried out using the USP apparatus 2 (paddle method, NTR-6100A, Toyama Sangyo Co., Ltd.,

Table 1 – Components and compositions for ER matrix tablets.							
Components	Compositions (%/tablet)						
	Rp. 1	Rp. 2	Rp. 3	Rp. 4	Rp. 5	Rp. 6	Rp. 7
Oxycodone HCl	8	8	8	8	8	11	5
HPMCAS-LF	30	–	30	43	26	26	26
HPC-H	–	30	30	20	37	37	37
HPC-SL	3	3	3	3	3	3	3
D-mannitol	58	58	28	25	25	22	28
Mg stearate	1	1	1	1	1	1	1
Total (mg)	150	150	150	150	150	100	200

Table 2 – pH of test media, media volume and residence time for dissolution test using USP apparatus 3 in this study.

pH of test media	Media volume (ml)	Residence time (h)
pH 1.2	250	1
pH 6.2	250	1.25
pH 6.5	250	1.25
pH 6.9	250	1.25
pH 6.2	180	19.25

Table 3 – Summary of parameters used for human PK simulation of oxycodone by GastroPlus.

Input parameters	Input value
Molecular weight	315.37
logD (pH 7.4)	1.44
Solubility (mg/mL) (pH 9.86)[a]	1.68
pKa [22]	8
Dose (mg)	10
Dose volume (ml)	250
Effective permeability (Human) (cm/s $\times 10 \wedge 4$)[b]	4.27
Body weight (kg)	70
Vc (l/kg)[c]	1.18
k12 (1/h)[c]	4.28
k21 (1/h)[c]	2.28
V_{max} (mg/l) [c]	8.29
CLr (l/h/kg) [23]	0.07

[a] Predicted by ADMET Predictor (ver. 6.0).
[b] Optimized by fitting to plasma concentration after oral administration of solution in GastroPlus.
[c] Optimized by PKPlus fitting to plasma concentration after intravenous administration in GastroPlus.

Japan) in 900 ml of dissolution medium at 37 ± 0.5 °C (n = 3 to 6). For this study, the dissolution mediums were the first fluid for disintegration test (pH 1.2) and the second fluid for disintegration test (pH 6.8), as noted in the Pharmacopoeia of Japan (JP). The paddle rotating speed was set at either 50, 100 or 200 rotations per min (rpm). In prior studies, Sako et al. examined the effect of paddle rotating speed on drug dissolution to assess whether or not *in vitro* tests correlated with *in vivo* conditions [19,20]. And in the Japanese guideline for bioequivalence studies, several dissolution conditions of pH (1.2 to 6.8) and rotating speeds (paddle method, 50 rpm to 200 rpm) are required variables used to assess the drug dissolutions in severe conditions of the GI tract [21]. Therefore, we selected the above dissolution conditions to evaluate the ER matrix tablets against mechanical strength and changing pH. Samples of 5 ml were withdrawn at appropriate dissolution timepoints and the sample volumes were replaced with the equal amount of blank medium. The release percent of oxycodone was analyzed by HPLC (Alliance2690, Waters Corporation, USA).

2.2.3. In vitro *dissolution test (USP apparatus 3)*
The dissolution experiments in the USP apparatus 3 (reciprocating cylinder, BIO-DIS, Varian, USA) were performed at a reciprocation rate of 10 dips/min using a cylinder with bottom mesh screens of 405 μm mesh size at 37 ± 0.5 °C (n = 3 to 6). Samples were withdrawn at appropriate dissolution timepoints and analyzed by HPLC. Other set conditions for the dissolution test are summarized in Table 2.

2.2.4. Analysis of oxycodone release by HPLC
Samples were filtered through 0.45 μm membrane filters (Ekicrodisk, 25 mm, Pall Corporation, USA). Samples of 5 μl were injected into a column (3.0 mm ID × 50 mm, 2.2 μm, Shimpack XR-ODS, Shimadzu Corporation, Japan) held at 50 °C and eluted with a mixture of pH 2.5 buffer solution and methanol (37:13) at a flow rate of 0.5 ml/min. Quantitation was based on peak area measurement at λ = 230 nm.

2.2.5. Human PK simulations of oxycodone by GastroPlus using in vitro *dissolution profiles of USP apparatus 3*
To simulate the absorption process of ER matrix tablets containing oxycodone hydrochloride, a human PK model for oxycodone was constructed using GastroPlus (version 9.0, Simulations Plus, Inc., USA), in which the gastrointestinal absorption was described by an advanced compartmental absorption and transit (ACAT) model. The physicochemical properties of oxycodone hydrochloride (such as diffusion coefficient, pKa and solubility) input into GastroPlus are shown in Table 3. PK pa-

rameters of oxycodone, except for renal clearance (CLr) and effective permeability (P$_{eff}$), were estimated by fitting the 2-compartment model to the plasma concentration-time profile following intravenous infusion (10 mg/8 h) and bolus (2 mg and 5 mg) administration using the PKPlus module of GastroPlus. The CLr was inputted as the reported value into the GastroPlus model. The P$_{eff}$ value was estimated by fitting the model to the plasma concentration-time profile following oral administration of oxycodone in solution (20 mg) under fasted conditions. Simulation of oxycodone plasma concentration-time profiles was conducted for a two 10 mg ER tablets dosing (20 mg oxycodone). The *in vitro* dissolution profile of the ER matrix tablets from the USP apparatus 3 was used for the human PK simulation.

2.2.6. Calculation of f$_2$ value between ER matrix tablet and reference products
The following equation defines f$_2$. T$_t$ and R$_t$ show the average dissolutions of the test and reference products at the time point (t), respectively, and n is the number of time points at which the average dissolutions are compared.

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2}} \right]$$

3. Results and discussion

3.1. In vitro *dissolution properties of ER matrix tablets: USP apparatus 2 (paddle method)*

Fig. 1 shows the dissolution profiles of three kinds of matrix formulations (HPMCAS-based matrix tablet, HPC-based matrix tablet and HPMCAS/HPC ER matrix tablet, see Table 1) in acidic and neutral media using the USP apparatus 2. Effects of medium

A

Fig. 2 – A picture of remaining tablet after 7h dissolution test in test medium (pH 1.2) using USP apparatus 2 (200 rpm). (A) Rp. 1: HPMCAS-based matrix tablet, (B) Rp. 3: HPMCAS/HPC ER matrix tablet.
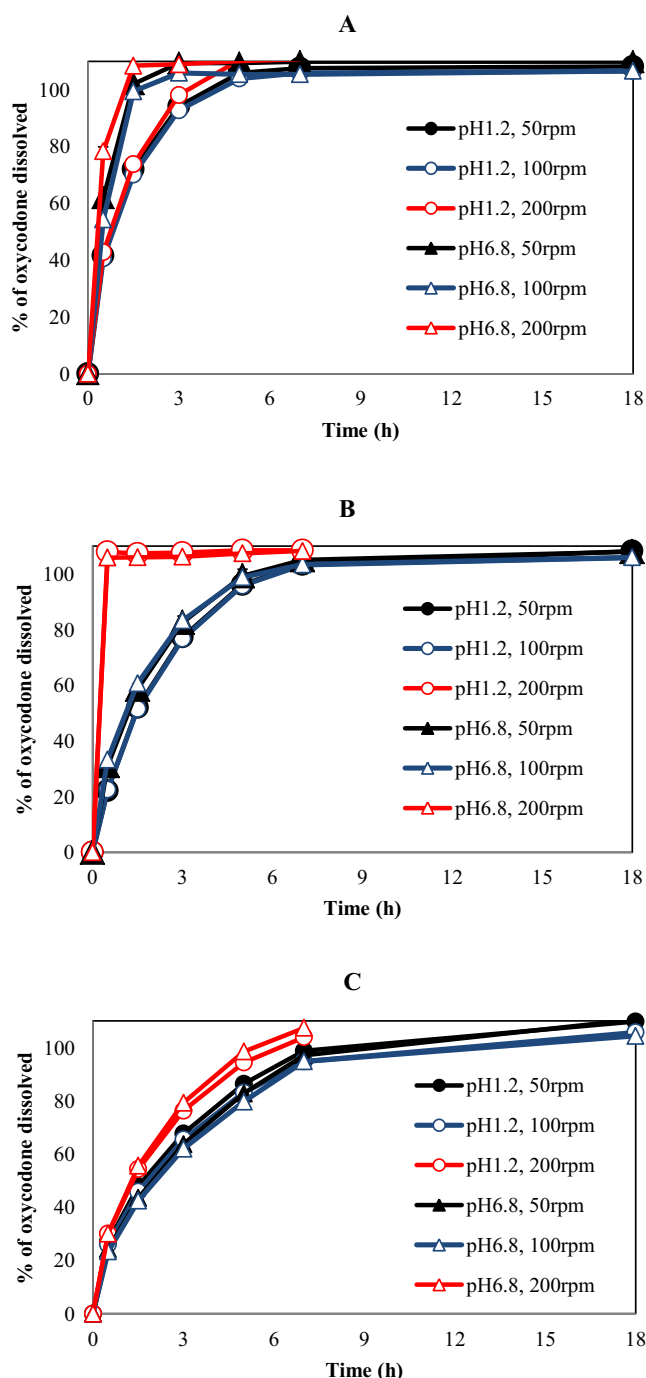
B

C

Fig. 1 – Dissolution profiles of oxycodone from ER matrix tablets in test media using USP apparatus 2. (A) Rp.1: HPMCAS-base matrix tablet, (B) Rp.2: HPC-based matrix tablet, (C) Rp.3: HPMCAS/HPC ER matrix tablet.

pH and paddle rotating speed on drug dissolution were examined to confirm the effects of pH and mechanical stress in the GI tract.

In the case of the HPMCAS-based matrix tablets (Rp. 1), it was observed that oxycodone hydrochloride was released on a pH-dependent basis due to the enteric properties of HPMCAS, and the drug release at pH 6.8 was faster compared with the

release at pH 1.2 (Fig. 1A). Paddle rotating speed did not affect the drug release from the HPMCAS-based matrix tablet. The HPMCAS-based matrix tablet could keep its tablet shape after dissolution tests at pH 1.2 at a 200 rpm paddle rotating speed, even after 7 h (Fig. 2A).

In the case of the HPC-based matrix tablets (Rp. 2), the drug release was not affected by the pH of the test medium, but the dissolution rate was increased with the faster paddle rotating speed (Fig. 1B). The drug release at the paddle rotating speed of 200 rpm was very rapid in both the acidic and neutral media, and more than 90% of the dose was released within 30 min. The HPC-based matrix tablet could not keep its tablet shape and disintegrated in the vessels within 30 min at a 200 rpm paddle rotating speed.

On the other hand, in the case of the HPMCAS/HPC ER matrix tablets (Rp. 3), the drug release was not affected by the pH of the test medium, and was hardly affected by the paddle rotating speed (Fig. 1C). The HPMCAS/HPC ER matrix tablet could keep its tablet shape after dissolution tests at pH 1.2 at 200 rpm even if after 7 h, and the tablet was swollen compared to the HPMCAS-based matrix tablet due to additional hydrophilic polymer (HPC) (Fig. 2B). For the formulations with different ratios of HPMCAS/HPC (Rp. 4 [HPMCAS/HPC (2:1)], Rp. 5 [HPMCAS/HPC (2:3)]), the drug release was not affected by the pH of the test medium or paddle rotating speed in both acidic and neutral mediums (Fig. 3, Table 4). The dissolution speed was affected by the amount of extended-release polymer (HPMCAS+HPC) versus oxycodone (Rp. 7 > Rp. 5 > Rp 6). To examine the drug release mechanism, the kinetics of the drug released using the USP apparatus 2 (50 rpm) were analyzed by applying the empirical exponential equation ($M_t/M_\infty = kt^n$) (Table 4). For matrix tablets, an n value of ~0.5 indicates diffusion control and an n value of ~1.0 indicates erosion control. The n values of the HPMCAS/HPC ER matrix tablet (Rp. 3 to Rp. 7) were found to be between 0.50 and 0.65 in the acidic and neutral media. These results indicated that the drug release from the HPMCAS/HPC ER matrix tablet was classified as a combination of diffusion and erosion control. And in terms of the ratio of HPMCAS and HPC, n values of the HPMCAS/HPC (2:1) ER matrix tablet (Rp. 4) were more close to 0.5 (diffusion control) than that of the HPMCAS/HPC (2:3) ER matrix tablet (Rp. 5 to Rp. 7) in each of the mediums. This indicates that HPMCAS, the hydrophobic polymer, is responsible for diffusion control and HPC, the hydrophilic polymer, is responsible for erosion control.
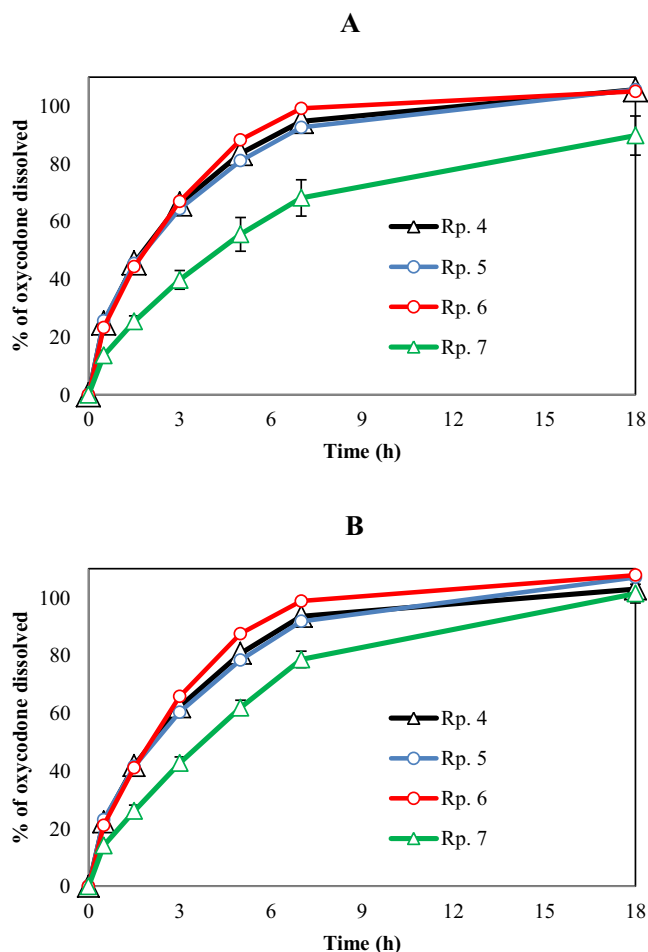
A

B

Fig. 3 – Dissolution profiles of oxycodone from the HPMCAS/HPC ER matrix tablets in test media using USP apparatus 2. (A) pH 1.2, (B) pH 6.8.

3.2. In vitro dissolution profiles of the HPMCAS/HPC ER matrix tablets: compared with the reference product (OxyContin): USP apparatus 3 (reciprocating cylinder apparatus)

Fig. 4 shows the dissolution profiles of HPMCAS/HPC ER matrix tablets (Rp. 5 to Rp. 7) and the reference product, OxyContin, using USP apparatus 3. The dissolution condition of apparatus 3 was set using examples from the physiology condition
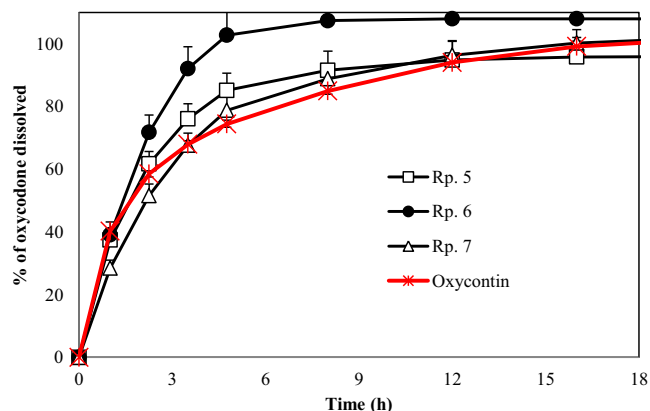

Fig. 4 – Dissolution profiles of oxycodone from the HPMCAS/HPC ER matrix tablets and OxyContin using USP apparatus 3.

(Human–physiological-fasted) of GastroPlus as an *in vivo* dissolution condition. Regarding the HPMCAS/HPC ER matrix tablets, the dissolution rate decreased with the increase of the amount of granules for extended release (Fig. 4). Therefore, the dissolution rate of the HPMCAS/HPC ER matrix tablet can be controlled and adjusted by the amounts of HPMCAS and HPC. Compared with the reference product, Rp. 5 and Rp. 7 showed similar dissolution profiles (Rp. 5; f2 = 55, Rp. 7; f2 = 62) and especially the dissolution profiles of Rp. 5 and Rp. 7 were shown to be close to that of the reference product in the early phase and the late phase, respectively. Regarding the tablet shape using USP apparatus 3, the HPMCAS/HPC ER matrix tablet could keep its tablet shape in the mimicked gastric condition and finally dissolved in the neutral medium. On the other hand, OxyContin kept its tablet shape until the last point of observation.

3.3. Simulation of PK parameter after oral administration of the HPMCAS/HPC ER matrix tablet to humans by GastroPlus

The absorptions simulated by GastroPlus for the HPMCAS/HPC ER matrix tablets and the reference product are shown in Fig. 5. For this simulation, dissolution profiles shown in Fig. 4 were used as *in vivo* dissolution profiles. Regarding the reference product, OxyContin, Mandema et al. reported the pharmacokinetic data of two 10 mg OxyContin single dosing (C_{max}: 18.6 ± 6.1 ng/ml, AUC_{0-t}:

Table 4 – Release exponent (n) value of oxycodone and the effect of paddle rotating speed from matrices calculated from dissolution data.

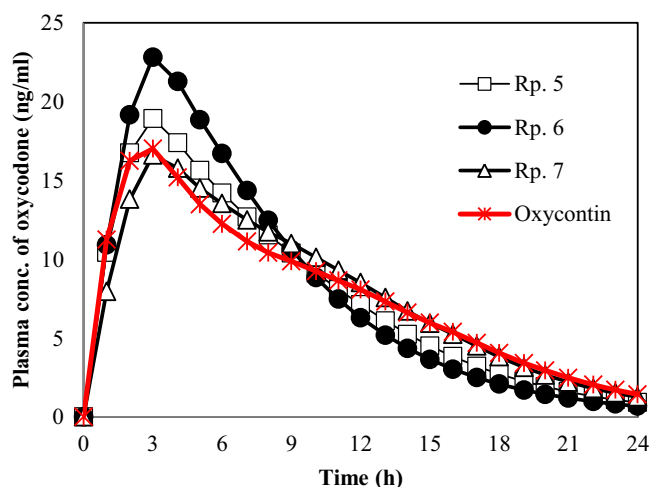| Formulations		n Value		Effect of paddle rotation speed ($D_{1.5h, 200\ rpm}/D_{1.5h, 50\ rpm}$)	
		pH 1.2	pH 6.8	pH 1.2	pH 6.8
Rp. 1	HPMCAS	0.46 ± 0.01	–	1.03	–
Rp. 2	HPC	0.71 ± 0.03	0.55 ± 0.01	2.06	1.81
Rp. 3	HPMCAS/HPC (1:1)	0.51 ± 0.01	0.54 ± 0.01	1.13	1.28
Rp. 4	HPMCAS/HPC (2:1)	0.50 ± 0.01	0.53 ± 0.01	1.15	1.24
Rp. 5	HPMCAS/HPC (2:3)	0.54 ± 0.01	0.56 ± 0.01	1.14	1.33
Rp. 6	HPMCAS/HPC (2:3)	0.64 ± 0.03	0.65 ± 0.03	1.25	1.24
Rp. 7	HPMCAS/HPC (2:3)	0.62 ± 0.04	0.65 ± 0.05	1.26	1.02

Fig. 5 – Simulation of oxycodone plasma concentration-time profiles.

199.7 ± 65.3 ng-h/ml, T_{max}: 2.62 ± 1.07 h) [24]. The simulated PK parameters after oral administration of OxyContin were estimated accurately (Table 5). The plasma concentration-time profiles simulated after oral fasted administration of Rp. 5 and Rp. 7 were more similar to that of the reference product than compared to each simulation curve of Rp. 6, and especially Rp. 5 was acceptable from the viewpoint of the absorption behavior of the upper small intestine (up until 3 h).

Based on the simulated results, the *in vivo* performance of the HPMCAS/HPC ER matrix tablet was the same as the reference product, OxyContin. In fact, the HPMCAS/HPC ER matrix tablet (Rp. 5) was bioequivalent to OxyContin under fasted and fed conditions in a human clinical pharmacokinetic study [25]. In this clinical study, the ratios for C_{max} and AUC_{last} under the fasted condition were 112% and 98.4%, respectively. On the other hand, according to the simulated result, the ratios for C_{max} and AUC_{last} were 110% and 98.3%, respectively; these simulated results were similar to the *in vivo* study. OxyContin is a matrix tablet to which the AcroContin delivery system has been applied. The AcroContin delivery system is an improvement upon the Contin System, and is well-known to show pH-independent drug release, and allows for uniform release throughout the GI tract [13,14]. Our results estimated that the HPMCAS/HPC ER matrix tablet could control drug release appropriately in the human GI tract without dose dumping, and showed an ideal PK profile comparable to OxyContin.

Based on some reports, from the viewpoint of prediction of physical variables such as pH and mechanical stress, it is difficult to correlate the entire *in vivo* release with the *in vitro* release determined only by a single method at a stirring rate [26]. In this study USP apparatus 3 was used as a bio-relevant dissolution method for selection of a candidate formulation with consideration for the *in vivo* performance. To simulate the absorption process of ER matrix tablets, a human PK model for oxycodone was constructed using physiologically based pharmacokinetic (PBPK) modeling in GastroPlus. As described above in this section, the candidate formulation of the HPMCAS/HPC ER matrix tablet including oxycodone could show *in vivo* performance comparable to OxyContin. Thus the methodology for the combination of the dissolution tests of the USP apparatus 3 and the PBPK modeling in GastroPlus is applicable for prediction of *in vivo* performance of a candidate formulation [27–29].

3.4. *In vitro dissolution profiles of the HPMCAS/HPC ER matrix tablet: USP apparatus 2 (paddle method), in 40% ethanol*

Oxycodone hydrochloride, used in this study, is one of the opioid drugs listed in schedule II of the Drug Enforcement Administration (DEA) [30]. In 2005 the FDA withdrew a hydromorphone modified release drug formulation (hydromorphone: schedule II in DEA), Palladone, from the US market, since taking it together with alcohol fatally increased the peak plasma concentrations of hydromorphone [11]. Subsequently, alcohol-induced dose dumping effects in control release dosage forms have received increased attention, especially for opioid drugs [10]. In the case of Palladone, the drug release rate with 40% ethanol increased (about 1.5 folds, D_{2h}) compared to without ethanol [31]. Dissolution profiles of the HPMCAS/HPC ER matrix tablet (Rp. 5) with or without ethanol in test medium are shown in Fig. 6. For the HPMCAS/HPC ER matrix tablet (Rp. 5) alcohol-induced dose dumping was not confirmed, and the dissolution profile of the HPMCAS/HPC ER matrix tablet at pH 1.2 with 40%

Table 5 – Human PK parameters for oxycodone simulated by GastroPlus and clinical data from Mandema et al.

Formulations		C_{max} (ng/ml): (Ratio[a], %)	AUC $_{0-t}$ (ng-h/ml): (Ratio*, %)	T_{max} (h)
OxyContin	Simulated data	17.2	190.5	2.55
	Clinical data[b]	18.6 ± 6.1	199.7 ± 65.3	2.62 ± 1.07
	Prediction error[c]	8%	5%	3%
Rp. 5	Simulated data	19.0	187.2	3.27
		(110%)	(98.3%)	
Rp. 6	Simulated data	23.2	197.9	3.46
		(135%)	(104%)	
Rp. 7	Simulated data	17.0	197.7	3.48
		(98.8%)	(104%)	

[a] Calculated as following equation.
Ratio of C_{max}: (C_{max} of HPMCAS/HPC ER matrix tablet)/(C_{max} of OxyContin) × 100.
Ratio of AUC: (AUC $_{0-t}$ of HPMCAS/HPC ER matrix tablet)/(AUC $_{0-t}$ of OxyContin) × 100.
[b] Clinical data from Mandema et al. [25].
[c] Prediction error (%) (OxyContin) = |Observed value − Simulated value|/Observed value.
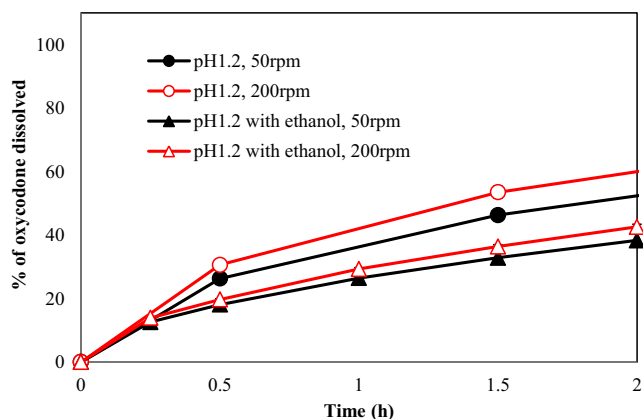
Fig. 6 – Dissolution profiles of oxycodone from the HPMCAS/HPC ER matrix tablets in test media (pH 1.2 with or without ethanol) using USP apparatus 2.

ethanol was shown to be slower than at pH 1.2 without ethanol (about 0.8 folds, D_{2h}). In the case of OxyContin, drug release was also not affected by addition of 40% ethanol (data not shown). Alcohol-induced dose dumping is influenced by physico-chemical factors (drug solubility, wettability and hardness of dosage form) and characteristics of the matrix polymer [32,33]. Oxycodone hydrochloride is a hydrophilic drug and insoluble in ethanol. Regarding the characteristics of polymers, HPMCAS is insoluble, but HPC is soluble in ethanol. Therefore, the characteristics of HPMCAS and its water solubility prove advantageous in the prevention of alcohol-induced dose dumping from the HPMCAS/HPC ER matrix tablet.

3.5.   The drug release mechanism from the HPMCAS/HPC ER matrix tablet

From the above results, the drug release from the HPMCAS/HPC ER matrix tablet in the GI tract was estimated as shown in Fig. 7. Inside of the tablet, drug substance, HPMCAS and HPC-H in granules for extended release and filler formed the matrix structure.

In the stomach (Fig. 7A), HPMCAS in the HPMCAS/HPC ER matrix tablet is insoluble due to its enteric property in the acidic region. HPC swells when it borders on water, and forms a gel layer around the tablet. Tiwari et al. reported that incorporation of ethylcellulose (hydrophobic polymer) in the hydrophilic matrix was found to control the drug release to some extent, which could be attributed to the reduced entry of solvent into the matrix due to the presence of the hydrophobic matrix [34]. In this study HPMCAS, the hydrophobic polymer, is responsible for diffusion control and HPC, the hydrophilic polymer, is responsible for erosion control in terms of the kinetics of drug release. Also, the HPMCAS/HPC ER matrix tablet expressed a sufficient strength against mechanical stress and the matrix of diffusion barrier and gel formed allowed it to keep its tablet shape in the acidic media. Thus, the tablet did not disintegrate and the tablet shape did not change markedly.

On the other hand, on and after the small intestine (Fig. 7B), HPMCAS in the HPMCAS/HPC ER matrix tablet is soluble due to its enteric property. HPC, a pH independent polymer, forms a gel layer around the tablet, the same as in the acidic region. Streubel et al. explained that the drug of a matrix tablet containing HPMC and HPMCAS is released by diffusion through the swollen polymer network [18]. So, it is estimated that in neutral medium HPMCAS and HPC dissolve by degrees and create a polymer network by HPC's filling of the pores created by HPMCAS. In regard to the kinetics of drug release, the HPMCAS/HPC ER matrix tablets were classified as a combination of diffusion and erosion control (n values were 0.50 to 0.65). Thus HPMCAS is dissolved by degrees due to the pH of the intestinal juice, ER dissolution profiles are provided, and drug is released by diffusion through the erosible matrix of HPC and dissolving HPMCAS in the lower GI tract.
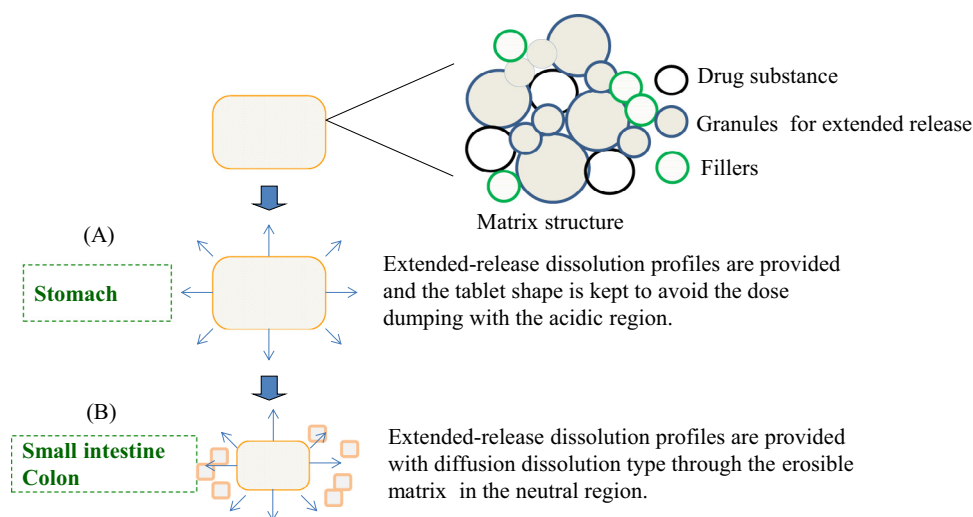

Fig. 7 – The schematic description of drug release from the HPMCAS/HPC ER matrix tablet in the GI tract. (A) The mechanism in stomach, (B) the mechanism in and after small intestine.

4.   Conclusion

An ER matrix tablet with a combination of HPMCAS and HPC was characterized with regard to its dissolution properties. The dissolution profile from the HPMCAS/HPC ER matrix tablet could be controlled and showed a constant extended-release profile in various test media. Also, the HPMCAS/HPC ER matrix tablet was evaluated to have sufficient strength against mechanical stress. Regarding its *in vivo* performance, it is estimated that the HPMCAS/HPC ER matrix tablet is similar to the reference product based on the simulation of the PK profile after oral administration to humans. These results suggest that the combination of HPMCAS and HPC showed robust dissolution against pH and paddle rotating speed, and therefore indicates an appropriate extended-release profile in humans.

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