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Research paper

Release characteristics and in vitro–in vivo correlation of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture via osmotic pressure and swelling

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Abstract

This study attempted to characterize the influence of core and coating formulations on the release profiles to establish in vitro/in vivo correlations of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture based on three core tablet formulations (A-core: HPMC 50+4000 cps, B-core: E10M, and C-core: K100M) coated with various thicknesses of a semipermeable ethylcellulose membrane plasticized with HPMC 606 (Pharmacoat 606) at different ratios with/without adding various amounts of water to dissolve it in the coating solution. Drug release behaviors were investigated using apparatus II in four media of pH 1.2 solution, pH 6.8 buffer, deionized water, and a NaCl solution rotated at 75, 100, and 150 rpm. Pilot studies of the in vivo pharmacokinetics were conducted as well for comparison with the in vitro results. Results demonstrated that drug release from the three kinds of core tablets in deionized water increased with an increasing stirring rate, and decreased with an increasing viscosity grade of HPMC used in the core formulations. A significant promotion of drug release from core tablets was observed for the three levels of NaCl media in comparison with that in deionized water. Results further demonstrated that a slightly slower release rate in pH 1.2 solution and a faster release rate in pH 6.8 buffer than that in deionized water were observed for the A-core and B-core tablets, with the former being slower than the latter. However, similar release rates in the three kinds of media were observed for C-core tablets, but they were slower than those for the A- and B-core tablets. Dissolution of coated tablets showed that the controlling membrane was ruptured by osmotic pressure and swelling which activated drug release with a lag time. The lag time was not influenced by the pH value of the release medium or by the rotation speeds. The lag time increased with a higher coating level, but decreased with the addition of the hydrophilic plasticizer, Pharmacoat 606, and of the water amount in the coating solution. The lag time also increased with a higher concentration of NaCl in the medium. The release rate after the lag time was determined by the extent of retardation of gelation of HPMC in the core tablet based on the ionic strength of the medium. Results of the three pilot crossover studies for the exemplified pulsatile systems indicated that the lag time for the in vivo plasma profile was well correlated with that determined from the in vitro release profile in pH 1.2 solution and the in vivo release rate was better reflected by that performed in pH 6.8 buffer.

Keywords: Ethylcellulose; Hydroxypropylmethylcellulose (HPMC); Pulsatile Release; Membrane Rupture; Lag time

1. Introduction

The concepts of the chronopharmacokinetics and chronotherapy of drugs have been extensively utilized in clinical therapy for improving drug efficacy and preventing side effects and tolerance of drugs [1–3]. In order to emulate

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innate circadian rhythms, a reasonable and generally accepted rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than continuous delivery at predetermined times and/or sites following oral administration [4–7]. In general, pulsatile drug delivery systems can be classified into time-controlled and site-specific delivery systems. Drug release from the former group is primarily activated by plug ejection or a barrier coating that dissolves, erodes, or ruptures after a certain lag time [8–10], while release from the latter group is primarily regulated by the biological environment in the gastrointestinal tract such as by the pH or the presence of enzymes [11,12].

Based on the plug ejection mechanism, the Pulsicap device was designed to release drug formulations by ejecting a swollen hydrogel plug from the capsule at a predetermined time after ingestion [13]. This technology was further simplified by replacing sliding hydrogels with an erodible tablet [14]. Sangalli et al. reported that Chronotopic™ designed to attain delayed and/or time-dependent colon-specific release consists of a drug-loaded core coated with a swellable hydrophilic polymer (HPMC E50), which is responsible for the lag phase preceding the onset of release [11]. The lag time and the drug release rate for a tablet-in-capsule pulsatile drug delivery system can be modulated by changing the formulation of the plug and the fill material, and immediate drug release after a designated lag time can be obtained if the plug is pushed out by the CO_2 gas generated by the interaction of $NaHCO_3$ and citric acid [15].

Coating with a high viscosity grade HPMC (100,000 cps) follows the erosion mechanisms, and a time-controlled release tablet with a designated lag time can be achieved depending on the erosion rate which is controlled by coating conditions such as the HPMC concentration, ethanol/water ratio as the coating solvent, the coating level, and the swelling (mixing) time of the coating solution [16]. Similarly, the start of drug release from dry-coated tablets with water-soluble gel-forming and swelling

Table 1
Pharmaceutical compositions of A-, B-, C-core tablets with a semipermeable ethylcellulose (EC) membrane coating

Formula	Inner core			Coating layer			Initial rate (%/h) (Lag time, h) In Deionized water
	HPMC 50 cps	HPMC 4000 cps	HPMC E10M	HPMC K100M	EC:HPMC 606	Coating level (%)	
Plain core (A)	20	20			—	—	32.5 ± 3.1 (0.0 ± 0.0)
A1.8E1H-a	20	20			1.8:1	2.7	14.9 ± 1.2 (2.0 ± 0.2)
A1.8E1H-b	20	20			1.8:1	3.2	11.5 ± 3.7 (2.6 ± 0.8)
A1.8E1H-c	20	20			1.8:1	3.6	8.0 ± 0.4 (2.7 ± 0.2)
Plain core (B)			40		—	—	27.7 ± 2.5 (0.0 ± 0.0)
B1.8E1H-a			40		1.8:1	2.4	7.8 ± 1.4 (0.5 ± 0.3*)
B1.8E1H-b			40		1.8:1	3.1	9.6 ± 0.6 (1.4 ± 0.2*)
B1.8E1H-c			40		1.8:1	3.6	6.6 ± 1.1 (2.8 ± 0.1*)
B1.5E1H-a			40		1.5:1	4.3	5.7 ± 2.3 (4.9 ± 0.1§)
B1.5E1H-b			40		1.5:1	6.4	4.0 ± 0.4 (7.6 ± 0.3§)
B1.5E1H-c			40		1.5:1	8.5	4.2 ± 0.2 (10.9 ± 0.6§)
B1.5E1H-d			40		1.5:1	10.6	4.0 ± 0.1 (13.2 ± 1.0§)
B1.5E1H-3a			40		1.5:1[a]	4.0	10.6 ± 2.4 (1.3 ± 0.1)
B1.5E1H-3b			40		1.5:1[a]	6.0	9.5 ± 2.1 (1.5 ± 0.1)
B1.5E1H-3c			40		1.5:1[a]	8.0	6.3 ± 1.1 (1.7 ± 0.2)
B1.5E1H-5a			40		1.5:1[b]	4.0	8.7 ± 1.3 (1.2 ± 0.2)
B1.5E1H-5b			40		1.5:1[b]	6.0	9.3 ± 3.3 (1.4 ± 0.2)
B1.5E1H-5c			40		1.5:1[b]	8.0	8.0 ± 1.4 (1.5 ± 0.2)
B1.5E1H-7a			40		1.5:1[c]	2.0	10.3 ± 1.6 (0.2 ± 0.2)
B1.5E1H-7b			40		1.5:1[c]	4.0	9.3 ± 1.4 (0.3 ± 0.03)
B1.5E1H-7c			40		1.5:1[c]	5.6	6.4 ± 1.2 (0.3 ± 0.1)
B1.5E1H-7d			40		1.5:1[c]	8.0	6.0 ± 0.8 (0.3 ± 0.1)
B1E1H-a			40		1:1	4.3	6.5 ± 2.3 (1.8 ± 0.2)
B1E1H-b			40		1:1	6.4	7.1 ± 1.0 (2.1 ± 0.1)
B1E1H-c			40		1:1	8.5	5.6 ± 1.4 (2.3 ± 0.3)
B1E1.5H-a			40		1:1.5	4.0	16.5 ± 0.8 (0.4 ± 0.1)
B1E1.5H-b			40		1:1.5	6.0	12.8 ± 1.2 (0.7 ± 0.1)
B1E1.5H-c			40		1:1.5	8.0	11.8 ± 2.2 (0.9 ± 0.1)
Plain core (C)				40	—	—	18.1 ± 2.1 (0.0 ± 0.0)
C1E1H-a				40	1:1	4.0	3.8 ± 1.0 (1.2 ± 0.1¶)
C1E1H-b				40	1:1	6.0	3.5 ± 0.5 (2.6 ± 0.1¶)
C1E1H-c				40	1:1	8.0	7.3 ± 0.7 (3.7 ± 0.3¶)

[a] Addition of 3%.
[b] Addition of 5%.
[c] Addition of 7% distilled water to the coating solution.
*,§,¶ Statistically significant linear correlation between lag time and coating level ($p < 0.05$).

materials such as HPC [17], HPMC [18], HEC [19], and an alginate-chitosan ion complex [20,21] as the outer layer is controlled by the erosion rate of the outer layer and the speed of water penetration into the outer layer.

Pulsatile delivery based on a rupturing mechanism with the aid of osmotic pressure was invented by Baker [22]. In general, rupture times are best controlled by varying the membrane materials and/or membrane thickness. Razaghi et al. further investigated the influence of incorporating a swellable polymer of PEO (polyethylene oxide) in osmotically rupturable tablets on the rupture time and subsequent drug release [23]. A novel pulsed-release system based on a bilayer-coated tablet containing an osmotically active agent was developed by Zhang et al. with HPMC and a mixture of Eudragit RS and RL, respectively, being applied as the swelling layer and semipermeable outer coat [24]. Bussemer et al. evaluated a pulsatile drug delivery system consisting of a drug-containing hard gelatin capsule, a swelling layer, and an insoluble polymeric coating; they concluded that the lag time was controlled by the hydration/expansion of the swelling layer and subsequent complete rupturing of the polymeric coating [25]. The osmotic rupture mechanism was found to play an important role in controlling the lag time and drug dissolution for the compression-coated tablet prepared with micronized ethylcellulose as the outer layer [26,27].

In our previous study, a lag time method produced by varying the coating level of Eudragit RS (plasticized with 20% TEC) on drug-containing pellets to release drug in a pulsed fashion to various sites in the GI tract was proposed [28]. Similarly, the lag times exhibited by PVA (polyvinyl acetate) swelling-controlled release systems (SCRSs) were controlled by the coating level of the membrane, which was composed of ethylcellulose (EC), HPMC, and TEC (70:30:20) and was shown to be dependent on the rupture of the coated membrane which was proposed to be caused by the swelling of PVA [29]. Since it is possible that both Eudragit RS and EC membranes can be made to be semipermeable, swelling caused by either osmotic pressure or a swellable polymer in the core tablet can be used to rupture the membrane to initiate drug release. In this study, the underlying mechanism responsible for the rupture of coated membranes of EC for achieving the pulsatile release by controlling the lag time was elucidated, and the influence of core and coating formulations on the release characteristics was examined for the establishment of in vitro/in vivo correlations of pulsatile pattern.

2. Experimental procedures

2.1. Materials

Doxazosin mesylate (Code No. 100041, purity 100.9%) was supplied by Dr. Reddy's laboratory (India). Ethylcellulose (EC, 10 cps) was purchased from Aqualon (USA). Hydroxypropyl methylcellulose (HPMC) of various grades (60SH-50, 60SH-4000, and Pharmacoat 606) was obtained from Shin-Etsu (Tokyo, Japan). Hydroxypropyl methylcellulose E10M and K100M were from Colorcon (London, UK). All materials were used as received, and all other chemicals were of reagent grade. DOXABEN XL® (formulated with the gastrointestinal therapeutic system containing 5.093 mg doxazosin mesylate equivalent to 4 mg doxazosin) used as the reference for in vitro dissolution and in vivo study was supplied by Pfizer Inc. Prazosin HCl (Lot No. 048H463631, purity 99%) used as the internal standard was purchased from Sigma–Aldrich Co. (St. Louis, MO, USA).

2.2. Methods

2.2.1. Production of tablets

According to the formulation lists in Table 1, the core tablet excipients were blended for 10 min in a Turbulablender (W.A. Bachhofen Maschinenfabrik, Basel, Switzerland), followed by the addition of magnesium stearate (1.0% w/w) and Aerosil 200 (1.0% w/w). The powder mixture was further blended for 5 min. The core tablets (with a diameter of 6 mm, a biconvex, shape, a hardness of 8–10 kg, and an average tablet weight of 160 mg) were compressed using a rotary tabletting machine (Korsch Type PH100, Korsch Pressen, Berlin, Germany).

2.2.2. Coating of core tablets

The coating solution was prepared by dissolving EC in 95% alcohol, and then HPMC 606 was added while stirring. After that, the water content designated as shown in Table 1 was added, and the resulting solution was adjusted with 95% alcohol such that it had a final solid content of 7% (w/w). A batch size of 2 kg (100 g of designated tablets and 1900 g of a placebo) was placed in the coating machine (Super coater, Model YC-SC-40F, Yenchen, Taiwan). The process conditions were as follows: inlet temperature of 43–45 °C, outlet temperature of 33–35 °C, a spray rate of 10–18 g/min, a nozzle diameter of 1 mm, a roller speed of 5 rpm, an air flow rate of 3.3 m^3/min, and an atomizing air pressure of 45 psi. The coated tablets were further dried in a coating pan for 15 min at 40 °C after the coating process was completed. Tablets were then placed in an oven at 40 °C for 2 h to remove any residual solvent. The increase in weight percent after coating was determined as the coating level.

2.2.3. Dissolution study

The USP XXIV paddle method (37.0 ± 0.5 °C, at 50, 100, or 150 rpm, with 500 ml of deionized water (DDW), a 0.1 N HCl solution, pH 6.8, phosphate buffer (PBS), and an NaCl solution, $n = 3$) was used to study the drug release from the tablets (Vankel VK700, Varian Inc., Cary, NC, USA). Samples were withdrawn at predetermined time intervals that could appropriately reveal the release profiles. The amount of doxazosin mesylate released was assayed with a UV spectrophotometer (V-550, Jasco, Tokyo, Japan) at a λ_{max} wavelength of

256 nm. The assay method was validated in the concentration range of 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, and 20.0 μg/ml. The intraday correlation was $y = 0.0714x + 0.0022$ ($r^2 = 0.9999$) with a precision (CV%) of 0.2557–5.4714 and an accuracy (RSE%) of −1.5298 to 1.6583; while the inter-day correlation was $y = 0.0716x + 0.0007$ ($r^2 = 0.9999$) with a precision (CV%) of 0.5777–7.6956 and an accuracy (RSE%) of −2.0794 to 5.1445. In vitro initial release rate (RR, %/h) and lag time (LT, h) were determined from each individual release profile and average and standard derivation were reported.

2.2.4. Clinical pilot study

Volunteers over the age of 20 years and body weight at approximately 55–85 kg and in good health (free from significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal and hematological disease) as determined before and after PK study by medical history, physical and psychiatric examination, EKG and routine laboratory screening tests (blood glucose, albumin, globulin, urea, creatinine, uric acid, cholesterol, triglyceride, GOT, GPT, LDH, total and differential white cell counts, RBC, hemoglobin, hematocrit, and routine urinalysis) were recruited after signing an informed consent agreement approved by the Ethics Committee of Taipei Medical University Hospital. Three pilot studies utilizing a crossover design (one week washout period) were conducted with three subjects in the fasted state for each study. After dosing, heparinized venous blood samples (10 ml) were collected by means of an indwelling venous cannula in the cubital vein according to a predetermined time schedule, which included a blank sample just prior to dosing and then samples at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 24, and 36 h after dosing. Plasma was immediately separated by centrifugation at 1690*g* for 10 min, then transferred to suitably labeled tubes, and stored at −20 °C until analysis. Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature were performed at 30 min, 8, 14, 24, 36 h after dosing. The plasma drug concentration was assayed with a validated high-performance liquid chromatographic (HPLC) method. The HPLC system consisted of a Hitachi L-7100 pump, an L-7200 autosampler, an L-7485 FL detector, and an L-7300 column oven (30 °C). A C_{18} column (Luna C_{18}, 5 μm, 4.6 × 150 mm) was employed with a mobile phase consisting of 65% methanol and 35% of 5 mM KH_2PO_4 at a flow rate of 1 ml/min. The eluent was monitored with a fluorescence detector at a wavelength of 246 nm for excitation and 389 nm for emission. Prazosin was used as the internal standard at a concentration of 50 ng/ml. The assay method was validated in the concentration range of 0.5, 1, 2, 5, 10, 20, 50 and 100 ng/ml. The accuracy values were between −13.2% and 9.7% both intra- and inter-day. The precision ranged from 1.1% to 4.7% and from 2.6% to 8.8% for intra- and inter-day, respectively. Three QC samples (1.5, 15 and 80 ng/ml) were assayed along with the analysis of plasma concentrations and also demonstrated acceptable accuracy and precision as −2.7% to 5.7% and 1.2% to 3.7%, respectively.

In vivo absorption rate (K_a, h^{-1}) and lag time (LT, h) were determined from each individual plasma profile with the assumption of one compartmental model with the first-order absorption rate and lag time by PK modeling method (fitting with WinNonlin®, version 2.1, Pharsight Corporation, USA) and Wagner–Nelson method (with EXCEL). Average and standard derivation were reported for three subjects for each formulation.

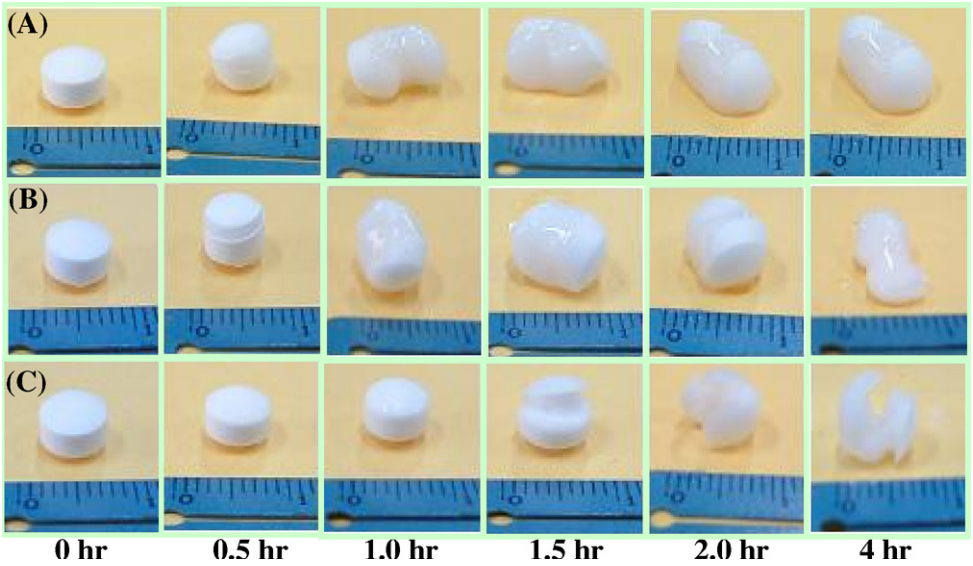

Fig. 1. Morphological photographs of formulation B1.5E1H-7d at various time intervals under dissolution testing in (A) deionized water, (B) pH 6.8 buffer, and (C) a 1 M NaCl solution (at 150 rpm and 37 °C).

3. Results and discussion

A pulsatile release system activated by membrane rupture was designed based on three core tablet formulations (with either the A-, B-, or C-core) using viscosity grades of HPMC (50+4000 cps, E10M, and K100M, respectively) coated with various thicknesses of an EC membrane plasticized with HPMC 606 at different ratios with/without adding various amounts of water to dissolve it in the coating solution. Detailed formulation designs for the core tablet and membrane compositions are listed in Table 1. The pulsatile release pattern due to membrane rupture for the designated system is typically exemplified by the B1.5E1H-7d formulation (designated as a B-core tablet formulation coated with 8% of the EC membrane at a ratio of EC/HPMC of 1.5:1 with the addition of 7% water to the coating solution) in various media as shown in Fig. 1. Results demonstrated that after immersion in the three media, coated tablets gradually swelled to various extents, and then the coated membrane ruptured to expose the core tablet in the form of a hydrogel. Differences in the time to membrane rupture in different media were in the order of deionized water < pH 6.8 buffer < 1.0 M NaCl. This demonstrates differences in the lag times for drug release. A smaller extent of swelling before rupture was also exhibited for coated tablet immersed in the 1.0 M NaCl solution compared to that in deionized water and the pH 6.8 buffer. Further, complete dissolution of the hydrogel within 4 h after rupture was observed when dissolution was conducted in a 1.0 M NaCl solution, whereas a greater portion of the hydrogel remained within this time period for dissolution in deionized water compared to that in the pH 6.8 buffer. This indicates that the salt concentration (i.e., the ionic strength) may have had a dominant influence on both membrane rupture and dissolution of the hydrogel, which in turn regulated the lag time by the former and the drug release rate by the latter.

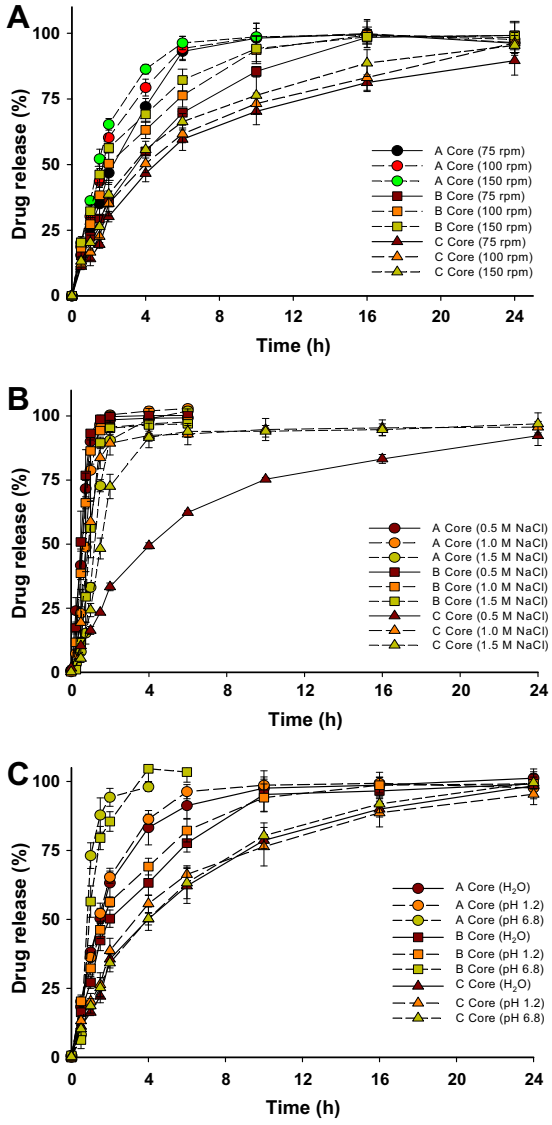

Fig. 2. Drug release profiles of three core formulations (A) in deionized water with different stirring rates (75, 100, and 150 rpm, $n = 3$), (B) in deionized water with different concentrations of NaCl (0.0, 0.5, 1.0, and 1.5 M at 150 rpm, $n = 3$), and (C) at different pH values (deionized water, pH 1.2, and pH 6.8 at 150 rpm, $n = 3$).

The in vitro dissolution of three core tablet formulations designated the A-, B-, and C-cores was first examined in deionized water at different stirring rates and in various media with different pH values and NaCl concentrations at the highest stirring rate. Results are illustrated in Fig. 2. As revealed in Fig. 2A, drug release from the A-core tablet in deionized water increased with an increasing stirring rate. This was true for the other two core tablets (B- and C-cores) regardless of which viscosity grade of HPMC was utilized. Comparisons among them show a greater difference in the release profile from three core tablets with various viscosity grade of HPMC when a higher stirring was used in the dissolution study. This indicates that a stirring rate was necessary to be higher enough to differentiate the influence of various viscosity grades on the drug release. Therefore, the highest stirring rate of 150 rpm was employed in the following dissolution study.

When dissolution was conducted in media containing various concentrations of NaCl as shown in Fig. 2B, a significant promotion of drug release from the three core tablets was observed at the three levels of NaCl media compared to that in deionized water at a stirring rate of 150 rpm. Further, the influence of the NaCl concentration in the media on the drug release from A- and B-core tablets was similar, with a slightly slower release of drug in the 1.5 M NaCl solution. But the drug release from the C-core tablet formulation was significantly influenced by the concentration of NaCl in the medium in the order of 0.5 M < 1.5 M < 1.0 M. It was also observed that gelation of the three different viscosity grades of HPMC (50, 4000 cps, and E10M) in the medium containing three different levels of NaCl did not occur, whereas that of K100M HPMC did not occur only in the 1.0 and 1.5 M NaCl media. This indicates that the hydration and gelation of K100M HPMC were

less sensitive to the concentration of NaCl than were the other three viscosity grades of HPMC. The inhibition of HPMC gelation in the presence of NaCl resulted in an increase in the drug release rate. This explains why the slowest release rate was observed for C-core tablets in 0.5 M NaCl medium. Furthermore, a slower release rate from the three core tablet formulations in the 1.5 M NaCl medium could be attributed to a slower rate of water uptake (data not shown); the slowest rate of water uptake among the three different core tablet formulations by C-core tablets (containing K100M HPMC) was observed in deionized water. This further explains why the release rate of core tablets in 0.1 M NaCl medium is faster than that in 1.5 M NaCl medium.

The effects of pH on the release rate of drug from the three core tablets at the same stirring rate of 150 rpm are illustrated in Fig. 2C. Results demonstrated that the release rate in deionized water was slightly slower than that in pH 1.2 medium (0.1 N HCl solution), and a faster release rate was observed in pH 6.8 medium (phosphate-buffered solution, 50 mM) for the A-core tablet formulation that utilized HPMC 50+4000 cps. The same trend of release rates in the three kinds of media as that for the A-core tablet formulation was found for B-core tablets formulated with E10M, but rates were slower than that for A-core tablets in the respective media. Similar release rates in the three kinds of media with slower rates than for A- and B-core tablets were observed for C-core tablet formulated with HPMC

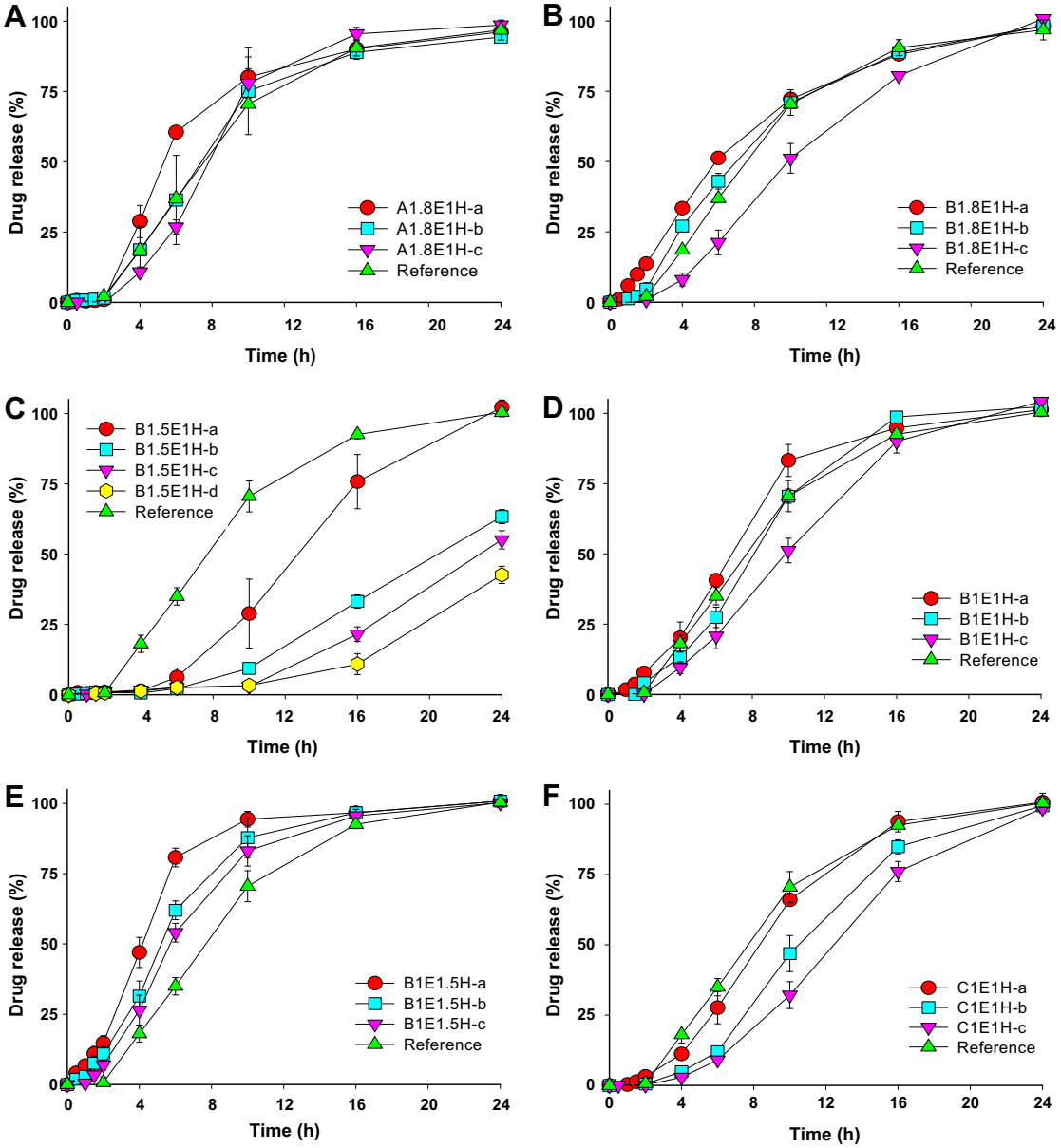

Fig. 3. Drug release profiles in deionized water (150 rpm, $n = 3$) for (A) A-core tablets coated with a membrane of EC: HPMC (1.8:1) in various thicknesses (A1.8E1H-a to A1.8E1H-c); B-core tablets coated with a membrane of (B) EC/HPMC (1.8:1), (C) EC/HPMC (1.5:1), (D) EC/HPMC (1:1), or (E) EC/HPMC (1:1.5) in various thicknesses; and (F) C-core tablets with a membrane of EC/HPMC (1:1) in various thicknesses.

K100M. This indicates that the release rate in the three kinds of media followed the same order as the viscosity grade of HPMC utilized to formulate the core tablet, with the higher viscosity grade of HPMC having a slower release rate. Furthermore, the influence of pH value on the release rate exhibited the following order of deionized water ≅ pH 1.2 < pH 6.8 for both A- and B-core tablets, with insignificant differences in release rates with respect to pH values for C-core tablets. Since a profound effect of NaCl concentration (ionic strength) on the drug released from A- and B-core tablets and a small effect on C-core tablets were shown as described above, the faster release observed for A- and B-core tablets in pH 6.8 medium at a concentration of 50 mM might be attributed to the ionic strength of the pH 6.8 medium being capable of retarding the gelation of both HPMC 50+4000 cps and E10M but not K100M.

The release profiles in deionized water at a stirring rate of 150 rpm are illustrated for three coated tablets (A-, B-, and C-cores) coated with various thicknesses of the EC membrane plasticized with HPMC 606 at different ratios

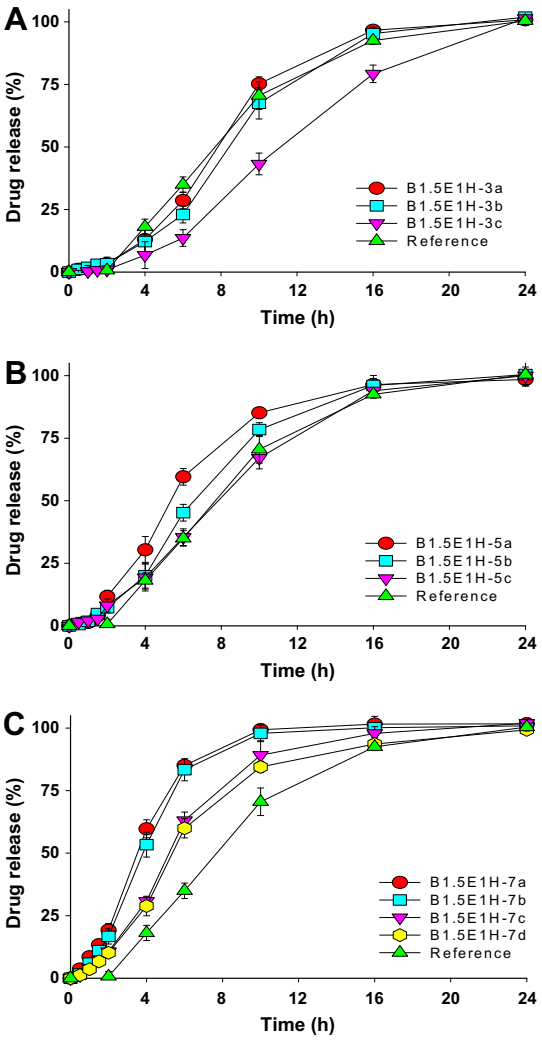

Fig. 4. Drug release profiles in deionized water (150 rpm, $n = 3$) for B-core tablets coated with a membrane of EC/HPMC (1.5:1) with the addition of (A) 3%, (B) 5%, or (C) 7% water in various thicknesses.

(Fig. 3) with adding various amounts of water to the coating solution (Fig. 4). The lag times and release rates after the lag time were determined from the release profiles, and results are shown in Fig. 5 and Table 1. The release rate in deionized water decreased with increasing thickness of the coated EC membrane for all coated tablets. For the same ratio of EC/HPMC in the membrane coated at a similar thickness as shown in Fig. 3 (3A and 3B = 1.8:1; 3D and 3F = 1:1), the release rate after membrane rupture decreased with the increasing viscosity grade of HPMC used in the core tablet as evidenced in Fig. 3A (HPMC 50+4000 cps) versus Fig. 3B (HPMC E10M) and Fig 3D (HPMC E10M) versus Fig. 3F (HPMC K100M). For those with the same B-core tablet coated at a similar thickness as shown by Fig. 3C–E, the release rates after membrane rupture, in the order of 3C < 3D < 3E, increased with the increasing fraction of hydrophilic HPMC in the membrane composition as evidenced by the ratio of EC/HPMC which followed the same order of 3C (1.5:1) < 3D (1:1) < 3E (1:1.5). For the same B-core tablet formulations coated at the same thickness with the same EC/HPMC ratio (1.5:1) as shown in Fig. 4, the release rate seemed to increase with the increasing added amount of water in the coating solution (4A: 3%; 4B; 5%; and 4C: 7%), which correlates with a decrease in the lag time as a result of membrane rupture. Those results indicate that the release of drug from a designated pulsatile system is mainly regulated by two factors: the controllability of the core tablet formulation and the lag time induced by rupture of the membrane.

Demonstrated by statistically significant linear correlation as shown in Fig. 5, the lag time determined from the release profiles in deionized water proportionally increased with the increasing thickness of the coated EC membrane only when higher viscosity grades of HPMC (E10M and K100M) (B1.8E1H in Fig. 5A and C1E1H in Fig. 5B) were used in the core tablet, when no water was added to the coating solution (B1.5E1H in Fig. 5C), and when the ratio of EC/HPMC in the membrane was higher than 1.5:1 (B1.8E1H and B1.5E1H in Fig. 5D). This indicates that the increase in the fraction of hydrophilic HPMC in the EC membrane or the addition of water to the coating solution to dissolve HPMC led to an increase in the hydrophilicity of EC membranes such that they became highly permeable to water with the gradual disappearance of the lag time effect due to the thickness of the EC membrane. Furthermore, it was observed that the lag time was reduced for those coated tablets containing a higher viscosity grade of HPMC at a lower level of coating thickness. Taken together, this was attributed to the swelling ability of the higher viscosity grade of HPMC in the core tablet that was only capable of assisting the rupture of EC membranes coated at a lower level but had a decreasing effect with an increasing level of coating thickness, leading to the resultant influence on the lag time for coated tablets with different thicknesses. Therefore, it was concluded that the lag time for designated pulsatile systems based on the rupture of the coated membrane could be controlled by adjusting

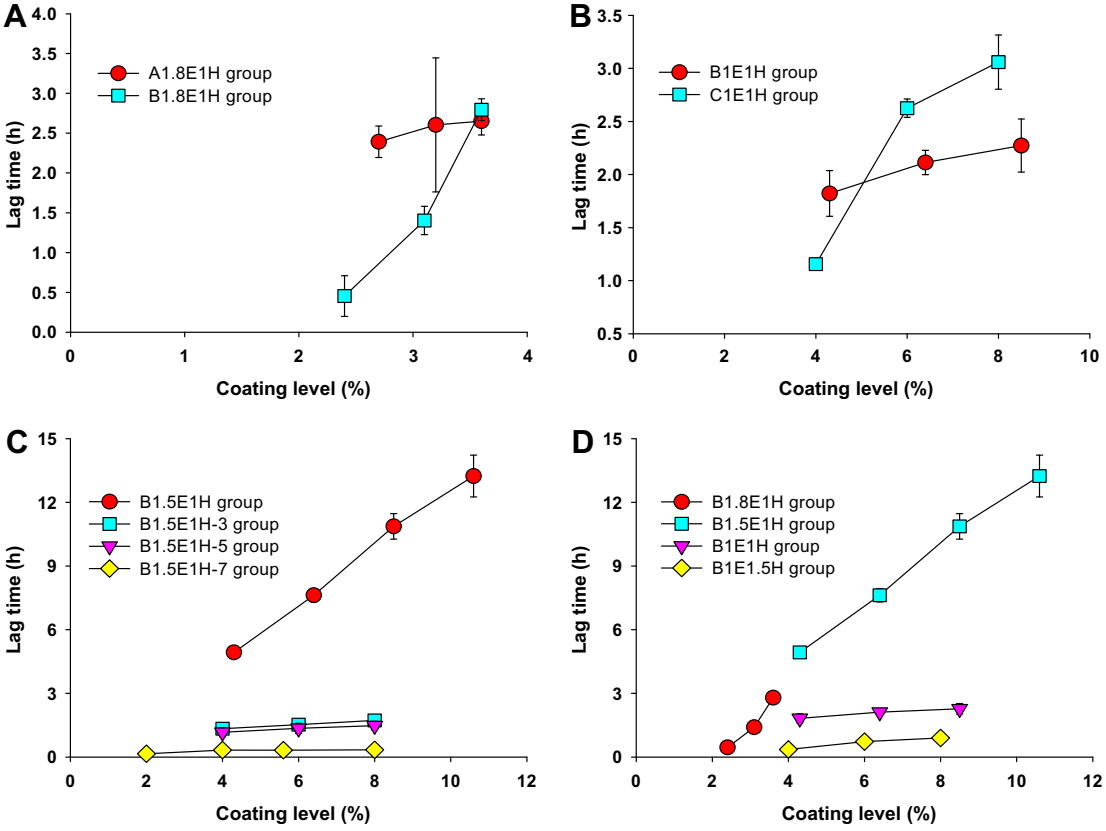

Fig. 5. Lag time of coated tablets. Effect of the core composition: (A) HPMC 50+4000 cps versus E10M; (B) E10M versus K100M; (C) effect of water amounts in the coating solution; (D) effect of Pharmacoat 606 in the EC membrane; ($n = 3$).

the water permeability of the coated membrane and its thickness and the swelling ability of the core tablet in the exposed medium.

The release profiles in pH 1.2 and pH 6.8 media at a stirring rate of 150 rpm for those exemplified coated tablets were compared to that in deionized water. Results are illustrated in Fig. 6 and reveal that the rate of drug released in the medium was in the order of pH 1.2 < deionized water < pH 6.8 for those coated tablet formulations. However, differences among the release rates in the three media were reduced with an increasing coating thickness at the same membrane composition (1.8E1H-a in Fig. 6A vs. A1.8E1H-c in Fig. 6B); even smaller differences among release rates were in evidence when the hydrophilicity of the membrane was increased for the same core formulation (B1.8E1H-c in Fig. 6C vs. B1.5E1H-7d in Fig. 6D); and differences among the release rates in the three media became insignificant when K100M HPMC (C1E1C-b in Fig. 6F) was used instead of E10M (B1E1H-7d in Fig. 6E) in the core tablet at the same membrane composition and coated thickness. Furthermore, it was found that a pulsatile release pattern appeared after a lag time for those formulations with the fastest release rate in pH 6.8 (Fig. 6A, C, and E), and the lag time for those having the slowest release rate in pH 1.2 seemed to be slightly longer (Fig. 6A, C, and E). This can be explained by the fact that the gelation of the three viscosity grades of HPMC (50+4000 cps and E10M, but not K100M) in pH 6.8 was hindered leading to faster release after the lag time with exposure of the core tablet to pH 6.8 medium. The osmotic effect of NaCl added to the pH 1.2 medium (~34 mM) caused an increase in the lag time by delaying water diffusion across the EC membrane, and the extent of its influence decreased with increasing hydrophilicity or decreasing semipermeability of the EC membrane. However, the effect of NaCl at a concentration of 34 mM on the hindrance of gelation of HPMC seemed to be less profound than that caused by potassium phosphate monobasic at a concentration of ~50 mM in pH 6.8 buffer. Therefore, the dominant influence on the drug release rate after the lag time from the designated pulsatile system in pH 6.8 and pH 1.2 media appeared to be the gelling effect and osmotic effect, respectively. The osmotic effect on the lag time in pH 1.2 medium was, as expected, dependent on the species of osmogents and their concentrations. Furthermore, the small influence on the gelation of K100M HPMC by both the pH 1.2 and pH 6.8 media makes it the most appropriate for controlling the drug release rate in the core formulation.

The release profiles for those exemplified coated tablet formulations were further evaluated in media containing various concentrations of NaCl (0.0, 0.5, 1.0, and 1.5 M) at a stirring rate of 150 rpm, and results are illustrated in Fig. 7. It demonstrates that the lag time increased with the increasing concentration of NaCl in the medium, and

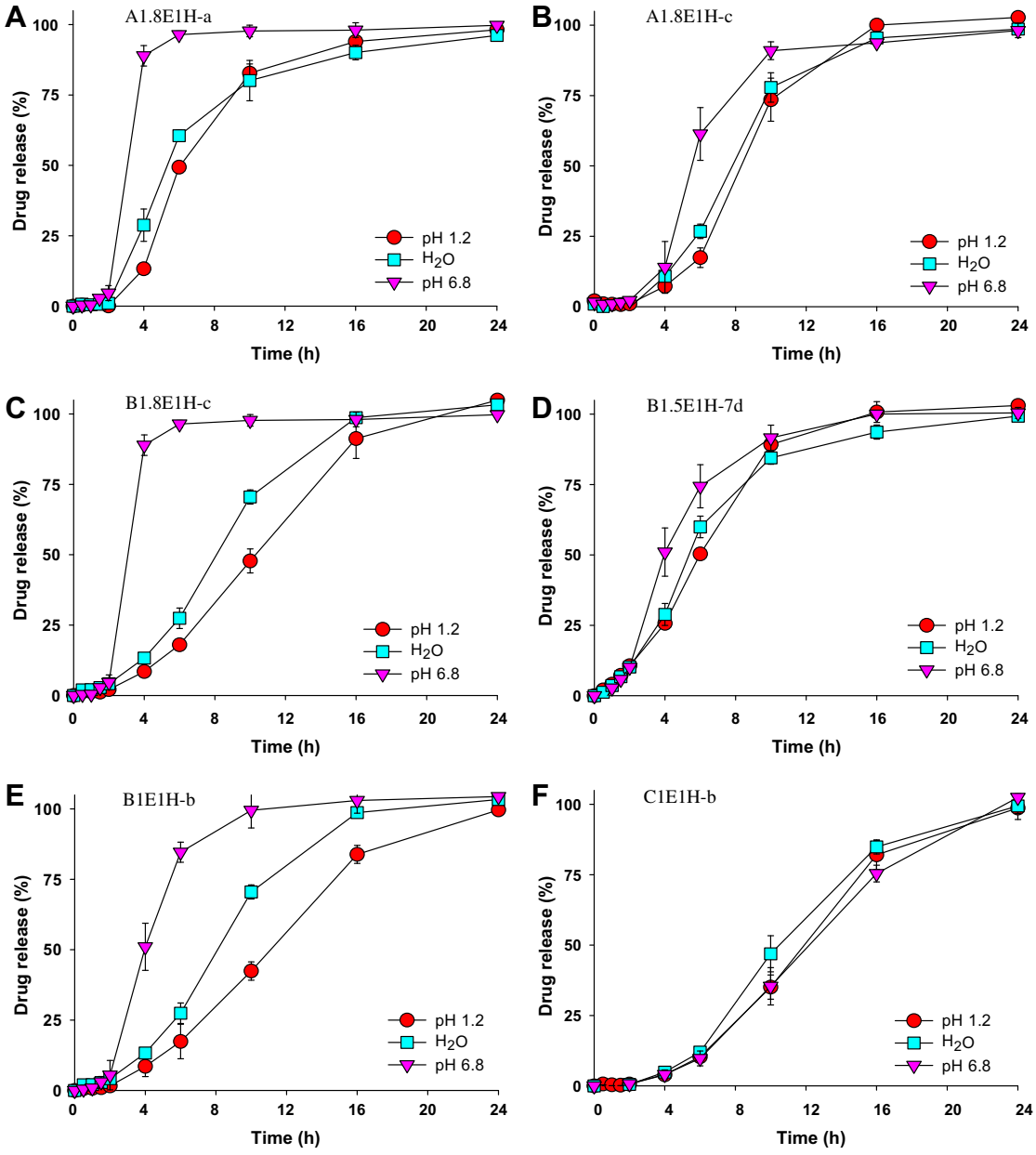

Fig. 6. Drug release profiles of (A) A1.8E1H-a, (B) A1.8E1H-c, (C) B1.8E1H-c, (D) B1.5E1H-7d, (E) B1E1H-b, and (F) C1E1H-b in a, pH 1.2, HCl solution, deionized water, and pH 6.8 buffer (150 rpm, $n = 3$).

the release profiles after the lag time showed a pulsatile pattern for all exemplified coated tablet formulations except that for C1E1H-b, which showed a sustained release manner after the lag time (exceptionally so in the 1.0 M NaCl solution). The osmotic effect of NaCl on the lag time was more profound when the EC membrane was thicker (A1.8E1H-a in Fig. 7A < A1.8E1H-c in Fig. 7B) and when the EC membrane was less hydrophilic (B1.8E1H-c in Fig. 7C < B1H1-b in Fig. 7E < B1.5E1H-7d in Fig. 7D). As discussed above, the gelation of HPMC (50+4000 cps and E10M) was hindered, and water diffusion across the EC membrane was delayed in the presence of NaCl, leading to the release rate after the lag time appearing to be pulsatile and the lag time increasing either with increasing NaCl concentration in the medium, with an increasing membrane thickness, or with decreasing hydrophilicity of the membrane. Further, K100M HPMC was able to gelify in the presence of NaCl at a concentration up to 0.5 M as demonstrated in Fig. 2D. Therefore, membrane rupture after the lag time had partially exposed the coated tablet to the medium caused by a lower concentration of NaCl than that in the medium contacted by those exposed HPMC surfaces resulting in a slower release rate with the exception of that in 1.0 M NaCl. It was concluded that the lag time and release profile for the designated pulsatile systems were dominantly determined by the osmotic effect in the former and by the ionic strength in the latter. In vitro initial release rate and the lag time were determined for

individual release profile of those exemplified coated formulations and plain B-core in all media examined and results are listed in Table 2.

Three pilot crossover studies were conducted to correlate the in vitro release patterns with the resultant plasma profiles for the exemplified pulsatile systems with reference to DOXABEN XL®, and results are illustrated in Fig. 8. There showed no adverse reaction during three pilot PK studies as indicated by vital signs measured. As shown by the first pilot study in Fig. 8A, a pulsatile pattern of plasma concentrations after a 2-h lag time was demonstrated by A1.8E1H-a. However, a slow increase then a plateau of plasma concentrations without a lag time was observed for the B-core formulation since it did not have a coated membrane. The lag time for A1.8E1H-a was similar to the reference formulation but it had a sharper plasma profile after that, which greatly differed from the plateau plasma concentration expressed by the reference formulation. Since the pulsatile system was first exposed to gastric acid after oral administration and then moved from the stomach to the intestines after a certain period of time, it was expected that the lag time for pulsatile systems should be highly correlated in pH 1.2, and the release rate after the lag time was similar

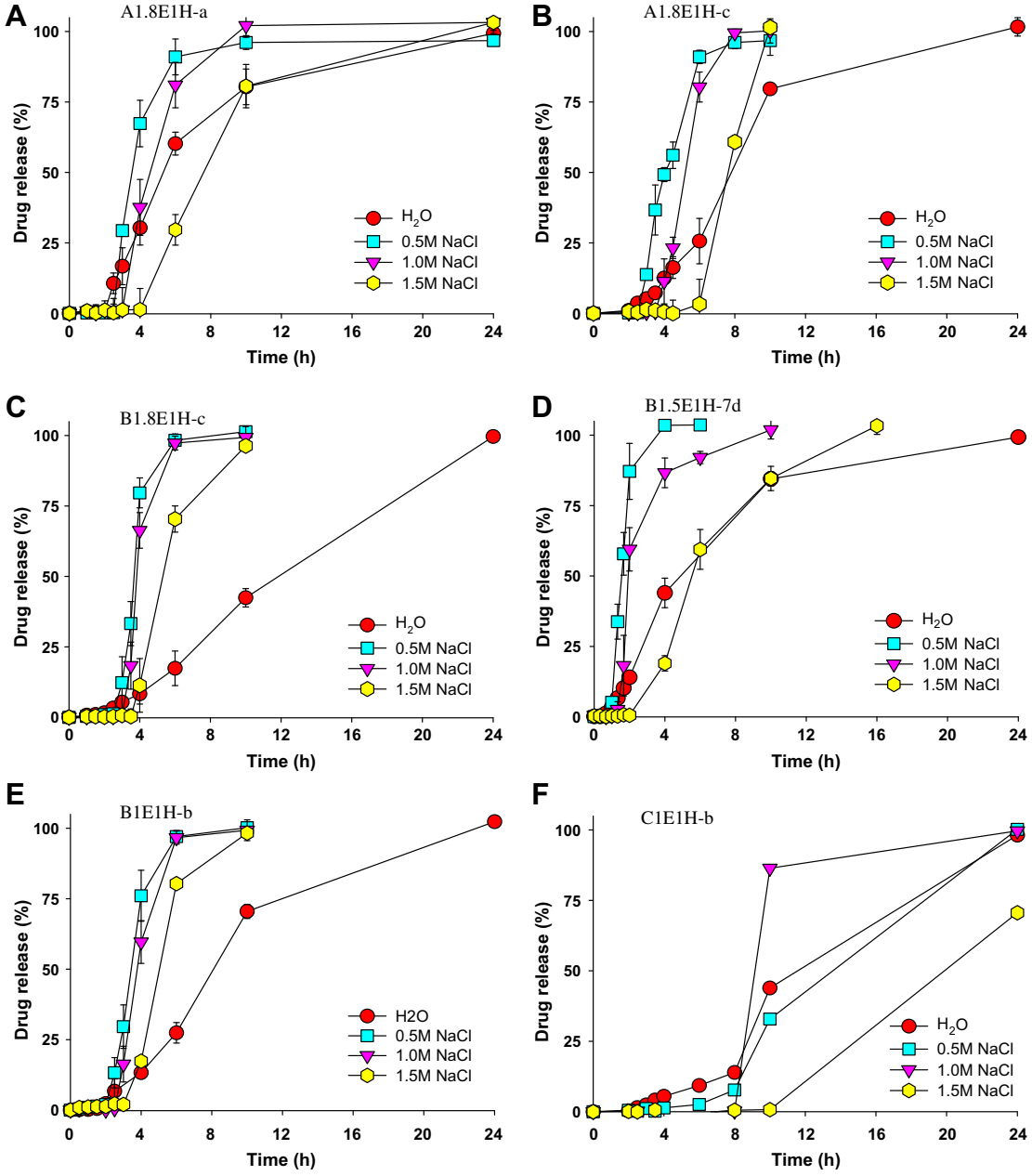

Fig. 7. Drug release profiles of (A) A1.8E1H-a, (B) A1.8E1H-c, (C) B1.8E1H-c, (D) B1.5E1H-7d, (E) B1E1H-b, and (F) C1E1H-b in a NaCl solution with different concentrations (150 rpm, $n = 3$, for C1E1H-b, $n = 1$).

Table 2
In vitro initial release rate (%/h) and lag time (h) determined from the dissolution profiles of exemplified formulations conducted in various media and in vivo absorption rate constant (K_a,h^{-1}) and lag time (h) from plasma profiles

Formula	Initial rate (%/h) (lag time, h)						K_a (h^{-1}) (lag time, h)	
	Deionized water	pH 1.2	pH 6.8, PBS	0.5 M NaCl	1.0 M NaCl	1.5 M NaCl	PK model fitting	Wagner–Nelson
Plain core (A)	32.5 ± 3.1 (0.0 ± 0.0)	31.5 ± 2.5 (0.0 ± 0.0)	72.5 ± 3.5 (0.0 ± 0.0)	91.1 ± 4.6 (0.0 ± 0.0)	79.5 ± 8.3 (0.0 ± 0.0)	14.5 ± 3.9 (0.0 ± 0.0)	—	—
A1.8E1H-a	14.9 ± 1.2 (2.0 ± 0.2)	12.2 ± 1.5 (2.3 ± 0.2)	42.1 ± 5.3 (1.9 ± 0.1)	19.3 ± 3.7 (1.1 ± 0.3[*])	25.9 ± 3.9 (2.8 ± 0.2[*])	13.2 ± 2.8 (3.8 ± 0.6[*])	1.76 ± 0.26 (3.83 ± 0.03)	0.81 ± 0.68 (3.20 ± 1.04)
A1.8E1H-c	8.0 ± 0.4 (2.7 ± 0.2)	4.1 ± 0.5 (1.9 ± 0.2)	14.8 ± 7.9 (2.3 ± 0.2)	34.0 ± 5.2 (2.5 ± 0.2[§])	32.7 ± 4.0 (3.6 ± 0.1[§])	28.8 ± 4.6 (5.9 ± 0.5[§])	0.13 ± 0.07 (5.67 ± 0.25)	0.26 ± 0.06 (5.76 ± 1.84)
Plain core (B)	27.7 ± 2.5 (0.0 ± 0.0)	27.3 ± 3.7 (0.0 ± 0.0)	73.2 ± 5.9 (0.0 ± 0.0)	101.8 ± 8.7 (0.0 ± 0.0)	76.8 ± 6.8 (0.0 ± 0.0)	26.8 ± 6.2 (0.0 ± 0.0)	0.29 ± 0.03 (0.55 ± 0.11)	0.45 ± 0.56 (0.61 ± 0.37)
B1.8E1H-c	6.6 ± 1.1 (2.8 ± 0.1)	5.7 ± 0.7 (2.7 ± 0.2)	19.8 ± 3.7 (1.6 ± 0.5)	67.3 ± 5.4 (2.9 ± 0.3[¶])	65.3 ± 7.1 (3.1 ± 0.3[¶])	28.5 ± 3.2 (3.5 ± 0.2[¶])	0.70 ± 0.15 (4.99 ± 0.11)	0.29 ± 0.12 (7.09 ± 2.51)
B1.5E1H-7d	6.0 ± 0.8 (0.3 ± 0.1)	7.3 ± 0.2 (0.5 ± 0.0)	16.9 ± 2.6 (1.1 ± 0.4)	80.8 ± 3.5 (0.9 ± 0.2[¥])	84.7 ± 6.2 (1.3 ± 0.2[¥])	20.2 ± 1.3 (3.1 ± 0.3[¥])	1.73 ± 0.52 (2.54 ± 0.15)	0.59 ± 0.14 (1.61 ± 0.45)
B1E1H-b	5.6 ± 1.4 (2.3 ± 0.3)	4.0 ± 0.2 (1.6 ± 0.4)	42.1 ± 6.0 (1.9 ± 0.2)	37.8 ± 2.2 (2.1 ± 0.2[#])	40.0 ± 3.2 (2.5 ± 0.2[#])	26.9 ± 3.2 (3.1 ± 0.3[¶])	0.71 ± 0.08 (3.91 ± 0.06)	0.51 ± 0.07 (3.70 ± 0.05)
Plain core (C)	18.1 ± 2.1 (0.0 ± 0.0)	16.3 ± 1.7 (0.0 ± 0.0)	16.6 ± 4.0 (0.0 ± 0.0)	14.7 ± 2.7 (0.0 ± 0.0)	60.0 ± 5.7 (0.0 ± 0.0)	32.7 ± 5.7 (0.0 ± 0.0)	—	—
C1E1H-b	7.3 ± 0.7 (3.7 ± 0.3)	5.3 ± 0.2 (3.6 ± 0.3)	5.4 ± 0.3 (3.6 ± 0.2)	7.5 ± 0.0 (6.1 ± 0.0)	43.1 ± 0.0 (8.0 ± 0.0)	5.0 ± 0.0 (9.9 ± 0.0)	0.09 ± 0.13 (8.93 ± 0.57)	0.15 ± 0.08 (8.34 ± 3.09)

Designation is the same as Table 1.
[*] $p < 0.00061$.
[§] $p < 0.000035$.
[¶] $p < 0.04749$.
[¥] $p < 0.0001$.
[#] $p < 0.00383$.

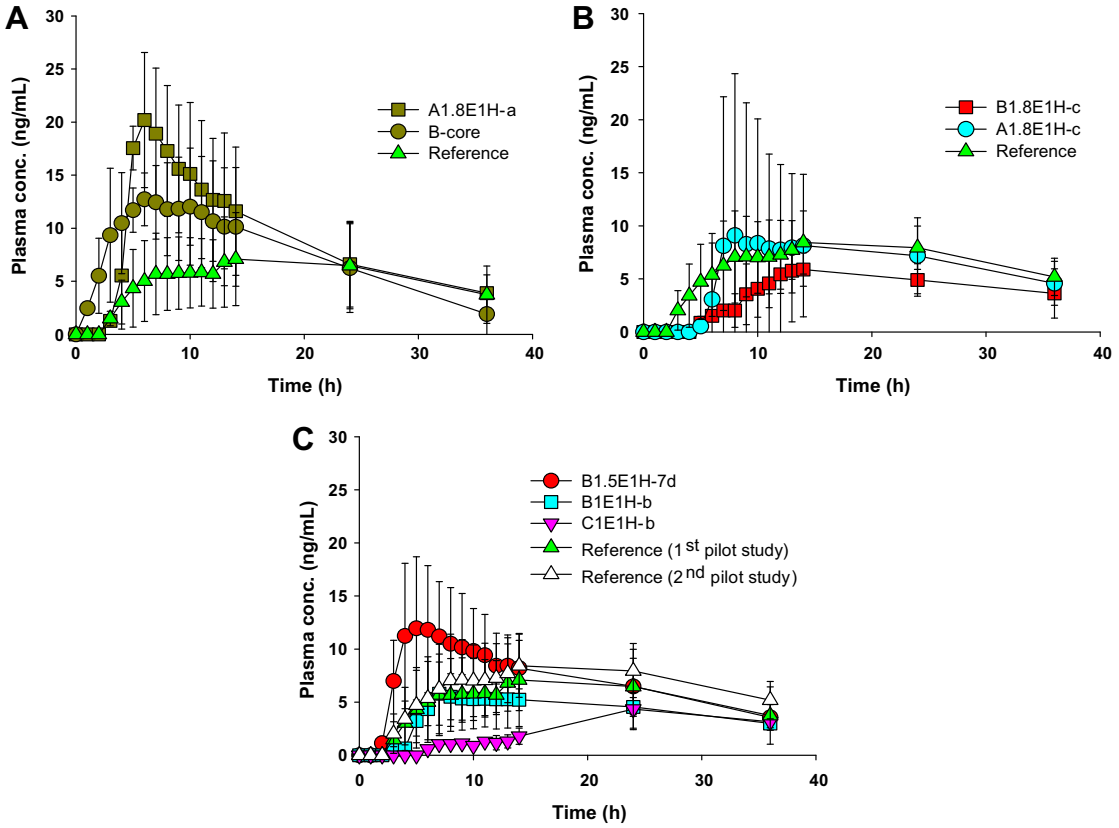

Fig. 8. The mean plasma concentration profiles for (A) A1.8E1H-a, B-core, and the reference; (B) B1.5E1H-7d, B1E1H-b, C1E1H-b, and the reference; and (C) B1.8E1H-c, A1.8E1H-c ($n = 3$).

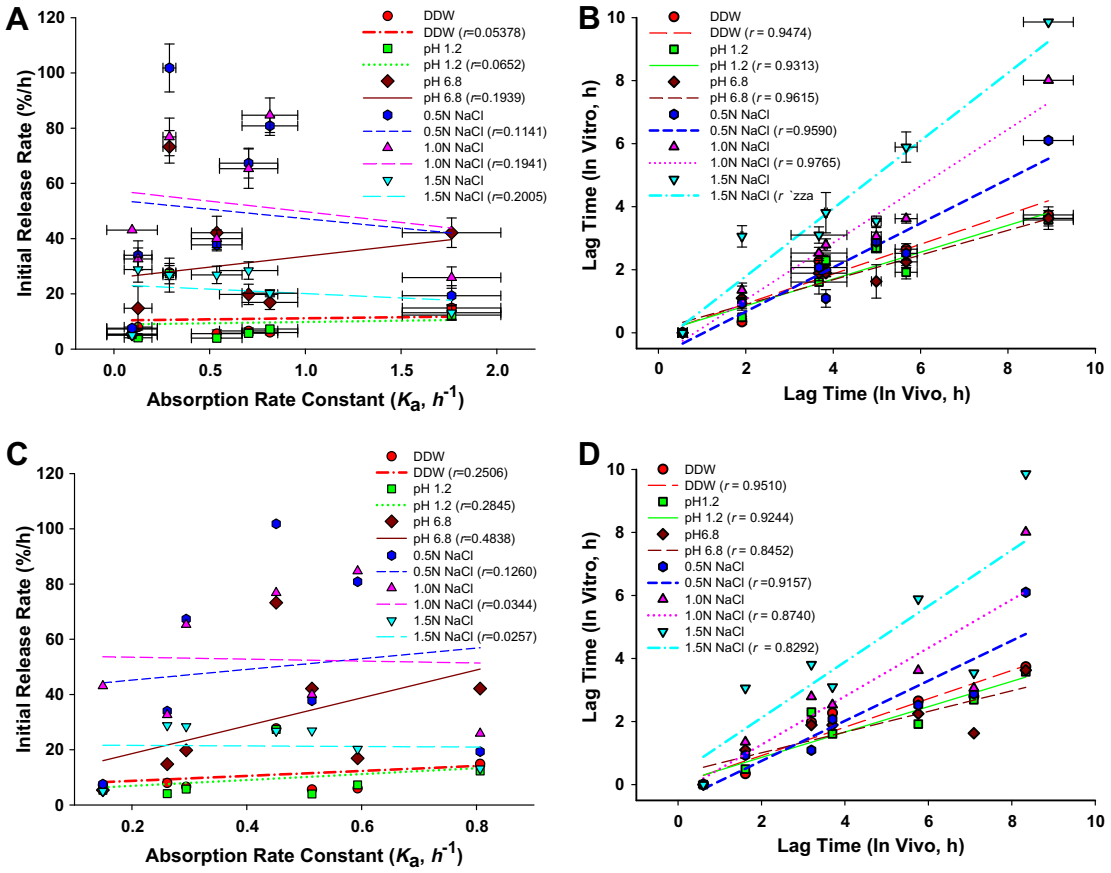

Fig. 9. Linear correlations between in vitro initial release rate (%/h) and in vivo absorption rate constant (K_a, h^{-1}) calculated by PK modeling method (A) or Wagner–Nelson method (C) and between in vitro lag time (h) and in vivo lag time (h) determined by PK modeling method (B) or Wagner–Nelson method (D).

to that in pH 6.8 if the lag time was longer than 2 h. As shown in Fig. 6A, a 2-h lag time in pH 1.2 and the pulsatile release following the lag time in pH 6.8 for A1.8E1H-a were consistent with its resultant plasma concentration, whereas a slower release rate following the same 2-h lag time in pH 1.2 resulted in a slower increase in the plasma concentration after the lag time that was inconsistent with the in vivo plasma concentration observed. Because of this, it was concluded that the lag time for the in vivo plasma profile was well correlated with that determined from the in vitro release profile in pH 1.2, and the in vivo release rate was better reflected by that performed in pH 6.8.

In a second pilot study as shown in Fig. 8B, the plasma profile after oral administration demonstrated a longer lag time and a slower in vivo release for A1.8E1H-c than for B1.8E1H-c. In comparison, it was found that the lag time for the in vivo plasma profile was correlated with that determined from the release profile in pH 1.2 for both with a slightly longer lag time for A1.8E1H-c than that for B1.8E1H-c. It is likely that the release rate after the lag time was similar to that in pH 6.8 with a faster release for B1.8E1H-c than that for A1.8E1H-c. Furthermore, a longer lag time in pH 1.2 and a slower release rate in pH 6.8 for A1.8E1H-c than that for A1.8E1H-a led to a longer lag time with a slower increase in the plasma profile for the former than for the latter. In a third pilot study shown in Fig. 8C, the plasma profile after oral administration demonstrated a 2-h lag time and a faster in vivo release rate for B1.8E1H-c, a 4-h lag time and a slower in vivo release rate for B1E1H-b, and a 5-h lag time and the slowest in vivo release rate for C1E1H-b. In comparison, it was also found that the lag time and release rate for the plasma profile were well correlated with those determined from the release profiles in pH 1.2 and pH 6.8 media, respectively. Therefore, the same conclusion was reached as above that the lag time and in vivo release rate of plasma profile can be well correlated with those determined from the in vitro release profiles in pH 1.2 and pH 6.8 media, respectively.

In vivo absorption rate constant (K_a, h^{-1}) and the lag time (h) were determined from each individual plasma profile for those exemplified coated formulations conducted in PK study with the assumption of one compartmental model with first-order absorption rate and lag time utilizing PK modeling method and Wagner–Nelson method, and results are also listed in Table 2. A correlation between in vitro release rate (%/h) (or in vitro lag time (h)) and in vivo absorption rate constant (K_a, h^{-1}) (or in vivo lag time (h)) calculated by two methods

was constructed in Fig. 9A, B and C, D, respectively. It demonstrated that a higher correlation coefficient was observed for the correlation between in vitro release rate in, pH 6.8, PBS and in vivo absorption rate constant calculated by two methods (Fig. 9A and C). On the other hand, the lag time determined from release profiles in DDW and, pH 1.2, HCl media was correlated well with in vivo lag time calculated by two methods (Fig. 9B and D). This result was consistent with the conclusions described above that the lag time and in vivo release rate of plasma profile can be well correlated with those determined from the in vitro release profiles in pH 1.2 and pH 6.8 media, respectively.

4. Conclusions

The designated pulsatile system characterized in this study demonstrated that after oral administration, the membrane rupture determined the lag time for pulsatile release which was mainly caused by the osmotic effect of the coated semipermeable membrane in pH 1.2 (0.1 N HCl solution) medium, but was synergistically promoted by the swellability of those excipients added to the core tablet only with a reduced thickness or an increased hydrophilicity of the coated membrane. The coated membrane was ruptured after a lag time to expose the core tablet in the form of a hydrogel, and the gelation and dissolution of the corresponding hydrogel in pH 6.8 buffer in turn regulated the release profile of the drug. From establishing an in vitro/in vivo correlation of the pulsatile pattern, we concluded that the desired lag time can be adjusted by the thickness and the hydrophilicity of the coated membrane. The release rate after the lag time can be adjusted as a pulsatile release pattern using the HPMC 60SH type (E10M) and a controlled release pattern using the HPMC 90SH type (K100M).

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