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Release mechanisms of acetaminophen from polyethylene oxide/polyethylene glycol matrix tablets utilizing magnetic resonance imaging

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ABSTRACT

Release mechanism of acetaminophen (AAP) from extended-release tablets of hydrogel polymer matrices containing polyethylene oxide (PEO) and polyethylene glycol (PEG) were achieved using flow-through cell with magnetic resonance imaging (MRI). The hydrogel forming abilities are observed characteristically and the layer thickness which is corresponding to the diffusion length of AAP has a good correlation with the drug release profiles. In addition, polymeric erosion contribution to AAP releasing from hydrogel matrix tablets was directly quantified using size-exclusion chromatography (SEC). The matrix erosion profile indicates that the PEG erosion kinetic depends primarily on the composition ratio of PEG to PEO. The present study has confirmed that the combination of *in situ* MRI and SEC should be well suited to investigate the drug release mechanisms of hydrogel matrix such as PEO/PEG.

1. Introduction

In an effort to improve quality of life among patients, researchers have developed controlled-release technologies using hydrogel-forming polymers. Hydroxypropyl methylcellulose (HPMC) is the most common material as a hydrogel matrix for controlled-release tablets and capsules due to its safety, chemical stability, and compatibility with many drugs. The drug release characteristics of HPMC matrices have been extensively investigated (Alderman, 1984; Ford et al., 1985a,b, 1987, 1991; Rao et al., 1990; Salomen et al., 1979). Recently, polyethylene oxide (PEO), which is highly soluble in water and has high gelability and low toxicity, has been proposed as an alternative hydrophilic polymer to HPMC for use in extended-release systems controlled by the drug self-diffusion and the polymeric matrix erosion (Graham and McNeill, 1984; Kim, 1995, 1998; Sako et al., 1996; Sako, 1998; Yang et al., 1996). Sako et al. (1996) developed enhanced PEO hydrogel matrix tablets containing polyethylene glycol (PEG), which can be used as a hydrophilic component to promote the uptake of water into tablets and accelerate complete gelation within a few hours. They revealed that the combined use of PEO and PEG has enabled the stable, sustained release of drugs throughout the gastrointestinal tract, including the colon, where water availability is limited. Further, there has also been a number of studies on the drug release behavior from PEO matrices (Kojima et al., 2008; Maggi et al., 2002; Wu et al., 2005).

Evaluation of a drug release mechanism generally involves characterization using drug release profiles, which are determined by collecting fractions of the dissolution media and measurement using high-performance liquid chromatography (HPLC) or ultraviolet–visible (UV–vis) spectroscopy. However, for more complex systems comprised of a number of functional polymeric excipients, thorough comprehension of the drug release mechanism is difficult using cumulative drug release profiles alone. In particular, hydrogel matrix tablets are required a certain amount of time before the testing fluid reaches the tablet core, and subsequently they swell characteristically. Maggi et al. (2000) reported that PEO matrices take approximately eight hours to reach the maximum swelling. Such previous findings have lent support to the belief that the kinetics of water ingress into tablets play an important role in controlling drug release from hydrogel matrices.

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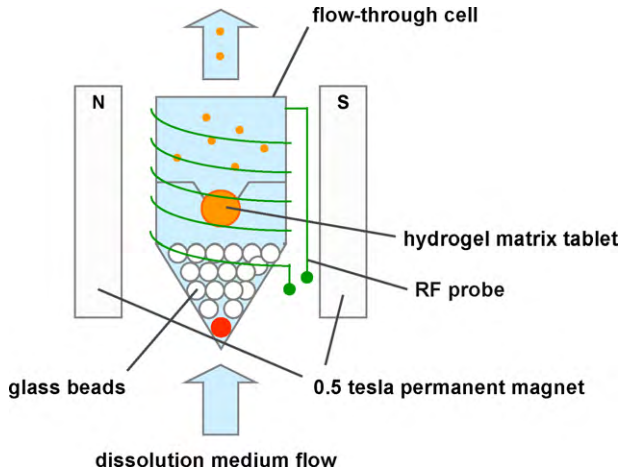

Fig. 1. Schematic illustration of flow-through cell apparatus fitted with a MRI.

In recent years, magnetic resonance imaging (MRI) has been used to explore the hydration phenomenon in pharmaceutical products using hydrophilic polymer matrices such as HPMC and PEO (Abrahmsén-Alami et al., 2007; Baumgartner et al., 2005; Fyfe et al., 2000; Kojima and Nakagami, 2002; Malaterre et al., 2009; Metz and Mäder, 2008; Richardson et al., 2005; Strübing et al., 2008; Tajarobi et al., 2009). Baumgartner et al. (2005) used MRI to quantitatively describe the swelling process seen in HPMC and hydroxypropyl cellulose (HPC) hydrogels on the basis of the concentration and mobility of water and the polymer as functions of time and distance. Abrahmsén-Alami et al. (2007) have developed a small release cell fitted in the MRI equipment, and revealed qualitatively and quantitatively the swelling and erosion behavior of PEO matrix tablet. Further, when MRI is combined with a flow-through cell apparatus for use in compendial analysis (European Pharmacopoeia, sixth ed., 2007; The Japanese Pharmacopoeia 15th ed., 2006; The United States Pharmacopeia 31-National Formulary 26, 2007) (Fig. 1), the physical changes in solid dosage forms can be examined in a dissolution test (Dorożyński et al., 2007; Fyfe et al., 2000; Kulinowski et al., 2008; Nott, 2010). Indeed, Fyfe et al. (2000) used such a combined system to assess drug delivery devices and thereby obtain a better understanding of drug delivery systems based on diffusion, dissolution, and osmosis mechanisms. Further, Dorożyński et al. (2007) and Kulinowski et al. (2008) carried out the compendial flow-through cell dissolution method for a HPMC matrix using two different solutions; fasted state simulating gastric fluid (FaSSGF) and fed state simulating gastric fluid (FeSSGF), under the continuous flow conditions to simulate *in vivo* conditions as closely as possible. However, the integrated investigation of the drug release mechanism from PEO hydrogel matrix tablet among the cumulative drug release profiles, the contribution of hydrogel matrix erosion and the conformation changes of the hydrogel under the compendial flow-through cell dissolution method have not been reported.

Here, to comprehensively examine the unique drug release mechanisms from PEO/PEG hydrogel matrix tablets, we used the combination of flow-through cell equipped with an MRI device to simultaneously evaluate the cumulative drug release profiles and internal states of tablets over time in a non-invasive and non-destructive manner. Further, the effect of polymeric erosion was assessed using size-exclusion chromatography (SEC), which was the most common way to obtain information about the molecular mass distribution of polymers (Abrahmsén-Alami et al., 2007; Kuga, 1981; Laguna et al., 2001). Acetaminophen (AAP) was used as a water-soluble drug, thereby enabling us to ignore the rate-determining step and instead focus on examining the drug release mechanism from PEO/PEG hydrogel matrices.

Table 1
Formulations of hydrogel matrix tablets loaded with AAP.

Tablets	Formulation		
	AAP (mg)	PEO (mg)	PEG (mg)
A PEO-7M/PEG (5:1)	20	150	30
B PEO-7M/PEG (1:1)	20	90	90
C PEO-7M/PEG (1:5)	20	30	150
D PEO-2M/PEG (5:1)	20	150	30
E PEO-2M/PEG (1:1)	20	90	90
F PEO-2M/PEG (1:5)	20	30	150

2. Materials and methods

2.1. Materials

AAP was purchased from API Corporation (Tokyo, Japan), and two kinds of PEO with average molecular weights of 7.0×10^6 (Polyox WSR 303, PEO-7M) and 2.0×10^6 g/mol (Polyox N60K, PEO-2M) were obtained from Dow Chemical (MI, USA). PEG with an average molecular weight between 7.3×10^3 and 9.3×10^3 g/mol (Macrogol 6000) was purchased from Sanyo Chemical Industries (Kyoto, Japan). All other chemicals used were of reagent grade.

2.2. Preparation of testing tablets

To avoid aggregation, the AAP and polymers (PEO and PEG) were passed through a sieve (355-μm aperture) before mixing. In total, six tablets were prepared with the concentration of AAP in each fixed at 10% (w/w). Polymer matrices of PEO and PEG mixtures were blended at weight ratios of 5:1, 1:1, and 1:5, respectively, and the tablets were designated A, B, C, D, E and F in Table 1. AAP was manually mixed with PEO and PEG in separate mortars for 5 min, and the resultant mixtures were compressed into 200-mg tablets in an autograph oil press (AGS-20kNG; Shimadzu, Kyoto, Japan) using 8 kN in applied force and a round-faced 8.0-mm diameter tooling.

2.3. Dissolution test

The *in vitro* drug release properties of the tablets were evaluated via the flow-through cell apparatus (DZ70; Pharma-Test AG, Hainburg, Germany) at a flow rate of 4 mL/min in a closed loop circuit containing 900 mL of dissolution test medium at 37 °C following the pharmacopoeia (European Pharmacopoeia, 6th ed., 2007; The Japanese Pharmacopoeia 15th ed., 2006; The United States Pharmacopeia 31-National Formulary 26, 2007). A flow-through cell was filled with 1-mm glass beads to create laminar flow, and a metal clip was used to hold the tablet in the original position. Distilled water was used as the medium, and was degassed by filtration in a vacuum before use, as described in the protocol (The United States Pharmacopeia 31-National Formulary 26, 2007), Every two hours, the dissolution medium was withdrawn from the dissolution vessels and the amount of AAP released from the tablets was measured using UV–vis spectroscopy at 280 nm (UV-2400PC; Shimadzu). In addition, the amounts of PEO and PEG eroded from the matrices were quantified by SEC, using a HPLC system (1200 series; Agilent Technologies, CA, USA) equipped with a charged aerosol detector (Corona CAD; ESA Biosciences, MA, USA) and a SEC column (TSK-GEL Alpha-3000; Tosoh, Tokyo, Japan; 7.8 mm i.d. × 30 cm, 7 μm). Purified water was used as a mobile phase for HPLC analysis, and the flow rate was 0.75 mL/min.

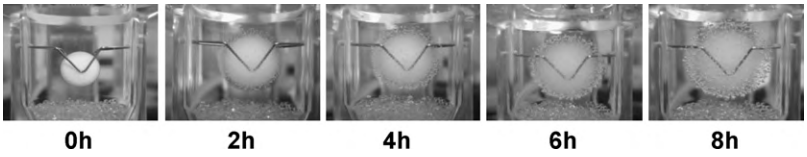

Fig. 2. Hydrogelation progress of Tablet A; PEO-7M/PEG (5:1) during flow-through cell dissolution test.

2.4. MRI scanning during the dissolution test

Our experiment combining MRI with a flow-through cell method was conducted using a bench-top MRI system (MARAN-iP; Oxford Instruments, Oxfordshire, UK) equipped with a 0.5 tesla permanent magnet system stabilized at 37 °C and operating at 20.6 MHz for ^{1}H NMR imaging. The testing conditions for flow-through cell were described in 2.3. MRI images were collected under the continuous medium flow conditions. To maintain the tablet in its original slice position for image acquisition, a plastic holder with a rubber retaining band was used instead of the original metal Pharmacopoeia clip, since a metal clip would have caused distortions in the magnetic field. T_1-weighted images were produced in the spin echo method. The signal intensity of the MRI pictures was defined as

$$S = M_0 \times \exp\frac{-\mathrm{TE}}{T_2} \times \left(1 - \exp\frac{-\mathrm{TR}}{T_1}\right) \quad (1)$$

where M_0 is magnetization, T_1 and T_2 are relaxation times, and TR and TE are repetition time and echo time, respectively. The imaging parameters were as follows: TR, 1 s; TE, 10 ms; the number of accumulations, 2; single image acquisition time, 4.3 min.; and temporal resolution of MRI data, 30 min. Resolution for the 128 × 128 pixel 2D images was 250 μm, with a slice thickness of 3 mm. In the present study, the image processing and analysis were carried out as with previous works using Image analysis and ImageJ software (Malaterre et al., 2009; Metz and Mäder, 2008).

2.5. Fourier transform infrared (FT-IR) spectroscopy

All IR spectra were measured at a resolution of 2 cm^{-1} using a FT-IR spectrometer (NICOLET 6700; Thermo Fisher Scientific, MA, USA) equipped with a diamond-ATR accessory and a deuterated triglycine sulfate detector. In order to acquire the IR spectra of both hydrogelling and non-hydrogelling parts, Tablet A was taken one hour after starting dissolution test. Tablet A was measured as a representative hydrogel matrix, because the two states are expected to be the same among six tablets. It was peeled and divided into the hydrogel layer and non-hydrogel core to understand the differences between the two states. A total of 64 scans were co-added to obtain spectra for each layer, the dried Tablet A, and water. All of the IR spectra were defined in absorbance units as

$$A = -\log_{10}\frac{R}{R_0} \quad (2)$$

where R and R_0 are the intensities of IR light from a sample and a reference compound, respectively.

3. Results

3.1. Dissolution study by flow-through cell

Photos were taken every two hours during the flow-through cell dissolution test for Tablet A (Fig. 2). These photos clearly show gradual swelling of the tablet over time, due to gelling of the hydrophilic matrix, and complete gelling within approximately 4 h.

Cumulated drug release curves for the tablets used in the present study indicated that the lower the concentration and molecular weight of PEO, the faster AAP released (Fig. 3). In particular, Tablet F showed much faster AAP releasing than the other tablets. These findings therefore suggested the possibility that the release mechanism of Tablet F differed from those of other tablets.

3.2. IR spectra

We investigated the types of water and the interaction between water and PEO/PEG matrix in the hydrogel using FT-IR spectroscopy. Fig. 4a showed IR spectra in the 4000–750 cm^{-1} region of dried Tablet A, water as a dissolution medium, and the surface of both the hydrogel layer and non-hydrogel core of Tablet A which was taken one hour after starting dissolution test. Figures 4b and 4c depicted enlarged spectra in the 3700–2700 and 1200–980 cm^{-1} regions, respectively. A relatively intense O-H stretching band (3700–3000 cm^{-1}), due to water penetration, could be seen in the hydrogel layer (blue line) and appeared strikingly similar to that for bulk water (light-blue line), indicating that much of the free water existed in the hydrogel layer. Interestingly, this O-H stretching band can also be observed in the non-hydrogel core (red line), although not in the dried tablet (green line), in a higher wavenumber (approximately 3500 cm^{-1}) than that for bulk water (light-blue line). This observation suggests the presence of non-freezing water in the non-hydrogel core (Morita et al., 2007; Tanaka and Mochizuki, 2004), indicating incomplete hydrogelling transformation. Further, as the dissolution medium penetrated into a tablet, a C–O stretching band at 1102 cm^{-1} (red line) shifted by approximately 20 cm^{-1} to a lower wavenumber (blue line) caused by the formation of hydrogen bonds between the C–O groups of PEO/PEG and water molecules (Fig. 4c). The C–O–C asymmetric stretching band at 1061 cm^{-1} assigned to a helical conformation of crystalline PEO/PEG (Brubach et al., 2004) disappeared in the spectrum of the hydrogel layer (blue line), indicating that the crystalline hydrophilic matrices were completely altered to an amorphous state by water penetration.

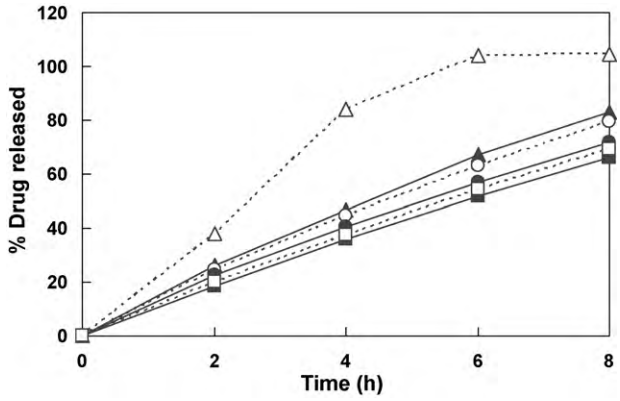

Fig. 3. Cumulative release profile of AAP; ■: Tablet A: PEO-7M/PEG (5:1), ●: Tablet B: PEO-7M/PEG (1:1), ▲: Tablet C: PEO-7M/PEG (1:5), □: Tablet D: PEO-2M/PEG (5:1), ○: Tablet E: PEO-2M/PEG (1:1), Δ: Tablet F: PEO-2M/PEG (1:5).

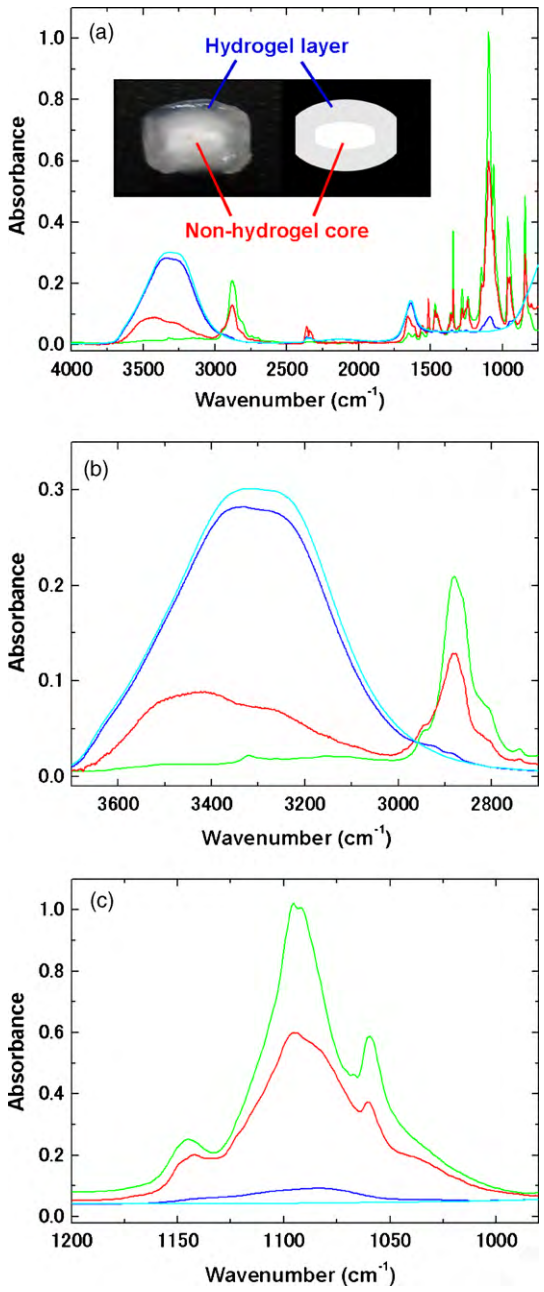

Fig. 4. ATR-IR spectra of dried Tablet A, water, and the surface of the hydrogel layer and non-hydrogel core parts of Tablet A, at one hour after the dissolution test in the 4000–750 cm^{-1} region (a), close-up spectra in the O–H stretching region (b), and close-up spectra in the C–O stretching region (c). Green line: dried Tablet A, blue line: surface of the hydrogel layer, red line: surface of the non-hydrogel core part, and light blue line: water.

3.3. MRI monitoring

^{1}H NMR images of each tablet during the flow-through cell dissolution test were shown in Fig. 5. In each image, non-hydrogelling layers were shown in black (extremely short T_2 relaxation time), hydrogelling layers in white (T_1 relaxation time: <1 s), and dissolution medium in gray (T_1 relaxation time: approximately 3 s). The high-intensity areas of the hydrogels in MRI images (white part, Fig. 5) had a smaller relaxation time (T_1) than bulk water (gray region, Fig. 5) due to the hydrogen bonds between the hydrophilic polymers and water (Fyfe and Blazek, 1997), as verified by IR study. Further, the IR study additionally indicated that the zero intensity region (black area) was a non-hydrogelling layer.

The time-dependence of the gelling process was quantified by plotting the changes in the non-hydrogelling regions (black area, Fig. 5) during the dissolution test (Fig. 6a). Changes in hydrogel thicknesses (white part, Fig. 5) during the dissolution test were shown in Fig. 6b. MRI studies suggest that the non-hydrogel area (black part) was reduced as the fluid was penetrated into a tablet (Fig. 6a). In the present study, all non-hydrogel portions of all tablets disappeared within approximately three hours, indicating that all of the tablets' matrices were hydrated and gelled. Further, from a different viewpoint, the MRI data shown in Fig. 6a indicate the fluid ingress behavior. For both the PEO-2M and PEO-7M formulations, the greater the concentration of PEG in tablets, the faster the penetration of dissolution medium. However, no significant difference in penetration process is observed between the two formulations.

Evaluation of changes in hydrogel layer thickness during the dissolution test indicated that their thicknesses increase with time, except in Tablets C and F (Fig. 6b). The differing findings with Tablets C and F are believed to be due to the higher content of PEG in these tablets when compared with the other tablets, as water-soluble PEG tends to accelerate tablet erosion. Further, tablets containing PEO-7M retained a much thicker hydrogel portion than tablets with PEO-2M. Taken together, these results suggest that the greater molecular weight and tangled structure of PEO-7M will allow it to form a more rigid hydrogel structure than PEO-2M.

Given the MRI findings of the present study, we hypothesize that the hydrogelation kinetics of the tablets depends only on the composition ratio of PEG to PEO. However, the behavior of hydrogel formation was not completely controlled by the concentration of PEG, on the other hand, the shape retention capability were strongly affected by the concentration of PEG as well as the molecular weight of PEO.

3.4. Erosion behavior of hydrogel matrices

Fig. 7a and b shows the erosion profiles of PEO and PEG quantified by SEC, respectively, for each formulation during flow-through cell dissolution study. These profiles appear to indicate that the accumulative erosion profiles of PEG depend primarily on the composition ratio of PEG to PEO, given that tablets with higher compositions of PEG showed quicker erosion of hydrogel matrices than those with lower compositions; similar patterns were also observed for PEO. Considering that PEG is more soluble and releasable than PEO, erosion of PEG should initiate and subsequently accelerate the erosion of PEO from the hydrogel.

Findings also showed that accumulative erosion profiles of PEO-2M exceeded those of PEO-7M, due to the differences in the molecular weight mentioned before. The characteristic erosion profiles observed for Tablet F may be explained by considering that the erosion effect of Tablet F's formulation, which included a relatively high concentration of PEG and the relatively low-molecular weight PEO-2M.

4. Discussion

4.1. Correlation between fluid ingress and AAP release behaviors

MRI findings in the present study suggest that the dissolution medium perfused the whole tablet within the first few hours (Fig. 6a), suggesting complete dissolution of AAP in the tablet within 3 h. However, as shown in Fig. 3, AAP was not fully released from the hydrogel matrices within the expected period, even though the tablet was completely infused with testing medium within the first few hours (see Figs. 2 and 6a). Indeed, the amount of drug released from Tablets A–F range between 40% and 80% at the sampling point

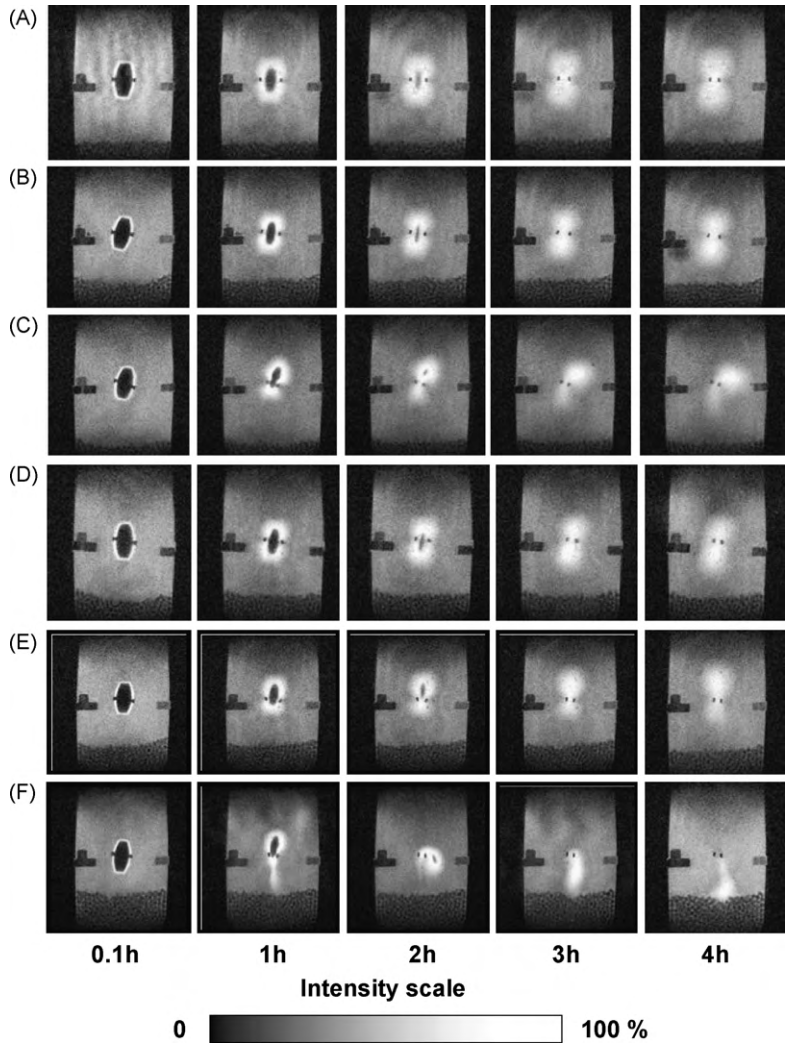

Fig. 5. MRI images of each formulation during flow-through cell dissolution test, taken every hour. From the top: (A) Tablet A: PEO-7M/PEG (5:1), (B) Tablet B: PEO-7M/PEG (1:1), (C) Tablet C: PEO-7M/PEG (1:5), (D) Tablet D: PEO-2M/PEG (5:1), (E) Tablet E: PEO-2M/PEG (1:1), and (F) Tablet F: PEO-2M/PEG (1:5).

of 4 h, indicating that there is no correlation between fluid ingress behaviors and the cumulative drug release profiles. Therefore, the contributions of both the drug self-diffusion and the matrix erosion which are well known controlling factors will be discussed below.

4.2. Diffusion of AAP from hydrogel matrices

To discuss the diffusion mechanism of AAP from PEO/PEG matrices, the relationship between hydrogel layer thicknesses and cumulative AAP release profiles was evaluated, with results showing a good correlation between their accumulated layer thicknesses measured by MRI every 30 min and the amount of drug released (Fig. 8). In the early phase of dissolution test, up to around 2 h after starting dissolution test, there were little differences in the amount of AAP released whose drug molecules were originally located near the surface of each tablet. On the other hand, after about four hours, the amount of drug released decreases with increasing drug diffusion length corresponding to the thicknesses of their matrix layers, prompting the conclusion that hydrogel layer thickness may affect the cumulative AAP release profile. Thus, the hydrogel layer thickness is regarded as the primary factor of controlling drug release by diffusion from the PEO/PEG matrices, except for in Tablet F, the erosion mechanism of which will be discussed below.

4.3. Erosion of hydrogel matrices

In the present study, we were able to precisely detect changes in hydrogel thicknesses during the dissolution test using MRI (Fig. 6b). However, estimating the contribution of hydrogel erosion to the drug release profile based solely on the MRI data proved difficult. Therefore, we used SEC to directly define the erosion profiles of each hydrophilic polymer over time in the dissolution test (Fig. 7).

Typically, hydrogel matrices constructed using high-molecular weight polymers do not show much erosion, particularly at early stages of dissolution, as their helical chains tend to form rigid interactions among polymer molecules. With regard to PEO, the crystalline portion was transformed into an amorphous (random) state, which improved the molecular and chain interaction when the compound was soaked in water (see Section 3.2). However, erosion and diffusion of both PEO and PEG were observed even for tablets with a high ratio of PEO to PEG (Fig. 7). SEC data suggest that once portions of PEO or PEG begin to erode, large pores form in the hydrogel matrix, possibly contributing to subsequent further erosion. The large amount of PEG and infusion of low-molecular weight PEO-2M in Tablet F may therefore explain the significantly faster release of not only AAP but PEO and PEG observed with this tablet in comparison with other tablets. These results indicate that SEC is useful for quantifying the amount of eroded matrices in discerning the release mechanism for controlled-release tablets.

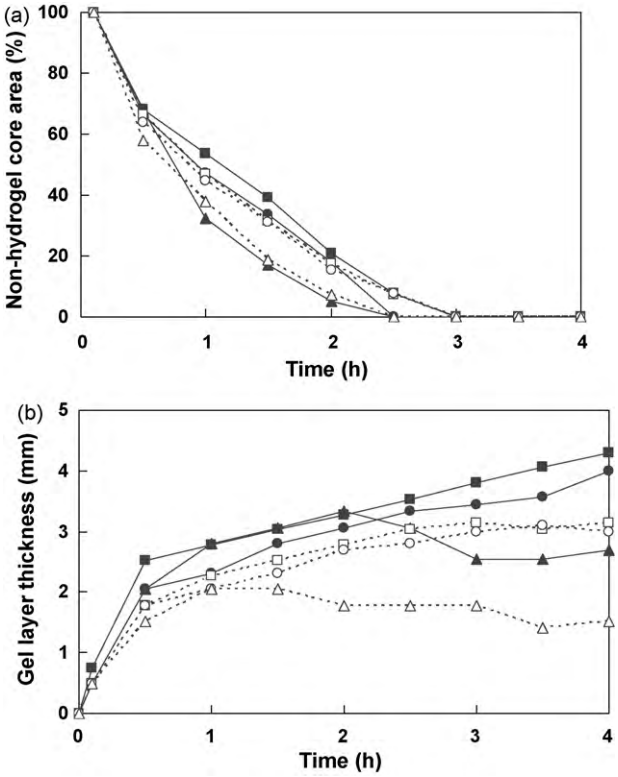

Fig. 6. Analysis graphs for MRI images of each tablet in the dissolution study. (a): Ratios of remaining portions of the non-hydogelling core to each initial area, (b): gel layer thickness. ■: Tablet A: PEO-7M/PEG (5:1), ●: Tablet B: PEO-7M/PEG (1:1), ▲: Tablet C: PEO-7M/PEG (1:5), □: Tablet D: PEO-2M/PEG (5:1), ○: Tablet E: PEO-2M/PEG (1:1), Δ: Tablet F: PEO-2M/PEG (1:5).

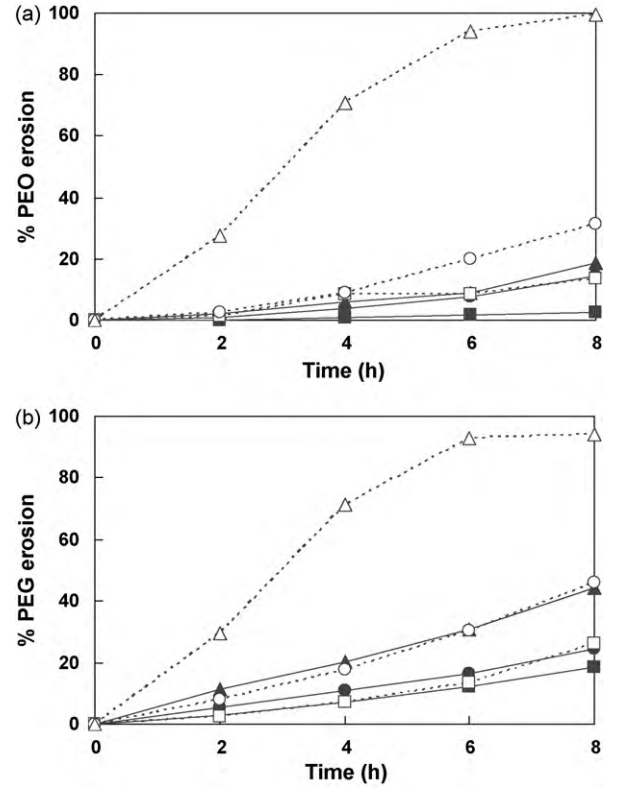

Fig. 7. Erosion profile of hydrogel matrices. (a): PEO, (b): PEG. ■: Tablet A: PEO-7M/PEG (5:1), ●: Tablet B: PEO-7M/PEG (1:1), ▲: Tablet C: PEO-7M/PEG (1:5), □: Tablet D: PEO-2M/PEG (5:1), ○: Tablet E: PEO-2M/PEG (1:1), Δ: Tablet F: PEO-2M/PEG (1:5).

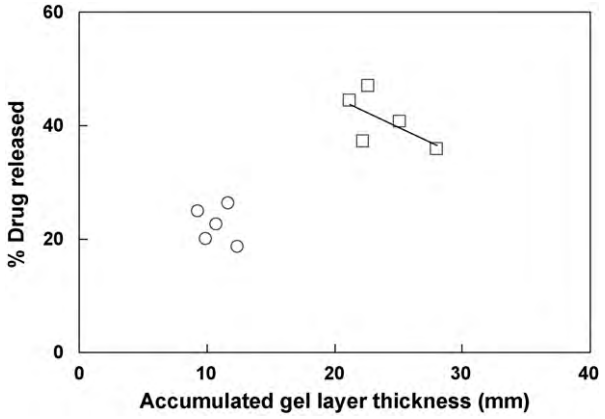

Fig. 8. Diagram describing the correlation between changes in accumulated hydrogel layer thickness measured by MRI every 30 min and the amount of AAP released. ○: after 2 h, □: after 4 h.

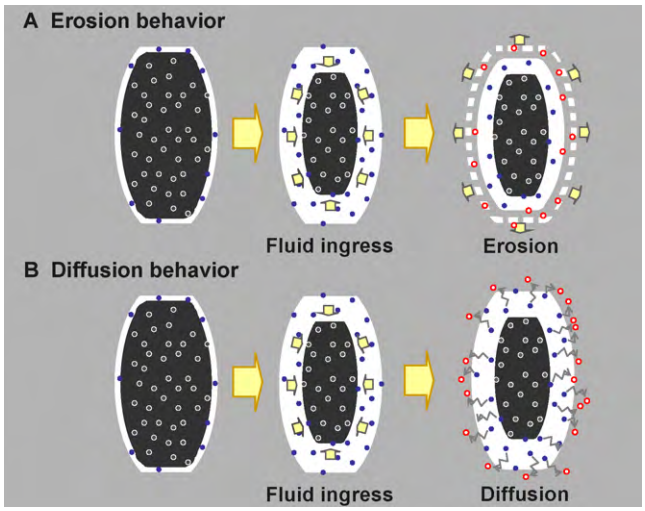

Fig. 9. Schematic illustration of drug release mechanism in PEO hydrogel matrix tablets. (A) Erosion behavior, and (B) diffusion behavior.

4.4. Release mechanisms on PEO/PEG hydrogel matrix tablets

A schematic illustration of the release mechanisms of AAP from PEO/PEG matrix tablets was presented in Fig. 9. As with the MRI images, the dark gray areas represent portions of the non-hydrogel core, while the white areas indicated portions of the hydrogel layer. Black, blue, and red particles represented non-dissolved AAP, dissolved AAP, and AAP released from the matrix, respectively.

Results from the present study indicate that the drug release mechanism of Tablet F is strongly controlled by the erosion of its hydrogel matrix (depicted as "Erosion" in Fig. 9). For this tablet, the erosion of PEG and PEO-2M occurs when the testing solution begins to penetrate into the matrix, and the erosion profiles of their hydrophilic materials are completely consistent with the release profile of AAP (see Figs. 3 and 7). In contrast, the AAP release in the other tablets (A, B, C, D, and E) is faster than their matrix erosion (see Figs. 3 and 7), indicating that the release mechanism of AAP is not controlled by matrix erosion, and is primarily dominated by the self-diffusion of AAP through the hydrogel layers (depicted as "Diffusion" in Fig. 9). Further, the cumulative drug release profiles are restrained with increasing hydrogel layer formation which is dependent on the composition of hydrogel matrices (depicted as "Fluid ingress" in Fig. 9).

With regard to Tablets A–E, we suspect that erosion of hydrogel matrices did indeed occur, as a measurable amount of PEO/PEG is found to be removed from the matrices (see Fig. 7). In the late stage of the dissolution test in particular, we suspect that the thinner the hydrogel layer becomes, the shorter the diffusion length for AAP. Thus, matrix erosion also affects the drug release behavior indirectly.

5. Conclusion

The AAP release mechanism from Tablet F which contains high PEG ratio to PEO and low molecular weight PEO is found to be strongly controlled by the erosion of the hydrogel matrix by SEC. On the other hand, the mechanism from the other tablets whose ratios of PEO to PEG is higher than that of Tablet F is not dominated by matrix erosion, and the contribution of the drug self-diffusion through the hydrogel layers is demonstrated by MRI.

Flow-through cell equipped with MRI and SEC are well suited to investigate the release mechanisms of hydrogel matrix tablets. With further development, this sort of combination study may aid in better understanding of the release mechanisms of pharmaceutical drug delivery system products.

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