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Research paper

Swelling kinetics of spray-dried chitosan acetate assessed by magnetic resonance imaging and their relation to drug release kinetics of chitosan matrix tablets

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ABSTRACT

Magnetic resonance imaging (MRI) was used to assess *in situ* swelling behaviors of spray-dried chitosan acetate (CSA) in 0.1 N HCl, pH 6.8 and pH 5.0 Tris–HCl buffers. The *in vitro* drug releases from CSA matrix tablets containing the model drugs, diclofenac sodium and theophylline were investigated in all media using USP-4 apparatus. The effect of chitosan molecular weight, especially in pH 6.8 Tris–HCl, was also studied. In 0.1 N HCl, the drug release from the matrix tablets was the lowest in relation to the highest swelling of CSA. The swelling kinetics in Tris–HCl buffers are Fickian diffusion according to their best fit to Higuchi's model as well as the drug release kinetics in all the media. The high swelling rate (k'_s) was found to delay the drug release rate (k'). The linear relationship between the swelling and fractions of drug release in Tris–HCl buffers was observed, indicating an important role of the swelling on controlling the drug release mechanism. Additionally, CSA of 200 and 800 kDa chitosan did not swell in pH 6.8 Tris–HCl but disintegrated into fractions, and the drug release from the matrix tablets was the highest.

1. Introduction

Swelling and erosion of pure polymers or drug–polymer matrices in dissolution media have been reported according to significant effects on controlled drug release systems including colonic drug delivery [1–5]. Although swelling properties of polymers were investigated by many techniques such as gravimetric technique and optical observation technique, there are some limitation, for example, the interference during weighing and error from removing excess solvent from the samples in gravimetric technique or the measurement of swollen gel under constrained condition in optical observation techniques [2,4–6].

Magnetic resonance imaging (MRI) is an outstanding technique from medical application to monitor swelling behavior of hydrophilic polymers especially in complicate drug delivery systems through nuclear magnetic resonance signal of the hydrogen nucleus, ^{1}H, the most sensitive signal [1,7–9]. MRI can also achieve full three-dimensional (3D) spatial resolution using orthogonal pulsed magnetic field gradients. Furthermore, MRI was applied to investigate swelling properties of many pharmaceutical materials, such as, hydroxypropyl methylcellulose (HPMC), starch, xanthan gum and bentonite [7,10–14].

Over the last decade, many colonic drug delivery systems have been developed in the treatment of colonic diseases, such as, colon cancer, amoebiasis and inflammatory bowel disease (IBD) to improve drug efficacy especially for local action and to prevent side effect of drugs [15]. Recently, chitosan, a cationic natural biopolymer produced by deacetylation of chitin, has been applied in various colon-specific drug delivery systems, especially in salt forms as lactate, glutamate, aspartate, hydrochloride and acetate [4,16,17]. Nonetheless, there are only a few studies on swelling behavior of chitosan in drug delivery systems, for example, polyelectrolyte complex microspheres and alginate beads coated with chitosan in various media using gravimetric methods. The drug release from the systems was controlled as enteric release according to the different swelling behavior in simulated gastric and intestinal fluid [18,19]. Nunthanid et al. studied the swelling of chitosan acetate in various media and its kinetics to explain the release of 5-aminosalicylic acid (5-ASA) from the compression coated tablets for colonic drug delivery using an optical observation method [4]. In the present study, MRI was used to observe real-time *in situ* swelling behavior of spray-dried chitosan acetate (CSA) compressed into tablets in various media, i.e., 0.1 N HCl, pH 6.8 and pH 5.0

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Tris–HCl buffers simulated to gastric fluid, small intestinal fluid, and colonic fluid of IBD patients, respectively [20]. The relationship between swelling and drug release kinetics from CSA matrix tablets containing diclofenac sodium (DS) and theophylline (TH) as an acidic and a basic model drug was investigated. The effect of molecular weight (MW) of chitosan on swelling and drug release in pH 6.8 Tris–HCl buffer was also examined.

2. Materials and methods

2.1. Materials

Chitosan (CS) with 87–89% degree of deacetylation and MW of 45 (CS45), 200 (CS200) and 800 (CS800) kDa were purchased from Seafresh Co. Ltd., Thailand (Lot Nos. COA050507, COA240702 and COA280604, respectively). DS and TH were purchased from Amoli Organics Ltd., India (Batch No. DS/0501/588A) and BASF Co. Ltd., (Lot No. 00099360-A), respectively. All other chemicals were of reagent grade.

2.2. Preparation of CSA

CSA was prepared from CS45, CS200 and CS800 by a spray drying technique as described in previous report [4]. Briefly, CS flakes were dissolved in an aqueous acetic acid solution. The solution was spray-dried by a spray dryer (model SD-60, Labplant, UK) under the following condition: 140 °C inlet temperature, 80–90 °C outlet temperature, and feeding rate of 5 mL/min. The obtained powders were collected and kept in a desiccator for further investigation.

2.3. Preparation of CSA and drug loaded CSA matrix tablets

To prepare CSA tablet for swelling study, CSA (300 mg) were compressed into tablets using a hydraulic press (Specac Inc., USA) at a fix compression force of 2 tons for 20 s with a 9.5-mm diameter flat-faced punch set.

Drug loaded CSA matrix tablets containing 275 mg of CSA and 25 mg of each model drug were also prepared under the same condition for *in vitro* drug release test.

2.4. Swelling study by MRI

An MRI instrument (Pharmasense™, Oxford Instruments, UK), as shown in Fig. 1, was used to investigate real-time *in situ* swelling and erosion behaviors of CSA tablets prepared from CS45. In general, MRI typically observes the mobile ^{1}H associated with the free water. If orthogonal magnetic field gradients are applied across the uniform static magnetic field during NMR acquisition, it is possible to spatially encode the signal in three dimensions. The signal intensity of a spin-echo image is dependent on the ^{1}H density which is related to water concentration as well as the T_1 (spin–lattice relaxation) and T_2 (spin–spin relaxation) values, which are related to water mobility [21]: this is given by the following equation:

$$\text{Signal intensity} \propto \text{PD} \cdot \exp(-\text{TE}/T_2) \cdot (1 - exp(-\text{TR}/T_1))$$

where TE and TR are the experimental echo and repetition time parameters, respectively. PD is the ^{1}H density. T_1/T_2 contrast images were used to highlight various features related to their water concentration and water-mobility.

In this experiment, CSA tablets were placed in various media, i.e., 0.1 N HCl, pH 6.8 and pH 5.0 Tris–HCl buffers which simulated to gastric fluid, small intestinal fluid, and colonic fluid of IBD patients, respectively. The images were captured every 10 min in black and white mode until the glassy core disappeared. The flow rate and temperature of the medium were controlled at

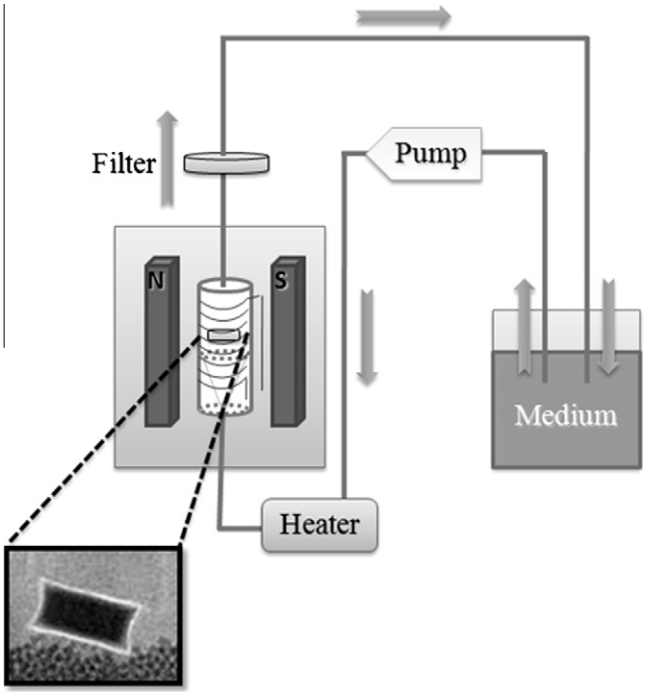

Fig. 1. Schematic diagram of an MRI instrument (Pharmasense™).

5 mL/min and 37 ± 0.5 °C, respectively. Contour lines were used to define and analyze the non-hydrated (glassy region) and hydrated (swelling or rubbery region) areas in rainbow mode by computer program (Mac-View Version 4, Mountech, Tokyo, Japan) (Fig. 2). Subsequently, the percentage of swelling was calculated by the following equation.

$$\text{Swelling } (\%) = \left[\frac{T_t - T_0}{T_0}\right] \times 100 \quad (1)$$

where T_0 is total cross sectional area of the original dry tablets and T_t is total cross sectional area (A + B in Fig. 2) of the swollen tablets measured at a time. Then, the percentages of swelling and glassy regions (mm^2) were plotted against time.

Furthermore, the swelling of CSA tablets prepared from CS200 and CS800 was also investigated in pH 6.8 Tris–HCl buffer.

2.5. In vitro release study

The release behavior of DS and TH from CSA matrix tablets in the same medium as in the swelling study was investigated using a flow-through cell dissolution apparatus (DZ1, Pharma Test, Germany). The 22.6-mm diameter flow cells were prepared by placing a 5-mm ruby bead in the apex of the cone and filling the cone with 1-mm glass beads in order to create laminar media flow. The matrix tablet was positioned in the cell on top of glass bead layers. To carry out the test, the medium was conveyed to the cells

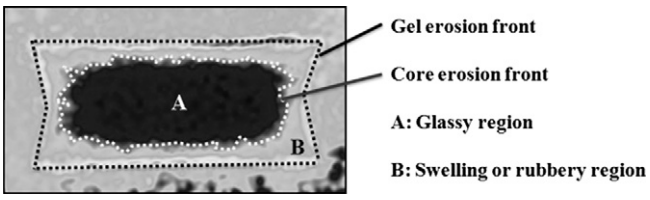

Fig. 2. Image diagram of a swollen CSA tablet from an MRI instrument in rainbow mode.

from the reservoir by the piston pump at a flow rate of 5 mL/min, 37 °C. The medium was collected at predetermined time intervals. The amount of drug was analyzed using UV-spectrophotometer (U-3300, Hitachi, Japan) at maximum wavelength of 271 nm for DS and 275 nm for TH. Additionally, the release profile of DS and TH from the matrix tablets of CSA prepared from CS with higher MW (CS200 and CS800) in pH 6.8 Tris–HCl buffer was also evaluated.

2.6. Relationship between swelling and drug release kinetics

The swelling and drug release kinetics of CSA tablets in each medium were calculated by the following equations [22,23];

Korsmeyer–Peppas model;

$$S = k_s t^n \quad (2)$$

$$M_t/M_\infty = kt^n \quad (3)$$

Higuchi's model;

$$S = k_s' t^{1/2} \quad (4)$$

$$M_t/M_\infty = k' t^{1/2} \quad (5)$$

First order kinetics;

$$\log S = k_s'' t \quad (6)$$

$$\log M_t/M_\infty = k\prime\prime t \quad (7)$$

Zero order kinetics;

$$S = k_s''' t \quad (8)$$

$$M_t/M_\infty = k''' t \quad (9)$$

where S, t, k_s, k_s', k_s'' and k_s''' are % swelling, time (h) and swelling constants of each model, respectively. M_t/M_∞, k, k', k'' and k''' are drug release fractions and drug release constants of each model, respectively. The graph between percentage of swelling and drug release fraction was also plotted to demonstrate their relationship.

3. Results and discussions

3.1. Swelling study by MRI

Fig. 3 shows MRI images of CSA tablets in various media, i.e., 0.1 N HCl, pH 6.8 and pH 5.0 Tris–HCl buffers. The images demonstrate high intensity of ^{1}H areas (white area) associated with water ingress of the hydrated area (swelling or rubbery region). The lower or zero intensity of ^{1}H regions (black area) represents for the non-hydrated area (glassy region). After exposure to the medium, the penetration of water into the tablets resulted in subsequent hydration/swelling and gel formation at the interface of the tablet and the medium. The gel erosion front moved outward, resulting in the expansion of swelling or rubbery region. In 0.1 N HCl, the most rapid swelling was observed and all the regions became gel after 420 min. This is because CS has a p*K*a value of about 6.2–7.0. Therefore, the amine functions of CS are protonated at lower pH. The ionization induces electrostatic repulsions between the polymer segments leading to high diffusion of solvent and high swelling rate of the polymer [24–26]. The swelling of CSA in both pH 6.8 and pH 5.0 Tris–HCl buffers was slower and the tablets tended to split at 430 and 560 min, respectively. The rate of water ingress into the inside core of the tablet, at pH 5.0, was slower than at pH 6.8 according to the higher gel formation as a barrier in the lower pH medium. As a result, the tablet splitting and rupture occurred owing to the swelling of partial hydrated inside CSA (Fig. 4). This result is in an agreement with the disintegration property of swelling polymers that used as tablet disintegrants such as gums and cellulose derivatives [27].

Fig. 5a demonstrates percentage of swelling of CSA in various media at various time intervals. The swelling of CSA in 0.1 N HCl was the highest and fastest where as the swelling rate of CSA in pH 6.8 and 5.0 was lower. This result is in consistency with the result from MRI mentioned above. However, CSA swelling in 0.1 N HCl reported by the previous research using an optical observation technique was the least according to the rapid gel erosion [4]. The different result was due to MRI technique could monitor the concentration of 1H which presented in water. Therefore, polymer swelling was accurately monitored while the optical observation

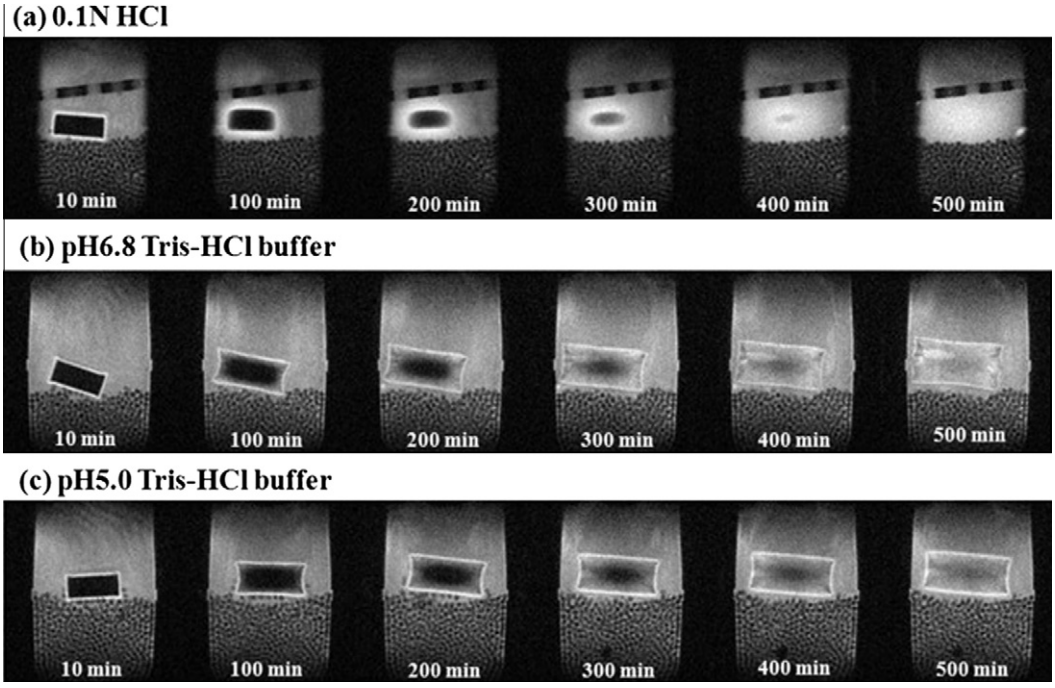

Fig. 3. MRI images of swollen CSA tablets prepared from CS45 in various media: (a) 0.1 N HCl, (b) pH 6.8 and (c) pH 5.0 Tris–HCl buffers.

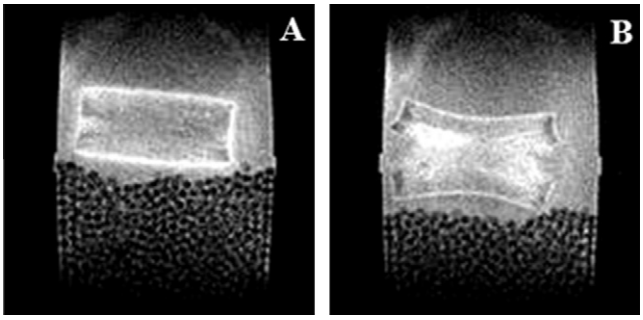

Fig. 4. Splitting of swollen CSA tablets prepared from CS45 at 1000 min, in (A) pH 5.0 and (B) pH 6.8 Tris–HCl buffers.

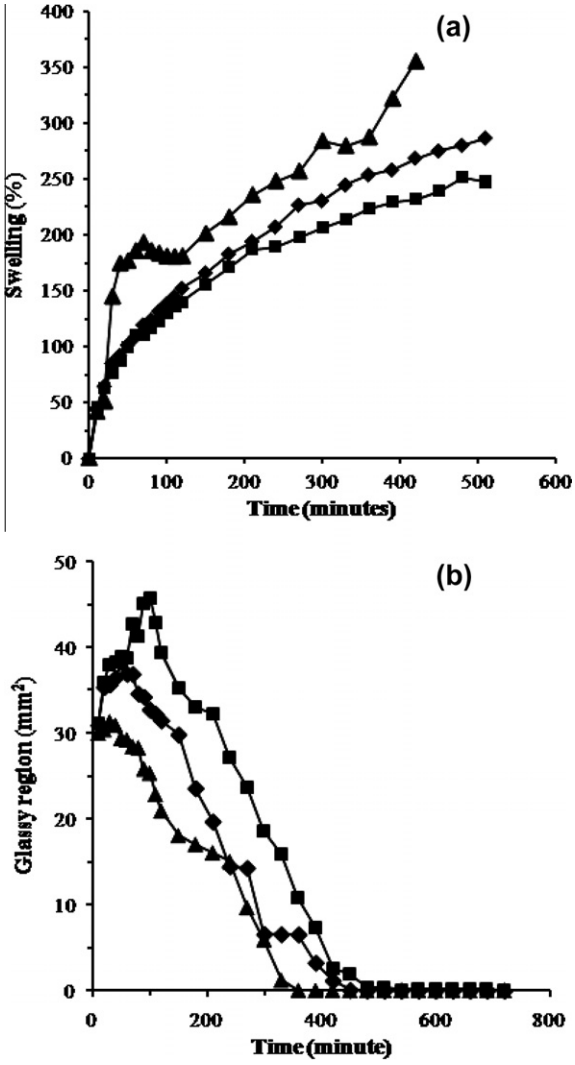

Fig. 5. (a) Percentage of swelling and (b) area of glassy region (mm^2) of CSA tablets prepared from CS45 in various media: 0.1 N HCl (▲), pH 6.8 (♦) and pH 5.0 Tris–HCl buffers (■) against time.

could not detect the exact boundaries between the clear hydrated gel and the solvent [10].

Fig. 5b shows the glassy region (black area inside the tablet) of CSA tablets in various pH media at various time intervals. The glassy region considerably expanded in higher pH media. For instance, at 100 min, the area increased from 30 mm^2 to 38.25 and 45.7 mm^2 in pH 6.8 and pH 5.0 buffers, respectively. This result is consistent with the previous studies by Ren et al. [28] and Sriamornsak et al. [29]. It could be explained that the pressure from the tablet compression process was released during gel formation resulted in the expansion of the glassy cores. Furthermore, the smaller expansion of the glassy region in pH 6.8 medium was due to the restriction of the more rigid structure of the outer gel layer as reported by Yao et al. that the elastic modulus of chitosan gel in an acid medium was higher than in an alkali medium [30].

Fig. 6 illustrates the swelling progress, in pH 6.8 Tris–HCl buffer, of CSA tablets prepared from CS with different MWs. It is apparent that CSA tablets made of CS200 and CS800 did not swell but began to disintegrate at 100 and 10 min, respectively, while that made of CS45 swelled and began to split at 430 min. The faster disintegration of the tablets made of CS with high MW was due to the higher porosity of CSA tablets as reported by Nunthanid et al., resulting in high water ingress rate into the tablets [16,31].

3.2. In vitro release study

In Fig. 7, the release profiles of DS and TH from CSA matrix tablets are demonstrated. It was found that the higher the percentage of gel swelling, the lower the drug release. In 0.1 N HCl, the drug release was the slowest according to the long distance of gel barrier retarding the drug diffusion into the medium. Furthermore, the release of DS was lower than that of TH, resulting from an interaction between COO^- functional group in the molecular structure of DS and the protonated NH_3^+ of CS. Puttipipatkhachorn et al. [32] reported that CS could interact with negatively charges of the acidic drugs and, thus retard the drug release. The effect of MW of CS on the drug release in pH 6.8 Tris–HCl buffer was also observed (Fig. 8). The drugs release from the tablets made of high MW CS was higher than those with low MW. This is probably due to the faster disintegration of high MW CSA tablets as presented by the MRI images in Fig. 6.

3.3. Relationship between swelling and drug release

Water uptake or hydration results in swelling of polymers, which is the main factor in controlling the drug release from the swelling system. To determine the relationship between swelling and drug release, kinetics of the swelling of CSA and the drug release of CSA matrix tablets prepared from CS45 in various media was analyzed by the application of Korsmeyers–Peppas, Higuchi's, first order and zero order kinetics models. As presented in Table 1, the swelling kinetics of CSA tablets in Tris–HCl buffers, pH 5.0 and 6.8, is Fickian diffusion, since they fitted well with both Higuchi's (r^2 in range of 0.993–0.994) and Korsmeyer–Peppas model (r^2 in range of 0.993–0.994 with n value close to 0.45 of a cylindrical shape). The results are in good agreement with the study of Bajpai et al. [33], which suggested that a Fickian diffusion is characterized by a solvent diffusion rate slower than the polymer relaxation rate. This was due to the fact that the polymer is in the rubbery state and polymer chains have a higher mobility that allows an easier penetration of the solvent [33]. In 0.1 N HCl, the swelling of CSA was not quite stable and did not fit with any kinetics models. This might was because of the very loose gel structure hence there was some interference from the gel erosion process. The results are consistent with Nunthanid et al. [4] who reported that CSA rapidly eroded in 0.1 N HCl. The drug release kinetics of DS and TH from the CSA matrix tablets made of CS45 in all media are Fickian diffusion as they best fitted with Higuchi's model (r^2 in range of 0.981–0.999) as presented in Table 2. Furthermore, the drug release from CSA matrix tablets made of high MW CS in pH 6.8 Tris–HCl buffer also obeyed Higushi's model, and their kinetics constants (k') were also higher than that of CS45 indicating the higher rate of drug release. In addition, as the swelling rate (k_s') was increased, the drug release rate (k') was decreased which

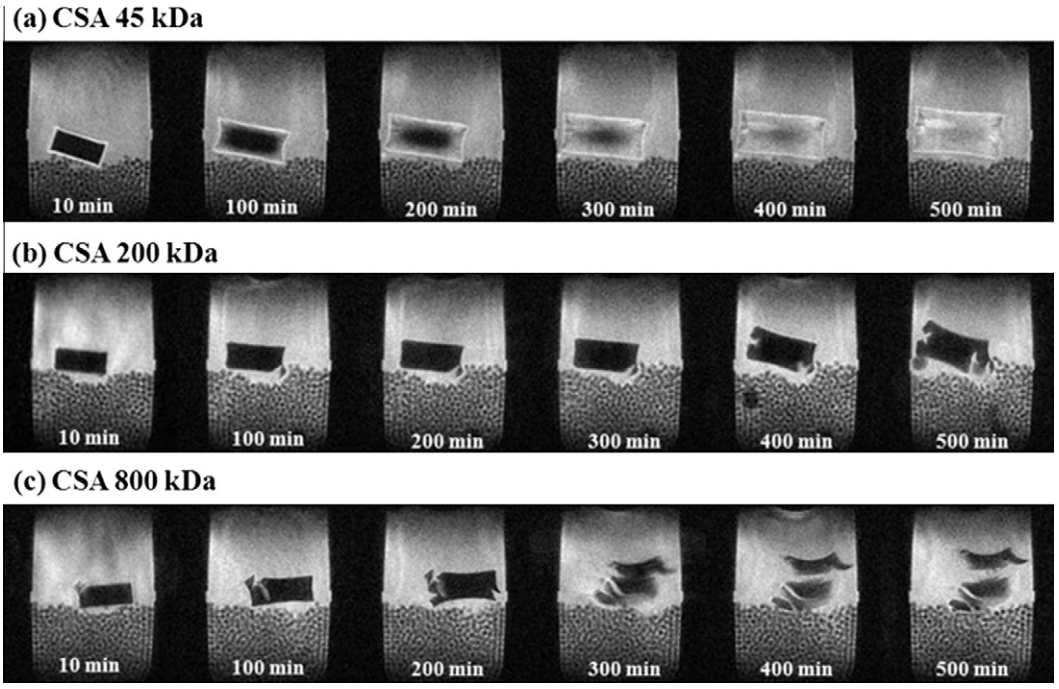

Fig. 6. MRI images of CSA tablets prepared from (a) CS45, (b) CS200 and (c) CS800.

implied that the high swelling rate delayed the rate of drug release from the matrix tablets. Fig. 9 shows the relationship between the release fraction of the model drugs (DS and TH) from CSA matrix tablets and percentage of CSA swelling. The linear relationship was found between the drug release and swelling in pH 6.8 and

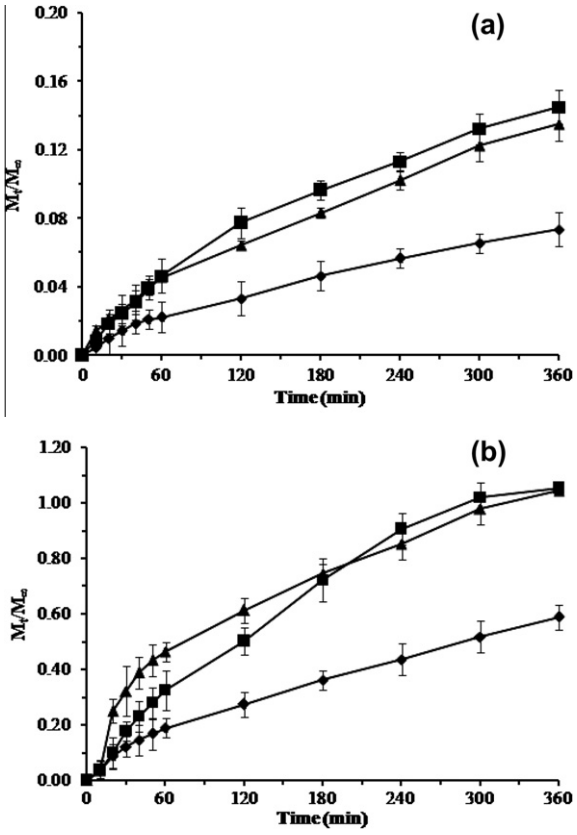

Fig. 7. The release profiles of (a) DS and (b) TH from CSA matrix tablets prepared from CS45 in 0.1 N HCl (▲), pH 6.8 (♦) and pH 5.0 (■) Tris–HCl buffers.

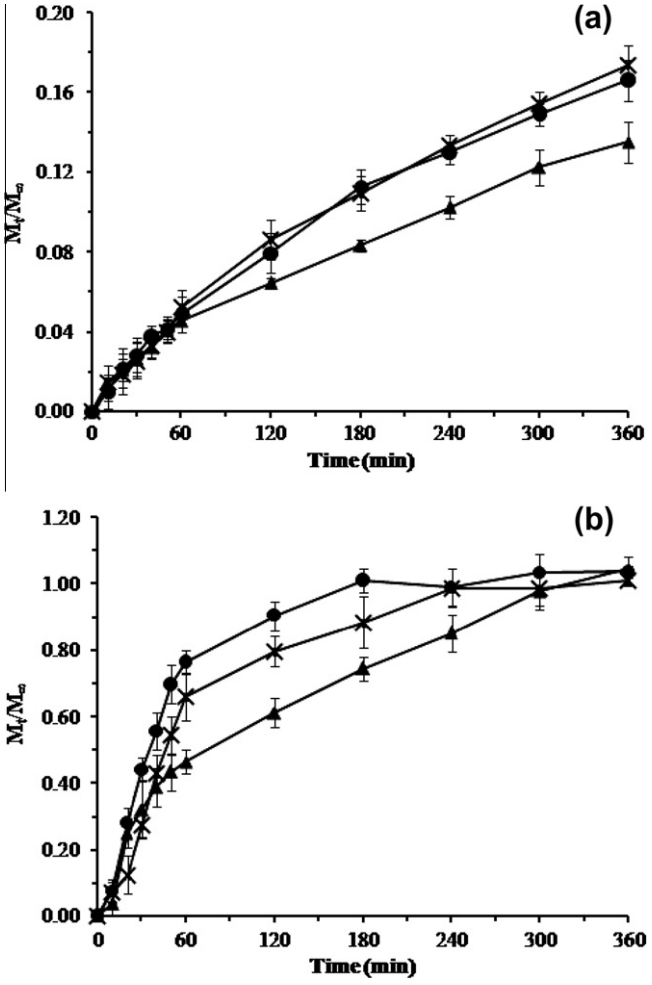

Fig. 8. The release profile of (a) DS and (b) TH from CSA matrix tablets in pH 6.8 Tris–HCl buffer prepared from CS45 (♦), CS200 (×) and CS800 (●).

Table 1
Swelling kinetics of CSA tablets prepared from CS45 in various media.

Sample	Swelling kinetics			
	$S = k_s t^n$ n (r^2)	$S = k_s' t^{1/2}$ k_s' (r^2)	Log $S = k_s'' t$ k_s'' (r^2)	$S = k_s''' t$ k_s''' (r^2)
CSA (CS45) 0.1 N HCl	0.575 (0.744)	15.65 (0.850)	0.003 (0.451)	3.394 (0.931)
CSA (CS45) pH 6.8 Tris–HCl	0.458 (0.993)	13.28 (0.994)	0.004 (0.858)	1.674 (0.890)
CSA (CS45) pH 5.0 Tris–HCl	0.448 (0.994)	11.83 (0.993)	0.003 (0.848)	0.551 (0.910)

Table 2
Release kinetics of DS and TH from CSA matrix tablets prepared from CS45 in various media and release kinetics of CSA matrix tablets prepared from CS200 and CS800 in pH 6.8 Tris–HCl buffer.

Sample	Release kinetics (DS)					Release kinetics (TH)		
	$M_t/M_\infty = kt^n$ n (r^2)	$M_t/M_\infty = k't^{1/2}$ k_s' (r^2)	Log $M_t/M_\infty = k''t$ k_s'' (r^2)	$M_t/M_\infty = k'''t$ k_s' (r^2)	$M_t/M_\infty = kt^n$ n (r^2)	$M_t/M_\infty = k't^{1/2}$ k' (r^2)	Log $M_t/M_\infty = k''t$ k'' (r^2)	$M_t/M_\infty = k'''t$ k_s' (r^2)
CSA (CS45), 0.1 N HCl	0.729 (0.981)	0.032 (0.993)	0.161 (0.775)	0.011 (0.982)	0.706 (0.978)	0.032 (0.995)	0.003 (0.755)	0.085 (0.993)
CSA (CS45), pH 6.8 Tris–HCl	0.500 (0.993)	0.061 (0.996)	0.146 (0.854)	0.021 (0.985)	0.498 (0.981)	0.055 (0.981)	0.002 (0.650)	0.203 (0.928)
CSA (CS45), pH 5.0 Tris–HCl	0.556 (0.945)	0.073 (0.996)	0.169 (0.780)	0.021 (0.977)	0.884 (0.962)	0.061 (0.995)	0.008 (0.689)	0.229 (0.959)
CSA (CS200), pH 6.8 Tris–HCl	0.745 (0.991)	0.085 (0.997)	0.171 (0.843)	0.023 (0.991)	1.304 (0.977)	0.163 (0.998)	0.022 (0.967)	0.805 (0.994)
CSA (CS800), pH 6.8 Tris–HCl	0.757 (0.991)	0.074 (0.996)	0.169 (0.793)	0.020 (0.979)	1.372 (0.967)	0.153 (0.999)	0.022 (0.843)	0.961 (0.984)

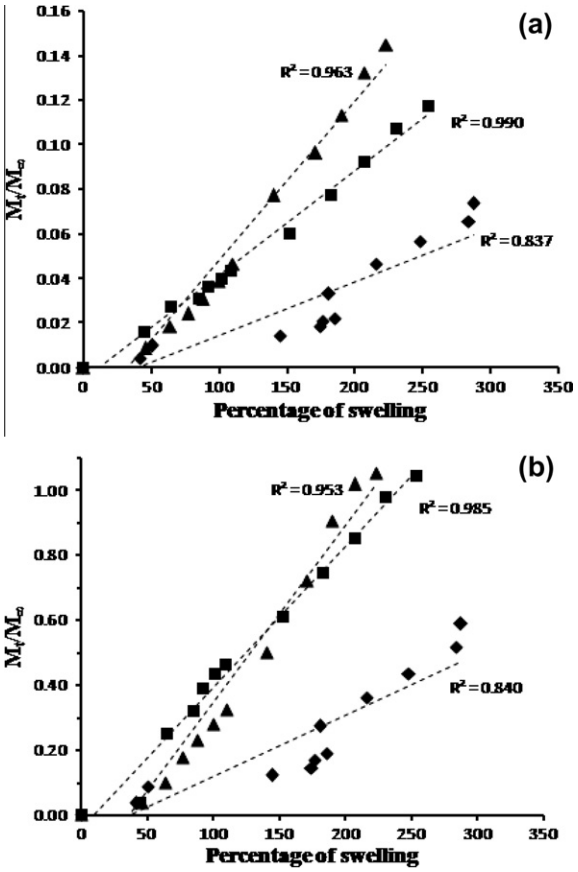

Fig. 9. Relationship between percentage of CSA swelling and (a) DS, (b) TH release fraction (M_t/M_∞) of CSA matrix tablets prepared from CS45 in 0.1 N HCl (▲), pH 6.8 (♦) and pH 5.0 (■) Tris–HCl buffers.

5.0 Tris–HCl buffers, indicating that the swelling behavior played an important role on controlling the drug release mechanism by diffusion. In 0.1 N HCl, the non-linearity relationships were observed which means that the diffusion of the drugs through the gel was not the key release mechanism of this system. It was consistent with the results of swelling kinetics which indicated the effect of gel erosion during the swelling process. However, the drug release kinetics obeyed Fick's law according to the long distance of gel barrier.

4. Conclusion

MRI technique combined with flow-through cell apparatus has been proven to be useful in the study of relationship between swelling and drug release kinetics of CSA matrix system. They reveal an important role of polymer swelling on drug release mechanisms follow Fickian diffusion control. In conclusion, CSA matrix system has a potential to provide enteric and colonic drug delivery purposes regarding the slowest drug release in simulated gastric fluid and the better release in simulated intestinal fluid and colonic fluid in IBD patients.

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