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Novel chitosan–magnesium aluminum silicate nanocomposite film coatings for modified-release tablets

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ABSTRACT

Chitosan (CS), a positively charged polysaccharide, and magnesium aluminum silicate (MAS), a negatively charged clay with silicate layers, can electrostatically interact to form nanocomposite films. In this study, CS–MAS nanocomposite films were evaluated for use in tablet film coating. Effects of CS–MAS ratio and coating level on water uptake and drug release from the coated tablets were investigated. Surface and film matrix morphology of the coated film and the effect of enzymes in the simulated gastro-intestinal fluid on drug release were also examined. The results demonstrated that the CS–MAS coated tablets had a rough surface and a layered matrix film, whereas a smooth surface and dense matrix film on the CS coated tablets was found. However, the CS–MAS coated tablets provided fewer film defects than the CS coated tablets. Nanocomposite formation between CS and MAS could retard swelling and erosion of CS in the composite films in acidic medium. The higher MAS ratio of the CS–MAS coated tablets gave lower water uptake and slower drug release when compared with the CS coated tablets. Moreover, the CS–MAS films on the tablets presented good stability towards enzymatic degradation in simulated intestinal fluid. The release of drug from the CS–MAS coated tablets could be modulated by varying CS–MAS ratios and coating levels. Additionally, drug solubility also influenced drug release characteristics of the CS–MAS coated tablets. These findings suggest that the CS–MAS nanocomposites displays a strong potential for use in tablet film coating intended for modifying drug release from tablets.

1. Introduction

Film coating of oral solid dosage forms provides many advantages in pharmaceutical manufacturing since it can overcome problems of unpleasant taste and odor of drugs, increase drug stability, and protect degradation of drugs from light, moisture, and oxidation processes (Nagai et al., 1997). Most importantly however, film coating can provide sustained drug release and protect the drugs from acid degradation in the gastro-intestinal tract (Wu et al., 1997). Synthetic cellulose derivatives, such as hydroxypropyl methylcellulose (Cao et al., 2004; Sangalli et al., 2004), and natural polymers, such as sodium alginate (Pongjanyakul et al., 2005) and chitosan (Nunthanid et al., 2002), have been previously used as coating materials for sustaining release of drug from the coated tablets.

Chitosan (CS), a positively charged polysaccharide consisting of N-acetyl-D glucosamine and D-glucosamine, has been used as a film coating material since it is biodegradable, biocompatible, physiologically inert, non-toxic (Illum, 1998; Krajewska, 2005), and possesses film forming properties (Senel et al., 2000; Nunthanid et al., 2001). Due to the high solubility in acidic media, tablets coated with CS films however, cannot sustain drug release in gastric conditions. For this reason, CS was blended with other substances in order to enhance acid stability of the films. It was found that CS could form polyelectrolyte complexes with anionic polymers, such as pectin (Fernández-Hervás and Fell, 1998; Macleod et al., 1999) and polyalkylenoxide–maleic acid copolymer (Yoshizawa et al., 2005), via electrostatic interaction. This led to retardation of acid swelling and improvement of film stability in gastric fluid.

Clays are composed of three-lattice layers, a central octahedral sheet of aluminum or magnesium and two external silica tetrahedron layers (Alexandre and Dubois, 2000). The silicate layer surface of clay has a negative charge, but weakly positive charges are present on the edges of the silicate layers. The silicate layers of clay can be separated and form three-dimensional structures when they are hydrated in water. It was found that CS can interact with several types of clay, such as montmorillonite (Roussy et al., 2005; Günister et al., 2007), magadiite (Liu et al., 2007), and rectorite (Wang et al., 2007). In our study, the interaction of CS and magnesium aluminum silicate (MAS) was investigated (Khunawattanakul et al., 2008).

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MAS is a mixture of colloidal montmorillonite and saponite (López-Galindo et al., 2007) that has been washed with water to optimize purity and performance and is employed as a pharmaceutical excipient due to its non-toxicity and non-irritation at levels used in drug formulations (Kibbe, 2000). Electrostatic interactions between CS and MAS cause a change in flow behavior and zeta potential of the composite dispersions. Moreover, the interaction of CS with MAS leads to flocculation in aqueous dispersions (Khunawattanakul et al., 2008). Recently, CS–MAS composite films were successfully prepared and characterized (Khunawattanakul et al., 2010). The CS–MAS composite films presented exfoliated and intercalated nanocomposites with properties dependent on the CS–MAS ratio used. For nanocomposite film formation it was not necessary to use heat treatment on the composite dispersion before film casting. The mechanical properties, particularly % elongation, of the CS films could be improved by nanocomposite formation of CS and MAS. Additionally, the CS–MAS films provided lower drug permeability than CS films. The drug permeation across the CS–MAS nanocomposite films occurred by diffusion processes through microchannels. Lower drug permeability and higher % elongation of the CS–MAS films indicated a strong potential for use as a coating film for modifying drug release from tablets.

In this study, we report for the first time about the use of the CS–MAS nanocomposite films for modifying drug release from tablets. The objective of this study was to evaluate the CS–MAS nanocomposite films as a coating material for tablets. Effects of CS–MAS ratio and coating level on water uptake and drug release from the coated tablets were investigated. Propranolol HCl (PPN), a cationic drug, and acetaminophen (ACT), non-electrolyte drug, were used as model compounds in this study. In addition, surface and film matrix morphology of the coated films, and the effect of enzymes in the gastro-intestinal tract on drug release characteristics were also examined.

2. Materials and methods

2.1. Materials

CS (molecular weight of 800 kDa) with an 85% degree of deacetylation was purchased from Seafresh Chitosan (Lab) Co., Ltd. (Bangkok, Thailand). MAS (Veegum® HV) was obtained from R.T. Vanderbilt Company Inc. (Norwalk, CT, USA). Propranolol HCl (PPN) and acetaminophen (ACT) were purchased from Changzhou Yabang Pharmaceutical Co., Ltd. (Jiangsu, China) and Praporn Darsut Ltd. (Bangkok, Thailand), respectively. Microcrystalline cellulose (Ceolus® PH102, Siam Chem-Pharm (1997) Co., Ltd., Bangkok, Thailand), spray-dried lactose (FlowLac® 100, Thai Meochems Co., Ltd., Bangkok, Thailand), magnesium stearate (Mallinckrodt Inc., USA), and colloidal silicon dioxide (Aerosil® 200, Degussa Japan Co., Ltd., Japan) were used as tablet excipients. Pancreatin (activity equivalent to 8× USP specification) extracted from porcine pancreas and pepsin (1:2500) extracted from porcine stomach mucosa were purchased from Sigma–Aldrich (St. Louis, MO, USA). All other reagents used were of analytical grade and used as received.

2.2. Preparation and evaluation of core tablets

Core tablets of PPN and ACT were prepared by a direct compression method. The tablets consisted of PPN or ACT (16.0%), microcrystalline cellulose (28.0%), spray-dried lactose (54.7%), colloidal silicon dioxide (0.3%), and magnesium stearate (1.0%, all percentages are by weight). The drug powder, microcrystalline cellulose, spray-dried lactose and colloidal silicon dioxide were mixed using a Y-shape mixer for 30 min. Then, magnesium stearate was incorporated into the mixture for 5 min before tabletting. An 8-mm biconvex punch and die was used. Core tablets were compressed using a single punch machine (YeoHeng Co., Ltd, Bangkok, Thailand), and tablet hardness was controlled in the range of 98–118 N. Average weight PPN and ACT core tablets obtained were 250.0 ± 3.1 and 250.0 ± 0.9 mg/tablet, respectively. Friability of both core tablets was less than 0.2%. The surface area of core tablets was calculated using the method of Bauer et al. (1998). The core tablets of PPN and ACT had a surface area of 1.86 ± 0.03 and 1.50 ± 0.05 cm^2/tablet, respectively. Both core tablets disintegrated in deionized water and 0.1 M HCl within 10 min (measured in a basket-rack assembly disintegration test apparatus (Model QC-21, Hansan Research, Northridge, CA)). The drug content in core tablets was extracted by using 0.1 M HCl and measured by UV-spectrophotometry (Shimadzu UV1201, Japan) at a wavelength of 289 and 265 nm for PPN and ACT, respectively. PPN core tablets contained 38.50 ± 0.92 mg/tablet ($n = 3$) of PPN whereas 40.20 ± 1.47 mg/tablet ($n = 3$) of ACT was found in ACT core tablets.

2.3. Coating of core tablets

CS and CS–MAS composite dispersions prepared using various CS–MAS ratios were used as coating materials. CS (1%, w/v) in 1% acetic acid was prepared and the CS dispersion was stirred overnight at room temperature. MAS (4%, w/v) was dispersed in hot water, then diluted with 10 mM acetate buffer at pH 4 to achieve a final concentration of 1% (w/v) MAS. The CS dispersion was mixed with various volumes of MAS dispersion to achieve CS–MAS ratios of 1:0, 1:0.2, 1:0.6, and 1:1 by weight. The volume of the composite dispersion was finally adjusted using 10 mM acetate buffer at pH 4. The composite dispersions were mixed for 5 min using a homogenizer and stored at room temperature for 24 h before coating.

The core tablets obtained were coated using a side-vented pan coating machine (Thai Coater Model FC15, Pharmaceuticals and Medical Supply, Thailand). The core tablets (900 g) were warmed in the coating pan under an inlet temperature of 70–75 °C and the coating pan was rotated at a rate of 10 revolutions/min. The spray rate of the coating dispersions was 4 ml min^{-1} under 0.38 mPa spray pressure. After the coating process, the coated tablets were stored in a dessicator prior to further examination.

The effect of CS–MAS ratio on characteristics of the coated tablets was investigated. The core tablets were coated with CS–MAS films with 1:0.2, 1:0.6, and 1:1 ratio of CS–MAS in the composite dispersion at a mean coating level of 4.3 mg cm^{-2}. CS coated tablets were also prepared at the same coating level. To investigate the effect of coating level, the core tablets were coated with the CS–MAS (1:1) composite films at the mean coating levels of 2.8, 4.3 and 8.6 mg cm^{-2}.

2.4. Scanning electron microscopy

Surface and film matrix morphology of the coated tablet were observed by scanning electron microscopy (SEM). The coated tablets and cross-sections of tablets were mounted onto stubs, coated with gold in a vacuum evaporator, and investigated using scanning electron microscopy (Joel Model JSM-6480LV, Tokyo).

2.5. Drug solubility studies

An excess amount of PPN or ACT was added into a test tube containing 10 ml of 0.1 M HCl or pH 6.8 phosphate buffer. Then, the tubes were shaken at 37 °C for 4–5 days until a saturated solution of drug was obtained. The concentration of PPN or ACT in the supernatant was analyzed using UV–visible spectrophotometry (Shimadzu UV1201, Japan) at a wavelength of 289 and 265 nm for PPN and ACT, respectively.

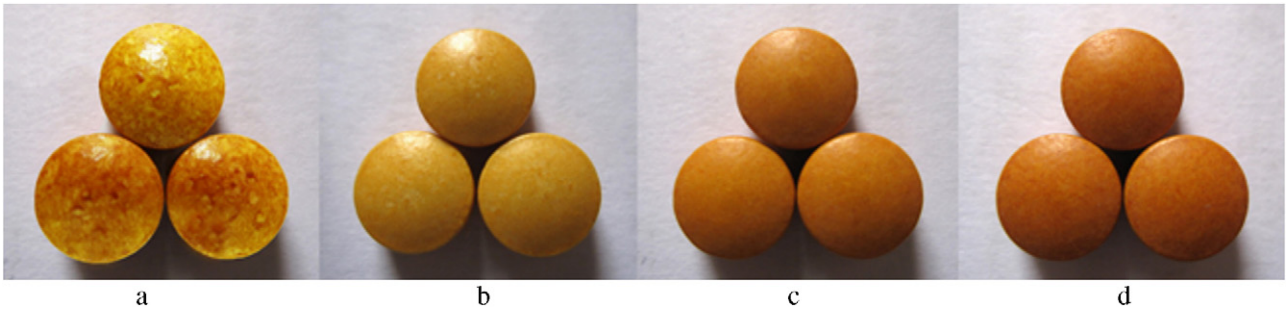

Fig. 1. Appearance of PPN-coated tablets with CS film (a), and CS–MAS films in the ratios of 1:0.2 (b), 1:0.6 (c), and 1:1 (d) at 4.3 mg cm^{-2} coating level.

2.6. In vitro release studies

Drug release from the coated tablets was characterized using a USP dissolution apparatus I (basket method). Dissolution media were 750 ml of 0.1 M HCl or pH 6.8 phosphate buffer at 37.0 ± 0.5 °C. The baskets were rotated at a rate of 50 revolution/min. At predetermined intervals, samples were collected and replaced with an equal volume of fresh medium. The concentration of drug released

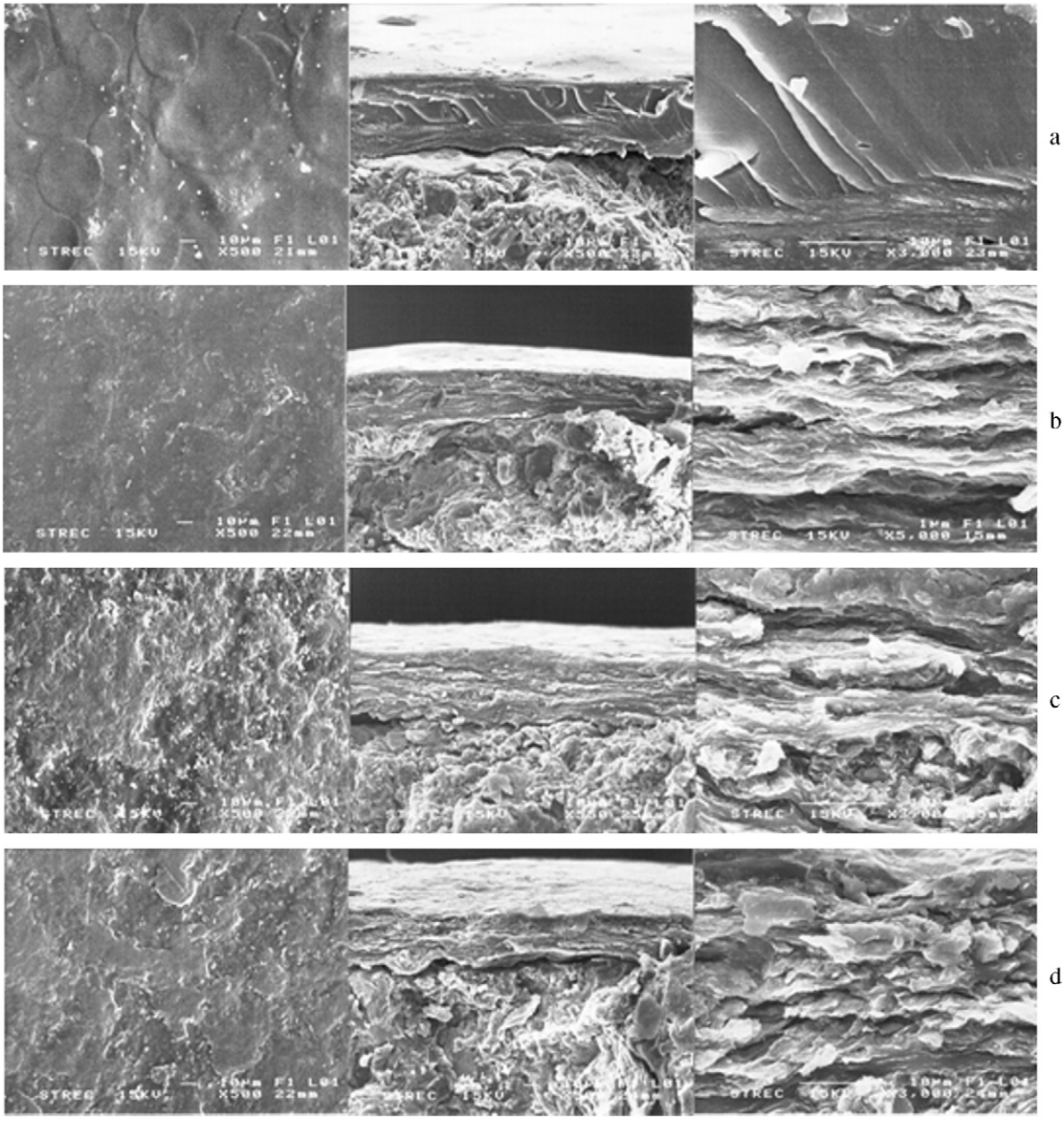

Fig. 2. SEM photographs of surface, cross-section and film matrix morphology of PPN-coated tablets with CS film (a), and CS–MAS films in the ratios of 1:0.2 (b), 1:0.6 (c), and 1:1 (d) at 4.3 mg cm^{-2} coating level.

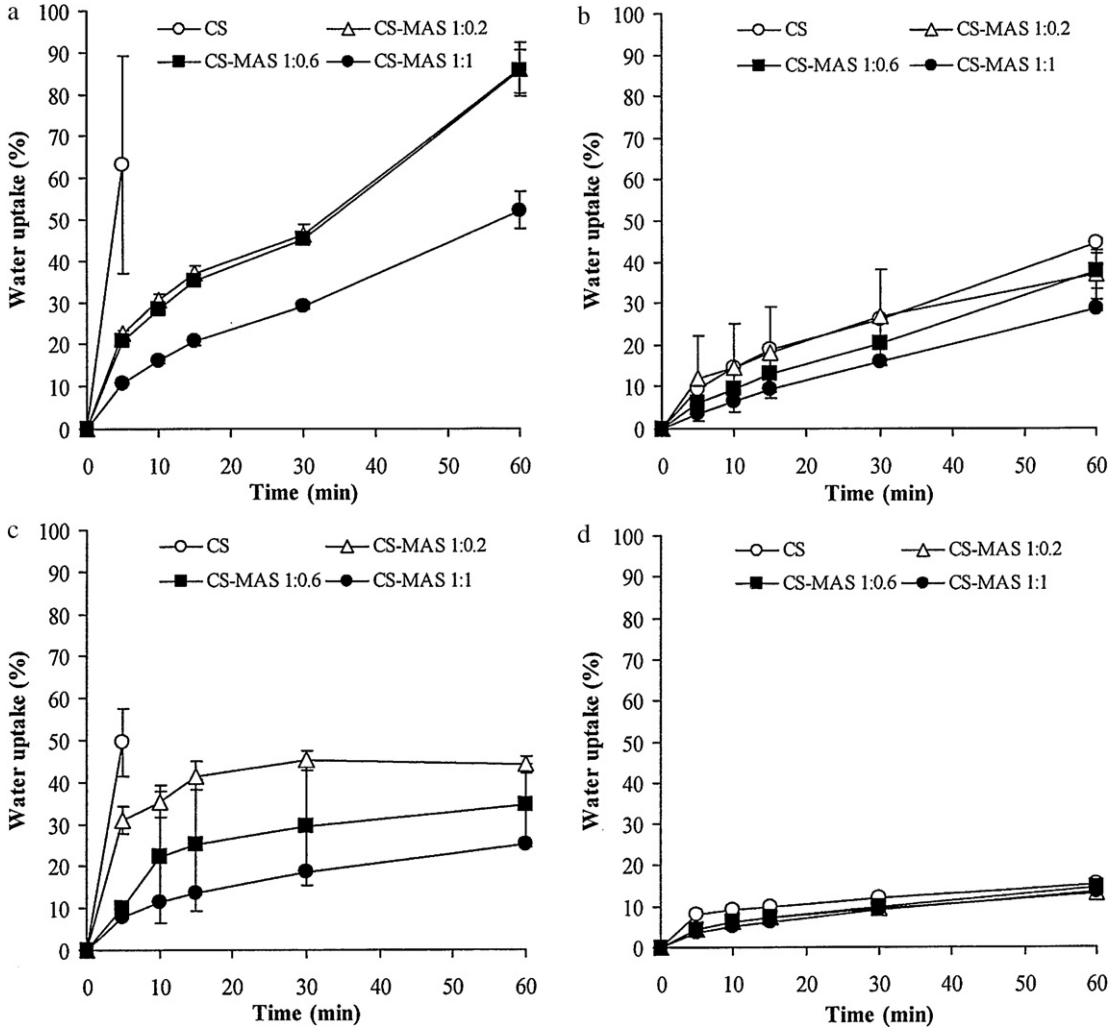

Fig. 3. Effect of CS–MAS ratio on water uptake of PPN-(a and b) and ACT-(c and d) coated tablets at 4.3 mg cm^{-2} coating level in 0.1 M HCl (a and c) and pH 6.8 phosphate buffer (b and d). Each value is the mean ± S.D., $n = 5$.

was assayed by using a UV–visible spectrophotometer (Shimadzu UV1201, Japan) at wavelength of 289 and 265 nm for PPN and ACT, respectively.

The effect of enzymes in the gastrointestinal tract on PPN release from the coated tablets was studied using simulated gastric fluid (SGF) with and without pepsin and simulated intestinal fluid (SIF) with and without pancreatin. SGF and SIF were prepared following the methods outlined in USP29/NF24. The collected samples were filtered using a cellulose acetate membrane (pore size 0.22 μm). The concentration of PPN released was determined using a UV–visible spectrophotometer at wavelength of 289 nm for SGF with and without enzyme and 310 nm for SIF with and without enzyme.

Drug release data of the coated tablets was evaluated using zero-order (Eq. (1)) and first-order (Eq. (2)) release kinetics:

$$F = K_0 t + B \tag{1}$$

$$-\mathrm{Log}(1 - F) = K_1 t \tag{2}$$

where F is fraction of drug released, t is time, and K_0 and K_1 are the zero-order and first-order release rate constants, respectively. B is a constant value and lag time of drug released from the coated tablets can be calculated using Eq. (1) when F equals zero.

2.7. Water uptake of coated tablets

Water uptake of the coated tablets in both 0.1 M HCl and pH 6.8 phosphate buffer was determined using USP dissolution apparatus I (basket) and the test conditions were the same as in the drug release study. The coated tablets were weighted (W_d), placed into baskets and immersed into the medium. At predetermined intervals, wet coated tablets were collected, carefully blotted with tissue paper to remove surface water and weighted (W_t) (Sungthongjeen et al., 2004). Water uptake of coated tablets could be calculated as follows:

$$\text{Water uptake}(\%) = \left(\frac{W_t - W_d}{W_d}\right) \times 100 \tag{3}$$

2.8. Statistical analysis

One-way analysis of variance (ANOVA) with the least significant difference (LSD) test for multiple comparisons and Student's t-test were used to compare the different results of drug release rate constant and lag time of the coated tablets. All statistical tests were performed using the software SPSS for MS Windows, release 11.5 (SPSS (Thailand) Co. Ltd., Bangkok, Thailand). The significance of the difference was determined at 95% confident limit ($\alpha = 0.5$) and considered to be significant at a level of P less than 0.05.

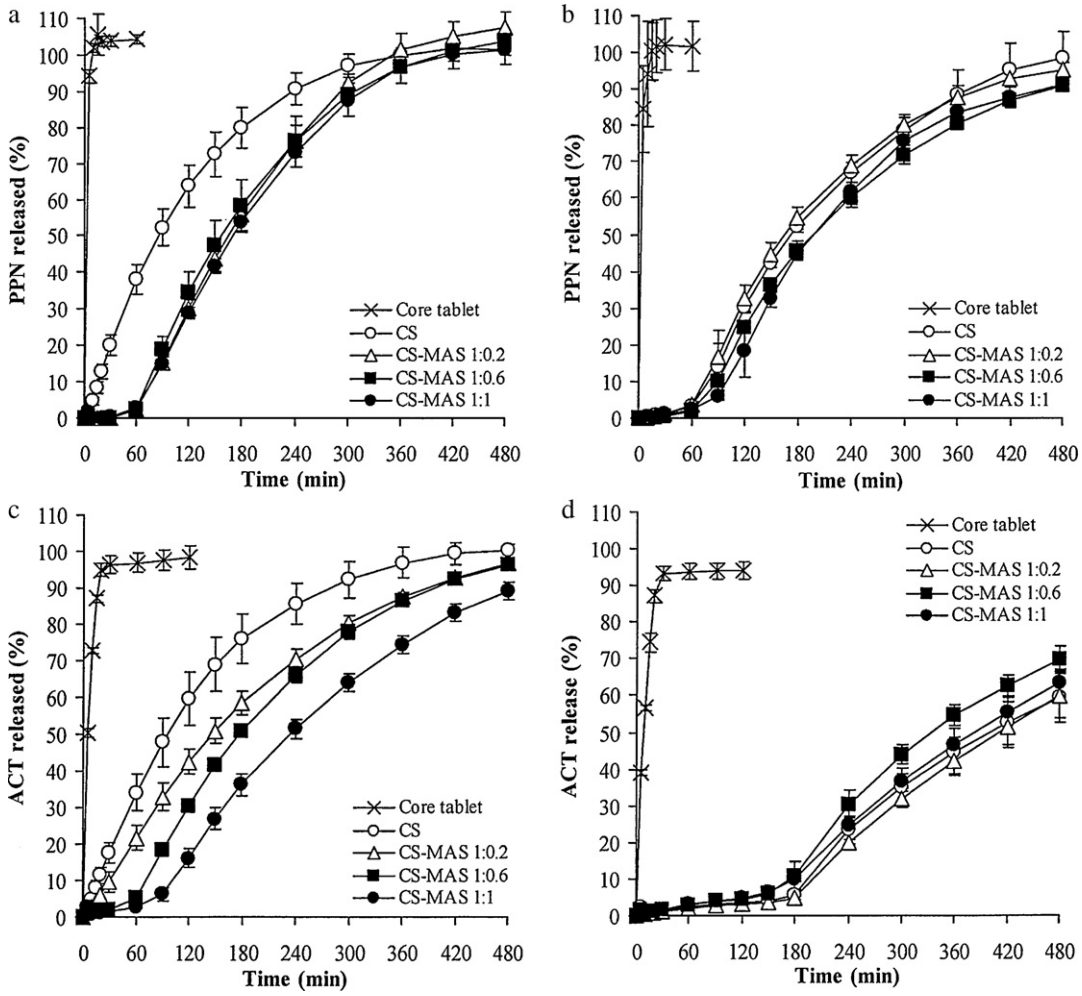

Fig. 4. Effect of CS–MAS ratio on drug release of PPN-(a and b) and ACT-(c and d) coated tablets at 4.3 mg cm^{-2} coating level in 0.1 M HCl (a and c) and pH 6.8 phosphate buffer (b and d). Each value is the mean ± S.D., $n = 3$.

3. Results and discussion

3.1. Appearance and morphology of coated tablets

Tablets coated using CS and CS–MAS nanocomposite films at various ratios had different visual appearances, which are presented in Fig. 1. The CS coated tablets showed a yellow and shrunken film, whereas the CS–MAS coated tablets had a brown, smooth and opaque film. Moreover, the CS coated tablets had more film defects than the CS–MAS coated tablets (Fig. 1). The microscopic morphology of the coated films, examined using SEM, is shown in Fig. 2. The CS coated tablets displayed a smooth surface and homogenous film matrix. This suggested that the tablets could be coated with CS, but film defect that was called picking (Rowe, 1997) could be visually observed (Fig. 1). Picking occurred from the film pull away from the surface core tablets in the initial period of the film coating process. In contrast, the CS–MAS coated films had rougher surfaces than the CS coated films, especially when using a higher ratio of MAS. The CS–MAS coated tablets displayed fewer film defects than the CS coated tablets because the stickiness of the coated tablets could be reduced during the coating process when incorporating MAS into the CS dispersions. The matrix morphology of the CS–MAS films showed a layer structure. This morphology was similar to free CS–MAS films that were prepared using a casting/solvent evaporation method (Khunawattanakul et al., 2010). The rough surface and layer structure of the films occurred because of the formation of CS–MAS flocculate particles in the dispersion (Khunawattanakul et al., 2010). Nevertheless, these findings suggest that CS–MAS dispersions have potential for use as coating materials and that the addition of MAS into the CS dispersion could reduce a film defects on the coated tablets.

3.2. Effect of CS–MAS ratio on water uptake and drug release

PPN and ACT core tablets were coated using CS and different ratios of CS–MAS composite dispersions at 4.3 mg cm^{-2} coating level. The water uptake of CS and CS–MAS coated tablets in 0.1 M HCl and pH 6.8 phosphate buffer is shown in Fig. 3. In 0.1 M HCl, water uptake of the CS coated tablets rapidly increased within the first 5 min of the test (Fig. 3a and c). CS with a pK_a of 6.2–7.0 (Hejazi and Amiji, 2003) can ionize and swell in acidic medium, leading to a loose CS film matrix and allowing water molecules to penetrate into the film. However, water uptake of the CS coated tablets could not be determined after 5 min because swelling and erosion of the CS films caused rupture of swollen tablets upon handling. On the other hand, tablets coated with the CS–MAS films at all ratios could be handled during the test, suggesting that the CS–MAS nanocomposite formation could retard swelling and erosion of CS in the composite films in acidic medium. It can be seen in Fig. 3 that the greater the MAS ratio added into the CS films, the lower the water uptake of the coated tablets. Water uptake of the CS and CS–MAS coated tablets obviously decreased in pH 6.8 phosphate buffer when compared with acidic medium. Moreover, water uptake determination of the CS coated tablets could

Table 1
Drug release characteristics of PPN and ACT coated tablets with CS and CS–MAS films at 4.3 mg cm^{-2} coating level.

Film component	PPN					ACT				
	0.1 HCl			pH 6.8 Phosphate buffer		0.1 HCl			pH 6.8 Phosphate buffer	
	Lag time (min)	$K_0 \times 10^2$ (min^{-1})	$K_1 \times 10^2$ (min^{-1})	Lag time (min)	$K_0 \times 10^2$ (min^{-1})	Lag time (min)	$K_0 \times 10^2$ (min^{-1})	$K_1 \times 10^2$ (min^{-1})	Lag time (min)	$K_0 \times 10^2$ (min^{-1})	$K_1 \times 10^2$ (min^{-1})
CS	<1	0.65 ± 0.08 (R^2 = 0.995)	0.38 ± 0.06 (R^2 = 0.999)	60.6 ± 14.0	0.51 ± 0.08 (R^2 = 0.996)	0.33 ± 0.10 (R^2 = 0.999)	<1	0.65 ± 0.09 (R^2 = 0.999)	0.39 ± 0.11 (R^2 = 0.999)	152.8 ± 1.5	0.26 ± 0.04 (R^2 = 0.985)	0.12 ± 0.02 (R^2 = 0.999)
CS–MAS												
1:0.2	55.0 ± 0.8	0.46 ± 0.04 (R^2 = 0.999)	0.33 ± 0.05 (R^2 = 0.999)	52.3 ± 6.1	0.46 ± 0.02 (R^2 = 0.988)	0.29 ± 0.03 (R^2 = 0.999)	6.3 ± 5.2	0.40 ± 0.03 (R^2 = 0.999)	0.24 ± 0.01 (R^2 = 0.999)	130.1 ± 15.9	0.19 ± 0.03 (R^2 = 0.999)	0.14 ± 0.02 (R^2 = 0.996)
1:0.6	52.4 ± 4.7	0.51 ± 0.11 (R^2 = 0.998)	0.32 ± 0.07 (R^2 = 0.999)	63.3 ± 14.3	0.44 ± 0.11 (R^2 = 0.993)	0.24 ± 0.01 (R^2 = 0.999)	36.5 ± 12.5	0.37 ± 0.04 (R^2 = 0.999)	0.25 ± 0.01 (R^2 = 0.999)	137.6 ± 12.6	0.28 ± 0.01 (R^2 = 0.993)	0.15 ± 0.01 (R^2 = 0.999)
1:1	54.3 ± 2.2	0.43 ± 0.02 (R^2 = 0.999)	0.31 ± 0.02 (R^2 = 0.999)	73.0 ± 25.5	0.44 ± 0.14 (R^2 = 0.998)	0.28 ± 0.07 (R^2 = 0.999)	72.1 ± 3.9	0.34 ± 0.02 (R^2 = 0.999)	0.20 ± 0.01 (R^2 = 0.999)	116.4 ± 0.6	0.19 ± 0.01 (R^2 = 0.995)	0.15 ± 0.03 (R^2 = 0.999)

Data are the mean ± S.D., n = 3.

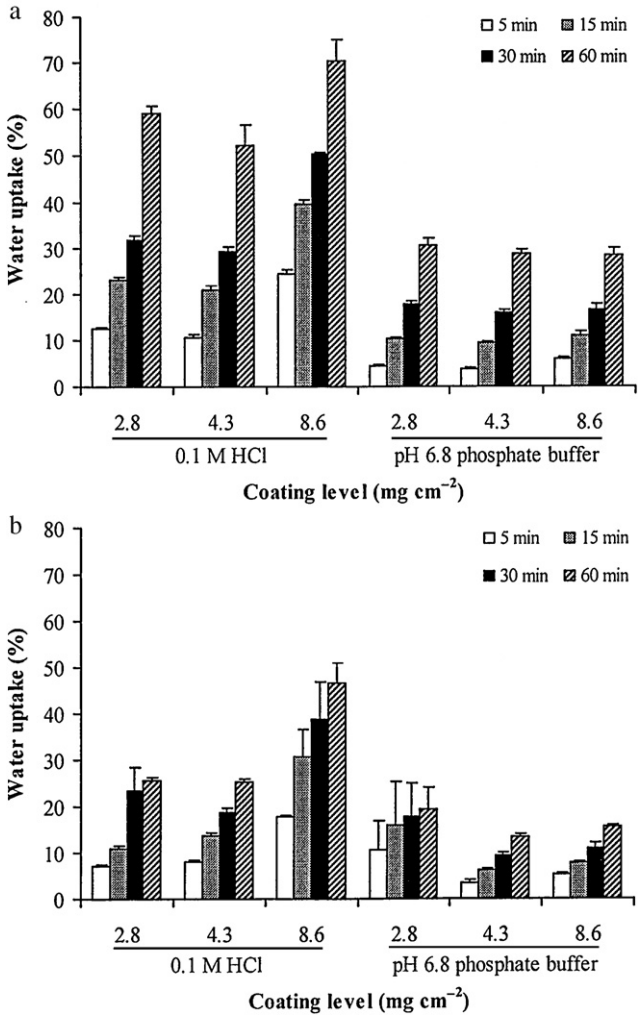

Fig. 5. Effect of coating level on water uptake of PPN-(a) and ACT-(b) coated tablets with CS–MAS (1:1) films in 0.1 M HCl and pH 6.8 phosphate buffer. Each value is the mean ± S.D., n = 5.

be performed at all timepoints. This indicated that CS could be cross-linked with phosphate anions bringing about an insoluble and stable film (Nunthanid et al., 2001), and leading to a restriction of water penetration into the coated tablets. Additionally, the coated PPN tablets showed a remarkably higher water uptake than the coated ACT tablets in both media, suggesting that drug properties in the core tablets influence water uptake of the coated tablets.

Drug release profiles of the PPN and ACT tablets coated with CS film and CS–MAS film at various ratios in 0.1 M HCl and pH 6.8 phosphate buffer are shown in Fig. 4. The zero-order release model could be used to calculate K_0 and lag time, whereas only K_1 was obtained from the first-order release model. Drug release rate constants and lag time are listed in Table 1. It was found that drug release data could be fitted to the zero-order release model ($R^2 > 0.99$) when drug release was less than 40–50% for PPN and 30–40% for ACT, whereas the first-order release model gave a good fit with 60–70% drug release for both PPN and ACT ($R^2 > 0.99$). The drug in the coated tablets could rapidly dissolve after the medium penetrated into the core of the tablets and a high concentration gradient of drug solution inside the coated tablets was created. Thus initially drug release was controlled by the coated films and a zero-order release kinetics was observed. After 30–50% of drug release, the drug concentration gradient in the coated tablets gradually decreased and could not maintain a constant drug concentration gradient, leading

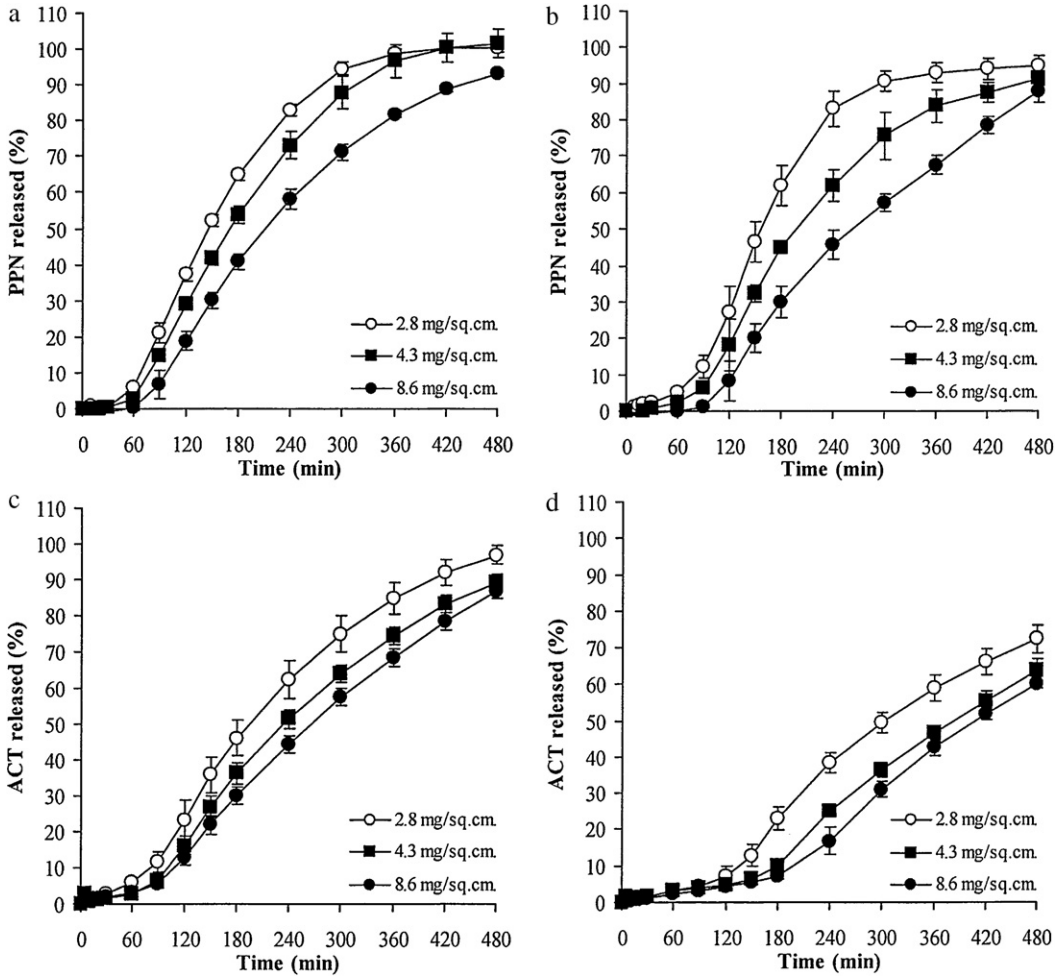

Fig. 6. Effect of coating level on drug release of PPN (a and b) and ACT (c and d) coated tablets with CS–MAS (1:1) films in 0.1 M HCl (a and c) and pH 6.8 phosphate buffer (b and d). Each value is the mean ± S.D., $n = 3$.

to a first-order release kinetics with higher % drug release. Although both K_0 and K_1 values could be used to compare the drug release rate in this study, the zero-order release model is preferred as two parameters, drug release rate constant and lag time, can be used for comparison.

Fig. 4 shows that the core tablets of PPN and ACT gave an immediate release of the drugs in both 0.1 M HCl and pH 6.8 phosphate buffer, and complete drug release was obtained within 15 and 30 min for PPN and ACT, respectively. In 0.1 M HCl, the CS coated tablets provided fast release of drug without lag time (Fig. 4 and Table 1). This result was in agreement with a study of Nunthanid et al. (2002), and was due to higher water uptake and swelling of the CS film in acidic conditions, resulting in greater drug permeability of the films. CS–MAS coated PPN tablets showed similar lag times and drug release rate constants (K_0) when increasing the MAS ratio in the coated films. It can be concluded that the greater water uptake of the PPN tablets coated with the CS–MAS films with various ratios was sufficient for dissolving the drug particles in the core tablets because of the high solubility of PPN in acidic medium (171.2 ± 0.6 mg ml^{-1}, $n = 3$). This caused a rapidly high PPN concentration gradient for drug diffusion, resulting in a similar release rate of PPN, independent of the CS–MAS ratio in the film.

On the other hand, increasing the MAS ratio in the CS–MAS films caused longer lag times and lower release rate constants of the CS–MAS coated ACT tablets in 0.1 M HCl. Moreover, the release rate constant of the CS–MAS coated ACT tablets was significantly lower ($P < 0.05$) than that of the CS–MAS coated PPN tablets when using the CS–MAS films at the ratios of 1:0.6 and 1:1 (Table 1). This is likely to be due to the lower solubility of ACT in 0.1 M HCl, which was found to be 23.0 ± 0.4 mg ml^{-1} ($n = 3$). In addition, water uptake of the ACT coated tablets decreased with increasing MAS ratio in the films. This suggested that the ACT tablets coated with CS–MAS (1:0.2) films contained enough water to dissolve the drug particles and built a high drug concentration gradient, resulting in a higher K_0 value and shorter lag time when compared with ACT tablets coated with CS–MAS films at higher MAS ratios. The coated films with higher MAS ratio could restrict water penetration into the coated tablets, leading to slower dissolution of ACT particles.

The CS coated tablets in pH 6.8 phosphate buffer had a lower drug release rate constant and a longer lag time than those in acidic medium (Table 1) and the drug release profiles of the CS coated tablets of both drugs were similar to those of the CS–MAS coated tablets (Fig. 4). The CS–MAS coated PPN tablets had longer lag times with increasing MAS ratio in the films, whereas similar release rate constants were found (Table 1). No difference in lag time and release rate constant of the CS–MAS coated PPN tablets in both 0.1 M HCl and pH 6.8 phosphate buffer were found. Moreover, the CS–MAS coated ACT tablets had a statistically longer lag time and lower release rate constant ($P < 0.05$) in pH 6.8 phosphate buffer when compared with drug release of the same tablets in acidic medium. Increasing the MAS ratio in the films did not obviously influence the ACT release characteristics in pH 6.8 phosphate buffer. The release characteristics of the CS and CS–MAS coated tablets in pH 6.8 phosphate buffer was different in 0.1 M HCl because the

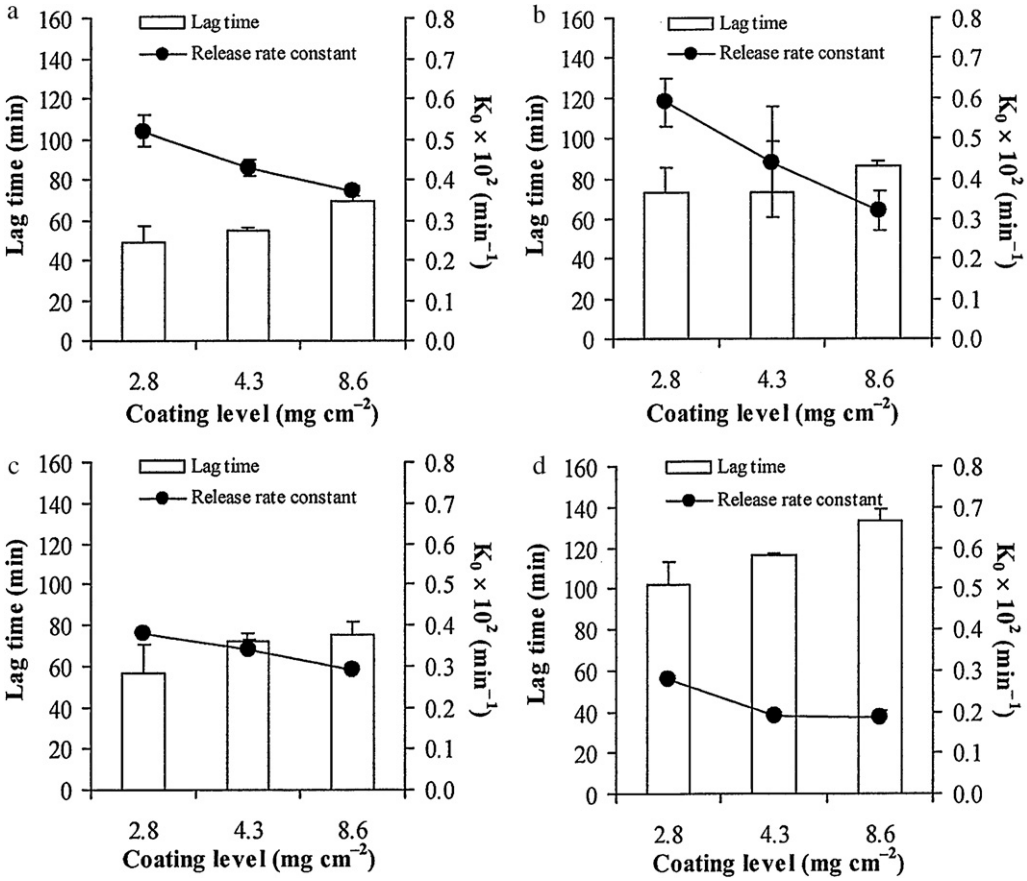

Fig. 7. Effect of coating level on lag time drug release rate constant of PPN (a and b) and ACT (c and d) tablets coated with CS–MAS (1:1) films in 0.1 M HCl (a and c) and pH 6.8 phosphate buffer (b and d). Each value is the mean ± S.D., $n = 3$.

cross-linking of CS in the films with phosphate anions in pH 6.8 phosphate buffer brought about a stable film, restricting water uptake of the coated tablets. This led to the similar drug release of the CS coated and CS–MAS coated tablets. However, the lower water uptake of the CS–MAS coated PPN tablets did not affect the dissolution of PPN particles and concentration gradient in the tablets because of the high solubility of PPN in pH 6.8 phosphate buffer (219.1 ± 4.1 mg ml^{-1}, $n = 3$). This resulted in the similar release profiles of PPN. In addition, the lag time of the CS–MAS coated PPN tablets increased with increasing MAS ratio. This was due to lower water uptake and the higher affinity of PPN with MAS in the composite films at high ratio of MAS (Khunawattanakul et al., 2010). Additionally, the CS–MAS coated ACT tablets provided longer lag times and lower release rate constants because of low solubility of ACT in pH 6.8 phosphate buffer (20.35 ± 0.40 mg ml^{-1}, $n = 3$) and low water uptake of the coated tablets.

The drug type used in this study influenced drug release characteristics and also water uptake of the coated tablets. PPN (MW of free base = 259.4) has a pK_a of 9.5 (Dollery, 1991). In this study, PPN is ionized and positively charged in both media. Interactions between PPN and MAS could have occurred via cation exchange, hydrogen bonding, and the water bridging mechanism (Rojtanatanya and Pongjanyakul, 2010). Therefore, PPN could interact with MAS in the CS–MAS coated film and this interaction could retard PPN release when compared with the CS coated films. In contrast, ACT is a weak acidic drug with a pK_a of 9.92 (Sinko, 2006). This suggests that ionization of ACT was very low in both 0.1 M HCl and pH 6.8 phosphate buffer, thus ACT was represented as a non-electrolyte molecule (Nakano et al., 1984; Terzyk et al., 2003). There are no reports about interactions between ACT and MAS. In addition, ACT (MW = 151.16) is a smaller molecule than PPN, thus ACT showed higher permeability through the CS–MAS film than PPN (Khunawattanakul et al., 2010). However, the CS–MAS coated ACT tablets gave a lower release rate constant than the CS–MAS coated PPN tablets in this study. This suggested that drug release depends on drug solubility in the tablet cores. The high solubility of PPN in both media caused fast dissolution of drug particles and the higher concentration of PPN inside the tablet led to increased water penetration into the tablet cores because of an osmotic pressure difference across the coated films. On the other hand, ACT with a comparatively low solubility could not induce water penetration into the tablet cores, leading to slow drug dissolution. This resulted in a higher drug release rate of PPN coated tablets when compared with ACT coated tablets and suggests that solubility of drugs here is the important factor for drug release from the coated tablets.

3.3. Effect of coating level on water uptake and drug release

The water uptake of the tablets coated with CS–MAS (1:1) films at different mean coating levels of 2.8, 4.3 and 8.6 mg cm^{-2} was examined (Fig. 5). In 0.1 M HCl, water uptake of the CS–MAS coated tablets increased rapidly within 5 min and increased gradually thereafter. Water uptake of the coated tablets increased with increasing coating level. In contrast, water uptake at each coating level was not different in pH 6.8 phosphate buffer, therefore, an effect of coating level on water uptake was found only in 0.1 M HCl. CS could still have swelled in acidic medium although its chains form nanocomposites with MAS. Swelling of CS loosened the film matrix structure and increased the matrix volume for adsorbing water. This suggests that the swollen films could adsorb water into the matrix films, resulting in higher water uptake when increasing the coating level. On the other hand, CS does not swell in pH 6.8

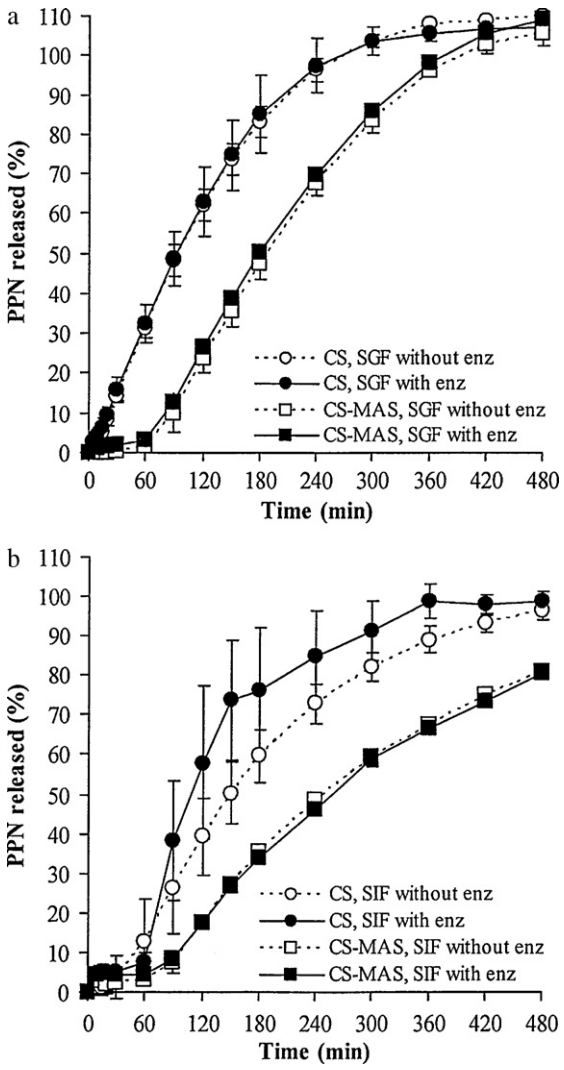

Fig. 8. PPN release profile of CS and CS–MAS (1:1) coated tablets in SGF (a) and SIF (b) with or without enzyme. Each point is the mean ± S.D., $n = 3$.

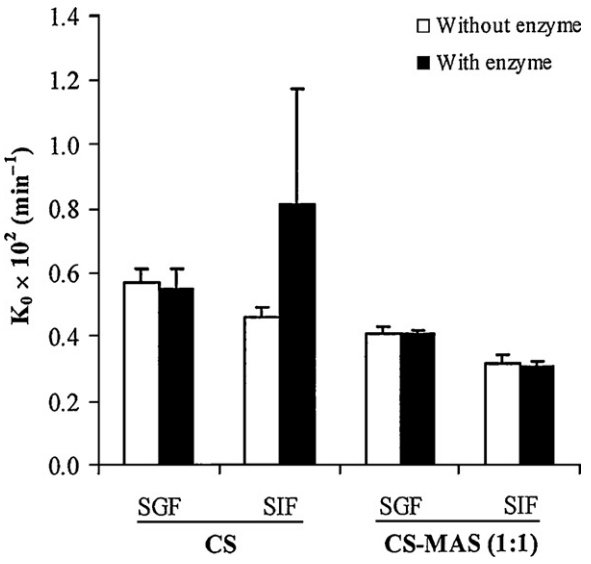

Fig. 9. Comparative PPN release rate constant of CS and CS–MAS (1:1) coated tablets in SGF and SIF with or without enzyme. Each value is the mean ± S.D., $n = 3$.

phosphate buffer, resulting in a similar water uptake of the coated films at all coating levels. Additionally, the use of PPN again resulted in a higher water uptake of the coated tablets compared to ACT.

The drug release profiles of the PPN and ACT tablets coated with CS–MAS (1:1) films at different coating levels are shown in Fig. 6. The effects of coating level on lag time and drug release rate constant (K_0) are presented in Fig. 7. It can be seen that an increase in coating level gave statistically longer lag time and lower drug release rate ($P < 0.05$) of the CS–MAS coated PPN and ACT tablets, especially in acidic medium. This resulted from the lower water uptake into the tablet cores and longer diffusional pathlength for drug permeation. Additionally drug solubility also affected the lag time and K_0 value of the coated tablets as was previously described. Overall these results suggest that drug release from the CS–MAS coated tablets can be modulated by varying coating levels of the coated films.

3.4. Effect of enzymes on drug release

The effects of pepsin and pancreatin on release of PPN from the CS and CS–MAS (1:1) coated tablets at 4.3 mg cm^{-2} coating level are presented in Fig. 8. PPN release from the CS and CS–MAS coated tablets was not different in SGF with and without pepsin. On the other hand, the CS coated tablets in SIF with pancreatin provided obviously faster PPN release than those in the medium without pancreatin (Fig. 9), whereas the CS–MAS coated tablets showed non different PPN release in SIF with and without pancreatin. This suggests that pancreatin in SIF affected release of PPN from the CS film coated on the tablets.

Several groups have investigated the chitosanolytic activity of pepsin (Tao et al., 2005; Vishu Kumar et al., 2007). The optimal condition for chitosanolytic activity of pepsin was pH 5 at 45 °C (Vishu Kumar and Tharanathan, 2004), which was different from the conditions used in this study (pH of 1.2 and 37 °C). Thus, no effect of pepsin on the CS and CS–MAS film coated tablets was found. Zhang et al. (2002) reported that depolymerization of CS in SIF was due to lipase in pancreatin causing a decrease in the specific viscosity of CS dispersions. Not only degradation of CS by lipase, but also proteolytic activity of pancreatin was considered. CS could be digested by pancreatin that possesses a proteolytic activity but cross-linked CS showed more resistance against enzymatic degradation (McConnell et al., 2008). In this study, the CS coated films could possibly be degraded by pancreatic lipase in SIF, hence the release of drug from the CS coated tablets in SIF with enzyme was faster than that in absent pancreatin medium. The drug release of the CS–MAS coated tablets was not affected by pancreatic lipase because the CS–MAS nanocomposites could form denser matrix structure of the films when compared with the CS films. Moreover, porcine pancreatic lipase has a molecular weight of 52,000 Da with Stokes radius of 3 nm (O'Connor and Bailey, 1988). It can be expected that the penetration of pancreatic lipase into the CS–MAS nanocomposite film was limited because of a large molecule with low diffusivity of pancreatic lipase. Additionally, the molecule size of pancreatic lipase was too large for attacking the CS molecules intercalated in the silicate layer of MAS, which the silicate layer space of the CS–MAS nanocomposites films was found to be 2 nm in the previous study (Khunawattanakul et al., 2010). This indicated that the CS–MAS (1:1) films coated on the tablets presented good stability towards enzymatic degradation in simulated intestinal fluid.

4. Conclusions

Both, CS and CS–MAS dispersions resulted in continuous coated films on tablets, but the CS–MAS coated tablets provided better visual appearance and fewer film defects than the CS coated

tablets. Nanocomposite formation between CS and MAS could retard swelling and erosion of CS in the composite films in acidic medium. The greater MAS ratio of the CS–MAS coated tablets provided lower water uptake and slower drug release when compared with the CS coated tablets. Moreover, the CS–MAS films coated on the tablets presented good stability towards enzymatic degradation in simulated intestinal fluid. The release of drug from the CS–MAS coated tablets could be modulated by varying CS–MAS ratios and coating levels, but was also dependent upon drug solubility. The findings indicated that the CS–MAS nanocomposite films can be used as a tablet coating material for modifying drug release from tablets.

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