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Alginate-magnesium aluminum silicate films: Effect of plasticizers on film properties, drug permeation and drug release from coated tablets

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Abstract

The effect of hydrophilic plasticizers, namely glycerin and polyethylene glycol 400 (PEG400), on physicochemical properties of sodium alginate-magnesium aluminum silicate (SA-MAS) microcomposite films was characterized and application of the films for controlling drug release from tablets was evaluated as well. The plasticizers could possibly interact with SA or MAS by formation of hydrogen bonding, as revealed using FTIR spectroscopy. PXRD studies presented that glycerin or PEG400 could intercalate into the silicate layers of MAS and higher crystallinity of the films with PEG400 was obtained. This led to a different thermal behavior of the films. Glycerin gave more flexibility of the films than PEG400. Incorporation of plasticizers into the films did not affect water uptake in acid medium, but increasing an erosion of the films because of the leaching of the plasticizers. Water vapor permeability of the films decreased with increasing amount of plasticizers in the range of 10–30% (w/w). Diffusion coefficient (D) of acetaminophen (ACT) across the films in acid medium increased with addition of the plasticizers because the leaching of plasticizers could reduce tortuosity of aqueous pore channels of the films. The tablets coated with plasticized films had a quite smooth surface without defect as shown by SEM. The ACT release profiles from the coated tablets showed a zero-order release kinetic with drug diffusion mechanism across in situ insoluble composite films in acid medium, and coating film swelling and erosion mechanism in pH 6.8 phosphate buffer. Moreover, neither the release rate nor the release pattern of the ACT coated tablets was obviously changed. The findings show that glycerin or PEG400 could improve physicochemical properties of the SA-MAS films and the plasticized films could control the drug release from tablets in gastro-intestinal condition.

Keywords: Sodium alginate; Magnesium aluminum silicate; Plasticizer; Composite film; Drug permeation; Coated tablet

1. Introduction

Sodium alginate (SA) is a sodium salt of alginic acid, a naturally occurring non-toxic polysaccharide found in brown algae. Alginate has been widely used as food and pharmaceutical additives, such as a tablet disintegrant and gelling agent. It contains two uronic acids, α-L-guluronic and β-D-mannuronic acids, and is composed of homopolymeric blocks and blocks with an alternating sequence (Draget, 2000). Gelation occurs by cross-linking of the uronic acids with divalent cations, such as calcium ion. This phenomenon has been used to prepare an alginate bead as a system for entrapping drugs (Badwan et al., 1985; Sugawara et al., 1994; Takka et al., 1998) and cells (Sugiura et al., 2005; Keshaw et al., 2005). A cross-linked film between SA and divalent ions has also been prepared and investigated some physical properties, such as mechanical properties (Remuñán-López and Bodmeier, 1997), water vapor transmission (Remuñán-López and Bodmeier, 1997) and drug permeability (Julian et al., 1988; Aslani and Kennedy, 1996; Remuñán-López and Bodmeier, 1997). Furthermore, in situ cross-linking of SA with calcium ion in a fluidized bed could form a coating film onto pellets, which led to a sustained-release delivery system (Abletshauser et al., 1993).

Magnesium aluminum silicate (MAS) is a mixture of montmorillonite and saponite clays (Kibbe, 2000), which have a layered structure. Each layer is constructed from tetrahedrally coordinated silica atoms fused into an edge-shared octrahedral plane of either aluminium hydroxide or magnesium hydroxide (Alexandre and Dubois, 2000; Kibbe, 2000). The layer structures of clays could be separated when they were hydrated in

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water. Once MAS is hydrated the weakly positive edges are attracted to the negatively charged faces. The attraction of face to edge of these colloidal layers creates a three-dimensional colloidal structure throughout the dispersion, which exhibited a thixotropic property (Zatz and Kushla, 1989). The charges on the layers of MAS lead to an interaction with anionic polymer, such as xanthan gum (Ciullo, 1981) and carbomer (Ciullo and Braun, 1991), which resulted in viscosity synergism. In addition, MAS could also improve a rheological property of SA gel that shifted from Newtonian flow to pseudoplastic flow with thixotropic property and drug release from the composite gels was retarded (Pongjanyakul et al., 2005a). This led to a study of physicochemical properties of the SA-MAS composite films. The SA and MAS could form a microcomposite film with improving mechanical properties, and retarding water uptake and drug permeability of the films. This composite dispersion could be used as a coating material for modifying drug release from tablets (Pongjanyakul et al., 2005b).

Plasticizers are usually high-boiling liquids of low molecular weight which should disperse as homogeneously as possible in the film formers to be modified. They could alter certain physical and mechanical properties by enhancing the mobility of the polymer chains (Bauer et al., 1998). Glycerin and polyethylene glycol400 (PEG400) have been widely used as a plasticizer in polymeric films (Heinämäki et al., 1994; Remuñán-López and Bodmeier, 1996; Honary and Orafai, 2002; Cervera et al., 2003; Krogars et al., 2003). Both plasticizers could change physical properties, especially mechanical and water vapor transmission properties, of polysaccharide films, including SA film (Remuñán-López and Bodmeier, 1996). In the case of clays, PEG could be adsorbed and intercalated into the silicate layers of clays (Billingham et al., 1997). Thus, it is interesting that addition of glycerin or PEG400 may improve physicochemical properties of the SA-MAS microcomposite films and the plasticized films may be used as a coating film for controlling drug release. This leads to the aims of this study on preparation of the SA-MAS microcomposite films incorporating various amounts of glycerin or PEG400 using casting/solvent evaporation process. Physicochemical properties of the films, such as thermal behavior, solid-state crystallinity, water uptake and erosion, mechanical properties, and water vapor and drug permeability, were investigated. FTIR spectroscopy was used to examine interaction between plasticizers and the components of the films. Additionally, the SA-MAS dispersions with plasticizers were evaluated as coating materials for controlling drug release of tablets.

2. Materials and methods

2.1. Materials

Low viscosity sodium alginate (SA, viscosity of 2% solution at 25 °C: 250 cps) was purchased from Sigma Chemical Company (MO, USA). MAS (Veegum® HV) and acetaminophen (ACT) were obtained from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA) and Praporn Darsut Ltd. (Bangkok, Thailand), respectively. Glycerin and PEG400 were purchased from Srichand United Dispensary Co., Ltd. (Bangkok, Thailand). Microcrystalline cellulose (Avicel® PH102, Asahi Chemical Industry Co., Ltd., Japan), 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. Other reagents used were of analytical grade and used as received.

2.2. Preparation of films

Films were prepared using casting/solvent evaporation technique, which have been previously reported (Remuñán-López and Bodmeier, 1997; Pongjanyakul et al., 2005b). SA (2 g) was dispersed in distilled water using homogenizer for 5 min, whereas MAS (2 g) was prehydrated with hot water for 15 min. The MAS dispersion was mixed into the SA dispersion using homogenizer for 5 min, and was then adjusted the volume with distilled water to 200 ml. The SA-MAS dispersion was kept for full hydration at room temperature overnight. Then, the dispersion was poured onto plastic plate (15 cm × 20 cm) and allowed to evaporate at 50 °C. The films were peeled off and kept in a desiccator. To incorporate plasticizer into the films, glycerin or PEG400 (10, 30 or 50% (w/w) based on SA) was mixed into the SA-MAS dispersion using homogenizer for 5 min before adjusting the final volume, and then the preparation was done as described above.

2.3. Characterization of composite films

2.3.1. Thickness of films

Thickness of dry and wet films was measured in 10 places using microprocessor coating thickness gauge (Minitest 600B, ElektroPhysik, Germany). The dry films (4 cm × 4 cm) were cut and placed on a control plate. The probe, which was connected with the measurement gauge and calibrated using a standard film, gently moved downward to touch on the film and the thickness of film was then measured. The films were subsequently placed in a small beaker containing 0.1 M HCl, which was shaken occasionally in water bath at 37.0 ± 0.5 °C for 15 min. The samples were taken and blotted to remove excess water. The thickness of wet films was immediately determined following the procedure mentioned above.

2.3.2. Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of samples were recorded with a FTIR spectrophotometer (Spectrum One, Perkin-Elmer, Norwalk, CT) using KBr disc method. Each sample was pulverized, gently triturated with KBr powder in a weight ratio of 1:100 and then pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4000 to 450 cm^{-1} at a resolution of 4 cm^{-1}.

2.3.3. Differential scanning calorimetry (DSC)

DSC curves of samples were recorded using a differential scanning calorimeter (DSC822, Mettler Toledo, Switzerland).

Each sample (2–3 mg) was accurately weighed into a 40 μl aluminum pan without an aluminum cover. The measurements were performed over 30–350 °C at a heating rate of 10 °C/min.

2.3.4. Powder X-ray diffractometry

Powder X-ray diffraction (PXRD) measurements of samples were performed on a powder X-ray diffractometer (Philips PW3710 mpd control, The Netherlands). The measurement conditions were a Cu radiation generated at 30 kV and 20 mA as X-ray source, angular 1–35°(2θ) and step angle 0.02°(2θ) s^{-1}.

2.3.5. Mechanical properties of films

The mechanical properties of films were measured using a Texture Analyzer (TA.XT plus, Surrey, UK). The films were cut into 10 cm × 1 cm strips, and kept in a chamber (55% RH, 25 °C) for 3 days before testing (ASTM, 2002; Honary and Orafai, 2002). The measurements were performed using a 5 kg load cell, a gauge length of 5 cm and a cross-head speed of 0.2 mm/s. The tensile stress was plotted against the percentage of elongation to give a stress–strain curve. The tensile strength, the percentage of elongation at break and Young's modulus were reported.

2.3.6. Water uptake and erosion of films

Water uptake and erosion of the films were carried out using gravimetric method. Films were weighed (W_0) and then soaked in 0.1 M HCl and shaken occasionally at 37.0 ± 0.5 °C. After a predetermined time interval, each film was withdrawn, blotted to remove excess water, immediately weighed (W_t) and then dried in a hot air oven at 50 °C to constant weight (W_d). The % water uptake and % erosion can be calculated from the following equation:

$$\text{water uptake}\,(\%) = \left(\frac{W_t - W_d}{W_d}\right) \times 100 \quad (1)$$

$$\text{erosion}\,(\%) = \left(\frac{W_0 - W_d}{W_0}\right) \times 100 \quad (2)$$

where W_0, W_t and W_d are the original, wet and dry weight of the films, respectively.

2.3.7. Water vapor permeability of film

Water vapor permeation (WVP) across the films was studied following the method of Remuñán-López and Bodmeier (1997). Discs were punched from the films, placed on open 5 ml glass vials containing 3.5 g silica gel beads and held in place with a screw lid having a 0.86 cm-diameter of test area (0.58 cm^2). The vials were placed in a dessiccator containing a saturated aqueous sodium chloride solution (75% RH) (Nyqvist, 1983). The dessiccator was kept in a room at 26.0 ± 1.0 °C, 55 ± 3% RH. The weight change was recorded periodically over 72 h. The WVP rate was obtained from the slope of relationship between the amount of water permeated and time. The WVP coefficient of the films was calculated using the following equation (Porter and Ridgway, 1982; Limmatvapirat et al., 2004):

$$\text{WVP coefficient} = \frac{Mh}{A\Delta P_v} \quad (3)$$

where M is the WVP rate, h is the mean thickness of the film, A is the area of the exposed film and ΔP_v is the vapor pressure difference.

2.3.8. Drug permeability of films

Permeability studies of acetaminophen (ACT) through the films were performed using a horizontal Side-Bi-Side diffusion cell (Crown Glass Co., Inc., Somerville, NJ) at 37.0 ± 0.5 °C. The films were clamped between donor and receptor compartments of 3 ml volume and the diffusional area was 0.66 cm^2. ACT (4 mg/ml) solution in 0.1 M HCl was placed in the donor compartment, while the receptor compartment was 3 ml of 0.1 M HCl. Both compartments were stirred continuously throughout the tests. At appropriate intervals, 2.5 ml aliquots of the receptor medium were withdrawn and immediately replaced with fresh medium. The amount of ACT was analyzed using UV–vis spectrophotometer at 265 nm (Shimadzu UV1201, Japan).

Drug permeation through a polymeric film was characterized under steady state conditions by means of Fick's first law, which can be expressed as (Martin, 1993; Pokharkar and Sivaram, 1996):

$$\frac{dQ}{A\,dt} = PC_0 \quad (4)$$

where dQ/Adt is the permeation flux which is the slope value calculated using linear regression analysis of the linear relationship between the amount of drug permeated and time, A is the surface area of the film which the diffusion is taking place, C_0 is the concentration of drug in the donor compartment which is assumed a constant throughout the test and P is the permeability coefficient. The apparent diffusion coefficient (D) can be estimated using the following equation:

$$t_L = \frac{h^2}{6D} \quad (5)$$

where t_L is the lag time which obtained from the x-intercept of the permeation profiles and h is the mean thickness of the films. Thus, the apparent partition coefficient (K) is obtained as follows:

$$K = \frac{Ph}{D} \quad (6)$$

2.4. Preparation of coated tablets

A single punch machine with biconvex 0.8-cm punch was used for preparing ACT tablets. The tablets were consisted of ACT 10%, Avicel® PH102 30%, Flowlac® 100 58.8%, colloidal silicon dioxide 0.2% and magnesium stearate 1% (w/w). The 2% (w/v) SA-2% (w/v) MAS dispersion was used as coating materials. To study the effect of plasticizer on characteristics of the coated tablets, glycerin or PEG400 (10, 30 and 50% (w/w) based on SA) was added into the SA-MAS dispersion. The film coating process was conducted using a side-vented coating pan (Thai Coater Model FC15, Pharmaceuticals and Medical Supply Ltd., Thailand). The coating conditions used were as follows: tablet weight 900 g, inlet air temperature 60–65 °C, spray rate 4 ml/min and spray pressure 0.28 MPa. The coating level was calculated

from weight gained of coating material by total surface area of core tablet.

2.5. Evaluation of coated tablets

2.5.1. In vitro release studies of coated tablets

A USP dissolution apparatus I (Hanson Research, USA) was used to characterize the release of drug from the tablets. The baskets were rotated with a rate of 50 rev/min at 37.0 ± 0.5 °C. The dissolution media used were 750 ml of 0.1 M HCl for 2 h and followed by 750 ml of pH 6.8 phosphate buffer. Samples (7 ml) were collected and replaced with a fresh medium at various time intervals. The amount of drug released was analyzed using UV–vis spectrophotometer (Shimadzu UV1201, Japan) at wavelength of 265 nm.

2.5.2. Scanning electron microscopic studies

The surface morphology and cross-section of the coated tablets were observed using scanning electron microscopy (SEM). Samples of the coated tablets were mounted onto stubs, sputter coated with a gold in a vacuum evaporator and photographed using scanning electron microscope (Jeol Model JSM-5800LV, Tokyo, Japan).

3. Results and discussion

3.1. Appearance and thickness of the films

SA-MAS films were prepared using casting/solvent evaporation method. All films were opaque. The films with glycerin or PEG400 were flexible than those without plasticizers. The dry and wet thicknesses of the films are shown in Table 1. The dry thickness of the films remarkably increased with increasing content of glycerin or PEG400 in the films. The wet thickness of the films measured after soaking in 0.1 M HCl for 15 min was obviously greater than the dry thickness, suggesting the films could absorb water and then swelling in an acid medium. The % thickness increased after hydration tended to increase with increasing content of glycerin, while the films with 10–30% PEG400 gave an increase of these values but decreased at 50% PEG400. This indicated that glycerin and PEG400 produced different characteristics of the films that will be further explained.

3.2. FTIR study

Molecular interaction of SA and MAS in the films has been reported in previous study (Pongjanyakul et al., 2005b). Carboxyl groups of SA could form electrostatic interaction with positive charged sites on the edges of MAS structure and hydrogen bonding with silanol groups on the surface of MAS. The effect of glycerin and PEG400 was observed at the O–H stretching peak of the films at 3438 cm^{-1} (Fig. 1c). This peaks shifted to lower wavenumber at 3422 cm^{-1} when the films added with 50% glycerin or PEG400 (Fig. 1d and e), which was resulted from the O–H stretching of glycerin and PEG400 at 3378 and 3380 cm^{-1}, respectively (data not shown). However, these peaks were sharper than the peak of the composite film. This indicated that the formation of hydrogen bonding between hydroxyl groups of the plasticizers and silanol groups on the surface of MAS, or carboxyl and hydroxyl groups of SA. This finding suggested an interaction of the plasticizers with MAS and SA that might cause a change in physicochemical properties of the films.

3.3. Thermal behavior of the films

DSC curves of the films are presented in Fig. 2. The film showed an exothermic peak and followed by an endothermic peak at around 205–215 °C, and a broad decomposition peak at 254 °C (Fig. 2c). Glycerin and PEG400 affected thermal property of the films. Firstly, the intensity of the exothermic and the endothermic peaks (205–215 °C) decreased with increasing content of glycerin or PEG400 and disappeared when either 50% glycerin or PEG400 was added, as shown in Fig. 2d–g. This suggested that glycerin and PEG400 might involve a recrystallization and a phase transition of the films after heat induction. Secondly, the decomposition peak of the films shifted to lower temperature at 220 °C for 50% glycerin and a little shift to 250 °C was found for 50% PEG400. These results suggested that glycerin and PEG400 could induce a different crystal structure of the films, which led to a change of thermal properties of the films.

Table 1
Effect of plasticizers on thickness and drug permeability of SA-MAS films

Film	Thickness[a] (μm)		Thickness increased after hydration[b] (%)	$P^c \times 10^5$ (cm/s)	Lag time[c] (min)	$D^c \times 10^7$ (cm^2/s)	K^c
	Dry	Wet					
SA-MAS	78.0 ± 1.1	159.4 ± 4.2	104.4	4.84 ± 0.28	5.91 ± 0.64	1.20 ± 0.14	6.44 ± 0.48
+10% Glycerin	78.6 ± 3.2	164.6 ± 7.9	109.4	5.15 ± 0.39	5.07 ± 1.04	1.53 ± 0.35	5.67 ± 1.05
+30% Glycerin	84.1 ± 1.7	180.3 ± 7.7	114.4	5.05 ± 0.15	4.91 ± 0.29	1.84 ± 0.11	4.95 ± 0.17
+50% Glycerin	91.4 ± 2.5	197.3 ± 11.9	115.9	5.76 ± 0.46	4.55 ± 1.59	2.64 ± 0.11	4.69 ± 1.36
+10% PEG400	77.3 ± 2.6	157.4 ± 5.3	103.6	4.78 ± 0.22	6.19 ± 0.67	1.12 ± 0.12	6.74 ± 0.45
+30% PEG400	81.7 ± 4.1	178.7 ± 7.7	118.7	4.81 ± 0.14	5.95 ± 0.52	1.50 ± 0.13	5.76 ± 0.34
+50% PEG400	96.2 ± 3.0	197.0 ± 10.8	104.8	4.69 ± 0.20	6.32 ± 0.37	1.71 ± 0.10	5.41 ± 0.42

[a] Data are mean ± S.D., $n = 10$.
[b] ((Mean wet thickness − mean dry thickness)/mean dry thickness) × 100.
[c] Data are mean ± S.D., $n = 3$. P, Permeability coefficient; D, diffusion coefficient; K, partition coefficient. Percentage of plasticizer added was based on the weight of SA.

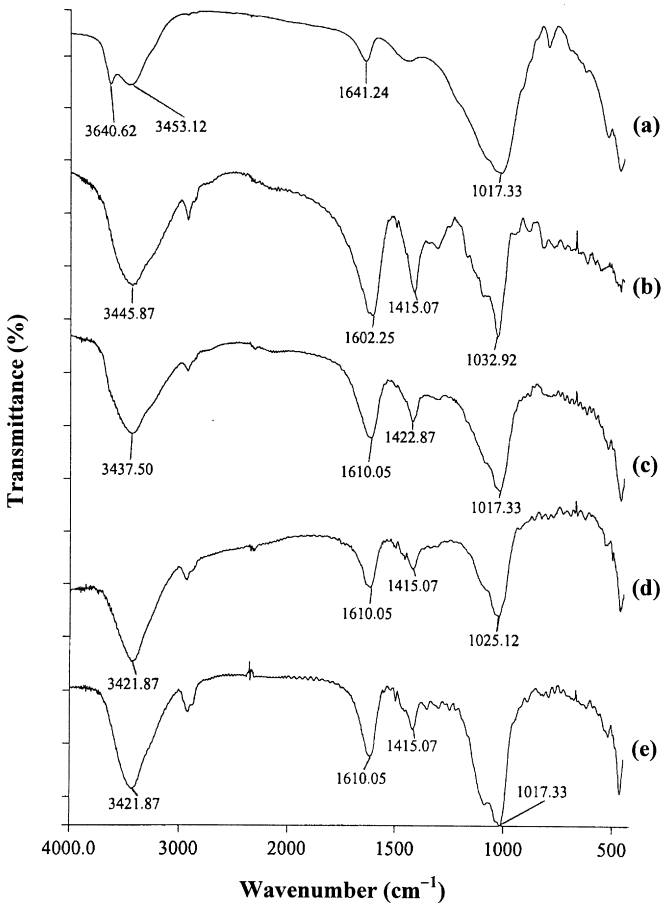

Fig. 1. FTIR spectra of MAS (a), SA film (b), SA-MAS films containing 0 (c), 50% glycerin (d) and 50% PEG400 (e).

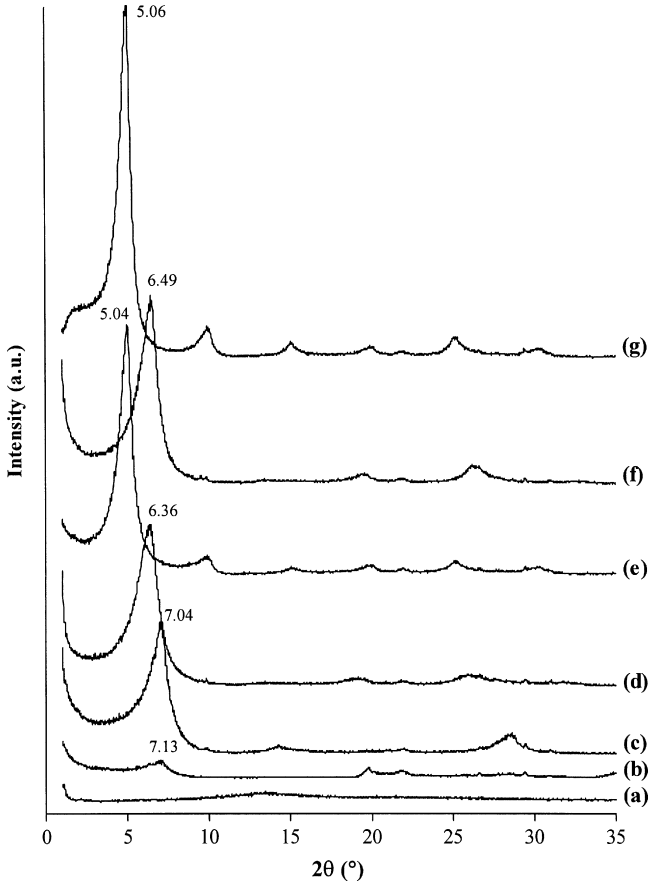

Fig. 3. Powder X-ray diffraction patterns of SA film (a), MAS (b), SA-MAS films containing 0% (c), 10% (d) and 50% (e) (w/w) glycerin, and 10% (f) and 50% (g) (w/w) PEG400.

3.4. Crystallinity of the films

The effect of glycerin and PEG400 on PXRD patterns of the films is shown in Fig. 3. SA film presented a broad peak at 13.3°(2θ) (Fig. 3a), which indicated an amorphous form of this film. MAS powder showed diffraction peaks at approximately 7.1°, 19.9°, 22.0° and 28.5°(2θ), indicating a crystalline form (Fig. 3b). The basal spacing at 7.1°(2θ) was 1.24 nm that was a thickness of the silicate layer in montmollilonite (Darder et al., 2003; Wang et al., 2005). The composite film showed a different PXRD pattern with MAS, but the basal spacing peak was not affected (Fig. 3c). This suggested a crystalline form of the film and SA could not intercalate into the silicate layers, so this composite film represented a phase-separated microcomposite

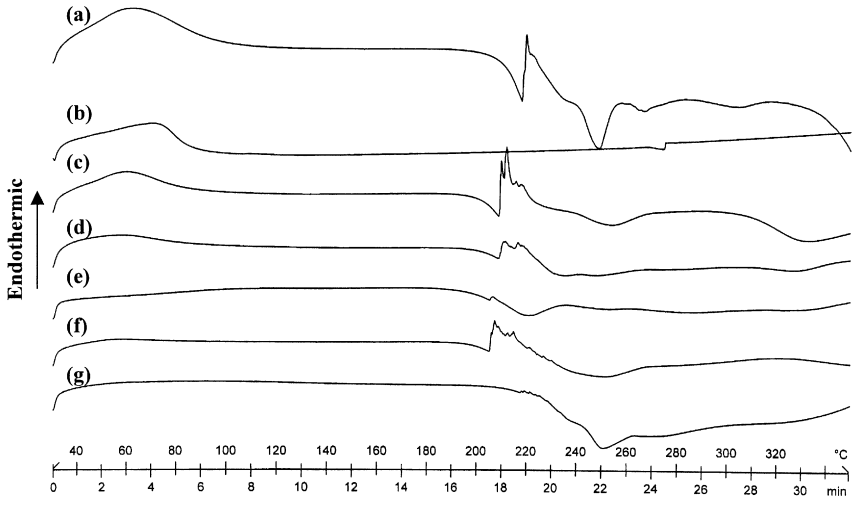

Fig. 2. DSC thermograms of SA film (a), MAS (b), SA-MAS films containing 0% (c), 10% (d) and 50% (e) (w/w) glycerin, and 10% (f) and 50% (g) (w/w) PEG400.

(Alexandre and Dubois, 2000; Pongjanyakul et al., 2005b). Furthermore, a stronger intensity of this peak was observed because of a reaggregation of MAS during drying process (Ogata et al., 1997; Lagaly, 1999). Addition of 10% glycerin or PEG400 caused a shift of the peak at 7.0°(2θ) of the films to around 6.4–6.5°(2θ) (Fig. 3d and f) and a change in overall PXRD pattern. This suggested the change in crystal structure of the films when the plasticizers were added and the intercalation of glycerin and PEG400 into the silicate layers, with the basal spacing in the range of 1.36–1.39 nm. Moreover, the films with higher quantity (30% and 50%) of glycerin or PEG400 also presented a different PXRD pattern from the unplasticized film and the films with 10% plasticizer. The diffraction peak of MAS was shifted from 7.04°(2θ) to around 5.04–5.06°(2θ) (Fig. 3e and g), indicating that the basal spacing of MAS was increased to about 1.75 nm. Billingham et al. (1997) reported that PEG could adsorb onto clay dispersion and insert between the silicate layers as one or two layers, which the basal spacing of the silicate layer was 1.86 nm. This suggested that two layers of plasticizers might be formed between the silicate layers when plasticizers were incorporated at the higher content (30–50%). Furthermore, the intensity of the peak at basal spacing increased with increasing content of glycerin and PEG400. This may be due to an increase stacking of the intercalated silicate layers (Sinha Ray et al., 2003), which resulted from the hydrogen bonding formation between plasticizers and silanol groups of MAS. Moreover, the intensity of this peak of the films with PEG400 was remarkably higher than those with glycerin. This also suggested a higher crystallinity of the plasticized films with PEG400, which caused a higher decomposition temperature in the DSC study.

3.5. Mechanical properties of the films

The tensile strength of the films decreased with increasing content of glycerin or PEG400 (Fig. 4a). Glycerin affected the tensile strength of the films more than PEG400. The elongation of the films increased with increasing amount of glycerin, whereas the films with PEG400 gave a higher elongation over the range of 10–30%, but the comparable elongation was found when adding 30% and 50% (Fig. 4b). Additionally, incorporation of glycerin and PEG400 caused a decrease in Young's modulus of the films. The plasticized films with 50% PEG400 gave remarkably higher Young's modulus than those with 50% glycerin (Fig. 4c).

Incorporation of glycerin or PEG400 caused a decrease in tensile strength and an increase in elongation of the films, leading to a decrease in Young's modulus of the films. This study indicated that glycerin gave a better plasticizing effect than PEG400. These results were similar to the previous study, which reported the effect of both plasticizers on SA films (Remuñán-López and

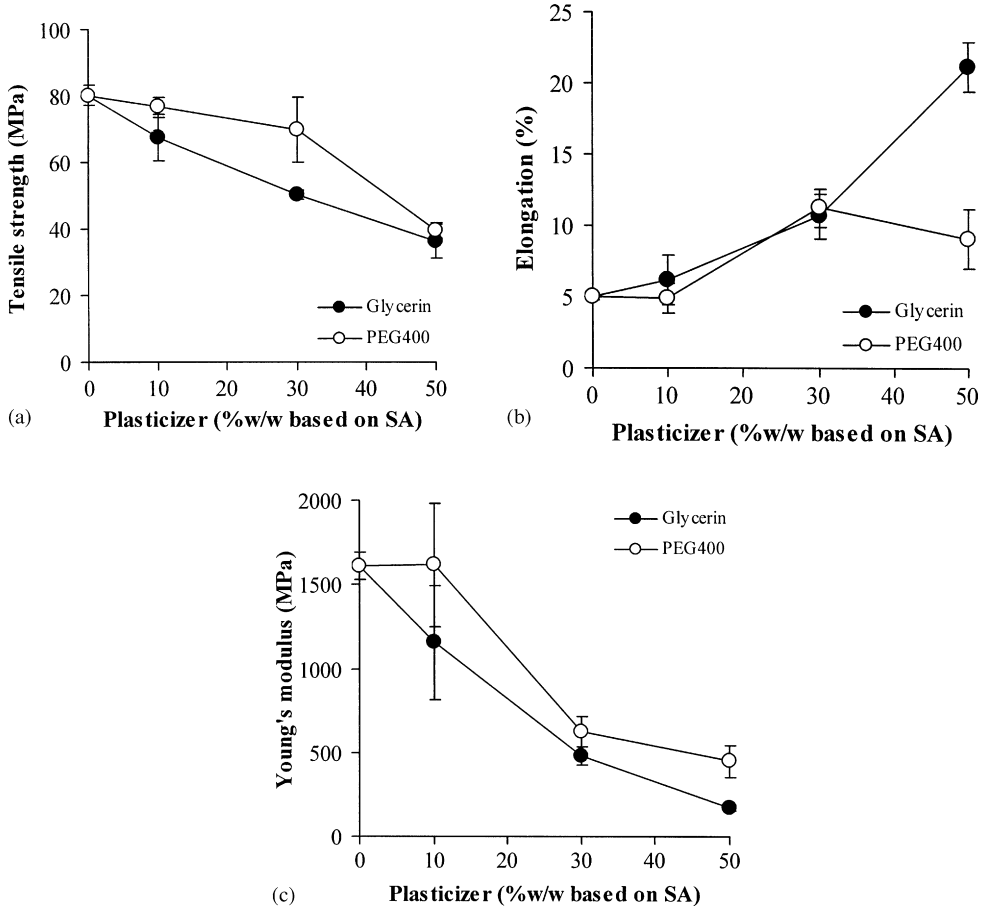

Fig. 4. Tensile strength (a), elongation (b) and Young's modulus (c) of SA-MAS films containing different contents of plasticizers. Each point is the mean ± S.D., $n = 4$.

Bodmeier, 1996). Glycerin is a smaller molecule than PEG400, so it could interpose the SA chain and interfere the formation of hydrogen bonging of intra- and inter-segmental of SA, thus decreasing rigidity of the SA structure. This suggested that plasticizers affected the mechanical properties of the films by interacting with SA. In addition, plasticizers were also intercalated into the silicate layers of MAS and subsequently changed the crystal structure formed. This may also affect the mechanical properties of the films. The higher crystallinity of the films with PEG400 resulted in higher rigidity of the films than those with glycerin.

3.6. Water uptake and erosion of the films

Water uptake and erosion of the films could be investigated in acid medium because SA was changed to unionized alginic acid and in situ insoluble films were formed. Other media, such as distilled water and pH 6.8 phosphate buffer, could not determine these parameters due to a fast swelling and dissolution of the films. The percent water uptake and erosion of the films in 0.1 M HCl at various times are shown in Fig. 5. The films with or without plasticizers gave a fast water uptake and reached an equilibrium about 10–30 min of the test. Incorporation of glycerin or PEG400 did not affect water uptake of the films, except the water uptake of the films with 50% plasticizers seemed to increase when compared with other films (Fig. 5a). A fast erosion of the films was also found to be about 14% at 5 min. The % erosion of the films with 10% plasticizers was comparable with the films without plasticizers. More than 10% glycerin or PEG400 caused a remarkable increase in erosion of the films. It can be observed that the erosion of the films without plasticizers and the films with glycerin reached equilibrium at 5 min, but that of the films with 30% and 50% PEG400 gradually increased with the time (Fig. 5b).

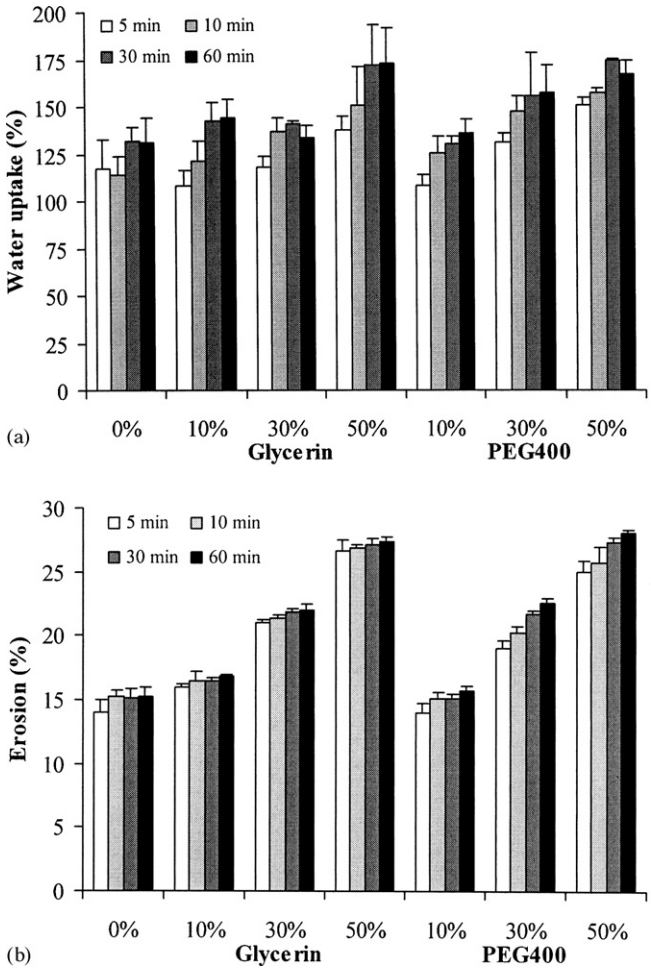

Fig. 5. Water uptake (a) and erosion (b) of SA-MAS films containing different contents of plasticizers. Each value is the mean ± S.D., $n = 4$.

In acid medium, SA was probably changed to water-insoluble alginic acid (Østberg et al., 1994), which led to in situ insoluble films. An erosion at initial 5 min was due to dissolution of some SA on the surface of the films. The additional erosion of the films was attributed to the leaching of plasticizers. The effect of the plasticizers on erosion was clearly observed when 30% and 50% plasticizers were added. This suggested that the certain amount of plasticizers that were intercalated between the silicate layers of the films could not leach out from the films. Thus, the films with 10% plasticizers showed comparable erosion with those without plasticizers. The further addition of 30–50% plasticizers resulted in gradual increase of erosion with increasing amount of plasticizers. At 30% and 50% plasticizers, the leaching of glycerin from the films was fast at initial 5 min and then constant, whereas the films with PEG400 provides a gradual increase of leaching with increasing time. This indicated that a larger molecule of plasticizer would diffuse from the films at a slower rate. The increase in erosion of the films by leaching of plasticizers did not obviously affect the water uptake of the films, suggesting that aqueous pore channels of the film did not increased, but seemed to increase in the films with 50% plasticizers. This indicated that a matrix structure of the films still formed after immersing in an acid medium because of the interaction of residual SA or alginic acid and MAS, and the intercalation of plasticizers with MAS structure.

3.7. Permeability of the films

The effect of glycerin and PEG400 on water vapor transmission of the films is presented in Fig. 6. Incorporation of both plasticizers caused a decrease in water vapor permeability (WVP) coefficient. A gradual decrease of WVP coefficient was found in the range of 10–30% plasticizers added, but the films with 50% plasticizers gave a higher WVP coefficient than those with 30% plasticizers. This finding is in agreement with the findings reported by Remuñán-López and Bodmeier (1996) in the case of free SA film with glycerin. It was possible to describe that plasticizers could penetrate between the chains of SA and the silicate layers of MAS, and then form intermolecular hydrogen bonding. This led to an increase in tortuosity of the pore channels in the films. Thus, WVP of the films with plasticizers was reduced. However, the WVP coefficient of the films with 50% plasticizers was increased because both plasticizers had a hygroscopic property, in which the excess amount of glycerin and PEG400 could absorb higher amount of water vapor into the film. This led to an increase in the WVP coefficient of the films.

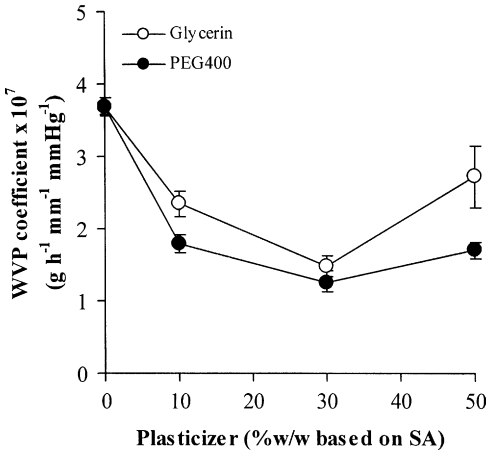

Fig. 6. Water vapor permeability coefficient of SA-MAS films containing different contents of plasticizers. Each point is the mean ± S.D., $n = 4$.

Moreover, the WVP coefficient of the films with PEG400 at various contents was lower than that of the films with glycerin. This was due to the higher crystallinity of the films with PEG400, as mentioned previously in PXRD studies. This finding suggested that the content of glycerin and PEG400 at lower than 30% based on SA content could retard the water vapor transmission of the films.

Drug permeability of the plasticized films in 0.1 M HCl was studied using acetaminophen (ACT) as a model drug because it was a weakly acidic non-electrolyte and had a less affinity on MAS (Pongjanyakul et al., 2005b). For this reason, ACT was a good model to study a change in permeability of the plasticized films. The permeation profiles of ACT across the films with both plasticizers showed a straight line with a lag time, suggesting that the drug permeation reached a steady state. The permeability coefficient (P) and lag time of ACT are shown in Table 1. The lag time of ACT across the films decreased with increasing content of glycerin, whereas it was not affected by incorporation of PEG400. The P values of ACT tended to increase with addition of glycerin, but the films with PEG400 showed a relatively constant of the P values which were not different from the unplasticized film. To compare the permeation of ACT through the films regardless of the effect of the thickness of the films, the apparent diffusion coefficient (D) values can be estimated using Eq. (5) and the wet thickness of the films was used for this estimation (Table 1). The higher the content of glycerin in the films, the greater the D values of ACT were observed. However, a slight increase of the D values was observed as amount of PEG400 was increased. Moreover, the films with glycerin gave higher D values than those with PEG400 at all levels of plasticizer added. A decrease in the apparent partition coefficient computed using Eq. (6) was found when glycerin and PEG400 were added.

The P values of ACT across the plasticized films had a little change when compared to the unplasticized films because addition of plasticizers did not obviously increase the water uptake of the films. Generally, the permeability of drug across thin films increased with increasing water content in the films (Lecomte et al., 2003), which led to a large aqueous pore channel. This indicated that aqueous pore channels of the hydrated films did not change. However, the consideration about the D values was an alternative way to study the microscopic structure change of the films when the plasticizers were added. It is clearly observed that the D values of the films increased with incorporation of plasticizers because the leaching of plasticizers from the film matrix led to decreasing tortuosity of aqueous pore channels in the films. The faster diffusion and the shorter lag time were thus obtained. Moreover, the K values were also decreased with addition of plasticizers. Both plasticizers could improve a hydrophilic property of the films. ACT was a non-electrolyte molecule and gave a low ionization in acid medium (Nakano et al., 1984). Therefore, an affinity of ACT to the plasticized films was reduced.

The films with glycerin and PEG400 showed different permeability properties. In the case of the microcomposite films, glycerin gave a more water vapor permeable films than PEG400. Furthermore, glycerin provided the higher P and D values, and the shorter lag time of drug permeation through the films in acid medium than PEG400. This was because PEG400 could form

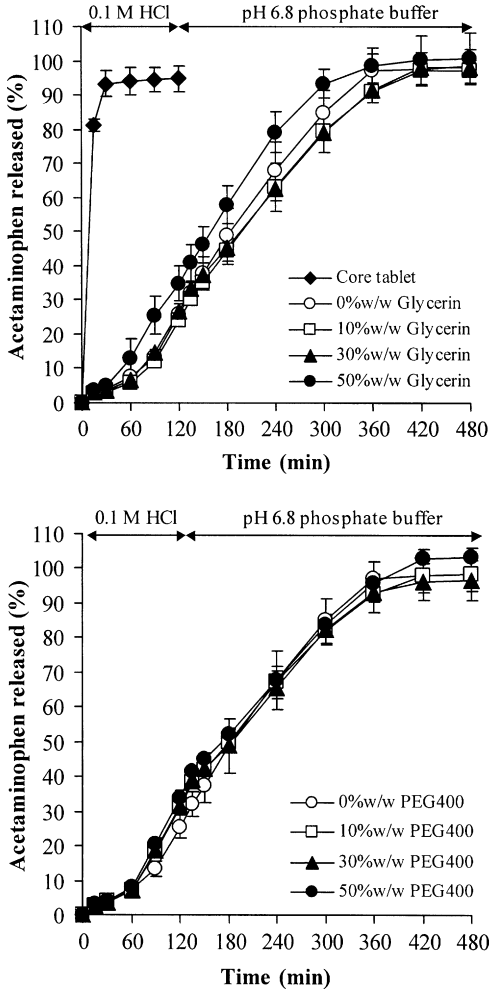

Fig. 7. Release profiles of acetaminophen from tablets coated with SA-MAS dispersion containing different contents of glycerin (a) and PEG400 (b). The coating level of the films was in the range of 4.3–4.7 mg/cm^2. Each point is the mean ± S.D., $n = 3$.

the composite films with the higher crystallinity. The denser matrix structure of the films with PEG400 was thus maintained when immersed in acid medium.

3.8. In vitro release studies of coated tablets

The SA-MAS dispersion could be used as a coating material for modifying drug release from tablets, as reported in our previous study (Pongjanyakul et al., 2005b). The effect of glycerin and PEG400 on the release of ACT coated tablets was investigated in this study. The ACT release profiles of core and coated tablets are presented in Fig. 7. The core tablet presented a fast and complete release of drug within 30 min. A slower drug release of the coated tablets was found and the relationship between drug released not more than 70% and time showed a good linearity ($R^2 > 0.97$) when using linear regression analysis for estimation. This suggested that the release of drug followed a zero-order kinetic with a lag time. The rate and lag time of drug release from the coated tablets are listed in Table 2. The lag time decreased with increasing content of glycerin and PEG400, whereas the

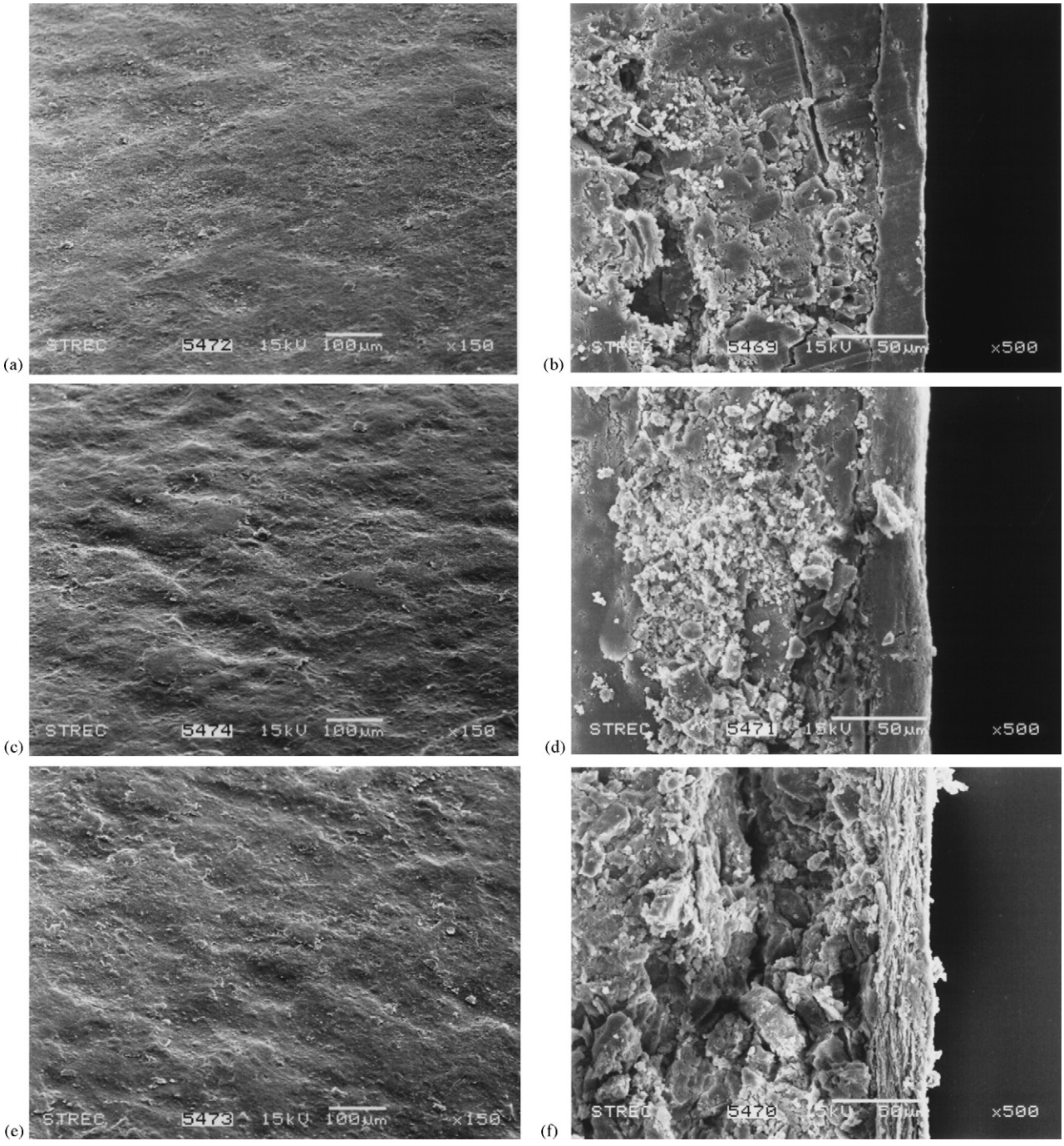

Fig. 8. SEM photographs of surface morphology (a, c and e) and cross-section (b, d and f) of acetaminophen tablets coated with SA-MAS film (a and b) and SA-MAS films containing 50% (w/w) glycerin (c and d) and 50% (w/w) PEG400 (e and f).

Table 2
Release characteristics of acetaminophen tablets coated with SA-MAS dispersion containing different contents of plasticizers

Coating component	Release rate (% min^{-1})	Lag time (min)	Amount of drug released at 2 h (%)
SA-MAS dispersion	0.35 ± 0.05 (R^2 = 0.994)	44.1 ± 3.6	25.5 ± 3.4
+10% Glycerin	0.31 ± 0.03 (R^2 = 0.995)	42.5 ± 4.5	24.0 ± 1.5
+30% Glycerin	0.32 ± 0.01 (R^2 = 0.990)	36.6 ± 3.9	26.6 ± 0.5
+50% Glycerin	0.37 ± 0.01 (R^2 = 0.998)	22.9 ± 14.9	34.7 ± 5.1
+10% PEG400	0.33 ± 0.02 (R^2 = 0.985)	30.9 ± 1.2	31.1 ± 1.5
+30% PEG400	0.33 ± 0.01 (R^2 = 0.972)	23.6 ± 3.6	31.8 ± 1.8
+50% PEG400	0.32 ± 0.02 (R^2 = 0.976)	27.0 ± 4.6	33.7 ± 2.2

Data are mean ± S.D., n = 3. Percentage of plasticizer added was based on the weight of SA.

release rates of all coated tablets were comparable. However, the different amount of drug released at 2 h (in acid medium) was observed (Table 2). Addition of glycerin and PEG400 tended to increase the amount of drug release in acid medium. Using SEM, the thickness of the films coated onto the core tablets at coating level of 4.3–4.7 mg/cm^2 was about 20–30 μm. The quite smooth films without defect were observed in all coated tablets, as shown in Fig. 8.

A slower drug release from the coated tablets was obtained when compared to the core tablets. This indicated that the coated films could control drug release in acid medium followed by pH 6.8 phosphate buffer. In acid medium, SA was probably changed to insoluble alginic acid (Østberg et al., 1994) and then formed in situ insoluble composite film, which acted as a rate-limiting step of drug release from the coated tablets. Subsequently, some alginic acids could be ionized and reconverted to SA in pH 6.8 phosphate buffer, leading to swelling and erosion of the films and drug release from the core tablets at the same time. Therefore, drug release profiles presented zero-order release kinetics.

It was observed that the lag times of drug release from the coated tablets (Table 2) were remarkably longer than those of drug permeated across the films in permeability study (Table 1). This was because of many processes involved before drug release from the coated tablets. When the coated tablets exposed an acidic medium, the insoluble composite membrane was formed that led to a restrictive water penetration into the tablets. Subsequently, drug particles slowly dissolved to create drug concentration gradient for diffusing through the membrane. However, drug concentration gradient in the wet coated tablets was possibly lower than that in the drug permeability testing. From these reasons, the longer lag time of the coated tablets was found.

The coat films with 10% and 30% glycerin provided longer lag time and lower amount of drug released at 2 h than those with 10% and 30% PEG and both parameters were comparable in 50% plasticizers (Table 2), although the cast films with glycerin gave higher drug permeability than those with PEG400 (Table 1). This may be due to different properties of films prepared from spray and cast methods. Sun et al. (1999) reported the differences in drug and water vapor permeability, and mechanical properties of ethylcellulose pseudolatex films produced using both methods. In addition, both methods also provided different mechanical properties of aqueous polymeric films (Obara and McGinity, 1994). Therefore, it was suggested that the films with PEG400 might possess higher drug permeability than those with glycerin when prepared using spray method. However, incorporating glycerin and PEG400 into the films could decrease lag time and increase amount of drug release in acid medium because glycerin and PEG400 could act as a channeling agent, which resulted from the leaching out of both plasticizers. Moreover, all coated tablets gave comparable drug release rate. This could be attributed to the couple mechanism for controlling drug release by drug diffusion across the insoluble films in acid medium, and erosion of the swollen films in pH 6.8 phosphate buffer. This finding suggested that the films with plasticizers could be applied as a coating film for controlled-release tablets in gastro-intestinal condition.

4. Conclusion

Incorporation of glycerin and PEG400 into the SA-MAS microcomposite films caused a change in thermal behavior, crystallinity, mechanical properties, water uptake and erosion, and permeability of the films. This was due to an interaction between plasticizers with both SA and MAS. Both plasticizers could intercalate into the silicate layers of MAS to form a different crystal structure. PEG400 provided the films with a higher crystallinity than glycerin. This led to a higher degradation temperature, a less flexibility and a less permeability to water vapor and drug of the films with PEG400. The SA-MAS dispersion with glycerin or PEG400 could produce a quite smooth film without defect onto the tablets, and zero-order release profiles were obtained. Moreover, both plasticizers did not accelerate the drug release and change the release kinetic of the coated tablets. This study suggested that SA-MAS dispersion with hydrophilic plasticizers, namely glycerin or PEG400, could form a flexible film with reducing water vapor transmission and the plasticized films presented a good potential for controlling drug release from tablets.

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