Table I. Component of NCT–MAS Complex-loaded SA Tablets Using Different Preparation pH Levels of Complexes

Component	Preparation pH of complexes		
	pH 4	pH 7	pH 9
NCT–MAS complexes (mg) (equivalent to 15 mg NCT)	166.0	129.0	120.0
SA (mg)	34.0	71.0	80.0
Magnesium stearate (mg)	2.0	2.0	2.0
Complex/SA ratio	1:0.20	1:0.55	1:0.67

Characterization of NCT–MAS Complex-Loaded SA Tablets

Thickness and Hardness

The thicknesses of the tablets were measured using a Vernier caliper (Mitutoyo, Japan). The hardness of the tablets was measured with a Stokes tablet hardness tester.

In Vitro Release Studies

NCT release from the NCT–MAS complex-loaded SA tablets was studied using two apparatus. NCT release from the whole tablets was studied using a USP dissolution apparatus 1 (basket method, VanKel VK200). The tablets were placed into the basket with a rotation speed of 50 rpm. The release medium was 500 ml of pH 6 phosphate buffer at 37.0 ± 0.5°C. Samples (7 ml) were collected and replaced with fresh medium at various time intervals. The amount of NCT released was analyzed using a UV–visible spectrophotometer (Shimadzu UV1201) at a wavelength of 259 nm.

Unidirectional release of NCT from the tablets was characterized using a modified USP dissolution apparatus 2, shown in Fig. 1. A 0.45-μm cellulose acetate membrane which had been hydrated in pH 6 phosphate buffer for 12 h was tightly attached at the lowest point of a polypropylene tube (inner diameter=1.8 cm) using a nylon cable tie. This tube was vertically placed in a dissolution vessel containing 300 ml of pH 6 phosphate buffer at 37.0 ± 0.5°C. The tube position was adjusted so that the membrane was wetted and in contact with the medium. The distance between the paddle and vessel bottom was set to 1 cm, and the rotation speed of the paddle was set to 50 rpm. The tablets were placed in the tube and wetted using 2 ml of phosphate buffer, pH 6. Samples (7 ml) were collected and replaced with fresh medium at various time intervals. The amount of NCT released was quantified with high-performance liquid chromatography (HPLC).

Table II. Component of NCT–MAS Complex-Loaded SA Tablets Using Different Complex/SA Ratios

Component	Complex/SA ratio			
	1:4	1:1.5	1:0.67	1:0
NCT–MAS complexes prepared at pH 9 (mg)	40.0	80.0	120.0	200.0
SA (mg)	160.0	120.0	80.0	0.0
Magnesium stearate (mg)	2.0	2.0	2.0	2.0
Amount of NCT (mg)	5	10	15	26.3

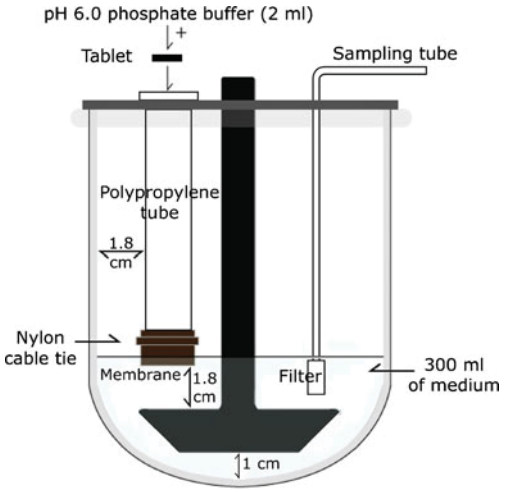

Fig. 1. Schematic presentation of the modified USP dissolution apparatus 2 for characterizing unidirectional NCT release and permeation of the buccal tablets

In Vitro Permeation Studies

NCT permeation of the tablets was also performed using a modified USP dissolution apparatus 2 (Fig. 1). Porcine esophageal mucosa was employed in this study because it has a lipid composition similar to porcine buccal mucosa, but a simpler preparation method (22). Esophageal mucosa of crossbred pig (hybrid kinds of Duroc Jersey–Landrace–Large White) with 80- to 100-kg weight was obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The porcine esophageal tube was opened longitudinally and immersed in 0.9% sodium chloride at 60°C for 1 min (22,23). The epithelium was then peeled away from the connective tissue and stored at −20°C. The frozen mucosal membranes were brought to room temperature by immersion in pH 7.4 isotonic phosphate buffer for 15 min. The mucosal membrane was then mounted and tightly attached to the end of a polypropylene tube. The dissolution vessel contained 300 ml of pH 7.4 isotonic phosphate buffer at 37.0 ± 0.5°C; the methods and experimental conditions were the same as the previous release study.

Analysis of Release and Permeation Data

The mechanisms of NCT release were determined both with a semi-empirical equation and a power law (24,25), shown in Eqs. 1 and 2, respectively, as follows:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

Table III. Characteristics of NCT–MAS Complexes Prepared at Different pH Levels

NCT–MAS complexes	Particle size (μm)	NCT content (% *w/w*)	NCT release rate (% $min^{-1/2}$)
pH 4	94.0±2.6	9.50±0.03	1.84±0.10 (R^2=0.993)
pH 7	82.1±2.4	12.20±0.02	2.22±0.06 (R^2=0.993)
pH 9	93.2±1.8	13.20±0.04	3.54±0.08 (R^2=0.991)

Data are the mean±SD, n=3

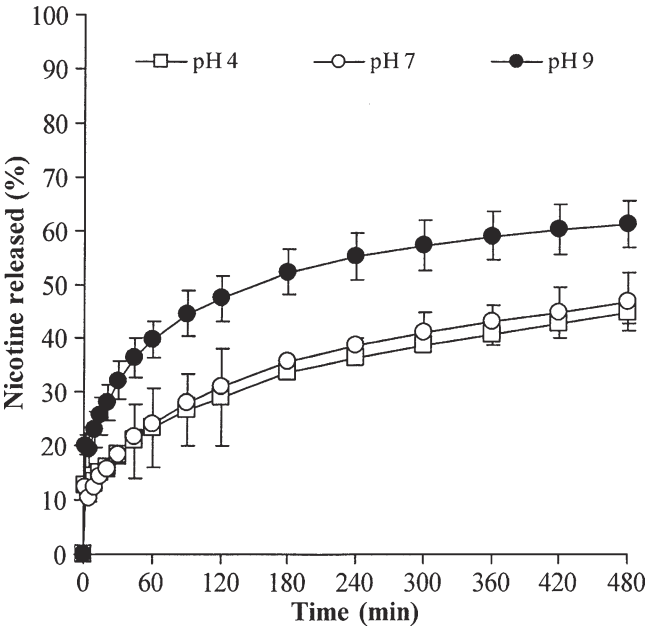

Fig. 2. NCT release profiles of the NCT–MAS complex particles prepared at different pH levels. Each *point* is the mean±SD, $n=3$

and

$$\log \frac{M_t}{M_\infty} = n \log t + \log k \tag{2}$$

where M_t/M_∞ is the fractional NCT release at time t, k is the kinetic constant, and n is the release exponent indicative of the drug release mechanism. A release exponent of $n=0.5$ indicates a diffusion-controlled drug release (Fickian diffusion), whereas a release exponent of $n=1$ corresponds to a polymer swelling/erosion-controlled release mechanism. Thus, release exponents between these two extreme values indicate a so-called anomalous transport—a complex transport mechanism that is a mixture of both drug diffusion and swelling/erosion of polymer (26).

The NCT release and permeation rates of the tablets were analyzed using both zero-order and Higuchi models (27), which can be expressed as Eqs. 3 and 4, respectively, as follows:

$$Q = K_0 t \tag{3}$$

and

$$Q = K_H t^{1/2}, \tag{4}$$

where Q is the amount of NCT released, t is time, and K_0 and K_H are the zero-order and Higuchi release rates, respectively.

Determination of Mucoadhesive Properties

The mucoadhesive properties of the tablets were measured using a texture analyzer (TA.XT plus, Stable Micro Systems, UK) with a 50-N load cell equipped with a bioadhesive test rig.

The tablet was attached to a 10-mm diameter cylindrical probe using a two-sided adhesive tape. Esophageal mucosa of pig was also obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The mucosal membrane from the porcine esophagus (about 2×2 cm) without heat treatment and elimination of the connective tissue that had been hydrated with pH 7.4 isotonic phosphate buffer for 20 min was placed on the stage of bioadhesive holder and gently blotted with tissue paper to remove excess water on the surface of the mucosal membrane. Next, 200 µl of pH 6 phosphate buffer was pipetted onto the membrane surface before testing. The probe and attached tablets were moved down at a constant speed of 1 mm s^{-1} with 0.5-N contact force and 2-min contact time. Immediately afterwards, the probe was moved upwards with a constant speed of 0.5 mm s^{-1}. The relationship between the force and tablet displacement was plotted. The maximum detachment force (F_{max}) and work of adhesion (W_{ad}, the area under the force *versus* distance curve) were calculated using the Texture Exponent 32 program version 4.0.9.0 (Stable Micro Systems).

Table IV. Physical Properties and NCT Release Characteristics of NCT–MAS Complex-Loaded SA Tablets

Tablets	Thickness (mm)	Hardness (N)	NCT release	
			Release exponent, n	Release rate (% min^{-1})
Preparation pH of complexes				
pH 4	1.46±0.02	70.6±2.7	1.05±0.07 (R^2=0.992)	0.14±0.01 (R^2=0.962)
pH 7	1.58±0.02	58.8±0.1	0.92±0.05 (R^2=0.990)	0.15±0.02 (R^2=0.980)
pH 9	1.61±0.01	60.8±2.7	0.98±0.07 (R^2=0.992)	0.15±0.03 (R^2=0.997)
Complex/SA ratio				
1:4	1.71±0.02	48.8±3.2	0.77±0.03 (R^2=0.992)	0.14±0.02 (R^2=0.996)
1:1.5	1.69±0.02	39.2±0.1	0.85±0.04 (R^2=0.992)	0.12±0.01 (R^2=0.999)
1:0.67	1.61±0.01	60.8±2.7	0.98±0.07 (R^2=0.992)	0.15±0.03 (R^2=0.997)
1:0	1.42±0.01	68.6±0.1	0.46±0.01 (R^2=0.972)	3.20±0.08[a] (R^2=0.988)
Pure SA	1.87±0.02	14.7±3.5	ND	ND
Pure MAS	1.31±0.01	36.3±4.4	ND	ND

Data are the mean±SD, $n=3$
ND not determined
[a] Calculated from Higuchi model (unit, % $min^{-1/2}$)

HPLC Condition for NCT Analysis

The concentration of NCT was determined using HPLC (Perkin Elmer Series, USA). Reversed-phase HPLC using a C-18 column (Waters Spherisorb® S5 ODS2, 5-μm particle size, 4.6 × 250 mm, Ireland) connected with a guard column was employed. The mobile phase was 0.05 M sodium acetate/methanol/triethylamine (88:12:0.5, *v*/*v*), and the final pH was adjusted to 4.2 with glacial acetic acid. The flow rate of the mobile phase was 1 ml min^{-1}, and the detector was a UV–visible detector at a wavelength of 259 nm. The retention time of NCT was approximately 7.0 min. Under these conditions, good linearity and reproducibility were shown over the range 1.0–100.0 μg ml^{-1} NCT.

FTIR Spectroscopy

The molecular interactions between SA and MAS in the tablets were investigated using an FTIR spectrophotometer (Spectrum One, Perkin Elmer, Norwalk, CT) and the KBr disc method. The residual mass of the swollen gel matrix tablets on the cellulose acetate membrane after the NCT release testing with the modified USP dissolution apparatus 2 ("In *Vitro* Release Studies") was collected, dried at 50°C, and gently ground with a mortar and pestle. Each sample was pulverized, gently triturated with KBr powder in a weight ratio of 1:100, and then pressed in a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4,000 to 450 cm^{-1} at a resolution of 4 cm^{-1}.

RESULTS AND DISCUSSION

Characteristics of NCT–MAS Complexes

Due to the molecular interactions between NCT and MAS via electrostatic force and hydrogen bonding (9), NCT–MAS complexes were formed and successfully prepared at pH 4, 7, and 9 using an adsorption method. The sizes of the NCT–MAS complex particles obtained fell into the range of 82.1–94.0 μm (Table III). The NCT content in the NCT–MAS complexes increased with increasing preparation pH (Table III). This was due to the denser matrix structure of the NCT–MAS complexes formed at acidic and neutral pH levels (8), resulting in a reduction of surface area for NCT adsorption. The NCT release profile of the complexes at different preparation pH levels is presented in Fig. 2. The NCT release percentage showed good agreement with the Higuchi model (R^2 higher than 0.99). This indicates that the NCT release kinetics from the complex particles is controlled by a matrix/particle diffusion mechanism (9). The complexes prepared at pH 9 gave a higher NCT release rate than those prepared at neutral and acidic pH levels (Table III). It is possible that the higher NCT content of the complexes prepared at pH 9 brought about a greater NCT concentration gradient in the complex particles, leading to faster NCT release. Moreover, the denser matrix formation of the complexes at pH 4 and 7 led to a lower NCT release rate than that of the complexes at pH 9.

Physical Properties of NCT–MAS Complex-Loaded SA Tablets

All mixtures prepared were easily compressed into tablets using a direct compression method. The thicknesses of the NCT–MAS complex-loaded SA tablets were in the range of 1.46–1.71 mm and are listed in Table IV. The tablets thus obtained were acceptable upon visual inspection, and acceptable hardness ranges from 39.2 to 70.6 N. Moreover, the hardness of pure SA and MAS tablets was found to be 14.7 and 36.3 N, respectively, suggesting that both materials

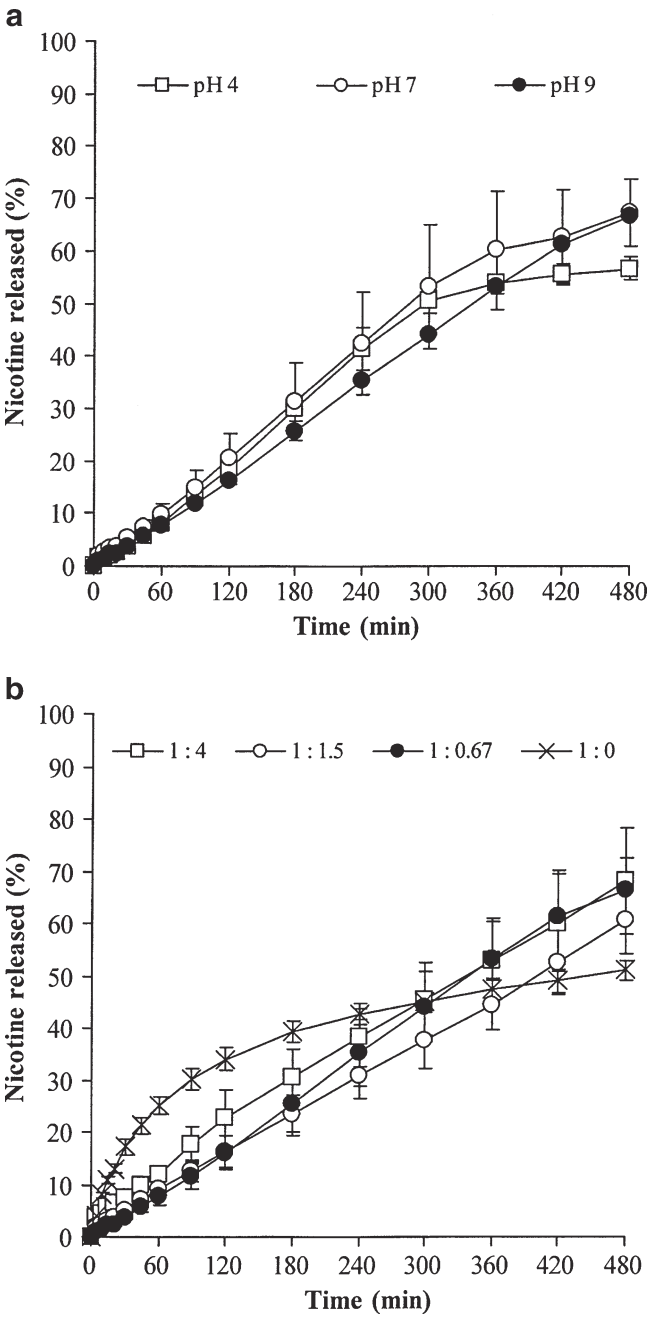

Fig. 3. NCT release profiles of the NCT–MAS complex-loaded SA tablets prepared using different preparation pH levels of complexes (**a**) and various complex/SA ratios (**b**). Each *point* is the mean±SD, $n=3$

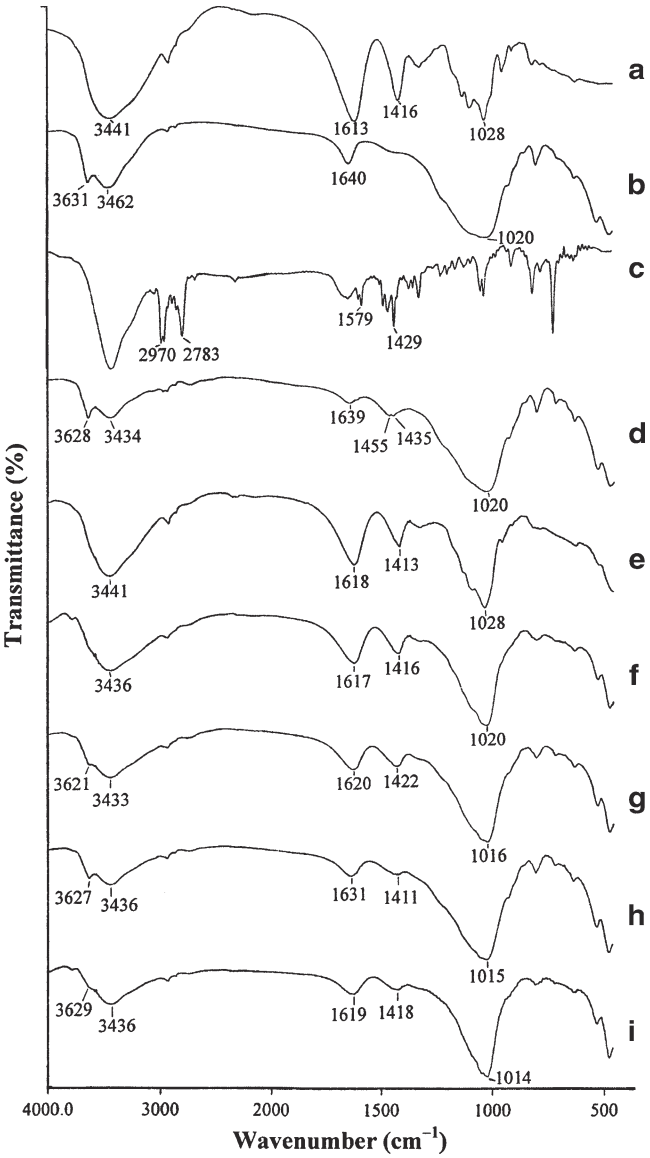

Fig. 4. FTIR spectra of SA tablet (*a*), MAS tablet (*b*), NCT (*c*), pH 9 NCT–MAS complex tablet (*d*), pH 9 NCT–MAS complex-loaded SA tablets using 1:4 (*e*), 1:1.5 (*f*) and 1:0.67 (*g*)complex/SA ratios, and NCT–MAS complex-loaded SA tablets using pH 4 (*h*) and pH 7 (*i*) complexes

have acceptable compressibility under pressure. Additionally, it was observed that pure MAS tablets had lower hardness than the pH 9 NCT–MAS complex tablets (1:0 complex/SA ratio), suggesting that the NCT adsorbed onto MAS may alter the surface interfacial properties of the MAS particles. This may lead to higher cohesive force at the contact surface after deformation of the NCT–MAS complex particles under compression.

NCT Release Characteristics of the Tablets

The NCT release profiles of the whole tablets in pH 6 phosphate buffer are shown in Fig. 3. The measured release of NCT from the NCT–MAS complex-loaded SA tablets (Table IV) fits well with the power law (Eq. 2; R^2 more than 0.99). The exponent n of the NCT–MAS complex-loaded SA tablets at all preparation pH levels was close to unity. This suggests that the NCT release was controlled by a polymer swelling/erosion mechanism and can be described using zero-order release kinetics. Additionally, increasing the SA ratio in the tablets led to a lower exponent value, particularly in the 1:4 and 1:1.5 complex/SA ratios. This indicates that the NCT release involved both a diffusion process through the swollen matrix and a swelling/erosion process of the SA. Moreover, the release process of the pH 9 NCT–MAS complex tablets without SA (1:0 complex/SA ratio) had an exponent value of

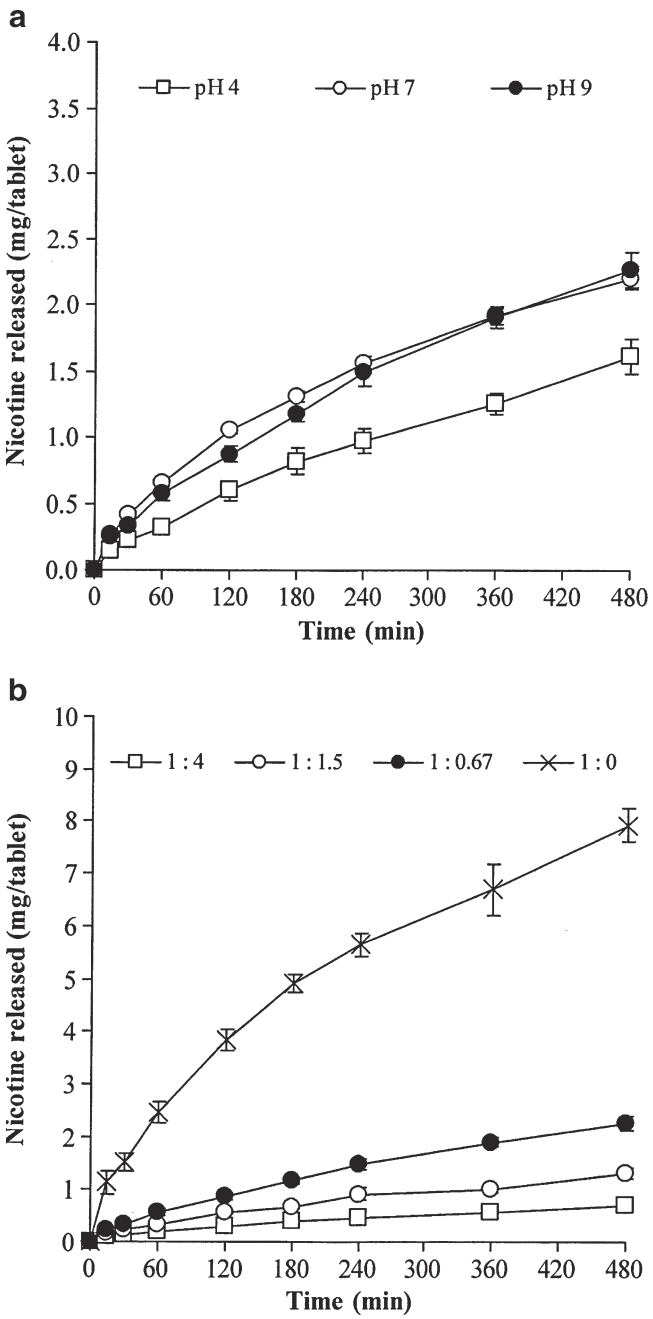

Fig. 5. Effect of preparation pH (**a**) and complex/SA ratio (**b**) on NCT release of NCT–MAS complex-loaded SA tablets using cellulose acetate as a membrane, measured using a modified USP dissolution apparatus 2. Each *point* is the mean±SD, $n=3$

0.46, the lowest that was found, suggesting that the NCT release was Fickian diffusion. Apart from NCT release mechanism, the NCT release rate of the whole tablets was calculated using the zero-order model (Eq. 3), as shown in Table IV. It was observed that the effect of preparation pH and the complex/SA ratio did not influence the NCT release rate. In contrast, the NCT release rate of the NCT–MAS complex tablets were well described by the Higuchi model, but not the zero-order model. The release rate of NCT from the tablets was lower than that of the complex particles (Table III) because of complex tablets' lower surface area for NCT release.

In this study, the observed NCT release from the NCT–MAS complex tablets without SA indicates a matrix/particle diffusion-controlled mechanism. Incorporation of a small amount of SA into the tablets could control the NCT release to achieve the zero-order release kinetics that was clearly observed in the tablets containing the complexes prepared at different pH levels. This indicates that the NCT release was controlled not only by matrix diffusion of the complex particles but also by the swollen gel matrix of SA formed around the tablets. However, the higher ratio of SA in the tablets caused the NCT release to be dominated by a matrix diffusion mechanism. We hypothesize that the greater amount of SA in the tablets may lead to higher viscosity and thickness in the swollen gel matrix during NCT release. Furthermore, it is interesting that all NCT–MAS complex-loaded SA tablets measured had a similar NCT release rate despite very different complex/SA ratios. It is possible that the swollen gel matrix may have changed during NCT release because of interactions between SA with MAS. We therefore investigated the molecular interactions of the tablet's components after drug release testing using FTIR spectroscopy.

Molecular Interaction of SA with MAS

The molecular interaction of SA with MAS in the swollen gel matrix was investigated in this study. SA showed stretching peaks from OH, COO^- (symmetric), and COO^- (asymmetric) at 3,441, 1,613, and 1,416 cm^{-1}, respectively (Fig. 4a). Figure 4b shows the peaks of MAS, such as hydroxyl stretching in SiOH (3,631 cm^{-1}), hydroxyl stretching in hydrogen-bonded water (3,462 cm^{-1}), hydroxyl bending (1,640 cm^{-1}), and stretching of Si–O–Si (1,020 cm^{-1}) (28). In the FTIR spectra of the pH 9 NCT–MAS complex tablets (Fig. 4d), a shift of the hydroxyl stretching peak of water hydrogen bonded to MAS to a lower wavenumber (3,462 to 3,434 cm^{-1}) was observed. A shift of the hydroxyl stretching peak of SiOH from 3,631 to 3,628 cm^{-1} was also observed. Moreover, the C–H bending on the pyridine ring of NCT was of low intensity and shifted from 1,429 cm^{-1} (Fig. 4c) to a higher wavenumber of 1,435 cm^{-1} (Fig. 4d). These results suggest that the amine group of the pyridine ring could interact with MAS via electrostatic forces and intermolecular hydrogen bonding (9). FTIR spectra of the pH 9 NCT–MAS complex-loaded SA tablets showed a shift of the SA COO^- stretching peaks (Fig. 4e–g) to a higher wavenumber, suggesting that the negative charge of the carboxyl groups of SA interacted electrostatically with the positively charged sites in the edges of MAS and could also create intermolecular hydrogen bonding with MAS silanol groups (11). Furthermore, the shift of the MAS Si–O–Si stretching peak to a lower wavenumber (from 1,020 to 1,016 cm^{-1}) could indicate intermolecular hydrogen bonding between SA and MAS. The pH 4 and 7 NCT–MAS complex-loaded SA tablets (Fig. 4h, i, respectively) also had spectra similar to those loaded with the pH 9 complexes. Unfortunately, the interaction of SA with NCT could not be clearly examined in this study. This may be due to a small amount of NCT remaining in the swollen gel matrix tablets. However, it is possible that NCT and SA could interact electrostatically because of their opposite charges, as well as through previously reported intermolecular hydrogen bonding (29). These findings indicate that SA can interact with MAS in the swollen gel matrix tablets, resulting in a denser matrix formation, thus modifying NCT release from the tablets. This was the reason describing why a small amount of SA could control the NCT release to achieve zero-order release kinetics. Additionally, the interaction of NCT with SA in the swollen gel matrix led to NCT release that was mainly controlled by swelling and erosion of the tablets.

Unidirectional Release and Permeation of NCT

Studies of the unidirectional NCT release and permeation of the NCT–MAS complex-loaded SA tablets were

Table V. NCT Release and Permeation Rate of NCT–MAS Complex-Loaded SA Tablets Tested Using Modified USP Dissolution Apparatus 2

		NCT release rate[a]		NCT permeation rate[b]	
Tablets	Release exponent, n	K_0 (μg min^{-1})	K_H (μg $min^{-1/2}$)	K_0 (μg min^{-1})	K_H (μg $min^{-1/2}$)
Preparation pH of complexes					
pH 4	0.70±0.01 (R^2=0.990)	3.18±0.26 (R^2=0.984)	77.2±6.6 (R^2=0.981)	0.97±0.10 (R^2=0.922)	43.1±2.6 (R^2=0.963)
pH 7	0.61±0.01 (R^2=0.997)	4.26±0.13 (R^2=0.955)	105.6±2.7 (R^2=0.994)	3.10±0.28 (R^2=0.979)	84.6±5.3 (R^2=0.980)
pH 9	0.66±0.04 (R^2=0.993)	4.51±0.23 (R^2=0.979)	109.8±5.2 (R^2=0.986)	4.88±0.30 (R^2=0.980)	131.6±7.4 (R^2=0.993)
Complex/SA ratio					
1:4	0.58±0.04 (R^2=0.989)	1.30±0.07 (R^2=0.992)	32.7±1.7 (R^2=0.989)	1.90±0.24 (R^2=0.982)	52.5±6.6 (R^2=0.989)
1:1.5	0.63±0.05 (R^2=0.991)	2.49±0.23 (R^2=0.966)	62.3±5.5 (R^2=0.981)	3.11±0.23 (R^2=0.986)	85.7±5.8 (R^2=0.990)
1:0.67	0.66±0.04 (R^2=0.993)	4.51±0.23 (R^2=0.979)	109.8±5.2 (R^2=0.986)	4.88±0.30 (R^2=0.980)	131.6±7.4 (R^2=0.993)
1:0	0.58±0.03 (R^2=0.991)	15.27±0.66 (R^2=0.937)	382.3±15.8 (R^2=0.995)	7.90±1.30 (R^2=0.955)	208.9±32.6 (R^2=0.996)

Data are mean±SD, n=3
[a] NCT release using cellulose acetate membrane
[b] NCT permeation using porcine esophageal membrane

performed using 0.45-μm cellulose acetate membrane and porcine esophageal membrane, respectively. The USP dissolution apparatus 2 was modified for measuring the NCT release and permeation of the buccal tablets. The advantages of this modified apparatus were its convenience of operation, high stirring efficiency, and large medium volume for maintaining the sink condition. The NCT release profiles of the NCT–MAS complex-loaded SA tablets from this study are shown in Fig. 5. The NCT release data fit well with the power law equation (Eq. 2), with R^2 >0.99 (Table V). The exponent obtained was in the range of 0.58–0.70, suggesting an anomalous release mechanism, *i.e.*, that drug diffusion and polymer swelling mechanisms controlled NCT release from the tablets. The exponent values obtained in this study were lower than those obtained from the release testing of whole tablets. This is due to the difference in release conditions and the surface area of the tablets exposed to the medium. Moreover, in the current study, erosion of the swollen gel matrix could not occur because of the use of cellulose acetate membrane as a barrier. The NCT release rates of the tablets were also calculated using the zero-order and Higuchi models, the results of which are listed in Table V. The NCT release rates showed a better fit with the Higuchi model than the zero-order model, as shown by the determination coefficient (R^2). The NCT release rate of the tablets increased with increasing preparation pH, even though the amount of SA used in the tablets using the complexes prepared at pH 4 was less than that in the complexes prepared at pH 7 and 9. This is due to the influence of the NCT release of the complex particles that was previously described in "Characteristics of NCT–MAS Complexes." An effect of the complex/SA ratio on NCT release was observed. Increasing the amount of complex in the tablets led to higher NCT release rates (Table V) by increasing the NCT concentration gradient for diffusion process. Moreover, the reduction of SA in the tablets decreased the swelling in the gel matrix that acted as a diffusion barrier for NCT. For this reason, the highest NCT release rate was found in the pH 9 NCT–MAS complex tablets without SA.

The permeation profiles of NCT from the NCT–MAS complex-loaded SA tablets across the mucosal membrane are shown in Fig. 6. NCT permeation rate was calculated using the zero-order and Higuchi models. The Higuchi model provided described the data better than the zero-order model (Table V), as was the case with the NCT release. This suggests that the rate-limiting step was not permeation across the mucosal membrane but NCT diffusion in the swollen gel matrix was. The preparation pH of NCT–MAS complexes had a clear effect on the NCT permeation rate (Fig. 6a and Table V). The tablets using the complexes prepared at pH 4 had the lowest NCT permeation rate with a very long lag time (the point of intersection with time axis); the highest NCT permeation rate was obtained from the complexes prepared at pH 9. This phenomenon occurred because the NCT molecules in the complexes formed at pH 4 were the protonated species (8) that possess lower permeability across the mucosal membranes (19,20). However, at pH 9, NCT is in its neutral species, which has higher mucosal permeability. Moreover, increasing the amount of SA in the tablets led to lower permeation rates of NCT (Table V). This was due to a slower NCT release in tablets with a higher ratio of SA. It was also observed that the permeation rates of NCT were greater than the NCT release rates in the pH 9 NCT–MAS complex-loaded SA tablets. This could be explained by the fact that the tablets composed of SA could absorb the medium through the pore channels of the cellulose acetate membrane used, whereas tablets rarely absorbed the medium when using the mucosal membrane due to the membrane's low water permeability. This resulted in increased swelling of the tablets during the release testing and led to the reduction of the concentration gradient and increase of the path length for NCT diffusion. Thus, the NCT release rate was possibly lower than the NCT permeation rate in this study.

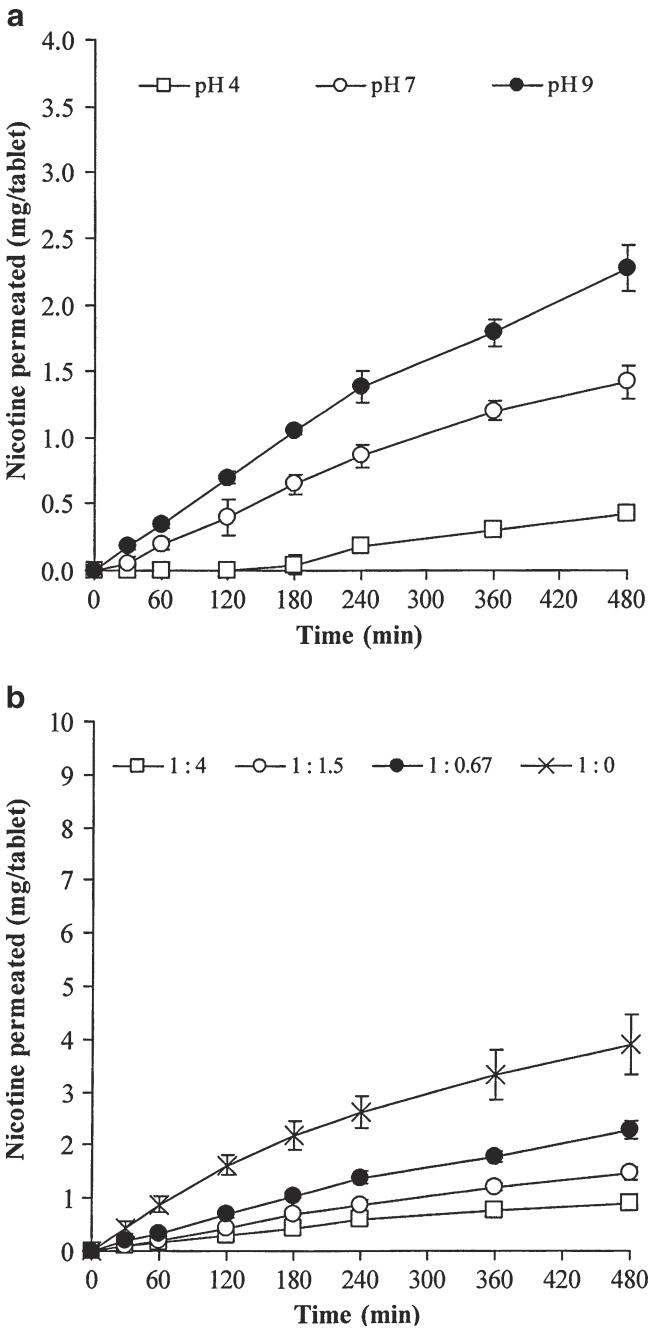

Fig. 6. Effect of preparation pH (**a**) and complex/SA ratio (**b**) on NCT permeation across porcine esophageal membranes of NCT–MAS complex-loaded SA tablets, measured using a modified USP dissolution apparatus 2. Each *point* is the mean±SD, n=3

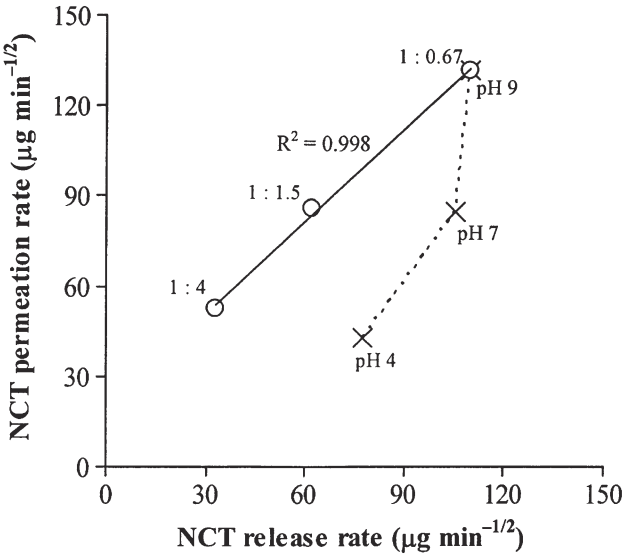

Fig. 7. Relationship between release rate and permeation rate of NCT from NCT–MAS complex-loaded SA tablets prepared using different preparation pH levels of complexes and complex/SA ratios

Relationship between the release rate and the permeation rate of NCT from the matrix tablets with various complex/SA ratios showed good linearity with R^2 higher than 0.99, as shown in Fig 7. It can be seen that the NCT permeation rate increased with increasing NCT release rate from the swollen matrix tablets. This suggested that the greater the NCT release rate, the higher the NCT concentration gradient on the surface of the mucosal membrane. This led to a higher NCT permeation rate as well. In contrast, the matrix tablets using NCT–MAS complexes prepared at different pH levels had not a linear relationship of both parameters. This was due to the low permeability across the mucosal membrane of protonated NCT released from the complexes prepared at acidic and neutral pH levels.

It is preferable to control the delivery of drugs via the drug delivery system rather than via the mucosal membrane. This study showed that the pH 9 NCT–MAS complex tablets without SA gave remarkably higher NCT release rates when compared with the NCT permeation rate, indicating that the permeation of NCT was controlled via the mucosal membrane. In contrast, the pH 9 NCT–MAS complex-loaded SA tablets gave similar release and permeation rates to NCT, suggesting that the delivery of NCT across the mucosal membrane was mainly controlled by the swollen gel matrix of the NCT–MAS complex-loaded SA tablets. This resulted from the molecular interaction of SA with MAS to form the gel matrix structure for controlling drug delivery.

Mucoadhesive Properties of the Tablets

The mucoadhesive properties, maximum detachment force (F_{max}), and work of adhesion (W_{ad}) of the tablets are presented in Fig. 8. The NCT–MAS complex-loaded SA tablets with different preparation pH levels had comparable F_{max} and W_{ad} values and did not differ from the mucoadhesive properties of SA tablets, although the amount of SA incorporated was quite low in the tablets. However, the pH 4 NCT–MAS complex-loaded SA tablets seemed to display the lowest F_{max} and W_{ad}. This is likely because these tablets used the smallest amount of SA. The complex/SA ratios used in the tablets affected the mucoadhesive properties. The F_{max} and W_{ad} of the tablets tended to decrease with decreasing SA amount in the tablets. Surprisingly, the pH 9 NCT–MAS complex tablets without SA showed large enough F_{max} and W_{ad} values for adhesion onto the mucosal membrane.

MAS has a silicate layer surface containing numerous hydroxyl groups which could possibly adhere to the mucosal membrane via hydrogen bonding with mucus. The NCT–MAS complex tablets possess mucoadhesive properties, suggesting that MAS still has enough hydroxyl groups to interact with mucus after the complexation with NCT. SA is a polysaccharide that possesses a mucoadhesive property (18,30,31) because it contains numerous hydrogen bond-forming groups, *i.e.*, carboxyl and hydroxyl groups. It has been proposed that the interaction between the mucus on mucosal membrane and hydrophilic polymers occurs by physical entanglement and chemical interactions, such as hydrogen bonding (31). Due to the mucoadhesive properties of SA and NCT–MAS complexes, the NCT–MAS complex-loaded SA tablets

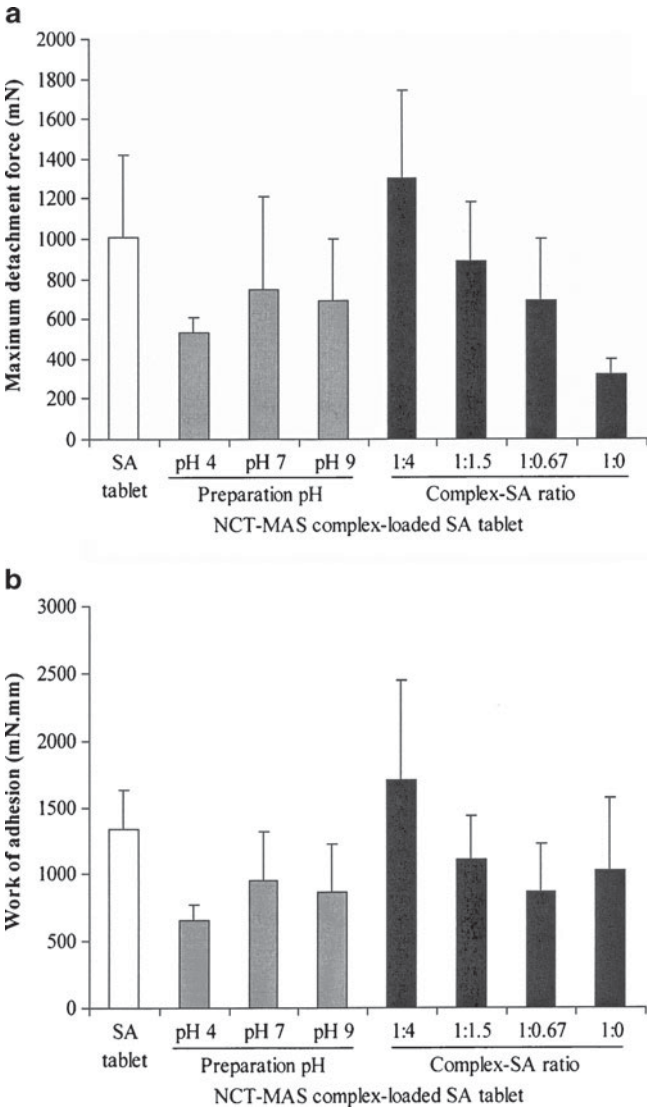

Fig. 8. Maximum detachment force (**a**) and work of adhesion (**b**) of the tablets. Each *bar* is the mean±SD, n=5

were sufficiently mucoadhesive for adhesion onto the mucosal membrane. However, the reduction of SA amount in the tablets caused a decrease of F_{max} and W_{ad}, suggesting that the swelling and physical entanglement of SA on the tablet surface was an important process for promoting the interaction with mucus.

CONCLUSION

The NCT–MAS complex-loaded SA tablets prepared using the direct compression method had favorable physical properties and gave a zero-order NCT release kinetic controlled by a swelling/erosion mechanism. The matrix tablets containing the NCT–MAS complexes prepared at pH 9 showed obviously greater NCT permeation rates than those containing the complexes prepared at acidic and neutral conditions. NCT release and permeation rates decreased with increasing SA amounts in the tablets. The use of the NCT–MAS complexes prepared at pH 9 in the tablets provided a highly effective NCT delivery across the mucosal membrane, which was controlled by the swollen gel matrix of the tablets. This resulted from the molecular interaction of SA with MAS to form the gel matrix structure that controlled the drug diffusion. Moreover, the presence of SA in the tablets could enhance the mucoadhesive properties of the tablets. This study suggests that SA could play an important role for controlling NCT release and enhancing the mucoadhesive properties of NCT–MAS complex-loaded SA tablets, and these tablets demonstrate strong potential for use as a buccal delivery system for NCT.

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Use of propranolol-magnesium aluminum silicate intercalated complexes as drug reservoirs in polymeric matrix tablets

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Running title: Propranolol-clay complexes as drug reservoirs in tablets

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The objective of the present study was to investigate the use of propranolol hydrochloride-magnesium aluminum silicate (PPN-MAS) intercalated complexes as drug reservoirs in hydroxymethyl propylcellulose (HPMC) tablets. HPMC tablets containing PPN-MAS complexes were prepared and characterized PPN release in comparison with PPN tablets and PPN-MAS physical mixture tablets. Additionally, the effect of HPMC viscosity grades, compression pressures, and calcium acetate incorporated on PPN release characteristics of the PPN-MAS complex tablets was also examined. The results showed that the PPN-MAS complex tablets gave higher tablet hardness than the PPN tablets containing pure and PPN-MAS physical mixture. The PPN release of the PPN-MAS complex tablets followed a zero-order release kinetic, whereas an anomalous transport was found in the PPN tablets and the PPN-MAS physical mixture tablets. The use of PPN-MAS complexes provided lower release rate than that of pure PPN. The PPN release rate of the PPN-MAS complex tablet significantly decreased with increasing HPMC viscosity grade. The higher compression pressure used could slow down the PPN released from these tablets. Furthermore, calcium ions incorporated could accelerate PPN release, particularly in acidic medium, because calcium ion could exchange with PPN molecules intercalated in the silicate layers of MAS. These findings suggest that PPN-MAS intercalated complexes showed strong potential for use as drug reservoirs in matrix tablets intended for modifying drug release.

Keywords: propranolol, magnesium aluminum silicate, complexes, hydroxypropyl methylcellulose, drug release; matrix tablets

Complexation between drugs and biocompatible materials has been used for improvement of drug solubility, drug stability, drug absorption and bioavailability[1]. In recent years, clays and biocompatible inorganic materials have been applied to adsorb the drugs onto their structures because they have a large specific surface area, good adsorption ability and cation exchange capacity[2,3]. Magnesium aluminum silicate (MAS), a mixture of natural montmorillonite and saponite clays[4], has a layered structure that is composed of tetrahedrally-coordinated silica atoms fused into an edge-shared octahedral plane of either aluminum hydroxide or magnesium hydroxide[4,5]. The negatively charged faces on the silicate layers of MAS have strong electrostatic interactions with amine drugs to form an intercalated complexes, which the drugs could intercalate into the silicate layers of MAS[6-8], thereby leading to the prolonged release of the drug. This finding recently led to potential application of drug-MAS complexes as drug carriers in matrix tablets for buccal delivery[9].

Propranolol hydrochloride (PPN), a secondary amine compound, was the first β–adrenoceptor blocking drug to achieve wide therapeutic use in angina and hypertension[10]. It has been selected as a drug candidate for developing sustained-release dosage forms[11-13] due to the short half life of PPN (3.9 h)[10]. However, many

researchers in development of PPN sustained-release dosage forms were met with problems, such as the difficulty to control drug release because of high aqueous solubility of PPN. This led to a large amount of polymer used in the matrix tablets for sustaining release of drug with high water solubility[14]. Recently, PPN could electrostatically interact with MAS to form intercalated complexes. The physicochemical properties of the complex particles were characterized and the PPN-MAS complexes showed sustained release of PPN after initial burst release[8]. Thus, it is interesting that the use of the PPN-MAS complexes as drug reservoirs in hydrophilic matrix tablets may modify drug release behavior when compared with the tablets contained with pure PPN.

Therefore, the aim of this work was to investigate physical properties and PPN release behavior of the matrix tablets containing PPN-MAS complexes as drug reservoirs by comparison with those containing pure PPN and PPN-MAS physical mixture. HPMC has been popularly used as a hydrophilic matrix-forming agent[14-17], and was employed in this study. Additionally, the effect of HPMC viscosity grades, compression pressures, and calcium acetate incorporated on PPN release characteristics of the PPN-MAS complex tablets was also examined.

MATERIALS AND METHODS:

MAS (Veegum®HV) and PPN were purchased from the R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA) and Changzhou Yabang Pharmaceutical Co., Ltd. (Jiangsu, China), respectively. Hydroxypropyl methylcellulose in the viscosity grades of 10-20 cP (low viscosity, LV-HPMC), and 40-60 cP (medium viscosity, MV-HPMC) was purchased from Onimax Co., Ltd. (Bangkok, Thialand). High viscosity grade HPMC (HV-HPMC), 80-120 cP, was obtained from S.M. Chemical Supplies Co., Ltd. (Bangkok, Thailand). All other reagents used were of analytical grade and used as received.

Preparation of PPN-MAS complexes:

A 4% w/v MAS suspension was prepared using hot water and cooled to room temperature prior to use. Next, 25 ml of the 4% w/v MAS suspension was mixed with 25 ml of the 1% w/v PPN deionized water solution in an Erlenmeyer flask. The pH of the PPN-MAS dispersion was adjusted by adding a small amount of 1 M HCl or 1 M NaOH into the flask while swirling and using a pH meter (Ion Analyzer 250, Coring, USA) to determine when the final pH of the dispersions was 7. Then the dispersions were incubated at 37 °C with shaking for 24 h to allow PPN adsorption into the MAS to

equilibrate. The PPN-MAS complexes were separated from the filtrates by filtration. Then, the complexes collected were redispersed in 25 ml of the 1% w/v PPN solution in an Erlenmeyer flask, and the mixture was incubated at 37 °C with shaking for 24 h for the second drug loading. The PPN-MAS complexes of the double drug loading were separated, washed and dried at 50 °C for 24 h. The dry PPN-MAS complexes were ground using a mortar and pestle, sieved for collecting the complex particles in the size range of 125-180 μm, and kept in a desiccator before use.

Scanning electron microscopy (SEM):

Particle shape and surface morphology of the MAS powder and the PPN-MAS complexes were observed using scanning electron microscopy (SEM). Samples were mounted onto stubs, sputter coated with gold in a vacuum evaporator, and photographed using a scanning electron microscope (Jeol Model JSM-6400, Tokyo, Japan).

Preparation of matrix tablets:

All tablets were prepared using the direct compression method. PPN-MAS complex tablet composed of 200 mg PPN-MAS complexes (equivalent to PPN 40 mg) and 600 mg HPMC for each. The complexes and HPMC were mixed in a rotomixer for 10 min; magnesium stearate (1 %w/w) was then blended with the mixture for 3 min before tabletting. The mixtures were filled into 12-mm flat-faced punches and dies, then applying 6.6, 8.8 or 11.0 MPa with a hydrostatic press (Model 3126, Shimadzu, Kyoto, Japan) without holding time. The tablets obtained were stored in a desiccator prior to use.

PPN tablets and PPN-MAS physical mixture tablets were prepared for drug release comparison with the PPN-MAS complex tablets. Each PPN tablet contained 40 mg PPN and 760 mg LV-HPMC. The PPN-MAS physical mixtures were prepared by mixing PPN and MAS in the ratio of 1:4 by weight. The PPN-MAS physical mixture tablets composed of 200 mg physical mixture (equivalent to PPN 40 mg) and 600 mg LV-HPMC. The next preparation method of these tablets was followed that mentioned above.

Effect of calcium acetate on PPN released from the PPN-MAS complex tablets was investigated in this study. The amount of calcium acetate added was 50, 100 or 150 mg in the PPN-MAS complex tablets that LV-HPMC amount was reduced to 550, 500 or 450 mg, respectively. The proceeded method was the same as mentioned previously.

Evaluation of matrix tablets:

Thickness and hardness. The thicknesses of the tablets were measured using a vernier caliper (Mitutoyo, Japan). The hardnesses of the tablets were measured using a tablet hardness tester (VanKel VK 200, USA).

In vitro release studies. PPN release of the tablets prepared was tested using a USP dissolution apparatus 1 (basket method, VanKel 7000, USA). The tablets were placed into the basket with a rotation speed of 100 revolutions/min. The release medium were 0.1 M HCl and pH 6 phosphate buffer in the volume of 750 ml and the temperature was controlled at 37.0 ± 0.5 °C. Twenty milliliters of samples were collected and replaced with fresh medium at various time intervals. The amount of PPN released was analyzed using a UV-visible spectrophotometer (Shimadzu UV1201, Japan) at a wavelength of 290 nm. In the case of calcium ion effect study, the release media were 0.1 M HCl and pH 6.8 Tris buffer containing 8.19 g/l sodium chloride and 0.32 g/l potassium chloride for simulating sodium and potassium ions in small intestine[18]. Tris buffer was used instead of phosphate buffer because calcium acetate could not completely dissolve in a phosphate ion-rich medium and an insoluble calcium phosphate was formed.

Analysis of PPN release:

The release mechanisms of PPN from the tablets were determined with a power law[19] as shown in Equations 1 and 2, respectively, as follows:

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Eq. 1}$$

and

$$\log \frac{M_t}{M_\infty} = n \log t + \log k, \qquad \text{Eq. 2}$$

where M_t/M_∞ is the fractional NCT release at time t, k is the kinetic constant, and n is the release exponent indicative of the drug release mechanism. A release exponent of n=0.5 indicates a diffusion-controlled drug release (Fickian diffusion), whereas a release exponent of n=1 corresponds to a polymer-swelling/erosion-controlled release mechanism. Thus, release exponents between these two extreme values indicates so-called anomalous transport-a complex transport mechanism that is a mixture of both drug diffusion and swelling/erosion of polymer.

The PPN release rate of the tablets was analyzed using both zero-order and Higuchi models[20], which can be expressed as Equations 3 and 4, respectively, as follows:

$$Q = K_0 t \qquad \text{Eq. 3}$$

and

$$Q = K_H t^{1/2}, \qquad \text{Eq. 4}$$

where Q is amount of PPN released, t is time, and K_0 and K_H are the zero-order and Higuchi release rates, respectively.

Matrix erosion studies:

Matrix erosion of the tablets containing calcium acetate was carried out in 0.1 M HCl and pH 6.8 Tris buffer with sodium chloride and potassium chloride. The method used in this study was modified from that of the previous report[21,22]. Weighed tablet (W_i) was placed in basket and subjected to the condition of the release studies described above. Each basket was taken out at 1 h and morphology of the swollen tablets was viewed using a digital camera (Canon Ixy 920iS, Japan). The baskets were placed in a small beaker, and then put in an oven at 50 °C until the constant weight of the tablet (W_d) was obtained. The %matrix erosion can be calculated using the following equation.

$$\text{Matrix erosion (\%)} = \left(\frac{W_i - W_d - W_r}{W_i} \right) \times 100 \qquad (2)$$

where W_r is the mean amount of PPN released during the release study.

Statistical analysis:

One-way analysis of variance (ANOVA) with the least significant difference (LSD) test for multiple comparisons and Student t-test were used to compare the significantly different results of thickness, hardness, and PPN release parameters of the tablets. All statistical tests were performed using the software SPSS for MS Windows, release 11.5 (SPSS (Thailand) Co. Ltd., Bangkok, Thailand).

RESULTS AND DISCUSSION:

Comparative physical properties and PPN release mechanism of the tablets:

The matrix tablets containing pure PPN, PPN-MAS physical mixture, and PPN-MAS complexes were successfully prepared by using the direct compression method. The LV-HPMC was used as a matrix-forming agent and the compression pressure applied was 11.0 MPa. The thickness of the tablets obtained was in the range of 5.75-6.44 mm (Table 1). The different hardness of the tablets was found that the PPN tablets showed the lowest hardness. The hardness of the PPN-MAS complex tablets was statistically higher ($P<0.05$) than that of the PPN-MAS physical mixture tablets. This

result suggested that incorporation of MAS in the tablets could increase tablet hardness due to a good compressibility behavior of MAS[9]. Moreover, particle and surface morphology of MAS (Fig. 1a and 1b) were different with those of the PPN-MAS complex particles (Fig. 1c and 1d). The PPN adsorbed onto the silicate layers of MAS could modify surface morphology of the PPN-MAS complex particles. The change of surface morphology as well as particle shape of the complex particles may lead to greater interparticle bonding and interlocking with LV-HPMC particles, resulting in higher tablet hardness.

PPN release profiles of the tablets containing pure PPN, PPN-MAS physical mixture, and PPN-MAS complexes are presented in Fig. 2. The PPN tablets gave a sustained release profile of PPN in both 0.1 M HCl and pH 6.8 phosphate buffer, whereas an immediately complete dissolution of pure PPN was obtained with in 2 min of the test (Fig. 2a, left panel). The PPN-MAS physical mixture tablets also showed a sustained release of PPN. The PPN-MAS physical mixture gave an incomplete dissolution of PPN with 65-75 % fast dissolution of PPN and followed with a decreased amount of PPN dissolved (Fig. 2b, left panel). This decrease was due to adsorption of PPN with MAS particles[8]. In contrast, the PPN-MAS complexes gave sustained release of PPN after an initial burst release. Incorporation of the PPN-MAS complexes into the matrix tablets could eradicate PPN burst release and could control PPN release (Fig. 2c, left panel).

The PPN release parameters of all tablets are listed in Table 1. The PPN-MAS complex tablets gave the highest release exponent, n value, which was found to be 0.98 in 0.1 M HCl and 0.89 in pH 6.8 phosphate buffer. These values suggested that the PPN release possibly followed a zero-order release kinetic. The release exponents of the PPN tablets and the PPN-MAS physical mixture tablets were in the range of 0.72-0.75 and 0.62-0.64, respectively, indicating an anomalous transport. The PPN release rates of the tablets were calculated using the zero-order and Higuchi models as shown in Table 1. The PPN release of the PPN tablets and the PPN-MAS complex tablets presented good fit with R^2 higher than 0.99 when using the zero-order model. On the other hand, the Higuchi model gave better fit with the PPN released from the PPN-MAS physical mixture tablet than the zero-order model. The PPN-MAS physical mixture tablets showed the lowest PPN release rate, whereas the highest release rate of PPN was found in the PPN tablets. Additionally, the PPN release rates of the PPN tablets and the PPN-MAS physical mixture tablets in 0.1 M HCl were higher than those in pH 6.8 phosphate

buffer. On the other hand, the lower PPN release of the PPN-MAS complex tablets in acidic medium was obtained when compared with that in neutral buffer.

The release exponent of the tablets could be used to describe PPN release mechanism from the matrix tablets. The PPN release mechanism model of the PPN tablets is illustrated in Fig. 2a, right panel. The PPN powders embedded in the matrix tablets could rapidly dissolve after the tablets exposed to dissolution medium owing to high water solubility of PPN. The PPN molecules diffused through a water-filled channel in the swollen matrix, which this process involved tortuosity of the matrix. However, the swollen HPMC matrix could be eroded due to disentanglement and dissolution of HPMC molecules. Thus, the drug release of the PPN tablets was mainly controlled by drug diffusion and polymer swelling/erosion mechanism. Additionally, PPN dissolution rate in the medium also involved the drug release mechanism. This can be seen that the PPN release rate in 0.1 M HCl was lower than that in pH 6.8 phosphate buffer because the PPN solubility in acidic medium was reported to be 225 mg/ml, whereas that in pH 6.8 phosphate buffer was 130 mg/ml[23]. This led to higher PPN release in acidic medium. This finding was in agreement with the previous study[24].

The PPN-MAS physical mixture tablets showed the other process that involved the PPN release (Fig. 2b, right panel). The matrix tablets could absorb water from the surrounding medium, leading to dissolution of PPN powders and swelling of MAS particles in the swollen tablets. According to high affinity of a negatively charged MAS with a positively charged PPN[8], an adsorption process of PPN molecules onto the surface of MAS particles was occurred. This resulted in slower PPN release and lower amount of PPN release at 7 h of the test; even through the erosion of the swollen matrix was progressed. Therefore, the release exponent of this tablet was smaller than that of the PPN tablets and the PPN released from this tablet can be described well with the Higuchi model. Moreover, the PPN release rate in acidic medium was also greater than that in pH 6.8 phosphate buffer because of higher PPN solubility and lower PPN affinity of MAS in acidic medium[8].

In the case of the PPN-MAS complex tablets, the PPN-MAS complex particles embedded in the matrix tablets could absorb dissolution medium that was composed of cations, such as hydrogen ion and sodium ion. The PPN intercalated in the silicate layers of MAS could be released by using a cation exchange process, and followed particle diffusion mechanism within the complex particles[8]. After that, the diffusion of PPN molecules through water-filled channels in the swollen matrix occurred, which the

erosion of swollen matrix was also progressed (Fig. 2c, right panel). Hence, the particle diffusion-controlled mechanism of the complex particles as drug reservoirs coupled with the drug diffusion and polymer swelling/erosion could control drug release with release exponent close to unity, indicating a zero-order release kinetic of this tablet. However, the PPN release rate in pH 6.8 phosphate buffer was higher than that in acidic medium that in contrast with the PPN tablets and the PPN-MAS physical mixture tablets. For explanation of this point, the matrix erosion of the PPN-MAS complex tablets at 1 h in both media was performed that the results were 20.5 ± 2.0 % (n=3) for 0.1 M HCl and 35.1 ± 6.7 % (n=3) for pH 6.8 phosphate buffer. This suggested that the faster erosion of the swollen matrix caused greater PPN release rate in pH 6.8 phosphate buffer. It was also indicated that the drug dissolution process did not involve the PPN release mechanism of the PPN-MAS complex tablets, but this process predominantly controlled the drug released from the PPN tablets and the PPN-MAS physical mixture tablets.

Effect of HPMC viscosity grade on PPN release:

The thickness and hardness of the PPN-MAS complex tablets prepared using different viscosity grades of HPMC and compression pressure at 6.6 MPa are listed in Table 2. The HPMC viscosity grade did not affect thickness of the tablets prepared. On the other hand, the tablet hardness significantly increased ($P<0.05$) with increasing viscosity grade of HPMC. The use of HV-HPMC presented the highest tablet hardness that was similar to the result of the previous study[25]. This result was due to a lower relative density of HV-HPMC when applying compression pressure[25].

The PPN release profiles of the PPN-MAS complex tablets prepared using different grades of HPMC in 0.1 M HCl are shown in Fig. 3. The release exponent, n value, of the tablets seemed to increase when increasing viscosity grade of HPMC (Table 2). The MV-HPMC and HV-HPMC tablets presented the n value close to unity. However, all tablets had better fit with the zero-order model than the Higuchi model. The PPN release rate, K_0, of the tablets statistically decreased ($P<0.05$) with increasing HPMC viscosity grade. Generally, increasing viscosity grade of HPMC brought about slower drug release from the HPMC tablets[26]. This result was because of a higher viscosity gel barriers created around the tablets when exposed to the dissolution medium. A higher viscosity gel barrier could retard water absorption rate that affected on an ion exchange process of the PPN-MAS complex particles and could reduce drug diffusivity in a water-filled channels due to increasing of tortuosity of swollen matrix. Additionally, slower matrix erosion of the swollen matrix occurred when HV-HPMC was used[27].

Effect of compression pressure on PPN release:

The thickness of the PPN-MAS complex tablets using LV-HPMC was significantly reduced ($P<0.05$) when increasing compression pressure (Table 3). In contrast, increase of compression pressure caused a significantly higher hardness of the tablets ($P<0.05$). These results were similar with the previous study[28]. It was indicated that the higher the compression pressure, the lower the porosity of the tablets was obtained, leading to decreasing of tablet thickness. Moreover, HPMC presented a plastic deformation under compression pressure, which greater compression pressure caused an increase of interparticle bonding of HPMC particles, resulting in higher tablet hardness[25].

The PPN release of the tablets using different compression pressures in 0.1 M HCl is shown in Fig. 4. It can be seen that the compression pressure affected PPN release. The release exponent of the tablets seemed to increase with increasing compression pressure (Table 3). The tablets using 11.0 MPa compression pressure gave the release exponent close to unity, indicative of the zero-order release kinetic. This led to a good fit of the PPN release with the zero-order model. The PPN release rate, K_0, decreased with increasing compression pressure and a significantly higher PPN release rate of the tablets using 11.0 MPa compression pressure was found ($P<0.05$) when compared with those using 6.6 MPa compression pressure. This finding was in contrast with the previous study that the compression pressure had a little influence on drug release from HPMC tablets[28-31]. The matrix erosion of the tablets was also investigated as shown in Table 3. It was shown that the tablets using different compression pressures had a similarity of the matrix erosion. This result suggested that higher tablet hardness did not influence water absorption and swelling processes of the tablets when exposed to dissolution medium. Thus, the interesting reason was a change of the PPN-MAS complex particles embedded in the matrix tablets under compression pressure. Previously, the drug-MAS complex particles without other excipients could be compressed as a tablet that provided a very high hardness[9]. This result led to slower drug release of the drug-MAS complex tablets when compared with the drug-MAS complex particles. For this reason, the PPN-MAS complex particles could possibly deform under higher compression pressure, which may cause a slower PPN release within the deformed complex particles. Hence, this finding suggested that the use of the PPN-MAS complexes as drug reservoirs in the HPMC tablets was sensitive with compression pressure rather than the HPMC tablets containing pure PPN.

Effect of calcium ion on PPN-MAS complex tablets:

The PPN-MAS complex tablets incorporated with various amounts of calcium acetate were prepared using LV-HPMC and 6.6 MPa compression pressure. The thickness of the PPN-MAS complex tablets tended to decrease when 150 mg of calcium acetate was incorporated (Table 4). In contrast, the tablet hardness significantly reduced ($P<0.05$) with adding 50 and 100 mg of calcium acetate, whereas a statistical increase of tablet hardness was found ($P<0.05$) in the tablets added with 150 mg of calcium acetate when compared with the control tablets. These results suggested that calcium acetate could reduce interparticle bonding of LV-HPMC when adding some of calcium acetate. However, the highest amount (150 mg) of calcium acetate caused an increase in tablet hardness because calcium acetate may have a good compressibility and may form interparticle bonding among itself that could be observed from a reduction of tablet thickness.

The PPN release profiles of the PPN-MAS complex tablets containing various amounts of calcium acetate in 0.1 M HCl and pH 6.8 Tris buffer are shown in Fig. 5a and 5b, respectively. Using 0.1 M HCl, the release exponent, n value, of the tablets was not affected by incorporation of calcium acetate that these values were over the range of 0.67-0.75 (Table 4). The matrix erosion of the swollen tablets statistically increased ($P<0.05$) when calcium acetate was added, but did not relate to the increase of calcium acetate amount. It can be confirmed by using photo image of the swollen tablets after 1 h of the release testing as presented in Fig. 6. The similarity morphology of the swollen tablets with or without calcium acetate was observed. However, the PPN release rate, K_0, of the tablets added with calcium acetate was significantly higher ($P<0.05$) than that of the control tablets. The greater the calcium acetate incorporated, the higher the PPN release rate was found. Apart from the result in acidic medium, the n value of the PPN release in pH 6.8 Tris buffer was close to unity when calcium acetate was incorporated into the tablets (Table 4). The swollen tablets showed higher %matrix erosion when incorporating calcium acetate (Table 4).The morphology of the swollen tablets with calcium acetate was changed (Fig. 6), indicating that incorporation of calcium acetate promoted matrix erosion of the swollen tablets in pH 6.8 Tris buffer. It was also observed that the matrix erosion of the tablets in pH 6.8 Tris buffer was greater than that in 0.1 M HCl. This result led to higher PPN release rate in pH 6.8 Tris buffer when compared with using acidic medium.

Calcium acetate could be dissolved for providing calcium ions in the swollen matrix tablets. The divalent calcium ions could accelerate an ion exchange process of the PPN-MAS complexes, resulting in higher release of PPN from the site of adsorption on the silicate layers of MAS. This occurrence led to higher release rate of PPN from the tablets. However, effect of calcium ions could be clearly observed when the matrix erosion of the swollen HPMC tablets occurred slowly and calcium ions had sufficient time for diffusion into the complex particles for ion exchange process. The phenomena mentioned could be found when using 0.1 M HCl as a dissolution medium. Increase of calcium acetate amount did not promote matrix erosion of the swollen tablets, which calcium ion could accelerate ion exchange process, resulting in higher PPN release rate. In contrast to the use of pH 6.8 Tris buffer, the matrix erosion of the swollen tablets progressed rapidly that the action of calcium ions could not completely occur. Thus, the higher release rate of the PPN-MAS complex tablets in pH 6.8 Tris buffer was mainly controlled by matrix erosion mechanism.

In conclusion, the PPN-MAS complex tablets were successfully prepared using the direct compression method and HPMC was used as a matrix-forming agent. The PPN-MAS complex tablets gave higher tablet hardness than the tablets containing pure PPN and PPN-MAS physical mixture. The PPN release from the PPN-MAS complex tablets followed a zero-order release kinetic because the release of PPN was controlled by many mechanisms, such as a cation exchange process, a particle diffusion-controlled mechanism of the complex particles, drug diffusion through water-filled channel in the matrix, and polymer swelling/erosion of HPMC. The PPN release rate of the PPN-MAS complex tablet decreased with increasing HPMC viscosity grade. The higher compression pressure used could slow down the PPN release from these tablets. Additionally, calcium salt incorporated into the tablets could accelerate PPN release, particularly in acidic medium, because calcium ion could exchange with PPN intercalated in the silicate layers of MAS. These findings suggest that PPN-MAS intercalated complexes can be used as drug reservoirs in polymeric matrix tablets intended for modifying drug release in oral drug delivery systems.

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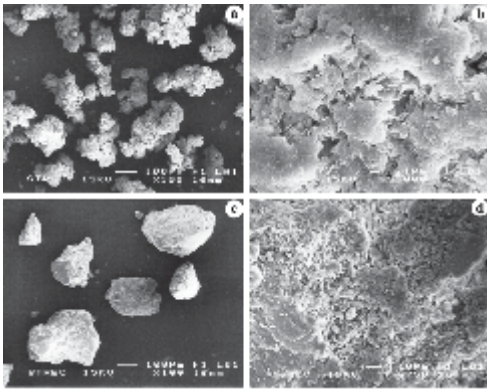

Fig. 1: Particle and surface morphology of MAS (a,b) and PPN-MAS complexes (c,d) used in this study.

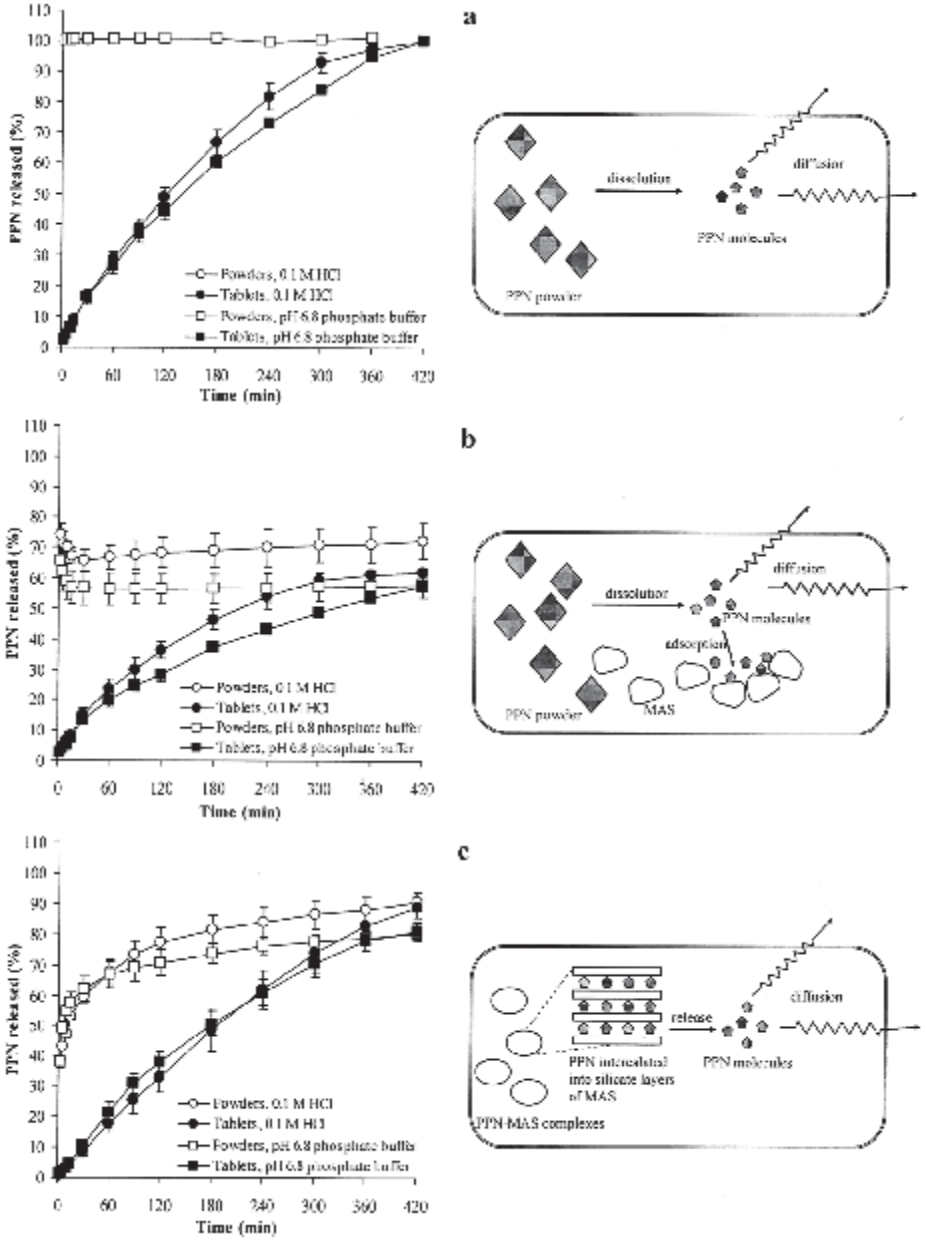

Fig. 2: PPN release profiles (left panel) and PPN release mechanism model (right panel) of HPMC matrix tablets containing pure PPN (a), PPN-MAS physical mixture (b) and PPN-MAS complexes (c). Each point in PPN release profiles is the mean ± SD, n=3.

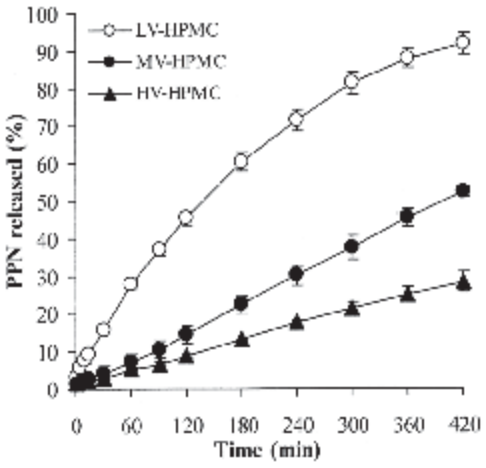

Fig. 3: Effect of viscosity grade of HPMC on PPN release of PPN-MAS complex-loaded HPMC tablets in 0.1 M HCl. Each point is the mean ± SD, n=3.

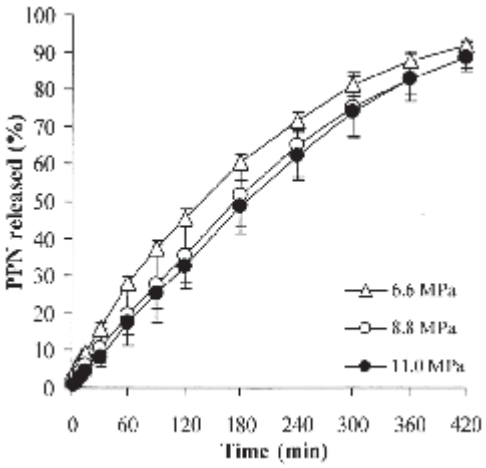

Fig. 4: Effect of compression pressure on PPN release of PPN-MAS complex-loaded HPMC tablets in 0.1 M HCl. Each point is the mean ± SD, n=3.

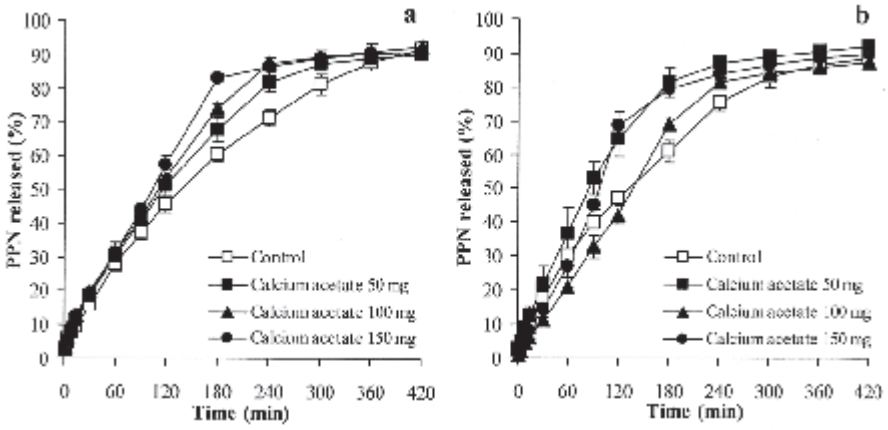

Fig. 5: Effect of calcium acetate amount on PPN release of PPN-MAS complex-loaded HPMC tablets in 0.1 M HCl (a) and pH 6.8 Tris buffer containing sodium chloride and potassium chloride (b). Each point is the mean ± SD, n=3.

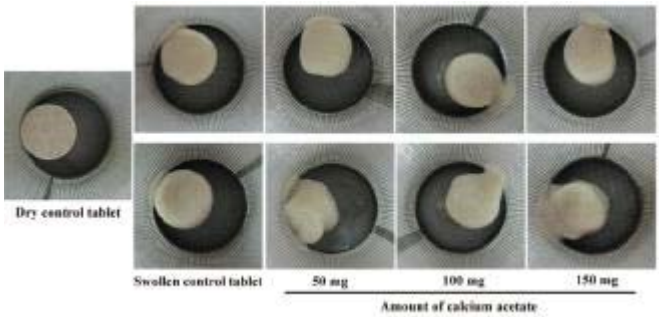

Fig. 6: Photo images of swollen matrix morphology of PPN-MAS complex tablets containing various amounts of calcium acetate in 0.1 M HCl and pH 6.8 Tris buffer after 1 h of release testing.

TABLE 1: PHYSICAL AND DRUG RELEASE CHARACTERISTICS OF HPMC TABLETS CONTAINING DIFFERENT FORMS OF PPN.

HPMC tablet	**Thickness**	**Hardness**	**n**		**K_H (% $min^{-0.5}$)**		**K_0 × 10 (% min^{-1})**	
	(mm)	**(N)**	**0.1 M HCl**	**Phosphate buffer**	**0.1 M HCl**	**Phosphate buffer**	**0.1 M HCl**	**Phosphate buffer**
Pure PPN	6.44 ± 0.02	86.6 ± 10.8	0.75 ± 0.02 (R^2=0.997)	0.72 ± 0.04 (R^2=0.987)	4.91 ± 0.37 (R^2=0.981)	4.49 ± 0.30 (R^2=0.983)	3.90 ± 0.30 (R^2=0.995)	3.60 ± 0.20 (R^2=0.991)
PPN-MAS physical mixture	5.83 ± 0.02	131.4 ± 4.3	0.64 ± 0.02 (R^2=0.992)	0.62 ± 0.03 (R^2=0.992)	3.76 ± 0.30 (R^2=0.994)	2.98 ± 0.05 (R^2=0.998)	2.20 ± 0.20 (R^2=0.965)	1.33 ± 0.01 (R^2=0.951)
PPN-MAS complexes	5.75 ± 0.03	179.1 ± 4.4	0.98 ± 0.02 (R^2=0.993)	0.89 ± 0.03 (R^2=0.990)	3.91 ± 0.60 (R^2=0.959)	4.28 ± 0.36 (R^2=0.976)	2.70 ± 0.44 (R^2=0.999)	2.90 ± 0.25 (R^2=0.987)

Data are the mean ± SD, n=3.
LV-HPMC was used to prepare the tablets at 11.0 MPa compression pressure.

TABLE 2: PHYSICAL AND DRUG RELEASE CHARACTERISTICS OF PPN-MAS COMPLEX-LOADED HPMC TABLETS PREPARED USING DIFFERENT VISCOSITY GRADES OF HPMC IN 0.1 M HCL.

Viscosity grade of HPMC	**Thickness (mm)**	**Hardness (N)**	**n**	**K_H (% $min^{-0.5}$)**	**$K_0 \times 10$ (% min^{-1})**
LV-HPMC (10-20 cP)	6.22 ± 0.02	78.5 ± 5.1	0.74 ± 0.03 (R^2=0.997)	4.79 ± 0.17 (R^2=0.984)	3.26 ± 0.01 (R^2=0.987)
MV-HPMC (40-60 cP)	6.13 ± 0.01	288.0 ± 15.0	0.92 ± 0.04 (R^2=0.993)	2.62 ± 0.16 (R^2=0.936)	1.20 ± 0.06 (R^2=0.998)
HV-HPMC (80-120 cP)	6.13 ± 0.01	332.4 ± 10.0	0.83 ± 0.05 (R^2=0.992)	1.40 ± 0.10 (R^2=0.941)	0.70 ± 0.06 (R^2=0.996)

Data are the mean ± SD, n=3.
Compress pressure used to prepare the tablets was 6.6 MPa and 0.1 M HCl was employed as a dissolution medium.

TABLE 3: PHYSICAL AND DRUG RELEASE CHARACTERISTICS OF PPN-MAS COMPLEX-LOADED HPMC TABLETS PREPARED USING DIFFERENT COMPRESSURE PRESSURES.

Compression pressure (MPa)	**Thickness (mm)**	**Hardness (N)**	**n**	**K_H (% $min^{-0.5}$)**	**$K_0 \times 10$ (% min^{-1})**	**Matrix erosion at 1 h (%)**
6.6	6.24 ± 0.02	78.5 ± 5.1	0.74 ± 0.03 (R^2=0.997)	4.79 ± 0.17 (R^2=0.984)	3.26 ± 0.01 (R^2=0.987)	20.7 ± 1.9
8.8	6.06 ± 0.02	124.5 ± 6.1	0.75 ± 0.10 (R^2=0.980)	4.31 ± 0.42 (R^2=0.960)	3.00 ± 0.21 (R^2=0.990)	18.7 ± 0.2
11.0	5.75 ± 0.03	179.1 ± 4.4	0.98 ± 0.02 (R^2=0.993)	3.91 ± 0.60 (R^2=0.959)	2.70 ± 0.44 (R^2=0.999)	20.5 ± 2.0

Data are the mean ± SD, n=3.
LV-HPMC was used to prepare the tablets and 0.1 M HCl was employed as a dissolution medium.

TABLE 4: PHYSICAL AND DRUG RELEASE CHARACTERISTICS OF PPN-MAS COMPLEX-LOADED HPMC TABLETS CONTAINING DIFFERENT AMOUNTS OF CALCIUM ACETATE.

Calcium acetate	**Thickness**	**Hardness**	**0.1 M HCl**			**pH 6.8 Tris buffer**		
	(mm)	**(N)**	**n**	**$K_0 \times 10$ (% min^{-1})**	**Matrix erosion at 1 h (%)**	**n**	**$K_0 \times 10$ (% min^{-1})**	**Matrix erosion at 1 h (%)**
0 mg (Control tablet)	6.22 ± 0.02	78.5 ± 5.1	0.74 ± 0.03 (R^2=0.997)	3.26 ± 0.01 (R^2=0.987)	20.7 ± 1.9	0.79 ± 0.03 (R^2=0.990)	3.38 ± 0.02 (R^2=0.972)	39.0 ± 0.5
50 mg	6.13 ± 0.01	51.3 ± 4.4	0.75 ± 0.03 (R^2=0.996)	4.07 ± 0.05 (R^2=0.991)	35.0 ± 1.4	0.79 ± 0.05 (R^2=0.997)	5.29 ± 0.03 (R^2=0.990)	51.2 ± 3.3
100 mg	6.23 ± 0.01	69.0 ± 2.5	0.67 ± 0.04 (R^2=0.999)	4.10 ± 0.01 (R^2=0.992)	31.6 ± 3.6	0.93 ± 0.05 (R^2=0.997)	3.49 ± 0.03 (R^2=0.998)	41.8 ± 5.1
150 mg	6.06 ± 0.02	93.8 ± 5.9	0.74 ± 0.06 (R^2=0.993)	4.45 ± 0.02 (R^2=0.995)	33.3 ± 6.1	0.82 ± 0.03 (R^2=0.991)	4.73 ± 0.02 (R^2=0.992)	53.9 ± 2.5

Data are the mean ± SD, n=3.
LV-HPMC was used to prepare the tablets at 6.6 MPa compression pressure.

Influence of pH Modifiers and HPMC Viscosity Grades on Nicotine-Magnesium Aluminum Silicate Complex-Loaded Buccal Matrix Tablets

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ABSTRACT

Hydroxypropyl methylcellulose (HPMC) tablets containing nicotine-magnesium aluminum silicate (NCT-MAS) complex particles and pH modifiers, namely sodium chloride, citric acid and magnesium hydroxide, were prepared using the direct compression method. The effects of HPMC viscosity grades and pH modifiers on NCT release and permeation of the matrix tablets were examined. The results showed that the higher the viscosity grade of HPMC that was used in the tablets, the lower the unidirectional NCT release rate was found to be. The unidirectional NCT permeation was not affected by the viscosity grade of HPMC because the NCT diffusion through the mucosal membrane was the rate-limiting step of the permeation. Incorporation of magnesium hydroxide could retard NCT release, whereas the enhancement of unidirectional NCT release was found in the tablets containing citric acid. Citric acid could inhibit NCT permeation due to the formation of protonated NCT in the swollen tablets at an acidic pH. Conversely, the NCT permeation rate increased with the use of magnesium hydroxide as a result of the neutral NCT that formed at a basic microenvironmental pH. The swollen HPMC tablets, with or without pH modifiers, gave sufficient adhesion to the mucosal membrane. Furthermore, the addition of magnesium hydroxide to the matrix tablets was the major factor in controlling buccal

delivery of NCT. This study suggests that the NCT-MAS complex-loaded HPMC tablets, which contained magnesium hydroxide, are potential buccal delivery systems of NCT.

KEY WORDS: pH modifier, Nicotine, Hydroxypropyl methylcellulose, Magnesium aluminum silicate, Buccal tablet

INTRODUCTION

Buccal drug administration provides several advantages when compared with oral drug administration. Buccal delivery allows drugs to avoid first-pass hepatic metabolism, resulting in greater bioavailability and facilitating drug withdrawal (1). Traditionally, the drug delivery system of this route is in the form of tablets and films. The films have been widely employed, but a large proportion of the drug dose could be swallowed before drug absorption occurs across buccal mucosa because of an initial burst release of the drug from the films (2). To solve this problem, a sustained-release tablet was designed to help reduce this unwanted effect and extend the duration of drug action. Moreover, the mucoadhesive properties of the tablets were also important because adhesion of the drug delivery system to the buccal mucosa was essential during administration (3). For this reason, tablet formulations of bioadhesive polymer were necessary to enhance the mucoadhesive property and sustain drug release. Hydroxypropyl methylcellulose (HPMC) has been widely used for this purpose (4-6).

Nicotine (NCT), obtained from tobacco plants, is a volatile and strongly alkaline liquid. NCT is highly soluble in both water and hydrophobic solvents (7). It has well-separated pK_a values; pK_{a1} and pK_{a2} are 3.04 and 7.84, respectively (8), which leads to the formation of diprotonated, monoprotonated, and neutral NCT at acidic, neutral and basic pH levels, respectively. NCT has been widely used in smoking cessation therapy for relieving withdrawal symptoms. It is a candidate for buccal delivery because of its low bioavailability after oral administration (7) and its ability to permeate buccal mucosa (8-10). Due to the volatility and susceptibility to oxidative degradation of free-base NCT, many researchers have sought an adsorbent material for NCT to prevent evaporation and improve stability. The adsorbents, such as

cellulose powder (11), cation exchange resin (12) and magnesium aluminum silicate (13), were employed to carry NCT in powdered form.

Magnesium aluminum silicate (MAS) is a mixture of montmorillonite and saponite clays (14), both of which have silicate layer structures. Each layer comprises tetrahedrally coordinated silica atoms fused into an edge-shared octahedral plane, with either aluminum hydroxide or magnesium hydroxide (14,15). The silicate layers of MAS have weakly positively charged edges and negatively charged surfaces. The negatively charged surfaces of the silicate layers strongly interact with NCT at different pH levels (16), leading to the formation of NCT-MAS complexes. This interaction allows NCT to intercalate into the silicate layers of MAS (13). The NCT-MAS complex particles could improve the thermal stability of NCT and give a sustained release of NCT after the initial burst release in pH 6 phosphate buffer (13). For these reasons, the NCT-MAS complex-loaded matrix tablets have been developed and evaluated (17). The complexes prepared at basic pH gave remarkably higher NCT permeation rates than those containing the complexes prepared at acidic and neutral pH levels. This result indicated that the pH level during the preparation method gave an NCT species that affected the mucosal delivery of NCT. Thus, modulating the microenvironmental pH of the tablets by adding pH modifiers may alter not only NCT release from the matrix tablets, but also NCT permeation through the mucosal membrane. The use of an additive in the NCT buccal tablets to increase pH, such as magnesium hydroxide, has been developed (18). Unfortunately, the effect the amount of pH increasing agent has on NCT release and permeation characteristics of the matrix tablets is not available in the literature.

Therefore, the aim of this study was to investigate the effect of pH modifiers, namely sodium chloride (neutral compound), citric acid (acidic compound) and magnesium hydroxide (basic compound), on NCT release and permeation of the matrix tablets containing NCT-MAS complexes prepared at basic pH. HPMC was used for this investigation because it is a non-ionic bioadhesive polymer that cannot electrostatically interact with positively or negatively charged compounds in the tablets. Moreover, the effect of the viscosity grade of HPMC on the characteristics of the NCT-MAS complex-loaded matrix tablets was also examined. Based on the results of NCT release and permeation, rate control of the NCT delivery was

investigated for a better understanding of when to incorporate pH modifiers into HPMC matrix tablets.

MATERIALS AND METHODS

Materials

MAS (Veegum®HV) and NCT were obtained from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA), and Fluka (Buchs, Switzerland), respectively. Hydroxypropyl methylcellulose, of viscosity grades of 10-20 cP (low viscosity, LV-HPMC) and 40-60 cP (medium viscosity, MV-HPMC), was purchased from Onimax Co., Ltd. (Bangkok, Thailand). High viscosity grade HPMC (HV-HPMC), 80-120 cP, was obtained from S.M. Chemical Supplies Co., Ltd. (Bangkok, Thailand). Sodium chloride, citric acid monohydrate and magnesium hydroxide were purchased from Merck Ltd. (Bangkok, Thailand). Magnesium stearate (Mallinckrodt Inc., St Louis, MO) was used as a lubricant for tableting. All other reagents that were used were of analytical grade and were used as received.

Preparation of NCT-MAS Complexes

A 4% w/v MAS suspension was prepared using hot water and was cooled to room temperature before use. An NCT solution (2 % w/v) was prepared using deionized water as the solvent. Fifty milliliters of the 4% w/v MAS suspension was then mixed with 50 ml of the 2% w/v NCT solution in an Erlenmeyer flask. The pH of the NCT-MAS dispersion was adjusted by adding small amounts of 1 M HCl into the flask while swirling until the final pH of the dispersions was at 9, as measured with a pH meter (WalkLAB TI9000, Singapore). To achieve NCT adsorption equilibrium on MAS, the dispersions were then incubated with shaking at 37 °C for 24 h (16). Following incubation, the NCT-MAS complexes were collected by filtration, washed twice using 20 ml of deionized water and dried at 50 °C for 24 h. The dry NCT-MAS complexes were ground using a mortar and pestle, sieved through a 180-µm sieve and stored in a desiccator.

Characterization of the NCT-MAS Complexes

Determination of NCT Content

Twenty-five milligrams of the NCT-MAS complexes were weighed and dispersed in 100 ml of 2 M HCl for 12 h. The supernatant was then collected and filtered, and the NCT content was analyzed using a UV-visible spectrophotometer (Shimadzu UV1201, Japan) at a wavelength of 259 nm.

Particle Size Determination

The particle sizes of the NCT-MAS complexes were measured using a laser diffraction particle size analyzer (Mastersizer2000 Model Hydro2000SM, Malvern Instrument Ltd., UK). The samples were dispersed in 70 ml of pH 6 phosphate buffer in a small volume sample dispersion unit and stirred at a rate of 50 Hz for 30 s before the measurement. The particle sizes (volume-weighted mean diameter) were reported.

Characterization of HPMC

Particle Size Determination

Particle sizes of HPMC powder with different viscosity grades were determined using a laser diffraction particle size analyzer (Mastersizer2000 Model Scirocco2000SM, Malvern Instrument Ltd., UK). The particle sizes (volume-weighted mean diameter) were presented.

Measurement of Viscosity

HPMC dispersions at a concentration of 2 % w/v in distilled water were prepared. The viscosity of the HPMC dispersion was investigated using a small sample adapter for the Brookfield digital rheometer (Model DV-III, Brookfield Engineering Labs. Inc., USA). The sample temperature was controlled at 32 ± 1°C. A rheogram of the samples was obtained by plotting between shear stress (y-axis) and shear rate (x-axis) at various revolution rates when a spindle (No. 34) was used. The slope of the rheogram was calculated as the viscosity of the dispersion.

Preparation of NCT-MAS Complex-Loaded HPMC Tablets

All tablets were produced using the direct compression method. Each tablet consisted of 120 mg NCT-MAS complexes (equivalent to 15.8 mg of NCT), 80 mg HPMC and 2 mg magnesium stearate. When a pH modifier was added, enough sodium chloride,

citric acid or magnesium hydroxide was added to give a final content of 5, 10, or 20 % w/w of the tablet weight. The NCT-MAS complexes were mixed with HPMC and pH modifier in a rotomixer for 3 min; magnesium stearate was then blended with the mixture for 1 min before tableting. The mixtures were filled into 10-mm flat-faced punches and dies, and then 23 MPa compression pressure was applied with a hydrostatic press (Model 3126, Shimadzu, Kyoto, Japan) without holding time. The resulting tablets were stored in a desiccator prior to use.

Characterization of NCT-MAS Complex-Loaded HPMC Tablets

Thickness and Hardness

The thicknesses of the tablets were measured using a vernier caliper (Mitutoyo, Japan). The hardnesses of the tablets were measured with a Stokes tablet hardness tester.

In Vitro Release Studies

NCT release of the NCT-MAS complex-loaded HPMC tablets was studied using two apparatuses. NCT released from the whole tablets was tested using a USP dissolution apparatus 1 (basket method, VanKel VK200, USA). The tablets were placed into the basket with a rotation speed of 50 revolutions/min. The release medium was 500 ml of pH 6 phosphate buffer, and the temperature was controlled at 37.0 ± 0.5 °C. Seven-milliliter samples were collected and replaced with fresh medium at various time intervals. The amount of NCT released was analyzed using a UV-visible spectrophotometer (Shimadzu UV1201, Japan) at a wavelength of 259 nm.

Unidirectional NCT release of the tablets was characterized using a modified USP dissolution apparatus 2 that was reported previously (17). Briefly, the distance between the paddle and vessel bottom was set to 1 cm, and the dissolution medium used was 300 ml of pH 6 phosphate buffer at 37.0 ± 0.5 °C. A cellulose acetate membrane (0.45-μm pore size), which had been hydrated in pH 6 phosphate buffer overnight, was tightly attached at the lowest end of a polypropylene tube (inner diameter =1.8 cm) using a nylon cable tie. This tube was vertically placed in a dissolution vessel, and the distance between the tube and the vessel wall was approximately 1.8 cm. The end of the tube was adjusted so that the membrane was

wetted and in contact with the medium. The tablets were placed into the tube and wetted using 2 ml of pH 6 phosphate buffer. The rotation speed of the paddle was set to 50 revolutions/min. Samples (7 ml) were collected and replaced with fresh medium at various time intervals. The amount of NCT released was analyzed using HPLC.

In Vitro Permeation Studies

Unidirectional NCT permeation of the tablets was also performed using a modified USP dissolution apparatus 2. Porcine esophageal mucosa was employed in this study because it had a lipid composition similar to porcine buccal mucosa, but a simpler preparation method (19). Esophageal mucosa of a crossbred pig (hybrid types of Duroc Jersey-Landrace-Large White) weighing 80-100 kg was obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The porcine esophageal tube was opened longitudinally and immersed in 0.9% sodium chloride at 60 °C for 1 min (19, 20). The epithelium was then peeled away from the connective tissue and stored at -20 °C. The frozen mucosal membranes were brought to room temperature by immersion in pH 7.4 isotonic phosphate buffer for 15 min. The mucosal membrane was then mounted and tightly attached to the end of a polypropylene tube. The dissolution vessel contained 300 ml of pH 7.4 isotonic phosphate buffer at 37.0 ± 0.5 °C; the methods and experimental conditions were the same as the previous release testing.

Analysis of NCT Release and Permeation

The release mechanisms of NCT released from the whole tablet and the unidirectional tablet were analyzed using a power law (21, 22) as shown in Equations 1 and 2, respectively, as follows:

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Eq. 1}$$

and

$$\log\frac{M_t}{M_\infty} = n\log t + \log k, \qquad \text{Eq. 2}$$

where M_t/M_∞ is the fractional NCT release at time t, k is the kinetic constant, and n is the release exponent indicative of the drug release mechanism. A release exponent of n = 0.5 indicates a diffusion-controlled drug release (Fickian diffusion), whereas a

release exponent of n = 1 corresponds to a polymer-swelling/erosion-controlled release mechanism. Thus, release exponents between these two extreme values indicate so-called anomalous transport, which is a complex transport mechanism that is a mixture of both drug diffusion and swelling/erosion of polymer.

The NCT release and permeation rates of the tablets were analyzed using both zero-order and Higuchi models (23), which can be expressed as Equations 3 and 4, respectively, as follows:

$$Q = K_0 t \qquad \text{Eq. 3}$$

and

$$Q = K_H t^{1/2}, \qquad \text{Eq. 4}$$

where Q is the amount of NCT released, t is time, and K_0 and K_H are the zero-order and Higuchi release rates, respectively.

Measurement of Mucoadhesive Properties

The mucoadhesive properties of the tablets were measured using a texture analyzer (TA.XT plus, Stable Micro Systems, UK) with a 50-N load cell equipped with a bioadhesive test rig.

The tablet was attached to a 10 mm diameter cylindrical probe using two-sided adhesive tape. Esophageal mucosa of pig was also obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The mucosal membrane from the porcine esophagus (approximately 2 cm × 2 cm), without heat treatment and elimination of the connective tissue that had been hydrated with pH 7.4 isotonic phosphate buffer for 20 min, was placed on the stage of the bioadhesive holder and gently blotted with tissue paper to remove excess water on the surface of the mucosal membrane. Next, 200 µl of pH 6 phosphate buffer was pipetted onto the membrane surface before testing. The probe and attached tablet were moved down at a constant speed of 1 mm s^{-1} with 0.5 N contact force and 2 min contact time. Immediately afterwards, the probe was moved upwards with a constant speed of 0.5 mm s^{-1}. The relationship between the force and tablet displacement was plotted. The maximum detachment force (F_{max}) and work of adhesion (W_{ad}, the area under the force versus distance curve) were calculated using the Texture Exponent 32 program version 4.0.9.0 (Stable Micro Systems, UK).

HPLC Condition for NCT Analysis

The NCT concentration of the samples from release and permeation testing was determined using HPLC (Perkin Elmer Series, USA). Reversed-phase HPLC using a C-18 column (Waters Spherisorb® S5 ODS2, 5-μm particle size, 4.6 × 250 mm, Ireland) connected to a guard column was employed. The mixture of 0.05 M sodium acetate:methanol:triethylamine in the ratio of 88:12:0.5 by volume was used as a mobile phase and the final pH of the mobile phase was adjusted to 4.2 with glacial acetic acid. The flow rate of the mobile phase was 1 ml min^{-1}, and the detector was a UV-visible detector at a wavelength of 259 nm. The retention time of NCT was approximately 7.0 min. Under these conditions, good linearity and reproducibility were shown over the range 1.0 - 100.0 μg ml^{-1} NCT.

Statistical analysis

One-way analysis of variance (ANOVA) with the least significant difference (LSD) test for multiple comparisons was performed using SPSS program for MS Windows, release 11.5 (SPSS Thailand Co., Ltd., Bangkok, Thailand), to assess the statistical significance of physical properties as well as NCT release and permeation rate of the tablets. The significance of the difference was determined at 95% confident limit (α = 0.5) and considered to be significant at a level of *P* less than 0.05.

RESULTS AND DISCUSSION

Characteristics of NCT-MAS Complexes and HPMC

The size of NCT-MAS complex particles was 94.03 ± 1.28 microns (n = 3) and the NCT content was 13.20 ± 0.04 % w/w (n = 3). The particle size of HPMC with different viscosity grades is listed in Table 1. The MV-HPMC showed the smallest particle size of 75.7 microns, whereas the particle sizes of the LV-HPMC and HV-HPMC were over the range of 96.2 - 106.8 microns. In the viscosity determination, the relationship between shear stress and shear rate provided good linearity, indicating Newtonian flow. Therefore, the slope of such a relationship was the viscosity of HPMC dispersion. The viscosity of HPMC dispersions, as shown in Table 1, was less than that claimed by the manufacturer due to the higher temperature used in this study.

Effect of HPMC viscosity grade on characteristics of NCT-MAS complex-loaded tablets

The thickness and hardness of the tablets that were prepared using different viscosity grades of HPMC are listed in Table 1. The HPMC viscosity grade did not affect the thickness of the tablets that were prepared. On the other hand, the hardness of the tablets statistically increased ($P < 0.05$) with increasing viscosity grade of HPMC, and the use of HV-HPMC presented the highest tablet hardness. This result was in agreement with the previous study (24). The tablets gave acceptable physical properties because HPMC had a good compressibility and showed plastic deformation under compression with small elastic recovery when using low compression speed (24), which was similar to the use of hydrostatic press for tableting that had a slow speed for tablet compression.

The NCT release of the whole tablets is presented in Fig. 1a, and the NCT release parameters are listed in Table 1. It can be observed that NCT release was not related to the viscosity grade of HPMC used. The release exponent, n value, of the MV-HPMC tablets was more than unity, whereas that of the LV- and HV-HPMC tablets was in the range of 0.61-0.77. This result suggested that the NCT release of the MV-HPMC tablets was controlled by a matrix erosion mechanism, whereas both NCT diffusion and matrix erosion controlled NCT release of the LV-HPMC and HV-HPMC tablets. The NCT release data of the MV-HPMC tablets showed good correlation when using the zero-order equation with R^2 higher than 0.99 (Table 1). In contrast, the Higuchi model presented a better determination coefficient (R^2) than the zero-order model for the LV- and HV-HPMC tablets. Furthermore, the MV-HPMC tablets provided the highest K_0 and K_H values. The LV-HPMC tablets gave lower K_0 and K_H values than the HV-HPMC tablets. Generally, increasing the viscosity grade of HPMC caused slower drug release from the HPMC tablets (25) due to a higher viscosity gel barrier that was created around the tablets when exposed to the dissolution medium. This phenomenon could be explained for only the NCT release of the LV- and HV-HPMC tablets, but not for the MV-HPMC tablets. The NCT release of the LV- and HV-HPMC tablets mainly followed a matrix diffusion controlled mechanism, indicating that a continuous gel barrier could be formed around the tablets. In the case of the MV-HPMC tablets, an incomplete swelling of MV-HPMC particles may have occurred because the fracture of some NCT-MAS

complex particles, which have a larger particle size than MV-HPMC powder, could cover the surface of the MV-HPMC particles that underwent plastic deformation under compression. Covering the surface of these particles resulted in a slow water uptake and swelling of the MV-HPMC particles to form a continuous gel barrier around the tablets. An incomplete gel formation may lead to rapid erosion and NCT release of the tablets.

Unidirectional release and permeation of NCT from NCT-MAS complex-loaded HPMC tablets using different viscosity grades of HPMC are shown in Fig. 1b and 1c, respectively. The release and permeation parameters of NCT are listed in Table 1. The release exponents of all tablets were over the range of 0.54-0.60. The NCT release rate computed using the Higuchi model gave a better determination coefficient than that using the zero-order model. For these results, it was indicated that the NCT release was controlled by a matrix diffusion controlled mechanism with only a small impact on polymer swelling, which can be observed from the value of the release exponent that was slightly higher than 0.5. The NCT release rate of the tablets using different viscosity grades of HPMC was related to the viscosity value of 2% w/v HPMC that could be represented by the viscosity of the gel barrier that formed surrounding the swollen tablets (Fig. 2). The NCT release rate tended to decrease with increasing viscosity of HPMC. This result was in contrast with the NCT release of the whole tablets because erosion of the swollen tablets did not involve the unidirectional release of NCT. Therefore, the gel barrier could be completely created on the surface of the swollen tablets that were located on the cellulose acetate membrane. Apart from the unidirectional release, the NCT permeation rate could be computed with both the Higuchi and the zero-order models. It can be observed that the NCT permeation rate did not change significantly when increasing the viscosity value of HPMC (Fig. 2). This result suggested that the NCT diffusion across the mucosal membrane was the rate-limiting step of the NCT permeation.

The mucoadhesive properties, F_{max} and W_{ad}, of the NCT-MAS complex-loaded matrix tablets when using different viscosity grades of HPMC are presented in Table 1. It was found that the viscosity grade of HPMC did not influence F_{max} and W_{ad} values on porcine esophageal mucosa. HPMC is a nonionic polymer that possesses a mucoadhesive property (1,26) because it contains numerous hydroxyl groups that can

form hydrogen bonds. It has been proposed that the interaction between the mucus on the mucosal membrane and hydrophilic polymers occurs by physical entanglement and chemical interactions, such as hydrogen bonding (26). Due to the mucoadhesive properties of HPMC and NCT-MAS complexes (17), the NCT-MAS complex-loaded HPMC tablets adhered sufficiently onto the mucosal membrane.

Effect of pH modifier on characteristics of NCT-MAS complex-loaded HPMC tablets

The NCT-MAS complex-loaded MV-HPMV tablet was selected as a control tablet for investigating the effect of pH modifiers including sodium chloride, citric acid and magnesium hydroxide, on characteristics of the tablets. Incorporation of pH modifiers caused a change in the thickness and hardness of the tablets (Table 2). The tablet thickness seemed to increase with increasing amounts of pH modifier. Incorporation of 5-20% sodium chloride did not affect the hardness of the tablets, whereas 20% citric acid caused a decrease in tablet hardness, but 5-10% citric acid caused no change. On the other hand, a small amount of magnesium hydroxide brought about a remarkable decrease in the tablet hardness, and a similar tablet hardness was found by further increasing the magnesium hydroxide content (10 and 20%) in the tablets. It is possible to explain that sodium chloride possessed an intermediate plastic deformation with a low degree of fragmentation under the compression pressure (27,28), which was similar to HPMC. Incorporation of sodium chloride into HPMC did not affect deformation and interparticle bonding, leading to no change in the tablet hardness when sodium chloride was added. Conversely, the highest quantity of citric acid significantly decreased the tablet hardness because large amounts of citric acid may reduce interparticle bonding of HPMC. Inorganic materials, such as magnesium hydroxide, that form hard and brittle particles (28) gave fragmentation under compression pressure. This deformation could obviously reduce interparticle bonding and interlocking of HPMC particles, resulting in a decrease in the tablet hardness.

The effect of pH modifiers on NCT release of whole tablets is presented in Fig. 3, and the release exponent of NCT is shown in Fig. 4a. As observed from the NCT release profiles, sodium chloride and citric acid could accelerate NCT release, but a retardation of NCT release was found in the tablets containing magnesium hydroxide. The release exponents of the tablets containing varying quantities of sodium chloride

and citric acid were higher than unity and similar to the control tablets. This finding indicated that a matrix erosion mechanism was the predominant factor in controlling NCT release. The NCT release rates of the tablets containing various contents of sodium chloride and citric acid are presented in Table 2. The NCT release of the tablets containing sodium chloride showed a good fit with the Higuchi model, whereas neither the Higuchi model nor the zero-order model could fit with that of the tablets adding citric acid, which could be observed from a determination coefficient that was smaller than 0.97. However, it was clear that sodium chloride and citric acid could promote release of NCT from the tablets, but the extent of release did not correlate with the amount of sodium chloride and citric acid that was added. It is possible that the high water solubility of sodium chloride and citric acid could accelerate the swelling and erosion of the HPMC tablets, which could cause matrix erosion of the tablets and a higher NCT release rate compared to the control tablets. Moreover, the high water solubility of citric acid, 1 g in 1.69 ml at 20 °C (29), gave a greater NCT release rate than sodium chloride, which has a water solubility of 1 g in 2.78 ml (29). In contrast to the tablets containing magnesium hydroxide, the release exponent was found to be in the range of 0.58-0.62 even though only a small content of magnesium hydroxide was added to the tablets. This range led to a good fit for NCT release with the Higuchi model (Table 2). The NCT release rate of the tablets with magnesium hydroxide was statistically lower ($P < 0.05$) than that of the control tablets. This finding suggested that incorporating magnesium hydroxide could reinforce and maintain the matrix of the tablets, which could result from an inorganic gel formation of magnesium hydroxide in the tablet matrix after being exposed to the dissolution medium, leading to retardation of matrix erosion and a matrix diffusion-controlled mechanism of NCT release.

The effect of pH modifiers on unidirectional NCT release from the tablets is shown in Fig. 5, and the release exponent is summarized in Fig. 4b. It can be observed that the release exponent of all tablets was over the range of 0.55-0.69, which is indicative of a drug diffusion and polymer swelling controlled mechanism. The addition of pH modifiers did not influence the NCT release kinetics. However, the release exponent of the unidirectional NCT release was obviously lower than that of the NCT release of the whole tablets, particularly the control tablets and the tablets containing sodium

chloride and citric acid (Fig. 4a), because of the limitation on the erosion process of the swollen matrix tablets when using a cellulose acetate membrane. The NCT release rate of the tablets is listed in Table 3. The Higuchi model gave a better fit with the release of NCT from the unidirectional test than the zero-order model. The addition of sodium chloride did not remarkably affect the release of NCT when compared with the control tablets. This result suggested that sodium ions dissolved in the swollen tablets could not accelerate an ion exchange process with NCT that was intercalated in the silicate layers of MAS. On the other hand, 10 and 20% citric acid could significantly increase the NCT release rate ($P < 0.05$) when compared with the control tablets. This result was similar to the previous report (30). This similarity was due to the higher water solubility of citric acid that could it allow it to be rapidly dissolved and leach out from the swollen tablets. This leaching led to a decrease in the tortuosity of the swollen matrix and resulted in faster NCT release. In the case of magnesium hydroxide, a significant retardation of NCT release ($P < 0.05$) was found in comparison with the control tablets but was not proportional to the content of magnesium aluminum silicate added. This result suggested that the formation of an inorganic gel of magnesium hydroxide could reinforce and increase the tortuosity of the swollen matrix, resulting in slower diffusion and release of NCT from the tablets. The unidirectional permeation of the tablets using porcine esophageal mucosal membrane was also investigated as shown in Fig. 6. The NCT permeation rates were calculated using the Higuchi and zero-order models and are reported in Table 3. The NCT permeation could be described using the zero-order model rather than the Higuchi model because of a greater determination coefficient value, suggesting that the NCT diffusion across the mucosal membrane was the rate-limiting step of the permeation. The tablets containing sodium chloride gave a similar NCT permeation rate when compared with the control tablets. The incorporation of citric acid gave a significantly lower NCT permeation rate ($P < 0.05$) than the control tablets, and 20% citric acid gave the highest retardation effect ($P < 0.05$). Citric acid could enhance the NCT release from the swollen matrix, but NCT molecules that were released did not readily permeate across the mucosal membrane because NCT in the protonated form under acidic conditions has a low permeability for the mucosal membrane (8,9). On the other hand, magnesium hydroxide provided a statistical enhancement in NCT permeation ($P < 0.05$) when compared with the control tablets, even through a small quantity (5%) of magnesium hydroxide was used. The basic microenvironmental pH

of the swollen tablets containing magnesium hydroxide could prevent the protonation of NCT, instead giving a neutral species that showed increased permeability across the mucosal membrane, leading to enhanced permeation of NCT. Additionally, the use of 10% magnesium hydroxide showed the highest NCT permeation rate, suggesting that microenvironmental basic pH in the swollen tablets could be sufficient for inducing the formation of neutral NCT. Curiously, the addition of more than 10% magnesium hydroxide did not enhance the NCT permeation.

The mucoadhesive properties of the tablets containing pH modifier are listed in Table 3. The pH modifiers that were added did not affect the F_{max} and W_{ad} values of the tablets, which suggested that the MV-HPMC particles still had swelling properties on the tablet surface that incorporated with the particles of pH modifiers. The rapid swelling and disentanglement of MV-HPMC molecules could interact with mucin on the surface of the porcine esophageal mucosa, which resulted in similar mucoadhesive properties when adding a pH modifier to the tablets.

Rate control studies of the matrix tablets

In the development of the drug delivery system, the delivery of drug to circulating blood must be controlled by the drug delivery system that is administered, which is not controlled by the mucosal membrane. Thus, the rate control studies of the NCT-MAS complex-loaded matrix tablets were modified from the method that was reported previously (31,32). The fractional rate control provided by the device (buccal tablet) and the mucosal membrane could be computed using the NCT release and permeation data from the unidirectional testing and the following equations:

$$\text{Fractional control by device } (F_d) = \frac{A_P}{A_R}$$

$$\text{Fractional control by mucosal membrane } (F_m) = (1 - F_d)$$

where A_P is the amount of NCT that permeates across the mucosal membrane at 8 h, and A_R is the amount of NCT released through the cellulose acetate membrane at 8 h. These equations are based on the same testing method of the unidirectional NCT release and permeation.

The fractional control by the buccal tablets is presented in Fig. 7. In the evaluation of different HPMC viscosity grades, the tablets using HV-HPMC gave a remarkably greater F_d value than those using LV- and MV-HPMC. This result suggested that an increase in swollen gel viscosity could retard and control NCT release onto the mucosal membrane before NCT permeation, leading to a decrease in NCT permeation. Moreover, incorporation of sodium chloride did not influence the F_d value when compared with the tablets using MV-HPMC (the control tablet). The reduction in the F_d value was found when adding citric acid because of lower permeability of the protonated NCT that formed on the mucosal membrane. On the other hand, the F_d values of the tablets containing magnesium hydroxide were close to unity. This result indicated that the NCT permeation across the mucosal membrane was identical with the release of NCT from the tablets because of the formation of neutral NCT under basic pH.

CONCLUSION

The NCT-MAS complex-loaded HPMC tablets were successfully prepared by the direct compression method. The higher the viscosity grade of HPMC that was used in the tablets, the lower the unidirectional NCT release rate that resulted. The unidirectional NCT permeation was not affected by the viscosity grade of HPMC. The incorporation of magnesium hydroxide could retard NCT release, whereas the enhancement of unidirectional NCT release was found in the tablets containing citric acid. Citric acid could inhibit the NCT permeation rate due to the formation of protonated NCT under acidic pH. Conversely, the NCT permeation rate increased with the use of magnesium hydroxide, resulting from a neutral NCT species that formed under basic pH. The swollen HPMC tablets, with or without pH modifier, showed mucoadhesive properties toward the mucosal membrane. Furthermore, the buccal delivery of NCT could be controlled mainly by the matrix tablets with the addition of magnesium hydroxide. This study suggests that the NCT-MAS complex-loaded HPMC tablets containing magnesium hydroxide presented a promising buccal delivery system of NCT.

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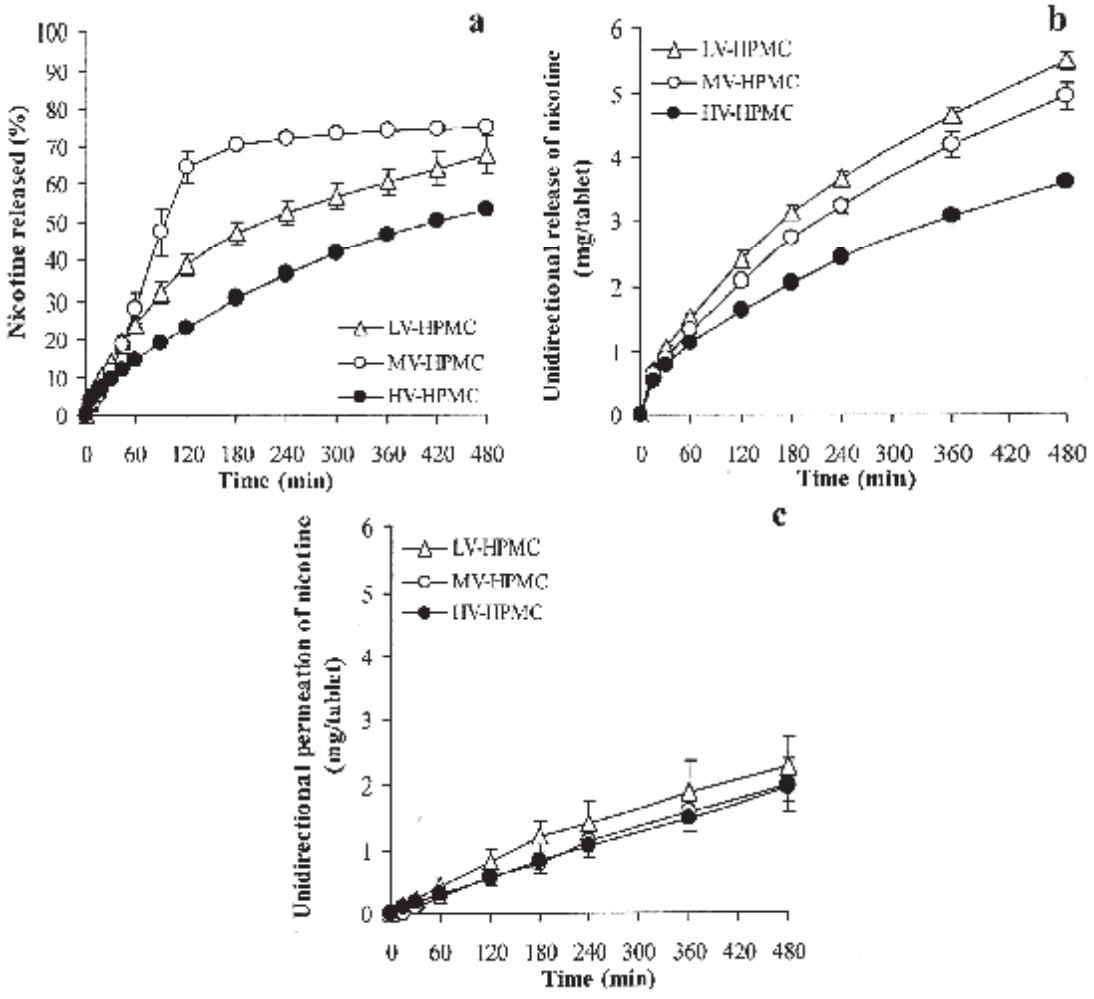

Fig. 1. NCT release profiles of whole tablets (a), and unidirectional NCT release (b) and permeation (c) of NCT-MAS complex-loaded HPMC tablets prepared using different viscosity grade of HPMC. Each value represents the mean ± SD of triplicate experiments.

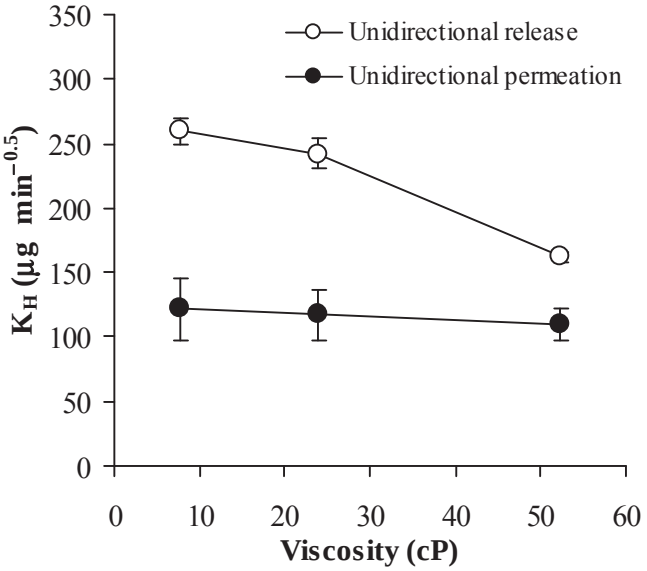

Fig. 2. Relationship between viscosity of 2%w/v HPMC dispersion and unidirectional release and permeation rate of tablets calculated using Higuchi's equation. Each point represented the mean ± SD of triplicate experiments.

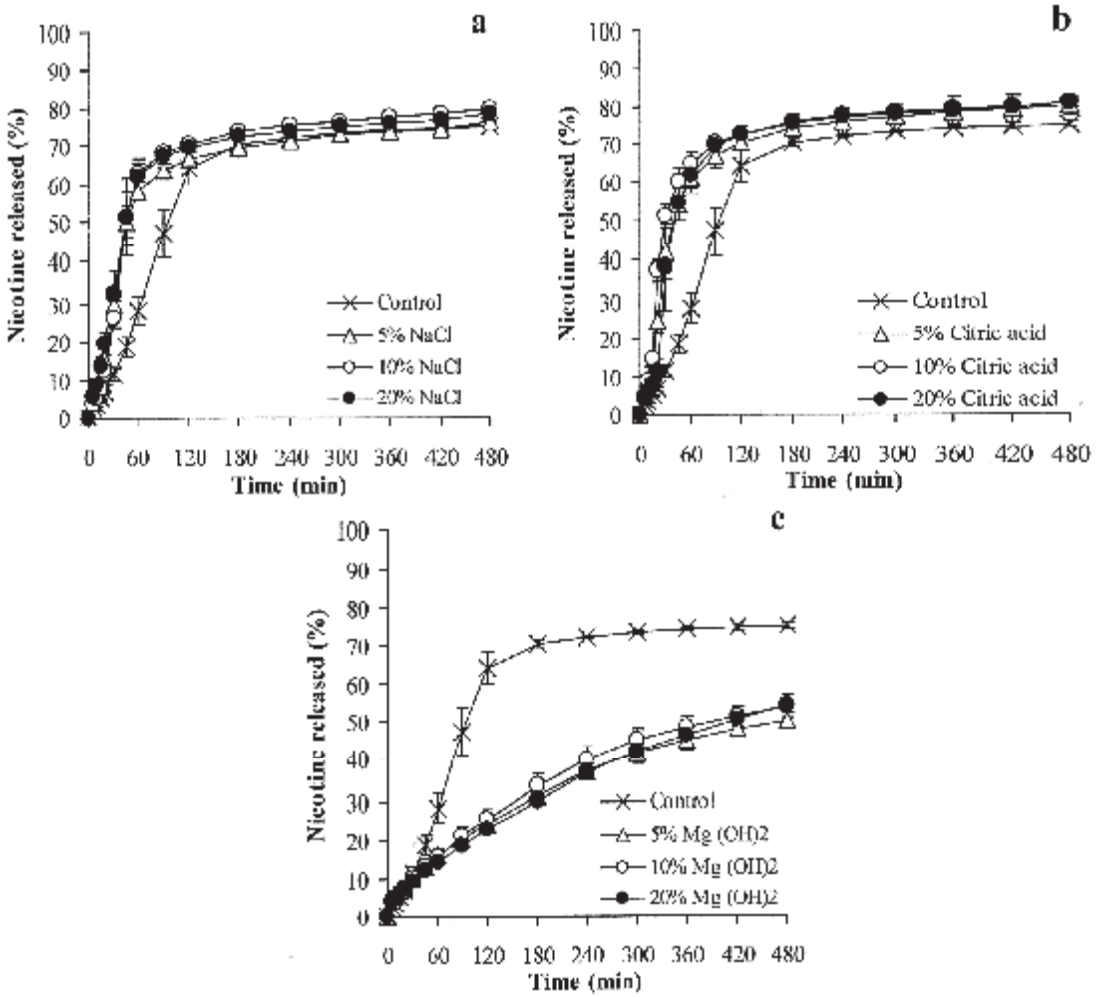

Fig. 3. Effect of pH modifiers on NCT release of whole tablets of NCT-MAS complex-loaded HPMC tablets containing various contents of sodium chloride (a), citric acid (b), and magnesium hydroxide (c). Each value represents the mean ± SD of triplicate experiments.

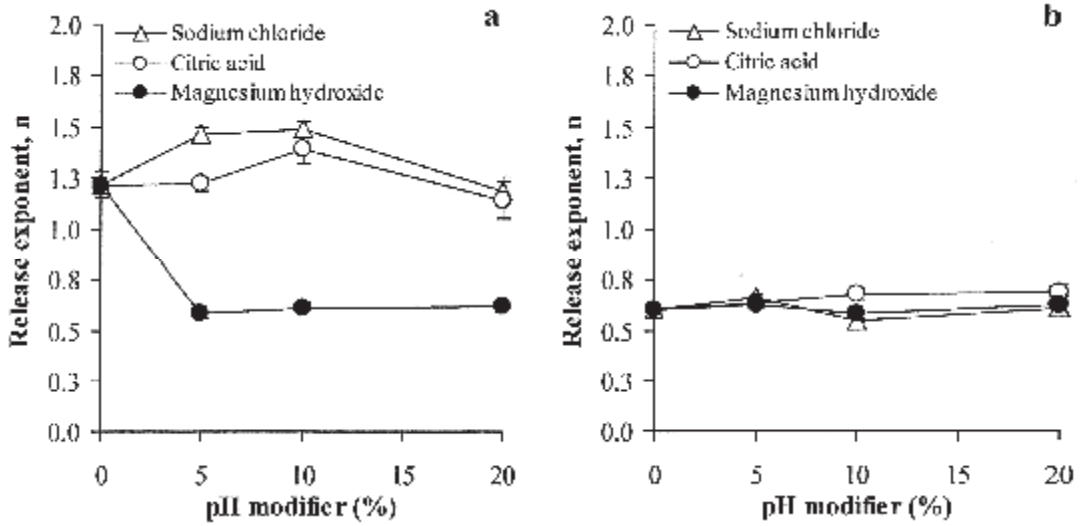

Fig. 4. Release exponent (n) of whole tablets (a) and unidirectional tablets (b) of NCT-MAS complex-loaded HPMC tablets prepared using different pH modifiers. Each value represents the mean ± SD of triplicate experiments.

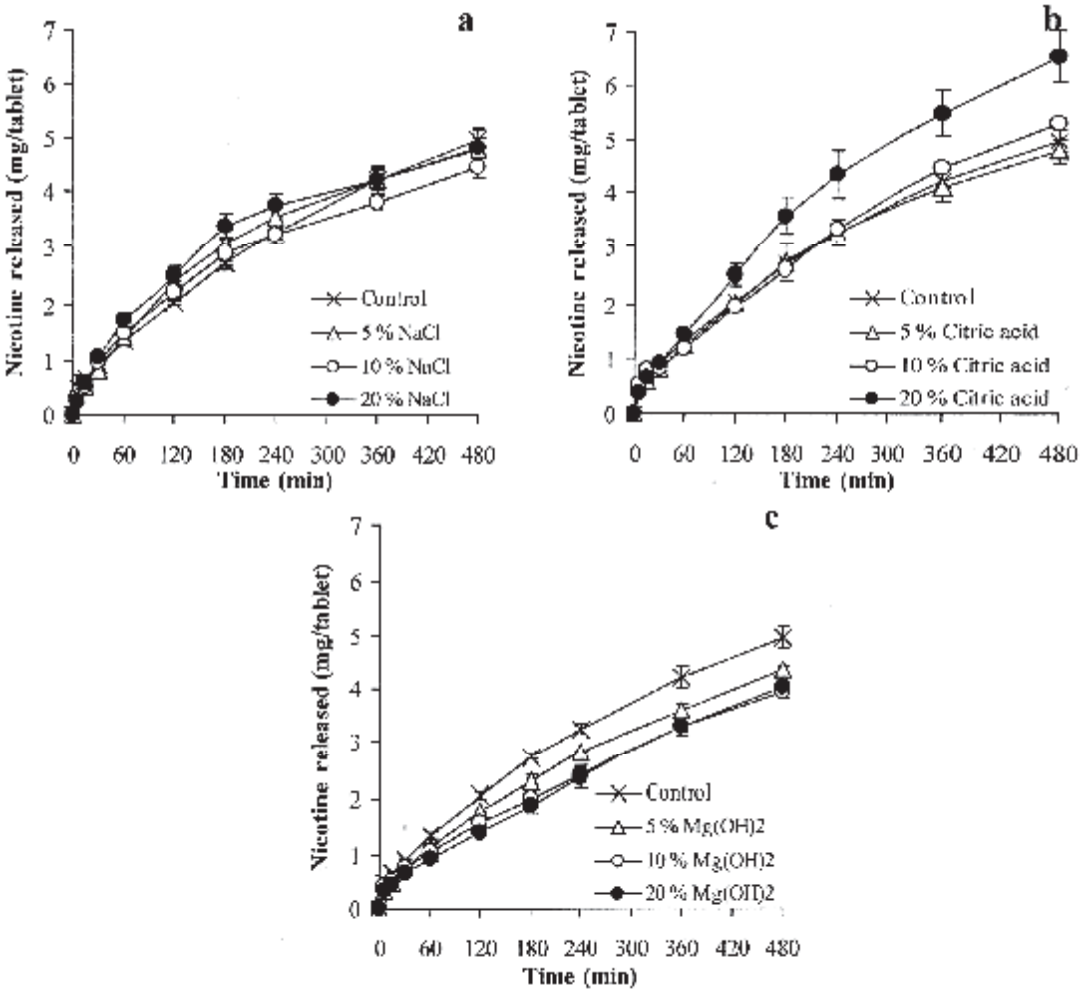

Fig. 5. Effect of pH modifiers on unidirectional NCT release of NCT-MAS complex-loaded HPMC tablets containing various contents of sodium chloride (a), citric acid (b), and magnesium hydroxide (c). Each value represents the mean ± SD of triplicate experiments.

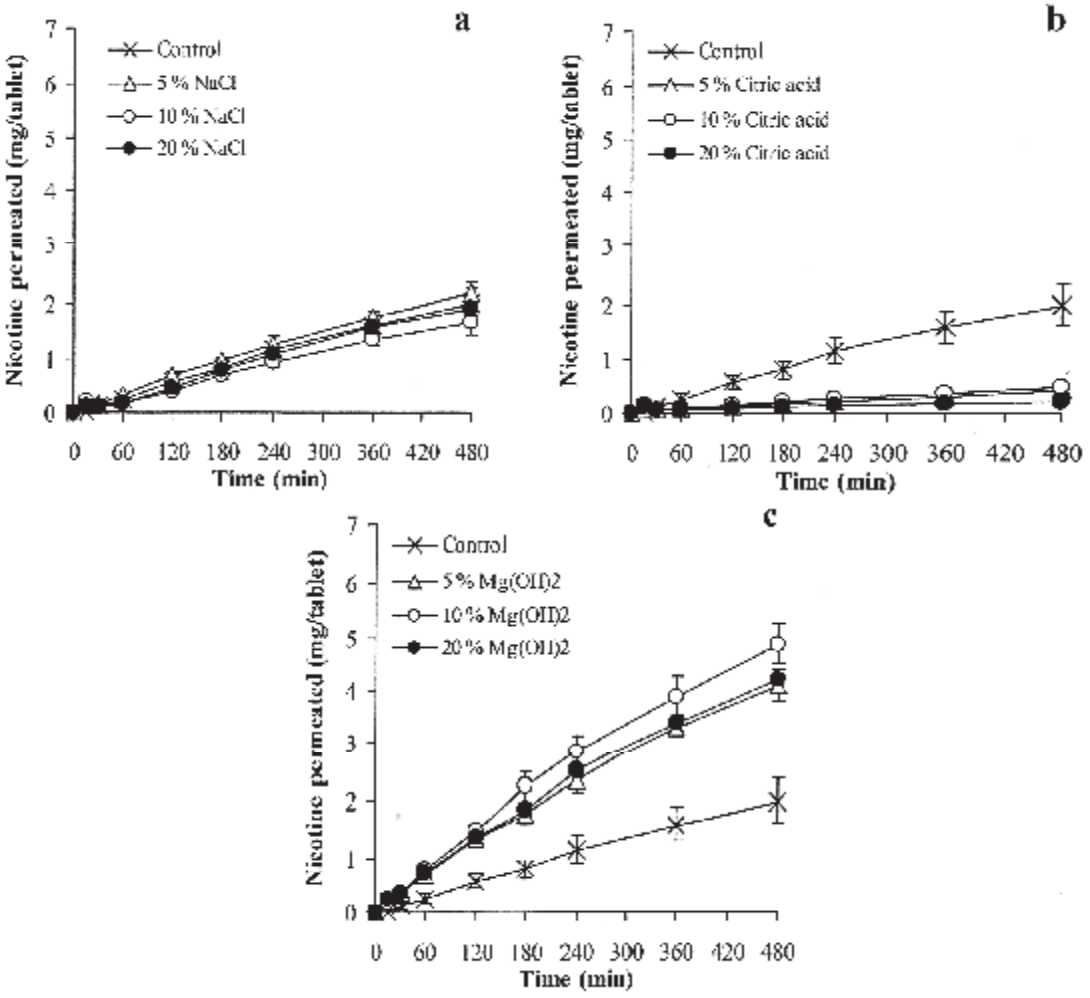

Fig. 6. Effect of pH modifiers on unidirectional NCT permeation of NCT-MAS complex-loaded HPMC tablets containing various contents of sodium chloride (a), citric acid (b), and magnesium hydroxide (c). Each value represents the mean ± SD of triplicate experiments.

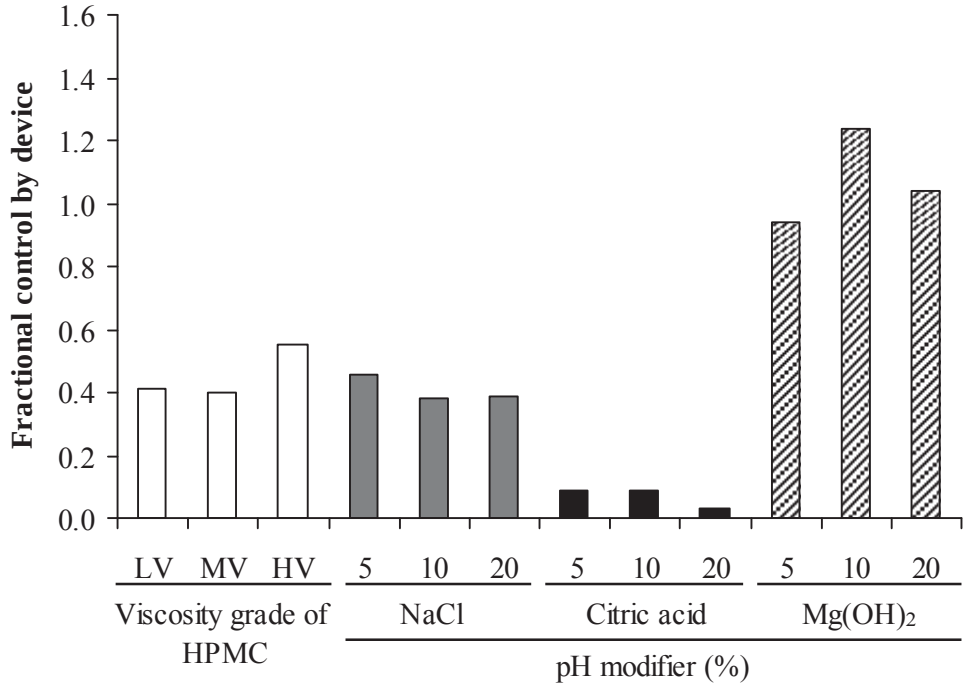

Fig. 7. Fractional control by device of NCT-MAS complex-loaded HPMC tablets prepared using different viscosity grades of HPMC and pH modifiers.

Table 1. Characteristics of HPMC powder and dispersion, and NCT-MAS complex-loaded matrix tablets prepared using different viscosity grades of HPMC.

HPMC characteristics	LV-HPMC	MV-HPMC	HV-HPMC
Powders			
Particles size[a] (μm)	106.8 ± 3.1	75.7 ± 0.2	96.2 ± 1.3
Dispersions			
Viscosity[a] (cP)	7.80 ± 0.02	24.00 ± 0.01	52.24 ± 0.01
Tablets			
Thickness[a] (mm)	1.81 ± 0.04	1.82 ± 0.03	1.83 ± 0.03
Hardness[a] (N)	66.6 ± 8.2	100.7 ± 3.5	118.4 ± 1.8
Release of whole tablets[a]			
n	0.77 ± 0.05 (R^2=0.996)	1.21 ± 0.06 (R^2=0.995)	0.61 ± 0.05 (R^2=0.991)
K_0 (% min^{-1})	0.21 ± 0.01 (R^2=0.939)	0.55 ± 0.05 (R^2=0.992)	0.11 ± 0.01 (R^2=0.939)
K_H (% $min^{-0.5}$)	3.84 ± 0.25 (R^2=0.995)	7.14 ± 0.72 (R^2=0.929)	2.63 ± 0.05 (R^2=0.996)
Unidirectional release[a]			
n	0.59 ± 0.02 (R^2=0.999)	0.60 ± 0.01 (R^2=0.997)	0.54 ± 0.01 (R^2=0.998)
K_0 (μg min^{-1})	10.57 ± 0.36 (R^2=0.973)	9.54 ± 0.46 (R^2=0.979)	6.61 ± 0.15 (R^2=0.973)
K_H (μg $min^{-0.5}$)	259.6 ± 9.6 (R^2=0.994)	242.1 ± 11.5 (R^2=0.994)	162.2 ± 4.2 (R^2=0.993)
Unidirectional permeation[a]			
K_0 (μg min^{-1})	4.66 ± 0.92 (0.969)	4.33 ± 0.75 (R^2=0.990)	3.96 ± 0.49 (R^2=0.997)
K_H (μg $min^{-0.5}$)	122.1 ± 24.2 (0.993)	117.3 ± 19.4 (R^2=0.985)	109.3 ± 12.3 (R^2=0.978)
Mucoadhesive property[b]			
F_{max} (mN)	541.5 ± 173.6	486.7 ± 122.3	600.3 ± 140.2
W_{ad} (mN mm)	525.7 ± 87.7	436.6 ± 93.3	577.5 ± 127.4

[a] Data are mean ± SD, n=3.
[b] Data are mean ± SD, n=5.

Table 2. Physical properties and NCT release rate of whole tablets of NCT-MAS complex-loaded MV-HPMC tablets containing different pH modifiers.

pH modifier	Thickness (mm)	Hardness (N)	K_0 (% min^{-1})	K_H (% $min^{-0.5}$)
Control tablet	1.82 ± 0.03	100.7 ± 3.5	0.55 ± 0.05 (R^2=0.992)	7.14 ± 0.72 (R^2=0.929)
5 % NaCl	1.83 ± 0.05	98.8 ± 2.2	1.30 ± 0.09 (R^2=0.993)	12.8 ± 0.84 (R^2=0.968)
10 % NaCl	1.96 ± 0.04	99.6 ± 2.7	1.25 ± 0.08 (R^2=0.980)	13.6 ± 0.96 (R^2=0.964)
20 % NaCl	2.01 ± 0.07	106.4 ± 4.5	1.18 ± 0.25 (R^2=0.993)	10.5 ± 2.16 (R^2=0.945)
5 % Citric acid	1.92 ± 0.05	98.8 ± 9.5	1.28 ± 0.12 (R^2=0.972)	11.5 ± 1.18 (R^2=0.949)
10 % Citric acid	1.94 ± 0.04	104.3 ± 9.5	1.52 ± 0.10 (R^2=0.915)	13.9 ± 0.91 (R^2=0.933)
20 % Citric acid	2.18 ± 0.03	70.6 ± 2.7	1.52 ± 0.19 (R^2=0.945)	14.9 ± 2.04 (R^2=0.922)
5 % $Mg(OH)_2$	1.83 ± 0.03	62.5 ± 3.6	0.10 ± 0.01 (R^2=0.951)	2.47 ± 0.13 (R^2=0.997)
10 % $Mg(OH)_2$	1.97 ± 0.03	59.4 ± 2.6	0.11 ± 0.01 (R^2=0.952)	2.71 ± 0.13 (R^2=0.996)
20 % $Mg(OH)_2$	2.01 ± 0.02	61.9 ± 4.9	0.11 ± 0.01 (R^2=0.977)	2.64 ± 0.06 (R^2=0.995)

Data are mean ± SD, n=3.

Table 3. Unidirectional release and permeation of NCT and mucoadhesive properties of NCT-MAS complex-loaded MV-HPMC tablets containing different pH modifiers.

pH modifier	Unidirectional NCT release[a]		Unidirectional NCT permeation[a]		Mucoadhesive property[b]	
	K_0 (μg min^{-1})	K_H (μg $min^{-0.5}$)	K_0 (μg min^{-1})	K_H (μg $min^{-0.5}$)	F_{max} (mN)	W_{ad} (mN mm)
Control tablet	9.54 ± 0.46 (R^2=0.979)	242.1 ± 11.5 (R^2=0.994)	4.33 ± 0.75 (R^2=0.990)	117.3 ± 19.4 (R^2=0.985)	486.7 ± 122.3	436.6 ± 93.3
5 % NaCl	9.43 ± 0.58 (R^2=0.932)	235.8 ± 13.6 (R^2=0.988)	4.58 ± 0.16 (R^2=0.992)	125.6 ± 4.3 (R^2=0.990)	435.7 ± 101.6	433.5 ± 169.6
10 % NaCl	9.98 ± 0.42 (R^2=0.926)	215.8 ± 9.8 (R^2=0.994)	3.59 ± 0.52 (R^2=0.992)	108.6 ± 13.7 (R^2=0.989)	437.5 ± 122.1	368.3 ± 67.2
20 % NaCl	9.45 ± 0.31 (R^2=0.895)	240.8 ± 9.4 (R^2=0.986)	4.16 ± 0.22 (R^2=0.989)	116.4 ± 6.4 (R^2=0.981)	446.7 ± 88.1	449.2 ± 160.5
5 % Citric acid	9.23 ± 0.50 (R^2=0.969)	237.6 ± 13.8 (R^2=0.995)	0.78 ± 0.08 (R^2=0.965)	19.24 ± 2.02 (R^2=0.942)	468.2 ± 96.3	461.7 ± 92.4
10 % Citric acid	10.19 ± 0.57 (R^2=0.987)	268.1 ± 5.2 (R^2=0.986)	0.91 ± 0.22 (R^2=0.989)	24.92 ± 5.99 (R^2=0.963)	485.0 ± 102.6	392.6 ± 108.2
20 % Citric acid	13.20 ± 1.25 (R^2=0.975)	336.8 ± 33.4 (R^2=0.993)	0.32 ± 0.03 (R^2=0.959)	8.90 ± 0.67 (R^2=0.945)	471.6 ± 89.6	464.2 ± 151.1
5 % $Mg(OH)_2$	8.44 ± 0.17 (R^2=0.977)	213.5 ± 4.4 (R^2=0.994)	8.39 ± 0.53 (R^2=0.993)	227.4 ± 13.4 (R^2=0.988)	548.6 ± 53.8	531.9 ± 42.0
10 % $Mg(OH)_2$	7.34 ± 0.22 (R^2=0.990)	188.1 ± 5.9 (R^2=0.989)	10.19 ± 0.91 (R^2=0.991)	277.0 ± 25.7 (R^2=0.990)	448.8 ± 76.3	420.4 ± 72.6
20 % $Mg(OH)_2$	7.76 ± 0.35 (R^2=0.993)	196.0 ± 8.2 (R^2=0.977)	8.63 ± 0.21 (R^2=0.991)	235.4 ± 5.9 (R^2=0.990)	452.9 ± 52.7	484.7 ± 42.3

[a] Data are mean ± SD, n=3. [b] Data are mean ± SD, n=5.

Nicotine-magnesium aluminum silicate microparticles surface-modified using chitosan for mucosal delivery

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Abstract

Magnesium aluminium silicate (MAS), a negatively charged clay, and nicotine (NCT), a basic drug, could electrostatically interact to form microparticles. Chitosan (CS) was used for surface modification of the microparticles formed and lyophilization method was applied in order to preserve the originally natural particle morphology of the microparticles. Physicochemical properties, NCT content, mucoadhesive properties, and release and permeation across porcine esophageal mucosa of the microparticles were investigated. The results showed that the microparticles obtained had an irregular shape and NCT content increased with increasing NCT ratios in the preparation. High molecular weight CS (800 kDa) could adsorb and change the microparticle surface to positive charge. CS molecules could intercalate into the MAS silicate layers and decrease crystallinity of the microparticles, leading to an increase in release rate and diffusion coefficient of NCT from the microparticles. Moreover, higher NCT permeation fluxes and mucoadhesive properties of the microparticles surface-modified with CS was found. However, the enhancement of NCT release and permeation, and also mucoadhesive properties was dependent upon molecular weight and concentration used of CS. This finding suggested that the NCT-MAS microparticles surface-modified with CS displayed a promising mucosal delivery system for NCT.

Keywords: Magnesium aluminum silicate, Nicotine, Chitosan, Microparticles, Mucosal delivery.

1. Introduction

Microparticles have been widely used as drug carriers which are very often proposed as drug delivery systems for continuous, targeted, sustained or controlled release of active substances (Agnihotri et al., 2004; Yamada et al., 2001). They can offer homogeneous and reproducible drug absorption, reduction of local irritation, and protection active substances against enzymatic degradation (Allémann et al., 1998). Almost of microparticles have been fabricated using natural and synthetic polymers as the main component. The polymeric microparticles can induce a mucoadhesive effect for increasing a contact time on mucosa, which can enhance drug delivery efficiency (O'Hagan, 1998; Smart, 2005).

Magnesium aluminum silicate (MAS) is a mix of montmorillonite and saponite clays (Kibbe, 2000). MAS presents a silicate layered structure, which is composed of two tetrahedral silicate sheets sandwich to alumina or magnesia octahedral sheet (Alexandre and Dubois, 2000; Kibbe, 2000). It is non-toxicity and non-irritation at the levels employed in pharmaceutical uses (Kibbe, 2000). Moreover, montmorillonite clays presented weak cytotoxicity and good adhesion to cell membrane (Salcedo et al., 2012; Hsu et al., 2012). The MAS silicate layers can be separated when they are hydrated in water. They present a negative charge with large surface area, leading to adsorption with a positively charged drugs. Recently, anionic clays have been used to adsorb drug molecules for enhancing drug stability (Perioli et al., 2012), reducing drug toxicity (Kevadiya et al., 2012) and improving drug efficiency (Perioli et al., 2006), because of drug intercalation into the interlayer spaces of clays.

Nicotine (NCT) is one of drug candidate for adsorbing onto MAS particles via mainly electrostatic interaction (Suksri and Pongjanyakul, 2008; Pongjanyakul et al., 2009). NCT is diprotic base, $pK_{a1} = 3.04$ and $pK_{a2} = 7.84$, resulting in the formation of diprotonated, monoprotonated and neutral species at acidic, neutral, and basic pH levels, respectively (Nair et al., 1997). Rapid interaction between MAS and NCT in neutral and acidic pH conditions lead to formation of NCT-MAS complex flocculates. The characteristics of the NCT-MAS complexes, which were prepared, dried and ground to small particles, were previously investigated (Pongjanyakul et al., 2009). However, drying and grinding process destroyed the particle morphology and characteristics in nature of the flocculate particles, which can be possibly fabricated as

microparticles. For better understanding of the NCT-MAS microparticles in nature, lyophilization technique was used in drying process for maintaining an original morphology of the NCT-MAS microparticles formed. Moreover, the NCT-MAS flocculates formed at acidic and neutral pHs were still have negative charge on the particle surface. It is interesting for modifying the particle surface to positive charge in order to enhance mucoadhesive properties of these microparticles. For this concept, chitosan (CS), which was a cationic polysaccharide and possessed mucoadhesive properties (He et al., 1998), was considered because it could interact and neutralize the MAS charge that was previously reported (Khunawattanakul et al., 2008)

In the present study, we report for the first time about the NCT-MAS microparticles without and with surface modification using CS. The microparticles were prepared using electrostatic interaction between NCT and MAS at pH 4 and 7, and dried using lyophilization method. Low and high molecular weight chitosan (LCS and HCS, respectively) were used for surface modification. The particle morphology, NCT entrapment efficiency, thermal behavior, crystallinity and mucoadhesive properties of the microparticles were investigated. Furthermore, NCT release and permeation across porcine esophageal mucosa were examined to evaluate a potential use for mucosal delivery.

2. Material and method

2.1. Materials

MAS (Veegum® HV in the granular form) was obtained from R.T. Vanderbilt Company, Inc.,USA. LCS (MW=80 kDa) and HCS (MW=800 kDa) with 85% degree of deacetylation were purchased from Seafresh Chitosan (Lab) Co. Ltd., Thailand. Nicotine (NCT) was obtained from Fluka, Switzerland. All other reagents used were of analytical grade and used as received.

2.2. Preparation of NCT-MAS microparticles

MAS dispersion (1% w/v) was prepared by dispersing MAS powder in hot deionized water and pH of the MAS dispersion was adjusted to 4 or 7 using 2 M HCl solution. NCT solution in the concentration of 2% w/v at pH 4 or 7 was also prepared in deionized water. To produce NCT-MAS microparticles, 12.5, 25, or 50 ml of 2% w/v NCT solution was dropped into 500 ml of 1% w/v MAS dispersion with stirring using

a propeller at 300 rpm. The mixture was stirred for 1 h before adjusting pH to 4.0 or 7.0 again by using 2 M HCl or 2 M NaOH. Then, the final volume of the mixture was adjusted to 625 ml using deionized water and the mixture was incubated at 37 °C with 75 oscillates/min shaking for 24 h in order to reach equilibrium of NCT adsorption. Then, 10 ml of the mixture was collected to investigate particles size and zeta potential of the wet microparticles. The microparticles were collected by vacuum filtration and washed twice with 25 ml of deionized water. Then, the microparticles were dispersed again in 50 ml of deionized water, and the mixture was frozen at –20 °C and dried using lyophilization method. After drying, the microparticles passed through 125-µm sieve were collected and kept in desiccator until test.

NCT-MAS microparticles surface-modified with CS could be prepared using the following method. Fifty milliliters of 2% w/v NCT solution at pH 4 were dropped into 500 ml of 1% w/v MAS dispersion at pH 4 with continuous stirring using a propeller at 300 rpm for 1 h. After that, 12.5, 25 or 50 of 0.5% w/v HCS or LCS in 0.1 M HCl was gradually poured into NCT-MAS dispersion with continuous stirred for 5 min before adjusting pH to 4.0 by using 2 M HCl or 2 M NaOH. Then, the mixture was adjusted the final volume to 625 ml with deionized water and incubated at 37 °C with 75 oscillates/min shaking for 24 h. The next process was the same as that mentioned above.

2.3. Particle size determination

The particle size of MAS in the dispersions and NCT-MAS microparticles was measured using a laser diffraction particle size analyzer (Mastersizer2000 Model Hydro2000SM, Malvern Instrument Ltd., UK). The samples were dispersed in 70 ml of distilled water in a small volume sample dispersion unit and stirred at a rate of 3,000 rpm for 30 s before the measurement. The volume weighted mean diameter was reported.

2.4. Zeta potential measurement

The zeta potential of MAS and wet NCT-MAS microparticles was determined using a laser Doppler electrophoresis analyzer (Zetasizer Model ZEN 2600, Malvern Instrument Ltd., UK). The temperature of the samples was controlled at 25 °C. The

samples were diluted using deionized water to meet a count rate more than 20,000 counts/s prior to the measurement.

2.5. Scanning electron microscopy (SEM)

The particle shape and surface morphology of MAS and microparticles were observed using SEM. Samples were mounted onto stubs then coated with gold in a vacuum evaporator, and photographed using a scanning electron microscope (Jeol Model JSM-6400, Tokyo, Japan).

2.6. Differential scanning calorimetry (DSC)

DSC thermograms of samples were recorded using a differential scanning calorimeter (DSC822, Mettler Toledo, Switzerland). Each sample (2–3mg) was accurately weighed into a 40-µl aluminum pan without an aluminum cover. The measurements were performed over 30–400 °C at a heating rate of 10 °C/min.

2.7. Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of samples were recorded with an FTIR spectrophotometer (Spectrum One, Perkin Elmer, Norwalk, CT) using the 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 10 min. The disc was placed in the sample holder and scanned from 4000 to 450 cm^{-1} at a resolution of 4 cm^{-1}.

2.8. Powder X-ray diffractometry

The X-ray diffractograms of each sample was 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 20mA as X-ray source, angular of 1–35° (2θ) and step angle of 0.02° (2θ)/s.

The thickness of the silicate layer of MAS could be computed by Bragg's equation:

$$n\lambda = 2d\sin\theta \qquad \text{Eq. 1}$$

where n is 1 (the first order reflection), λ is the wavelength of the X-ray (1.54Å), θ is the angle of the basal spacing peak of MAS, and d is the silicate layer thickness of MAS.

2.9. Determination of NCT content

Twenty milligrams of the microparticles were weighed and dispersed in 50 ml of 2 M HCl. The mixture was incubated at 37 °C in a shaking water bath for 24 h. Then, the supernatant was collected and filtered using cellulose acetate membrane (0.45-µm pore size). The NCT content was analyzed using a UV–visible spectrophotometer (Shimadzu UV1201, Japan) at a wavelength of 259 nm. The NCT entrapment efficiency could be computed according to the ratio of actual to the theoretical drug content in the microparticles.

2.10. In vitro NCT release studies

A modified Franz diffusion cell was used to characterize NCT release of NCT from the microparticles. The receptor compartment was 5.3 ml of pH 6 phosphate buffer and the temperature was controlled at 37.0 ± 0.1 °C with continuous stirring speed of 600 rpm. A 0.45-µm pore size cellulose acetate employed as a membrane in this study was hydrated with pH 6 phosphate buffer for 24 h and mounted on the receptor compartment. The cells were fixed and tightly fastened with a clamp. The amount of the microparticles equivalent to 3 mg NCT was contained in the donor compartment and 100 µl of pH 6.0 phosphate buffer was added for wetting the microparticles. At appropriated intervals, samples (0.4 ml) were collected from the receptor compartment and immediately replaced with fresh medium. The concentration of NCT released was analyzed using HPLC.

The NCT release kinetic mechanism was investigated using a particle diffusion controlled model (Bhaskar et al., 1986; Ni et al., 2008; Pongjanyakul et al., 2009), which can be expressed by the following equation:

$$-\ln(1-F) = 1.59\left(\frac{6}{d_p}\right)^{1.3} D^{0.65} t^{0.65} \qquad \text{Eq. 2}$$

where F is the fractional release of NCT from the microparticles at given time (t), d_p is the mean particle size of the microparticles, D is the apparent diffusion coefficient and t is time. This model can be investigated by simply testing for linearity between –ln(1-F) and $t^{0.65}$. The slope (release rate constant) of the straight line (estimated using linear regression analysis) was used to calculate the apparent diffusivity according to the following equation:

$$D = \frac{d_p^2}{36}\left(\frac{slope}{1.59}\right)^{1/0.65} \qquad \text{Eq. 3}$$

Additionally, the Higuchi model (Siepmann and Siepmann, 2009) was also used to describe the NCT released from the microparticles by diffusion mechanism, which could be expressed by Eq. 4 as follow:

$$F = kt^{1/2} \qquad \text{Eq. 4}$$

where k is release rate constant, and F is the fractional NCT release from the microparticles at given time (t).

2.11. In vitro NCT permeation studies

Porcine esophageal mucosa used as a mucosal membrane was obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The porcine esophageal tube was opened longitudinally and immersed in an isotonic saline solution at 60 °C for 1 min (Diaz-del Consuelo et al., 2005; Diaz-del Consuelo et al., 2007). The epithelium was peeled away from the connective tissue and then frozen at –20°C until further use (Caon and Simões, 2011). The modified Franz diffusion cell was also used for the NCT permeation study. Frozen membranes were brought to room temperature and pre-hydrated in pH 7.4 isotonic phosphate buffer solution for 60 min at 37 °C. The hydrated mucosal membrane was then mounted on a diffusion cell that contained pH 7.4 isotonic phosphate buffer solution as a receptor compartment. The amount of the microparticles equivalent to 3 mg NCT was contained in the donor compartment and 100 µl of pH 6.0 phosphate buffer was added for wetting the microparticles. At appropriated intervals, samples (0.4 ml) were collected from the receptor compartment and immediately replaced with fresh medium. The concentration of NCT released was analyzed using HPLC. Steady-state fluxes of NCT permeation across the mucosal membrane could be calculated from the linear relationship between cumulative amount of NCT permeated (µg cm^{-2}) and time (h) using linear regression analysis.

2.12. Measurement of mucoadhesive properties

The mucoadhesive properties of the microparticles were measured using a texture analyzer (TA.XT Plus, Stable Micro Systems, Haslemere, Surrey, UK) equipped with a 50-N load cell and bioadhesion test rig. Porcine esophageal mucosa was also used,

which was obtained from a local slaughterhouse (Non Muang Village, Khon Kaen, Thailand). The porcine esophagus (about 2 cm × 2 cm) without heat treatment and elimination of the connective tissue was hydrated with pH 7.4 isotonic phosphate buffer for 20 min prior to test.

Microparticles were compressed into a thin disc with a smooth surface for complete contact to the mucosal membrane. A 10-mm diameter punches and die was used. To prevent a stick of microparticles, the surface of lower and upper punches was covered with a Teflon sheet (0.5-mm thickness) before compression. Twenty milligrams of microparticles were filled in the die and compressed at a pressure of 6.2 MPa using a hydrostatic press (Model 3126, Shimadzu, Kyoto, Japan). The thin disc (approximately 250-μm thickness) was attached to a 10-mm diameter cylindrical probe of the bioadhesion test rig with double-sided adhesive tape. The hydrate membrane was placed on the stage of bioadhesive holder and gently blotted with tissue paper to remove excess water on the surface of the mucosal membrane. Next, 100 μl of pH 6.0 phosphate buffer was pipetted onto the membrane surface and then, the probe that had been attached with the thin disc was moved down at a constant speed of 1.0 mm s^{-1} with 1.0 N contact force and 2.0 min contact time. Immediately afterwards, the probe was moved upwards with a constant speed of 0.5 mm s^{-1}. The relationship between detachment force and disc displacement was recorded. The maximum detachment force (DF_{max}) and work of adhesion (W_{ad}, the area under the force versus distance curve) were calculated using the Texture Exponent 32 program version 4.0.9.0 (Stable Micro Systems, UK).

2.13. HPLC analysis

The concentration of NCT was determined by HPLC analysis (Agilent 1000 series, Agilent Technologies, USA). A Reversed-phase C-18 column (Water Spherisorb® S5 ODS2, 5 μm, 4.6 × 250 mm) with a guard column was connected to the HPLC instrument. The mobile phase was 0.05 M sodium acetate:methanol:triethylamine (88:12:0.5 v/v) and adjusted a final pH to 4.2 using glacial acetic acid. The flow rate of mobile phase was 1 ml min^{-1}, and samples were detected at a wavelength of 259 nm using a UV-visible spectrophotometric detector. The retention time of NCT was

approximately 6.7 min. Under these conditions, linearity and reproducibility were seen over the range of 1-50 μg ml^{-1} NCT.

2.14. Statistical analysis

One-way analysis of variance (ANOVA) with the least significant difference (LSD) test for multiple comparisons was performed using SPSS program for MS Windows, release 11.5 (SPSS (Thailand) Co., Ltd., Bangkok, Thailand). The significant difference of the results obtained was determined at 95% confident limit (α=0.5) and considered to be significant at a level of P less than 0.05.

3. Result and discussion

3.1. Particle morphology, zeta potential and NCT content of NCT-MAS microparticles

The particle size and zeta potential of MAS in the dispersion was found to be 4.47 ± 0.01 μm (n=3) and –33.5 ± 2.4 mV (n=3), respectively. Incorporation of NCT into MAS dispersion at pH 4 and 7 caused a formation of microparticles due to electrostatic interaction between a positively charged NCT and a negatively charged MAS. The wet microparticles prepared using 0.1:1 and 0.2:1 ratios of NCT and MAS at pH 4 gave smaller particle size than those at pH 7 (Table 1). This was due to the difference protonated NCT formed. The 12.7% neutral and 87.3% monoprotonated NCT were formed at pH 7, whereas NCT at pH 4 was composed of 8.4% diproptonated and 91.6% monoprotonated species. The diprotonated NCT formed at pH 4 had stronger attraction force for microparticle formation, resulting in denser structure of microparticles. However, neither preparation pH nor NCT-MAS ratios affected the zeta potential of the wet microparticles formed (Table 1). Surface modification using CS at pH 4 resulted in an increase in particles size and a reduction of negative charges of NCT-MAS microparticles (Table 1). This was due to electrostatic interaction of protonated CS with residue negative charge of MAS on the surface of the microparticles (Khunawattanakul et al., 2008; Khunawattanakul et al., 2010). Additionally, the microparticle surface could be changed to positive charge when using HCS in the concentration of 0.02 and 0.04% w/v, suggesting that the microparticles were completely coated with HCS at those concentrations. The higher the HCS concentration, the greater the quantity of HCS molecules coated on the microparticle surface that could be observed from the increase of positive charge of

the microparticles. Therefore, surface modification of the NCT-MAS microparticles was dependent on molecular weight and concentration of CS.

The particle sizes of the dry NCT-MAS microparticles without or with surface modification using CS tended to slight increase when compared with those of the wet microparticles (Table 1). This may be due to a particle aggregation during drying process. The particle and surface morphology of MAS and microparticles are presented in Fig. 1. MAS showed a granular form (Fig. 1a), whereas the NCT-MAS microparticles without and with surface modification using CS had an irregular shape (Fig. 1c and 1e, respectively). However, the surface morphology of the microparticles was similar to that of MAS (Fig. 1b, 1d and 1f). The particle and surface morphology of the NCT-MAS microparticles were remarkably different from those of the NCT-MAS complex particles that were prepared with the same procedure, dried at high temperature and ground to get small particles, which was previously reported (Pongjanyakul et al., 2009). It was suggested that the use of freeze-dried method in this study could maintain an originally natural particle morphology of the NCT-MAS microparticles prepared using an electrostatic interaction.

The NCT content in the NCT-MAS microparticles significantly increased ($P<0.05$) with increasing NCT ratio in the dispersion (Table 1). This suggested that NCT adsorption onto the MAS particles could be driven by higher concentration of NCT before reaching adsorption equilibrium. However, NCT entrapment efficiency of the microparticles statistically reduced ($P<0.05$) when the NCT ratio was increased, indicating that adsorption sites of MAS for NCT were limited and thus higher quantity of NCT remained in the supernatant after adsorption equilibrium. The NCT-MAS microparticles surface-modified with LCS and HCS showed 8.3-8.9 % w/w of NCT contents that was significantly decreased ($P<0.05$) when compared with that of the microparticles without surface modification (Table 1). It was suggested that a large molecules of CS added could exchange with NCT adsorbed onto the microparticles, resulting in reduction of NCT entrapment efficiency of the microparticles.

3.2. Molecular interaction of microparticle components

Molecular interaction of MAS, NCT and CS was investigated using FTIR spectroscopy and PXRD diffractometry. FTIR spectra of NCT showed hydroxyl stretching peak at 3413 cm^{-1}, C–H stretching peaks at 2781-2969 cm^{-1}, aromatic C=C stretching peak at 1593 cm^{-1}, aromatic C=N stretching peak at 1579 cm^{-1}, pyridinic C–H bending peaks of CH_2 groups at 1429-1478 cm^{-1}, pyridinic C–N stretching peak at 1027 cm^{-1}, and the out of plane stretching peak of C–H bond at 717 cm^{-1} as presented in Fig. 2a. The MAS presented hydroxyl stretching of SiOH, hydroxyl stretching of hydrogen bonded water, hydroxyl bending, and Si–O–Si stretching peaks at 3632, 3449, 1639, and 1016 cm^{-1}, respectively (Fig. 2b). The spectra of the pH 4 NCT-MAS (0.2:1) microparticles showed a shift of hydroxyl stretching peak of SiOH of MAS to lower wavenumber (Fig. 2c), indicating hydrogen formation of SiOH of MAS with an amine group of pyridine ring of NCT. Unfortunately, the change in the C–N stretching peak of NCT at 1027 cm^{-1} was not found because this peak was overlapped with the Si–O–Si stretching peaks of MAS. However, the new peak of protonated amine groups ($–NH^+$) at 2714 cm^{-1} was observed (Nakanishi and Solomon, 1977; Pongjanyakul et al., 2009). It is possible to expect that the change of pyridinic C–H bending peaks of CH_2 groups and the out of plane stretching peak of C–H bond of NCT suggested an electrostatic between the amine group of the pyridine ring and negatively charged MAS (Pongjanyakul et al., 2009). In the case of the NCT-MAS microparticle surface-modified with CS, the spectra of HCS showed the OH stretching peak, which overlapped with the N–H stretching, at 3449 cm^{-1}, the C–H stretching peak around 2922-2880 cm^{-1}, NH_2 bending (amide II) peak of primary amine at 1596 cm^{-1}, and the CH_2 bending peak at 1420 cm^{-1} (Fig. 2d). It was found that the HCS spectra peaks were not observed in the microparticle surface-modified with CS (Fig. 2e). This may be due to too low quantity of CS in the microparticles. However, the small peak of free hydroxyl groups around 3681-3683 cm^{-1} indicated strong interaction of MAS with NCT and HCS. The stronger vibration of free hydroxyl groups on the inner surface of MAS silicate layers could be occurred when NCT and CS could intercalate into the MAS silicate layers that was previously reported (Pongjanyakul et al., 2009; Khunawattanakul et al., 2010). Additionally, the molecular interaction of the three components could be confirmed using PXRD studies.

The PXRD pattern of MAS presented the basal spacing peak at 7.21 °(2θ) (Fig. 3, left panel), representing that the thickness of MAS silicate layer was 1.22 nm. The NCT-MAS microparticles prepared at pH 4 and 7 showed stronger intensity of the basal spacing peak at 5.95 and 6.03 °(2θ), respectively. This indicated that the thickness of MAS silicate layers was increased to 1.46 and 1.48 nm, respectively, because of NCT intercalation into the MAS silicate layers. Incorporation of LCS and HCS in the preparation process caused a reduction of the basal spacing peak intensity of MAS (Fig. 3, middle and right panels), indicative of lower crystallinity of the microparticle formed. The microparticle surface-modified with LCS and HCS at the concentration of 0.04% w/v showed an obvious shift of the basal spacing peak to 5.95 and 5.83 °(2θ), respectively. These results indicated that the thicknesses of MAS silicate layers of the microparticles were 1.48 and 1.51 nm for using LCS and HCS, respectively. Furthermore, the microparticles surface-modified with CS had lower intensity and slight broader basal spacing peak. This suggested that CS, which could be coated on the microparticle surface and intercalated into the silicate layers of MAS, could change and reduce crystallinity of the microparticles. Therefore, the schematic presentration model of NCT-MAS microparticles surface-modified with CS can be presented in Fig. 4, which was based on the data obtained. Additionally, this finding showed that CS could also intercalate into the MAS silicate layers after the formation of microparticles and HCS could possibly increase the thickness of MAS silicate layers more than using LCS.

3.3. Thermal behavior of the microparticles

NCT, a volatile liquid, showed a broad endothermic peak at 147 °C because of the evaporation of NCT (Fig. 5, left panel). MAS presented a broad endothermic around 70 °C that was ascribable the dehydration of free water residues. The NCT-MAS microparticles prepared at pH 4 showed a broad exothermic peak around 290-297 °C (Fig. 5, left panel), suggesting a decomposition of NCT adsorbed and intercalated in MAS (Pongjanyakul et al., 2009). It can be seen that increasing NCT ratio in the microparticles brought about higher temperature of NCT decomposition. The similar results were obtained from the microparticles prepared at pH 7. The DSC thermograms of the microparticles surface-modified with LCS and HCS are shown in the middle and right panels of Fig. 5, respectively. The microparticles surface-

modified with CS showed the similar DSC thermograms with those without CS. However, the decomposition temperature of NCT tended to increase when increasing CS concentration, particularly the use of HCS. This suggested that the CS surface modification could retard the decomposition of NCT in the microparticles.

3.4. NCT release studies

The NCT release profiles of the microparticles are presented in Fig. 6. The NCT-MAS microparticles prepared at pH 4 and 7 presented the similar NCT release profiles as shown in Fig. 6a and 6b, respectively. The microparticles prepared using NCT-MAS (0.2:1) ratio provided the highest amount of NCT released because the higher the NCT content in the microparticles, the greater the NCT concentration gradient for driving the NCT release. Additionally, incomplete NCT release of the microparticles was found because equilibrium of cation exchange process could be occurred and this resulted in a zipping of the silicate layer edge and a shortening of interlayer distance (Jung et al., 2008). These led to retention of NCT in the microparticles. The NCT release showed good fit with both Higuchi and particle diffusion-controlled models with determination coefficient (R^2) more than 0.92 (Table 2). This suggested that the NCT release kinetics from the microparticles was a matrix/particle diffusion-controlled mechanism. It was indicated that NCT adsorbed and intercalated in MAS silicate layers of the microparticles could rapidly exchange with small cations, such as sodium ions, in pH 6 phosphate buffer, and then an intra-particle diffusion of NCT molecules occurred that was the rate-limiting step of the release process. However, K_H and slope values statistically increased ($P<0.05$) with increasing NCT content in the microparticles, but preparation pH did not affect the NCT release (Table 2). The highest D value was obtained from the microparticles prepared using NCT-MAS (0.2:1) ratio that possessed the highest NCT content. The increase of NCT content caused a decrease of MAS matrix ratio that was a diffusion barrier of NCT release. Thus, a faster release and higher D value of NCT was obtained.

The microparticles surface-modified with LCS and HCS showed the similar pattern of NCT release as shown in Fig. 6c and 6d, respectively. The NCT release also displayed well fit with both Higuchi and particle diffusion-controlled models (Table 2). The amount of NCT released and NCT release rate (K_H and slope values) of the microparticles prepared using 0.04% w/v LCS, and 0.02 and 0.04% w/v HCS were

significantly higher ($P<0.05$) than those of the microparticles without surface modification. Moreover, the HCS could accelerate NCT release more than the use of LCS, leading to greater of D value of NCT. This result was in agreement with the previous report that showed the effect of CS in CS-clay nanocarriers for drug release (Yuan et al., 2010). It is possible to explain that the higher thickness of MAS silicate layers of the microparticles surface-modified using CS, which was tested using PXRD, brought about a greater water-filled channels and a reduction of tortuosity of matrix structure of the microparticles. Moreover, the CS molecules that were intercalated into the MAS silicate layer could prevent a zipping of the silicate layer edges after NCT release. This resulted in higher release rate and diffusion coefficient of NCT.

3.5. NCT permeation studies

NCT permeation profiles of the microparticles without and with CS are shown in Fig. 7. A linear relationship between NCT permeated and time was found, indicating a steady-state permeation of NCT across the mucosal membrane. The NCT permeation fluxes of the NCT-MAS microparticles prepared at pH 4 and pH 7 are presented in Fig. 8a. The higher NCT content in the microparticles caused an increase in NCT permeation fluxes due to greater release rate of NCT. Furthermore, preparation pH of the microparticles obviously influenced the mucosal permeation of NCT. The microparticles prepared at pH 7 provided significantly higher NCT permeation fluxes ($P<0.05$) than those prepared at pH 4. At pH 7, NCT molecules were composed of mono-protonated and neutral NCT, whereas the completely protonated NCT was formed at pH 4. The protonated NCT could only permeate through the mucosal membrane via aqueous pore pathway and possessed low permeability with the mucosal membrane (Chen et al., 1999; Adrian et al., 2006; Pongjanyakul and Suksri, 2010). This resulted in lower permeation fluxes of NCT at lower pHs.

The microparticles surface-modified with LCS and HCS also gave steady-state NCT permeation as presented in Fig. 7c and 7d, respectively. The NCT permeation fluxes obtained from the microparticles surface-modified with LCS seemed to decrease, but not different with that obtained from the unmodified microparticles (Fig. 8b). On the other hand, the microparticles surface-modified with 0.04% w/v of HCS displayed a statistically higher NCT permeation flux ($P<0.05$) than the unmodified microparticles.

This was due to a very high release rate of NCT that could create greater concentration gradient for driving NCT permeation across the mucosal membrane. Moreover, it was well known that CS could act as a permeation enhancer for the mucosal membrane. CS adsorbed onto the surface of the microparticles could possibly interact and disturb lipid organization of mucosa (Şenel et al., 2000; Şenel and Hıncal, 2001), resulting in higher permeation of NCT. Additionally, higher molecular weight CS was more effective permeation enhancing properties than lower molecular weight CS (Tengamnuay et al., 2000).

3.6. Mucoadhesive properties of the microparticles

The DF_{max} and W_{ad} values of the microparticles are listed in Table 2. It can be seen that the DF_{max} values tended to decrease with increasing NCT content in the microparticles, but in contrast with the W_{ad} value. Moreover, the preparation pH did not affect the mucoadhesive properties. The mucoadhesive properties of pure MAS were also investigated using the same procedure in this study. The DF_{max} and W_{ad} values of MAS were found to be 1284.0 ± 471.4 mN and 534.7 ± 249.3 mN mm (n=5), respectively. This indicated that MAS possessed mucoadhesive properties with the mucosal membrane. It can be explained that the MAS silicate layers containing many hydroxyl groups that could mainly interact with mucin on the mucosal membrane via hydrogen bonding. For this reason, interaction of MAS with NCT to form microparticles could reduce a quantity of hydroxyl groups on the surface of silicate layers, leading to a reduction of mucoadhesive properties of the microparticles, which could be obviously observed from the DF_{max} values.

The use of LCS in surface modification of the NCT-MAS mcroparticles did not affect the mucoadhesive properties (Table 2). In contrast, the microparticles surface-modified with 0.04% w/v HCS showed the highest DF_{max} value (Table 2). It was indicated that surface modification with 0.04% w/v HCS could enhance mucoadhesive properties, especially DF_{max} value. CS is a cationic polysaccharide that had good mucoadhesive properties (Grabovac et al., 2005). CS, which had pK_a approximately 6.5 (Wang et al., 2006), could form 76% of protonated species at pH 6 of the test, which possessed positively charged CS molecules to interact with a negatively charged mucin on the mucosal membrane via electrostatic force (He et al., 1998). This effect was dependent upon molecular weight of CS and quantity of CS

adsorbed onto the surface of microparticles. Furthermore, surface modification of the NCT-MAS microparticles with CS could potentially enhance biocompatibility of MAS because polymer-clay nanomaterials possessed a lower cytotoxicity than the use of clay alone (Depan et al., 2009; Hsu et al., 2012; Salcedo et al., 2012; Mieszawska et al., 2011).

4. Conclusions

NCT-MAS microparticles without and with surface modification using CS were successfully prepared using an electrostatic interaction and dried using lyophilization method. Originally natural particle morphology of the microparticles was irregular shape. Surface modification using CS caused an increase in release rate and diffusion coefficient of NCT from the microparticles because CS could intercalate into the MAS silicate layers and decreased crystallinity of the microparticles. Moreover, higher NCT permeation fluxes and mucoadhesive properties of the microparticles surface-modified with CS was found. However, the enhancement of NCT release and permeation, and also mucoadhesive properties was dependent upon molecular weight and concentration used of CS. This finding suggested that the NCT-MAS microparticles surface-modified with CS displayed a strong potential for mucosal delivery of NCT.

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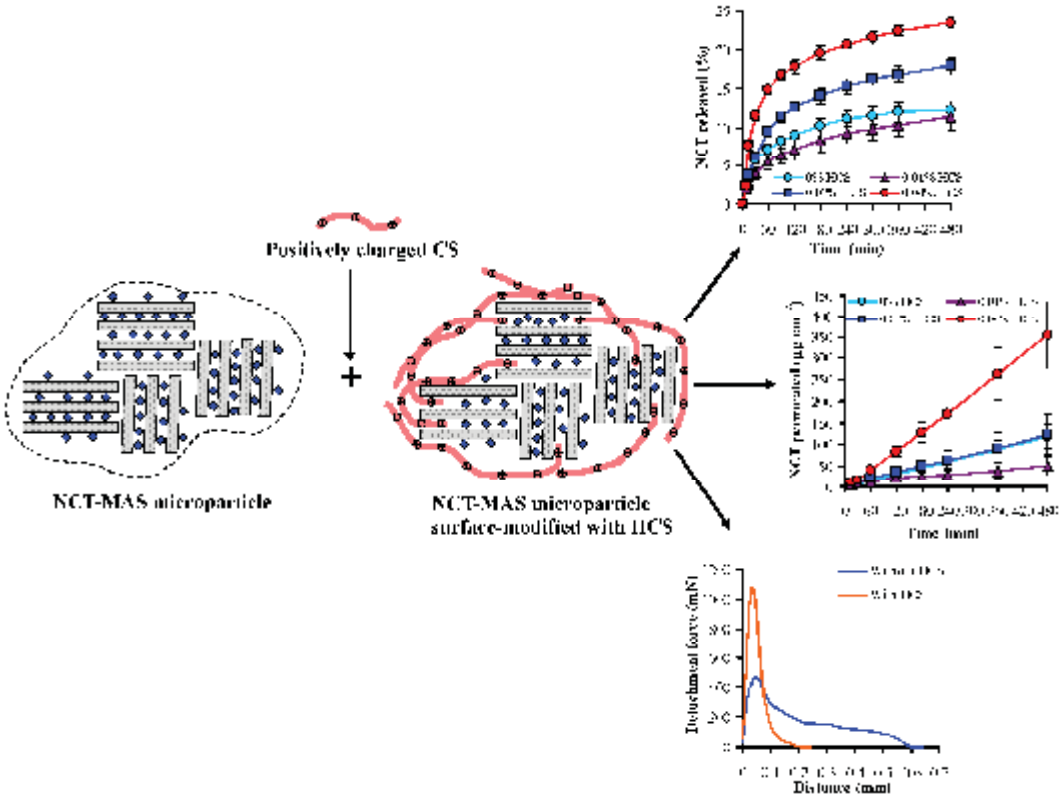
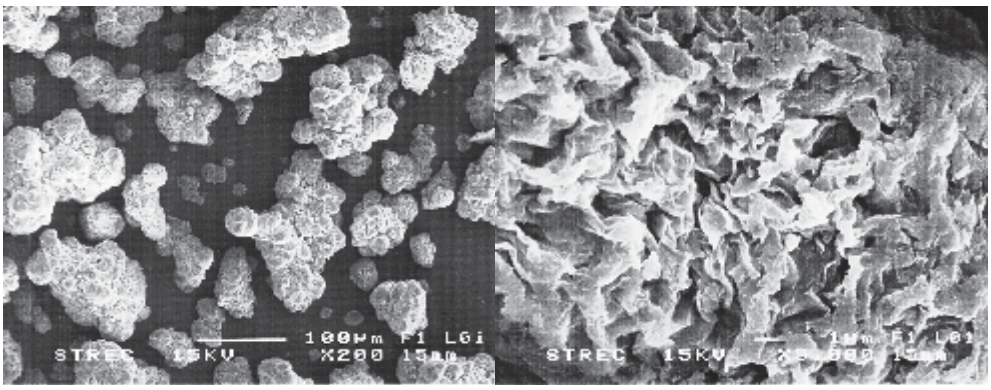
Graphical abstract





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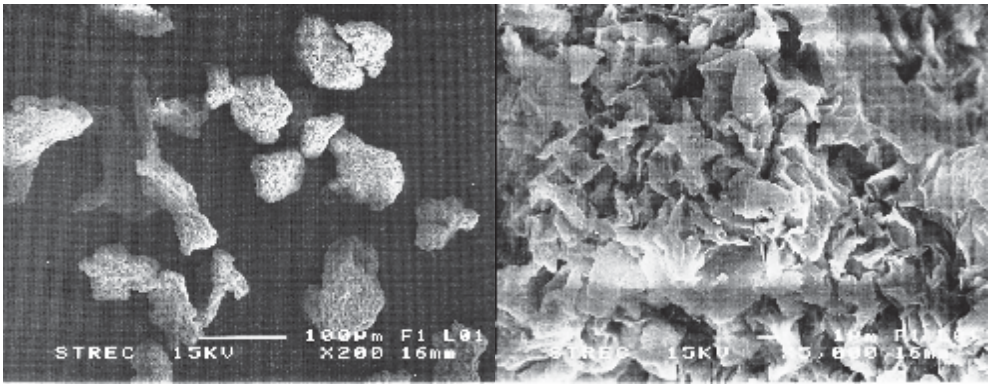

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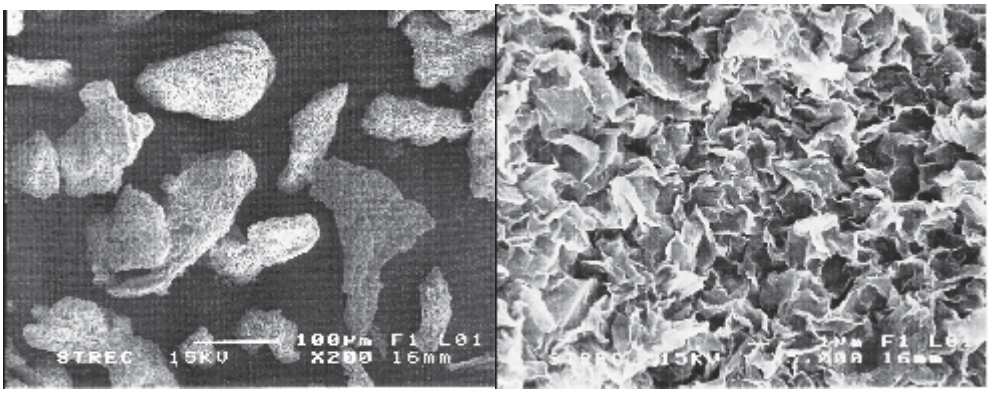

(e) (f)

Fig. 1. Particle and surface morphology of MAS (a,b), pH 4 NCT-MAS (0.2:1) microparticle (c,d), and pH 4 NCT-MAS microparticles surface-modified with 0.04% HCS (e,f).

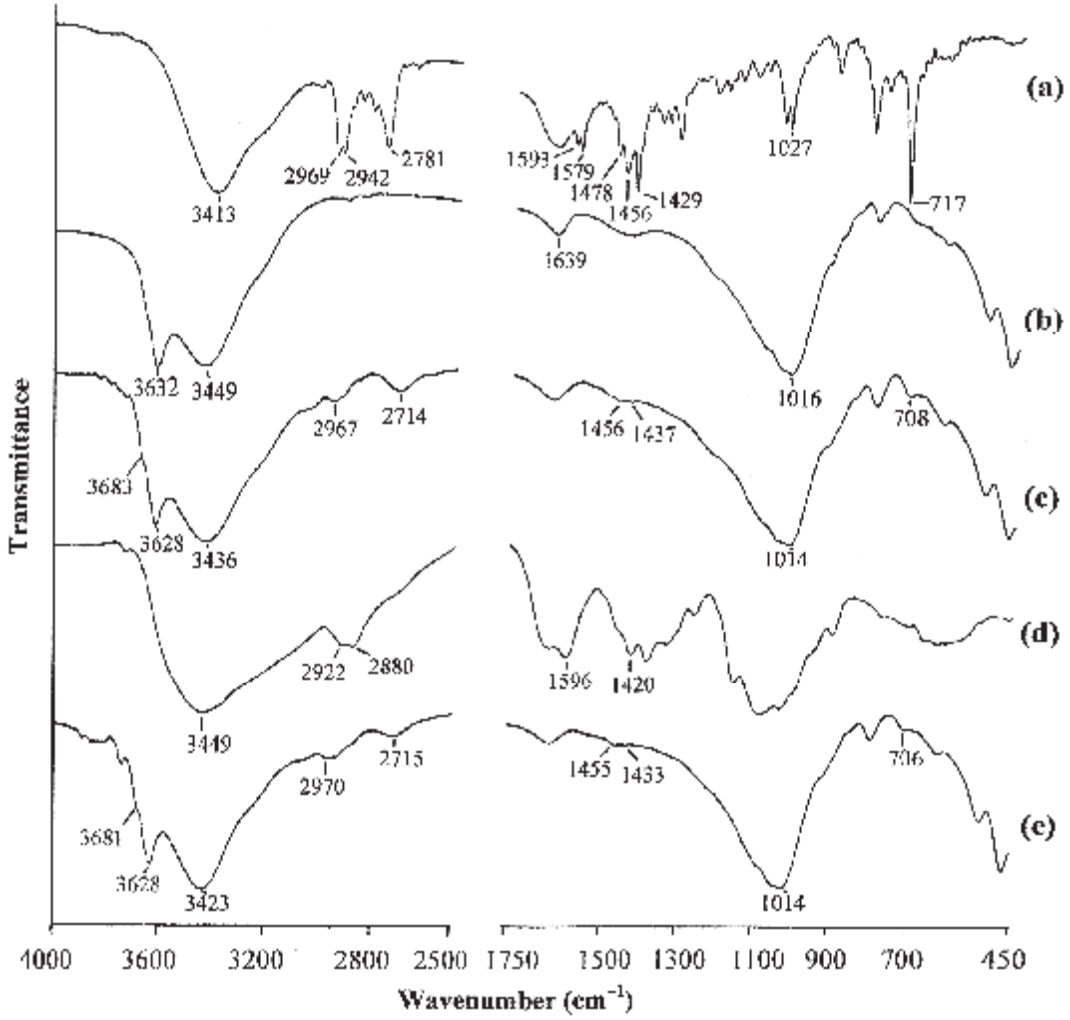

Fig. 2. FTIR spectra of NCT (a), MAS (b), pH 4 NCT-MAS (0.2:1) microparticles (c), HCS, and NCT-MAS (0.2:1) microparticles surface-modified with 0.04% HCS.

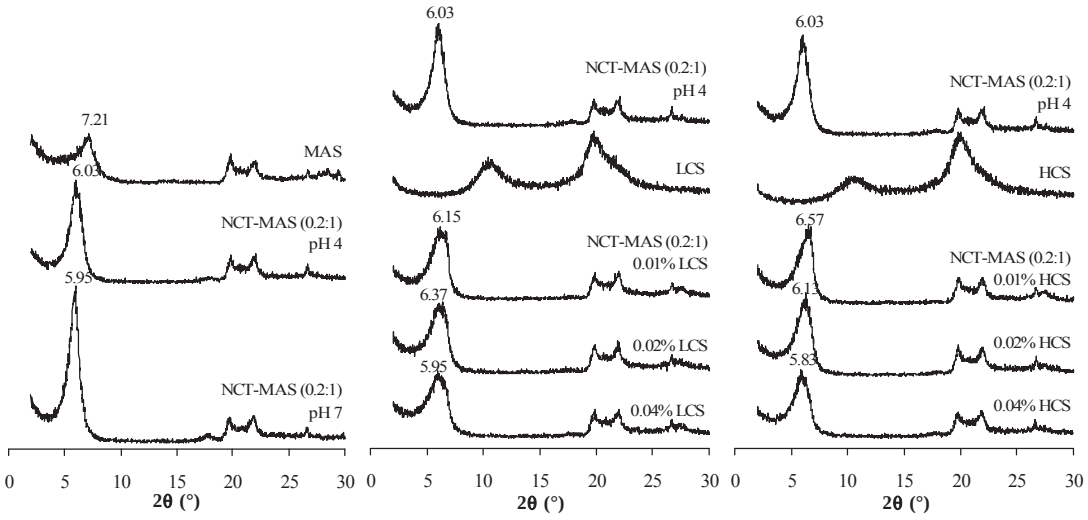

Fig. 3. PXRD patterns of MAS, CS, NCT-MAS microparticles, and NCT-MAS microparticles surface-modified with CS.

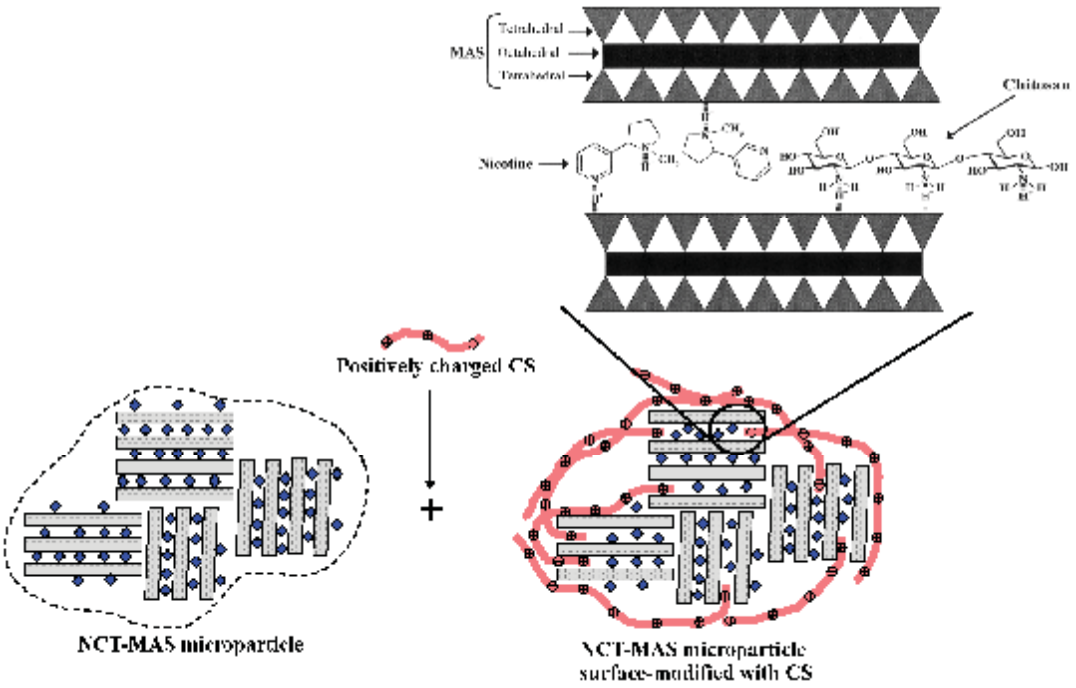

Fig. 4. Schematic representation of NCT-MAS microparticles surface-modified with CS.

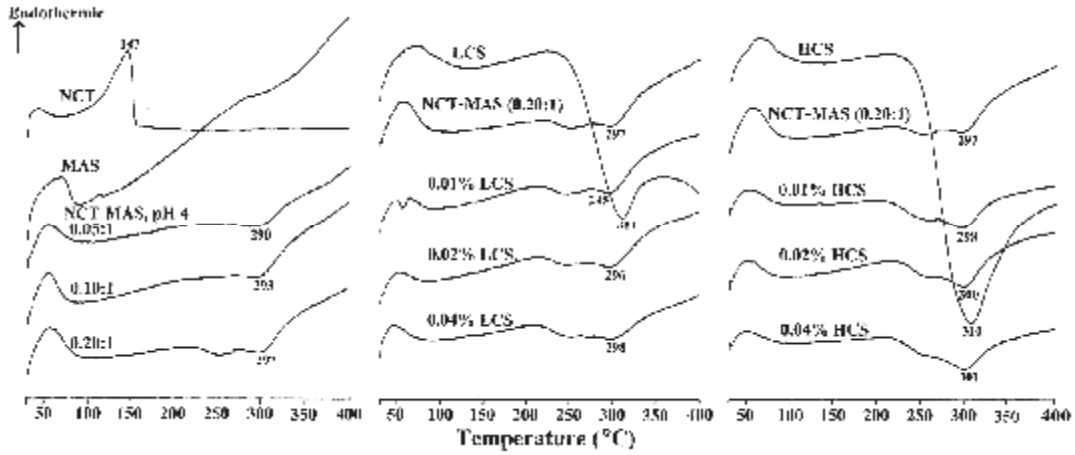

Fig. 5. DSC thermograms of NCT, MAS, CS, NCT-MAS microparticles, and NCT-MAS microparticles surface-modified with CS.

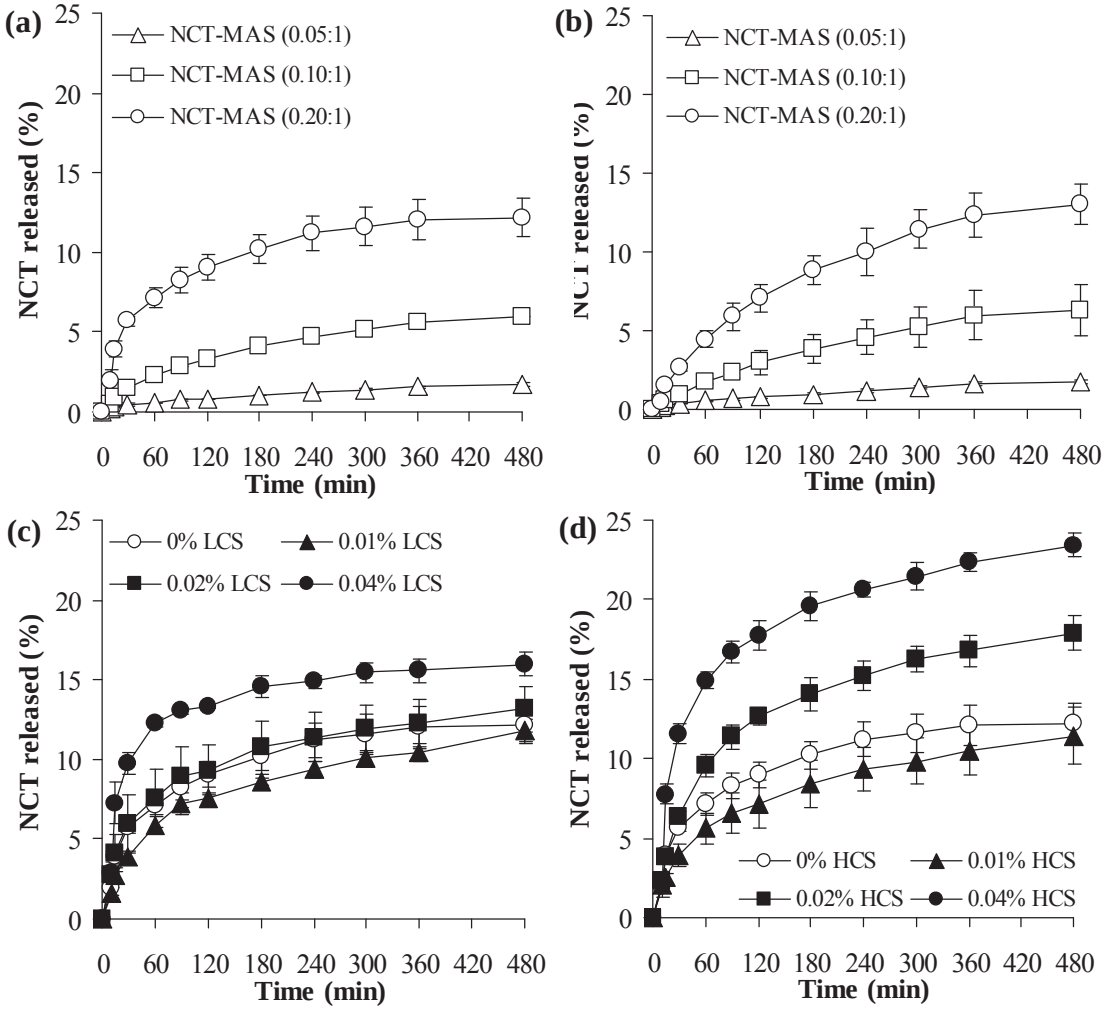

Fig. 6. NCT release profiles of NCT-MAS microparticles prepared at pH 4 (a) and 7 (b), and NCT-MAS microparticles surface-modified with LCS (c) and HCS (d). Each point is the mean ± S.D., n=3.

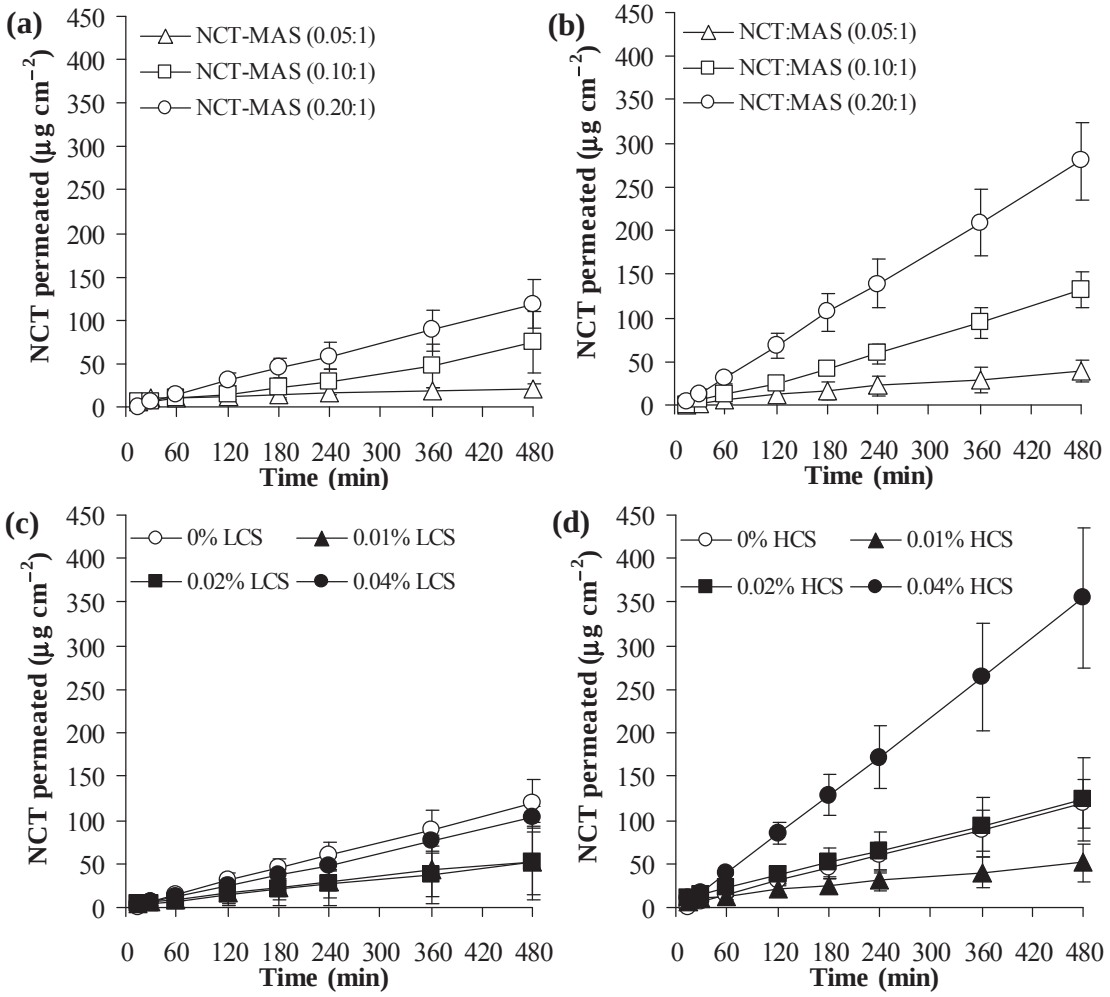

Fig. 7. NCT permeation profiles of NCT-MAS microparticles prepared at pH 4 (a) and 7 (b), and NCT-MAS microparticles surface-modified with LCS (c) and HCS (d). Each point is the mean ± S.D., n=3.

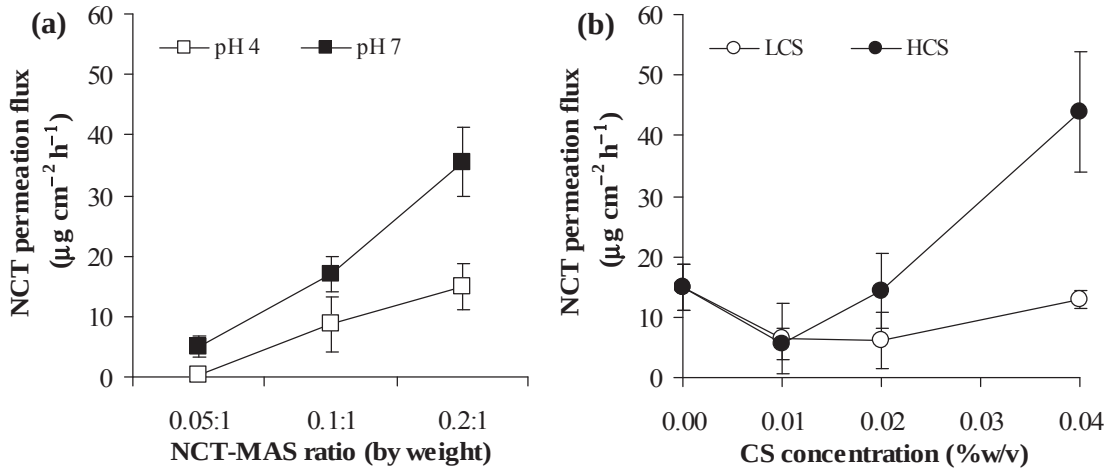

Fig. 8. Effect of preparation pH and NCT-MAS ratio (a), and CS (b) on NCT permeation flux across esophageal mucosal membrane of NCT-MAS microparticles. Each point is the mean ± S.D., n=3.

Table 1. Characteristics of wet and dry NCT-MAS microparticles with and without surface modification using CS.

Component and condition	Wet microparticles		Dry microparticles		
	Particle size (μm)	Zeta potential (mV)	Particle size (μm)	NCT content (%w/w)	NCT entrapment efficiency (%)
pH 7, NCT:MAS					
0.05:1	34.92 ± 0.26	-25.47 ± 1.99	96.91 ± 1.38	4.90 ± 0.07	102.80 ± 1.36
0.10:1	86.89 ± 1.57	-22.27 ± 3.28	80.54 ± 1.21	7.57 ± 0.05	83.32 ± 0.53
0.20:1	110.45 ± 0.89	-25.18 ± 2.53	74.73 ± 1.30	10.60 ± 0.14	63.57 ± 0.81
pH 4, NCT:MAS					
0.05:1	43.61 ± 0.86	-29.25 ± 1.11	103.82 ± 0.93	5.24 ± 0.23	110.01 ± 4.81
0.10:1	57.59 ± 0.61	-24.02 ± 3.63	84.23 ± 1.16	7.93 ± 0.07	87.20 ± 0.80
0.20:1	79.69 ± 0.98	-28.98 ± 2.19	108.97 ± 0.99	10.81 ± 0.49	64.85 ± 2.95
pH 4, NCT:MAS = 0.20:1					
LCS 0.01 %w/v	76.18 ± 4.00	-20.82 ± 0.55	101.53 ± 0.90	8.88 ± 0.06	53.29 ±0.37
0.02 %w/v	83.71 ± 0.51	-19.00 ± 1.11	113.64 ± 1.28	8.56 ± 0.05	51.37 ±0.29
0.04 %w/v	130.70 ± 1.02	-14.58 ±1.79	118.29 ± 1.43	8.30 ± 0.26	49.80 ±1.53
HCS 0.01 %w/v	83.84 ± 3.18	-5.67 ±2.19	120.24 ± 0.97	8.63 ± 0.04	51.77 ±0.23
0.02 %w/v	129.45 ± 3.97	24.82 ± 2.29	120.77 ± 0.81	8.58 ± 0.15	51.47 ±0.89
0.04 %w/v	211.17 ± 6.58	29.52 ± 1.51	134.84 ± 1.32	8.52 ± 0.13	51.13 ± 0.76

Data are the mean ± S.D., n=3.

Table 2. NCT release parameters and mucoadhesive properties of NCT-MAS microparticles with and without surface modification using CS.

Microparticles	Higuchi model [a]		Particle diffusion-controlled model [a]			Mucoadhesive properties [b]	
	$K_H \times 10^2$ ($min^{-0.5}$)	R^2	Slope $\times 10^3$ ($min^{-0.65}$)	R^2	$D \times 10^{12}$ ($cm^2\ s^{-1}$)	DF_{max} (mN)	W_{ad} (mN mm)
NCT-MAS (pH 7)							
0.05:1, 4.9 % NCT	0.09 ± 0.01	0.994	0.14 ± 0.01	0.992	0.25 ± 0.01	698.9 ± 248.3	681.8 ± 204.4
0.10:1, 7.6 % NCT	0.35 ± 0.10	0.997	0.61 ± 0.18	0.998	0.17 ± 0.08	492.2 ± 89.9	1101.2 ± 118.1
0.20:1, 10.6 % NCT	0.73 ± 0.10	0.995	1.29 ± 0.18	0.991	0.46 ± 0.09	265.5 ± 124.5	1299.4 ± 362.6
NCT-MAS (pH 4)							
0.05:1, 5.2 % NCT	0.08 ± 0.01	0.995	0.13 ± 0.01	0.992	0.26 ± 0.01	470.8 ± 204.5	377.8 ± 87.1
0.10:1, 7.9 % NCT	0.32 ± 0.01	0.992	0.52 ± 0.02	0.987	0.14 ± 0.01	511.3 ± 124.3	490.2 ± 38.0
0.20:1, 10.8 % NCT	0.75 ± 0.07	0.940	1.42 ± 0.14	0.922	1.23 ± 0.17	330.9 ± 144.5	1138.4 ± 258.3
Surface modification							
LCS 0.01 %w/v	0.67 ± 0.13	0.968	1.25 ± 0.30	0.952	0.81 ± 0.29	904.1 ± 178.6	657.6 ± 107.3
0.02 %w/v	0.82 ± 0.12	0.956	1.62 ± 0.25	0.942	1.51 ± 0.35	549.4 ± 99.3	388.2 ± 70.0
0.04 %w/v	1.10 ± 0.12	0.934	2.35 ± 0.24	0.928	2.87 ± 0.45	325.8 123.4	274.0 ± 65.1
HCS 0.01 %w/v	0.59 ± 0.12	0.982	1.07 ± 0.23	0.968	0.89 ± 0.28	310.1 ± 103.8	401.8 ± 162.9
0.02 %w/v	1.17 ± 0.06	0.965	2.28 ± 0.13	0.949	2.86 ± 0.25	514.3 ± 349.6	855.4 ± 391.2
0.04 %w/v	1.57 ± 0.02	0.971	2.92 ± 0.11	0.949	5.21 ± 0.31	1006.8 ± 288.2	811.6 ± 161.5

[a] Data are the mean ± S.D., n=3. [b] Data are the mean ± S.D., n=5.

แบบ สป/สผ/อสป/003-ก

สำหรับเจ้าหน้าที่

คำขอที่ .....

รับวันที่ .....

คำขอแก้ไขเพิ่มเติมคำขอรับสิทธิบัตร/อนุสิทธิบัตร

คำขอรับสิทธิบัตร/~~อนุสิทธิบัตร~~ เลขที่ .....1001000839.....

วันยื่นคำขอ ..... 27 พฤษภาคม 2553 .....

ชื่อที่แสดงถึงการประดิษฐ์/~~การออกแบบผลิตภัณฑ์~~ ...ยาเม็ดเมทริกซ์บรรจุสารประกอบเชิงซ้อนนิโคติน-เคลย์.....

ชื่อผู้ขอรับสิทธิบัตร/~~อนุสิทธิบัตร~~ .....มหาวิทยาลัยขอนแก่น .....

ข้อ 1. ข้าพเจ้า ..... นางจิราภรณ์ เหลืองไพรินทร์..... อยู่บ้านเลขที่ .....123.....ถนน.. มิตรภาพ.....สำนักงานบริหารจัดการทรัพย์สินทางปัญญา..... มหาวิทยาลัยขอนแก่น..... ตำบล/แขวง .... ในเมือง.....อำเภอ/เขต .....เมือง..... จังหวัด .....ขอนแก่น ..... โทรศัพท์ .....0-4336-4409 ... ซึ่งเป็นผู้~~ขอรับสิทธิบัตร/อนุสิทธิบัตร~~หรือตัวแทนของผู้ขอรับสิทธิบัตร/~~อนุสิทธิบัตร~~ที่ระบุข้างต้น ขอแก้ไขเพิ่มเติมคำขอรับสิทธิบัตร/~~อนุสิทธิบัตร~~ดังกล่าว ดังมีรายละเอียดตามที่แนบมาพร้อมนี้

ข้อ 2.ข้าพเจ้าขอยืนยันว่าการแก้ไขเพิ่มเติมนี้เป็นไปตามมาตรา 20 แห่งพระราชบัญญัติสิทธิบัตร พ.ศ. 2522 กล่าวคือ ไม่เป็นการเพิ่มเติมสาระสำคัญของการประดิษฐ์หรือการออกแบบผลิตภัณฑ์

วันที่ ..30... เดือน ..มิถุนายน..... พ.ศ. ...2553.....

ลายมือชื่อ .....

(..... นางจิราภรณ์ เหลืองไพรินทร์.....)

หมายเหตุ ให้ขีดข้อความที่ไม่ใช้ออก

คำขอรับสิทธิบัตร/อนุสิทธิบัตร

☑ การประดิษฐ์
☐ การออกแบบผลิตภัณฑ์
☐ อนุสิทธิบัตร

ข้าพเจ้าผู้ลงลายมือชื่อในคำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้ ขอรับสิทธิบัตร/อนุสิทธิบัตร ตามพระราชบัญญัติสิทธิบัตร พ.ศ 2522 แก้ไขเพิ่มเติมโดยพระราชบัญญัติสิทธิบัตร (ฉบับที่ 2) พ.ศ 2535 และ พระราชบัญญัติสิทธิบัตร (ฉบับที่ 3) พ.ศ 2542

สำหรับเจ้าหน้าที่	
วันรับคำขอ	เลขที่คำขอ
วันยื่นคำขอ	
สัญลักษณ์จำแนกการประดิษฐ์ระหว่างประเทศ	
ใช้กับแบบผลิตภัณฑ์ ประเภทผลิตภัณฑ์	
วันประกาศโฆษณา	เลขที่ประกาศโฆษณา
วันออกสิทธิบัตร/อนุสิทธิบัตร	เลขที่สิทธิบัตร/อนุสิทธิบัตร
ลายมือชื่อเจ้าหน้าที่	

1.ชื่อที่แสดงถึงการประดิษฐ์/การออกแบบผลิตภัณฑ์
ยาเม็ดเมทริกซ์บรรจุสารประกอบเชิงซ้อนนิโคติน-เคลย์

2.คำขอรับสิทธิบัตรการออกแบบผลิตภัณฑ์นี้เป็นคำขอสำหรับแบบผลิตภัณฑ์อย่างเดียวกันและเป็นคำขอลำดับที่
ในจำนวน คำขอ ที่ยื่นในคราวเดียวกัน

3.ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตร และที่อยู่ (เลขที่ ถนน ประเทศ)
1. มหาวิทยาลัยขอนแก่น
สำนักงานบริหารจัดการทรัพย์สินทางปัญญา ชั้น 3 อาคารสถาบันวิจัยและพัฒนา
มหาวิทยาลัยขอนแก่น อ. เมือง จ. ขอนแก่น 40002
2. สำนักงานกองทุนสนับสนุนการวิจัย (สกว.)
เลขที่ 979/17-21 ชั้น 14 อาคาร เอส เอ็ม ทาวเวอร์
ถนนพหลโยธิน แขวงสามเสนใน เขตพญาไท กรุงเทพมหานคร 10400

3.1 สัญชาติ ไทย
3.2 โทรศัพท์ 0-4320-2222-41
3.3 โทรสาร -
3.4 อีเมล์ -

4.สิทธิในการขอรับสิทธิบัตร/อนุสิทธิบัตร
☐ ผู้ประดิษฐ์/ผู้ออกแบบ ☑ ผู้รับโอน ☐ ผู้ขอรับสิทธิโดยเหตุอื่น

5.ตัวแทน(ถ้ามี)/ที่อยู่ (เลขที่ ถนน จังหวัด รหัสไปรษณีย์)
นางจิราภรณ์ เหลืองไพรินทร์
สำนักงานบริหารจัดการทรัพย์สินทางปัญญา
ชั้น 3 อาคารสถาบันวิจัยและพัฒนา มหาวิทยาลัยขอนแก่น
อ. เมือง จ. ขอนแก่น ประเทศไทย 40002

5.1 ตัวแทนเลขที่ 2217
5.2 โทรศัพท์ 0-4336-4409
5.3 โทรสาร 0-4336-4409
5.4 อีเมล์ ip@kku.ac.th

6.ผู้ประดิษฐ์/ผู้ออกแบบผลิตภัณฑ์ และที่อยู่ (เลขที่ ถนน ประเทศ)
6.1 รองศาสตราจารย์ ธเนศ พงศ์จรรยากุล คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น จ. ขอนแก่น 40002
6.2 นางสาวโสภาพรรณ กาญจนบัตร คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น จ. ขอนแก่น 40002

7. คำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้แยกจากหรือเกี่ยวข้องกับคำขอเดิม
ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตร ขอให้ถือว่าได้ยื่นคำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้ ในวันเดียวกับคำขอรับสิทธิบัตร
เลขที่ วันยื่น เพราะคำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้แยกจากหรือเกี่ยวข้องกับคำขอเดิมเพราะ
☐ คำขอเดิมมีการประดิษฐ์หลายอย่าง ☐ ถูกคัดค้านเนื่องจากผู้ขอไม่มีสิทธิ ☐ ขอเปลี่ยนแปลงประเภทของสิทธิ

หมายเหตุ ในกรณีที่ไม่อาจระบุรายละเอียดได้ครบถ้วน ให้จัดทำเป็นเอกสารแนบท้ายแบบพิมพ์นี้โดยระบุหมายเลขกำกับข้อและหัวข้อที่แสดงรายละเอียดเพิ่มเติมดังกล่าวด้วย

8.การยื่นคำขอนอกราชอาณาจักร

วันยื่นคำขอ	เลขที่คำขอ	ประเทศ	สัญลักษณ์จำแนกการประดิษฐ์ระหว่างประเทศ	สถานะคำขอ
8.1				
8.2				
8.3				

8.4 ☐ ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตรขอสิทธิให้ถือว่าได้ยื่นคำขอนี้ในวันที่ได้ยื่นคำขอรับสิทธิบัตร/อนุสิทธิบัตรในต่างประเทศเป็นครั้งแรกโดย
☐ ได้ยื่นเอกสารหลักฐานพร้อมคำขอนี้ ☐ ขอยื่นเอกสารหลักฐานหลังจากวันยื่นคำขอนี้

9.การแสดงการประดิษฐ์ หรือการออกแบบผลิตภัณฑ์ ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตรได้แสดงการประดิษฐ์ที่หน่วยงานของรัฐเป็นผู้จัด
วันแสดง วันเปิดงานแสดง ผู้จัด

10.การประดิษฐ์เกี่ยวกับจุลชีพ

10.1 เลขทะเบียนฝากเก็บ	10.2 วันที่ฝากเก็บ	10.3 สถาบันฝากเก็บ/ประเทศ

11.ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตร ขอยื่นเอกสารภาษาต่างประเทศก่อนในวันยื่นคำขอนี้ และจะจัดยื่นคำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้ที่จัดทำเป็นภาษาไทยภายใน 90 วัน นับจากวันยื่นคำขอนี้ โดยขอยื่นเป็นภาษา
☐ อังกฤษ ☐ ฝรั่งเศส ☐ เยอรมัน ☐ ญี่ปุ่น ☐ อื่นๆ

12.ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตร ขอให้อธิบดีประกาศโฆษณาคำขอรับสิทธิบัตร หรือรับจดทะเบียน และประกาศโฆษณาอนุสิทธิบัตรนี้ หลังจากวันที่ เดือน พ.ศ
☐ ผู้ขอรับสิทธิบัตร/อนุสิทธิบัตรขอให้ใช้รูปเขียนหมายเลข ในการประกาศโฆษณา

13.คำขอรับสิทธิบัตร/อนุสิทธิบัตรนี้ประกอบด้วย
ก. แบบพิมพ์คำขอ 2 หน้า
ข. รายละเอียดการประดิษฐ์ หรือคำพรรณนาแบบผลิตภัณฑ์ 8 หน้า
ค. ข้อถือสิทธิ 2 หน้า
ง. รูปเขียน 10 รูป 5 หน้า
จ. ภาพแสดงแบบผลิตภัณฑ์
☐ รูปเขียน รูป หน้า
☐ ภาพถ่าย รูป หน้า
ฉ. บทสรุปการประดิษฐ์ 1 หน้า

14.เอกสารประกอบคำขอ
☐ เอกสารแสดงสิทธิในการขอรับสิทธิบัตร/อนุสิทธิบัตร
☐ หนังสือรับรองการแสดงการประดิษฐ์/การออกแบบผลิตภัณฑ์
☐ หนังสือมอบอำนาจ
☐ เอกสารรายละเอียดเกี่ยวกับจุลชีพ
☐ เอกสารการขอนับวันยื่นคำขอในต่างประเทศเป็นวันยื่นคำขอในประเทศไทย
☐ เอกสารขอเปลี่ยนแปลงประเภทของสิทธิ
☐ เอกสารอื่น ๆ

15. ข้าพเจ้าขอรับรองว่า
☑ การประดิษฐ์นี้ไม่เคยยื่นขอรับสิทธิบัตร/ อนุสิทธิบัตรมาก่อน
☐ การประดิษฐ์นี้ได้พัฒนาปรับปรุงมาจาก.....

16.ลายมือชื่อ (☐ ผู้ขอรับสิทธิบัตร / อนุสิทธิบัตร; ☑ ตัวแทน)

(นางจิราภรณ์ เหลืองไพรินทร์)

หมายเหตุ บุคคลใดยื่นขอรับสิทธิบัตรการประดิษฐ์หรือการออกแบบผลิตภัณฑ์ หรืออนุสิทธิบัตร โดยการแสดงข้อความอันเป็นเท็จแก่พนักงานเจ้าหน้าที่ เพื่อให้ได้ไปซึ่งสิทธิบัตรหรืออนุสิทธิบัตร ต้องระวางโทษจำคุกไม่เกินหกเดือน หรือปรับไม่เกินห้าพันบาท หรือทั้งจำทั้งปรับ

หนังสือสัญญาโอนสิทธิขอรับสิทธิบัตร/อนุสิทธิบัตร

เขียนที่ มหาวิทยาลัยขอนแก่น
123 ถ. มิตรภาพ ต.ในเมือง อ. เมือง
จ. ขอนแก่น 40002

วันที่ 30 มิถุนายน 2553

สัญญาระหว่างผู้โอน 1.รองศาสตราจารย์ธเนศ พงศ์จรรยากุล และ 2.นางสาวโสภาพรรณ กาญจนบัตร ที่อยู่ คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น ต.ในเมือง อ. เมือง จ. ขอนแก่น รหัสไปรษณีย์ 40002 และผู้รับโอน คือ สำนักงานกองทุนสนับสนุนการวิจัย ในนาม ศาสตราจารย์ ดร. สวัสดิ์ ตันตระรัตน์ ผู้อำนวยการสำนักงานกองทุนสนับสนุนการวิจัย ที่อยู่ สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) เลขที่ 979/17-21 ชั้น 14 อาคาร เอส เอ็ม ทาวเวอร์ ถนนพหลโยธิน แขวงสามเสนใน เขตพญาไท กรุงเทพมหานคร 10400 โดยสัญญานี้ ผู้โอนซึ่งเป็นผู้ประดิษฐ์ "ยาเม็ดเมทริกซ์บรรจุสารประกอบเชิงซ้อนนิโคติน-เคลย์" ขอโอนสิทธิในการประดิษฐ์ดังกล่าว ซึ่งรวมถึงสิทธิขอรับสิทธิบัตร/อนุสิทธิบัตร และสิทธิอื่นๆ ที่เกี่ยวข้องให้แก่ผู้รับโอน เพื่อเป็นพยานหลักฐานแห่งการนี้ ผู้โอนและผู้รับโอนได้ลงลายมือชื่อไว้ข้างล่างนี้

(ลงชื่อ) ..... ผู้โอน
(รองศาสตราจารย์ ธเนศ พงศ์จรรยากุล)

(ลงชื่อ) ..โสภาพรรณ..กาญจนบัตร. ผู้โอน
(นางสาวโสภาพรรณ กาญจนบัตร)

ลงชื่อ) ..... ผู้รับโอน
(ศาสตราจารย์ ดร. สวัสดิ์ ตันตระรัตน์)

(ลงชื่อ).....พยาน
(นางสาวนฤมล เบญจปัก)

(ลงชื่อ).....พยาน
(นายเศกสิทธิ์ พรหมพฤฒา)

หนังสือมอบอำนาจ

มหาวิทยาลัยขอนแก่น
อ.เมือง จ. ขอนแก่น 40002

วันที่ 30 มิถุนายน 2553

โดยหนังสือฉบับนี้ ข้าพเจ้า สำนักงานกองทุนสนับสนุนการวิจัย โดย ศาสตราจารย์ ดร. สวัสดิ์ ตันตระรัตน์ ผู้อำนวยการสำนักงานกองทุนสนับสนุนการวิจัย ที่อยู่ สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) เลขที่ 979/17-21 ชั้น 14 อาคาร เอส เอ็ม ทาวเวอร์ ถนนพหลโยธิน แขวงสามเสนใน เขตพญาไท กรุงเทพมหานคร 10400 ขอมอบอำนาจและแต่งตั้งให้ นางจิราภรณ์ เหลืองไพรินทร์ อยู่บ้านเลขที่ 123 สำนักงานบริหารจัดการทรัพย์สินทางปัญญา มหาวิทยาลัยขอนแก่น ต.ในเมือง อ. เมือง จ.ขอนแก่น 40002 เป็นตัวแทนและผู้รับมอบอำนาจของข้าพเจ้ามีอำนาจในการยื่นขอรับสิทธิบัตร/อนุสิทธิบัตรและดำเนินการจดทะเบียนสำหรับสิทธิบัตร/อนุสิทธิบัตร จำนวน 4 เรื่อง คือ

1. ยาเม็ดเมทริกซ์บรรจุสารประกอบเชิงซ้อนนิโคติน-เคลย์
2. อนุพันธุ์แอนโดรกราโฟไลด์ การสังเคราะห์ และการใช้สารเหล่านั้น
3. ยาฉีดเมลาโทนิน
4. เฮดกิมบอลแอสเซมบลี้ (Head Gimbal Assembly) ที่ลดผลกระทบจากการรบกวนทางแม่เหล็กไฟฟ้า

โดยให้ตัวแทนดังกล่าวมีสิทธิลงชื่อในเอกสารทั้งมวลในนามของข้าพเจ้าแทนข้าพเจ้า แก้ไขเปลี่ยนแปลงเอกสารและเอกสารอื่นๆ ที่เกี่ยวข้อง รวมทั้งการอุทธรณ์ต่างๆ ด้วย

ข้าพเจ้าขอรับผิดชอบในการที่ผู้รับมอบอำนาจได้กระทำไปตามหนังสือมอบอำนาจ ที่เสมือนว่าข้าพเจ้าได้กระทำด้วยตนเองทั้งสิ้น

เพื่อเป็นหลักฐาน ข้าพเจ้าได้ลงลายมือชื่อไว้เป็นสำคัญต่อหน้าพยาน

รับรองสำเนาถูกต้อง

อากรแสตมป์ ๕ บาท อากรแสตมป์ ๕ บาท

(ลงชื่อ).....ผู้มอบอำนาจ
(ศาสตราจารย์ ดร. สวัสดิ์ ตันตระรัตน์)

อากรแสตมป์ ๒๐ บาท

(ลงชื่อ).....ผู้รับมอบอำนาจ
(นางจิราภรณ์ เหลืองไพรินทร์)

(ลงชื่อ).....พยาน
(นางสาวนฤมล เบญจปัก)

(ลงชื่อ).....พยาน
(นายเศกสิทธิ์ พรหมพฤฒา)

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Poster Legend

M1000 series: Monday afternoon session
W4000 series: Wednesday morning session
T2000 series: Tuesday morning session
W5000 series: Wednesday afternoon session
T3000 series: Tuesday afternoon session
R6000 series: Thursday morning session

DRUG DELIVERY - PHARMACEUTICAL TECHNOLOGIES (SMALL MOLECULE) / OTHER / FORMULATION

W4166 Formulation, Characterization, and Evaluation of TNP-470 Angiogenic Drug Loaded Albumin and Chitosan Microspheres
A. Siddig, S. Ayodele, L. Muscik, O. Oyelowo, X. Sun, D. Hass, K. Yeboah

W4167 Determination of the Molecular Properties of Polymethacrylic Acid Methyl Methacrylate Films Under Simulated Gastrointestinal Conditions
H. Fadda, J. Santos, D. Osman, A. Basit

W4168 Effect of Process Variables on Morphology of Voriconazole Formulations Produced by Thin Film Freezing
N. Beinborn, H. Lirola, R. Williams

W4169 Development, Formulation and Optimization of Polymer Based Films as Potential Buccal Delivery Systems Using Paracetamol and Ibuprofen as Model Drugs
H. Desai, B. Anghan, J. Boateng

W4170 Novel Lyophilization Cycle Development of Chitosan Based Formulation for Buccal Delivery Using Paracetamol as a Model Drug
I. Ayensu, J. Mitchell, J. Boateng

W4171 Withdrawn by Author

W4172 Manufacture of Pharmaceutical Relevant Material via Mechanochemistry Using Twin Screw Extrusion - Cocrystals and Salts
D. Daurio, J. MacLean, C. Medina, L. Li, K. Nagpudi, F. Alvarez-Nunez

W4173 Development of a Novel Mucoadhesive Patch for Intraoral Site-specific Controlled Release of Fenretinide
K. Desai, S. Mallery, G. Stoner, P. Larsen, S. Schwendeman

W4174 Biodegradable Thermoplastic Elastomer Grafts for Bone Tissue Regeneration
R. Dorati, C. Colonna, I. Genta, M. Hillmyer, L. Pitet, B. Conti

W4175 Working with Heckel Plots: Method for Checking the Plausibility of Force Displacement Data
K. Duchatsch, R. Lammens, B. Fretter

W4176 Delivery of Growth Factors Using Pluronic F127 Gel with Activator Role of Lactoferrin by Performing In Vitro Wound Healing Assay
G. Duman, D. Mercan, E. Yalvaç, D. Erol, E. Yesilada, F. Sahin

W4177 Studies to Investigate the Sensitivity of Operational Parameters on Drug Release Behavior in the USP Apparatus 4
J. Eaton, D. Tran, W. Hauck, E. Stippler

W4178 A Data Sharing Initiative on the Toxicity of Excipients
J. Edwards

W4179 Development of Ketoconazole/Ketorolac Mucoadhesive Gel for Treatment of Fungal Keratitis
M. El-Nabarawi, M. El-Miligi, H. El-Mofty, I. Khalil

W4180 Evaluation of a Novel Aqueous Wax Dispersion Rubicoat® for Moisture Barrier Applications
P. Pilgaonkar, M. Rustomjee, A. Gandhi, S. Chaudhari

W4181 Bioresponsive Camptothecin Delivery for Brain Cancer
V. Garripelli, S. Jo

W4182 Buccal Formulation Development Based on Novel In Situ Formation of Interpolymer Complex
A. Gupta, R. Gaud, G. Srinivasan

W4183 Enhanced In Vitro Transbuccal Delivery of Ondansetron HCl
L. Hu, B. Michniak-Kohn

W4184 Development of an Enteric Coating Process and Stability Evaluation of PCcaps™
B. Kadri, A. Johnson, D. Cartwright, M. Cappucci, P. Skultety

W4185 Use of Biorelevant Media for Assessment of Dissolution of a Poorly Soluble Weakly Basic Drug: Mosapride Citrate in the Form of Liquisolid Tablets
M. Badawy, A. Kamel, O. Sammour

✳ W4186 Alginate Matrix Tablets Containing Nicotine–Clay Complexes for Mucosal Delivery: Effect of Preparation Ph of Complexes ✳
S. Kanjanabat, W. Khunawattanakul, T. Pongjanyakul

W4187 Oral Transmucosal Drug Delivery System for Nicotine
B. Kilfoyle, H. Tan, B. Michniak-Kohn

W4188 Evaluation of the Properties of HPMC Capsules Manufactured Using Different Methods
T. Uyama, A. Inui, T. Kokubo

W4189 Evaluation of Ultrasonic Compaction Technology for Developing Solid Dispersions
M. Bordawekar, J. Bilotta, F. Seiler, R. Vippagunta, A. Subramony, L. Rabaglia, J. Lakshman, R. Panicucci

Alginate matrix tablets containing nicotine–clay complexes for mucosal delivery: Effect of preparation pH of complexes

S. Kanjanabat[1], W. Khunawattanakul[1], T. Pongjanyakul[1]

[1]Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand

Purpose.

To prepare and evaluate sodium alginate (SA) tablets containing nicotine–magnesium aluminum silicate (NCT–MAS) complexes prepared at different pHs.

Methods.

NCT–MAS complexes were prepared using an adsorption process at pH 4, 7, and 9. NCT–MAS complex particles obtained had 9-13%w/w of NCT. The tablets consisted of the NCT–MAS complexes equivalent to 15 mg of NCT, magnesium stearate (1%w/w) and appropriate amount of SA to adjust each tablet weight to 200 mg. The mixture obtained was filled into 10-mm diameter flat-faced punches and die, and compressed using a hydrostatic press. The NCT release from the tablets was performed using a USP dissolution apparatus I. The NCT permeated across porcine esophageal mucosa was conducted using a modified USP dissolution apparatus II. The concentration of NCT permeated was analyzed by HPLC. Additionally, the muco-adhesive properties of the tablets were determined using a texture analyzer.

Results.

The SA tablets containing NCT–MAS complexes prepared at various pHs showed good physical properties and the tablet thickness was over the range of 1.4-1.6 mm. The tablets obtained presented zero order kinetic of NCT release. The preparation pH of the NCT–MAS complexes did not affect the release of NCT. However, the tablets containing the complexes prepared at pH 9 gave the highest NCT permeated across porcine esophageal mucosa and the lowest NCT permeation was found in those containing the complexes prepared at acidic condition. This indicated that the complexes prepared at basic condition could liberate neutral NCT that had a high permeability with the mucosa. Furthermore, the SA tablets containing NCT–MAS complexes also presented sufficient muco-adhesive properties for adhesion to the mucosal membrane.

Conclusion.

The NCT–MAS complex-loaded SA tablets showed strong potential for mucosal NCT delivery systems and the highest NCT permeation was obtained when using NCT–MAS complexes prepared at basic condition.

This work was supported by the Thailand Research Fund, Bangkok, Thailand (Grant No. RSA5280013). Financial support from Graduate School, Khon Kaen University, Khon Kaen, Thailand, for S. Kanjanabat is gratefully acknowledged.

ALGINATE MATRIX TABLETS CONTAINING NICOTINE–CLAY COMPLEXES FOR MUCOSAL DELIVERY: EFFECT OF PREPARATION pH OF COMPLEXES

Sopaphan Kanjanabat, Wanwisa Khunawattanakul , Thaned Pongjanyakul

Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

Objective

To prepare and evaluate sodium alginate (SA) matrix tablets containing nicotine–magnesium aluminum silicate (NCT–MAS) complexes prepared at different pHs.

Methodology

Preparation of NCT–MAS complexes

The NCT-MAS dispersion in the weight ratio of 0.5:1 were prepared at pH 4, 7 and 9. Then, the dispersions were incubated at 37 °C with shaking for 24 h. After that, the NCT–MAS complexes were separated by filtration, washed 2 times with 20 ml of deionized water and dried overnight at 50 °C. The dry NCT–MAS complexes were ground using a mortar and and pestle, sieved through a 180-µm sieve and kept in a desiccator.

Preparation of SA matrix tablets containing NCT–MAS complexes

The tablets consisted of the NCT–MAS complexes equivalent to 15 mg of NCT, magnesium stearate (1%w/w) and appropriate amount of SA to adjust each tablet weight to 200 mg. The tablets were prepared by direct compression method. The mixture obtained was filled into 10-mm diameter flat-faced punches and die, and compressed using a hydrostatic press. The ingredients for each formulation is represented in table 1.

Table 1 Tablet compositions

Ingredient	pH 4	pH 7	pH 9
	mg/tablet		
NCT-MAS complexes	166	129	120
Sodium alginate (SA)	34	71	80
Magnesium stearate	2	2	2
Total weight	202		

Dissolution studies

The NCT release from the NCT-MAS complexes and the SA matrix tablets were performed using a USP dissolution apparatus I. The dissolution media are pH 6 phosphate buffer at 37°C. The samples were assayed at 259 nm by UV–visible spectrophotometer.

Permeation studies

The porcine esophageal mucosa was used as a mucosal membrane. The porcine esophageal tube was washed with pH 7.4 isotonic phosphate buffer. The mucosal membrane was separated by removing connective tissues and frozen at -20°C until further use. The NCT permeated across porcine esophageal mucosa was conducted using a modified USP dissolution apparatus II (Figure 1). Appropriate sections of mucosa were fixed under the polypropylene tube. The medium was pH 7.4 phosphate buffer isotonic at 37°C. The tablets were placed into the polypropylene tube, then 2 ml of pH 6 phosphate buffer was added. The concentration of NCT permeated was analyzed by HPLC.

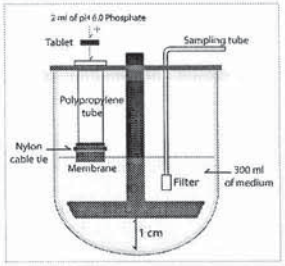

Figure 1
Modified USP dissolution apparatus II

Mucoadhesive studies

Porcine esophageal mucosa was used in this study. The mucoadhesive properties of the tablets were determined using a texture analyzer with 50 N load cell.

Results

The NCT content of the complexes prepared at pH 4, 7 and 9 were 9.50 ± 0.03, 12.21 ± 0.02 and 13.17 ± 0.04 %w/w, respectively. The NCT-MAS complexes prepared at various pHs had irregular shapes which different from the MAS particles as shown in Figure 1 (SEM).

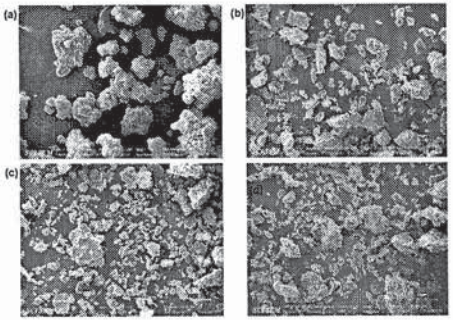

Figure 2
SEM photomicrographs of MAS granule (a) and NCT–MAS complexes prepared at pH 4 (b), 7 (c) and 9 (d).

The NCT release from the complexes increased with increasing pH of the preparation medium (Figure 3). The complexes prepared at various pHs showed similar release characteristics. The SA tablets containing NCT–MAS complexes prepared at various pHs showed good physical properties and the tablet thickness was over the range of 1.4-1.6 mm (Figure 4).

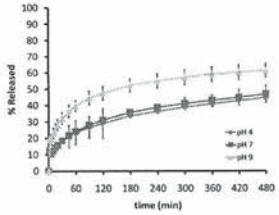

Figure 3
NCT release profile of NCT-MAS complexes prepared at different pHs in pH 6 phosphate buffer

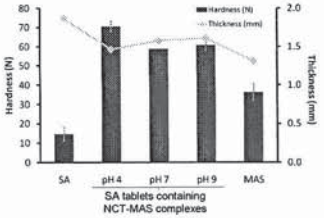

Figure 4
Thickness and hardness of matrix tablets

The preparation pH of the NCT–MAS complexes did not affect the NCT release from the SA tablets. The release exponent (n) values were ranged from 0.92 to 1.05, indicating swelling and erosion controlled release mechanism. These formulations also showed good fit to zero order model with R^2 0.996-0.997.

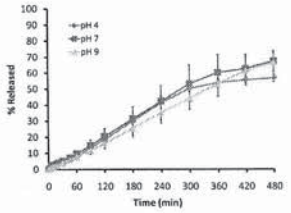

Table 2
NCT release kinetic of SA tablets containing NCT–MAS complexes in pH 6 phosphate buffer

Formulation	Zero order model		Power law
	K_0 (% min^{-1})	R^2	Release exponent (n)
pH 4	0.17 ± 0.01	0.996	1.05 ± 0.07
pH 7	0.17 ± 0.04	0.998	0.92 ± 0.05
pH 9	0.15 ± 0.03	0.997	0.98 ± 0.07

Figure 5 NCT release profile of SA tablets containing NCT–MAS complexes

The tablets containing the complexes prepared at pH 9 gave the highest NCT permeation across porcine esophageal mucosa. The lowest NCT permeation and the longest lag time were found in those containing the complexes prepared at acidic condition (Figure 6 and 7). This indicated that the complexes prepared at basic condition could liberate neutral NCT that had a high permeability with the mucosa.

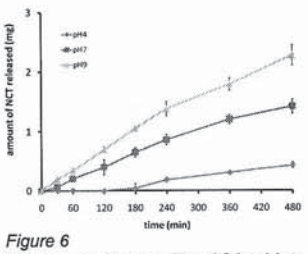

Figure 6
NCT permeation profile of SA tablets containing NCT–MAS complexes

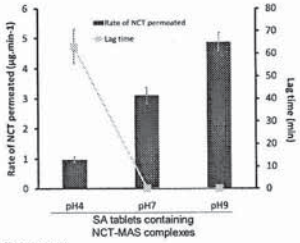

Figure 7
Permeation rate and lag time of NCT across membrane

Furthermore, the SA tablets containing NCT–MAS complexes also presented sufficient mucoadhesive properties for adhesion to the mucosal membrane. The preparation pH of the NCT–MAS complexes did not affect on mucoadhesive properties. (Figure 8).

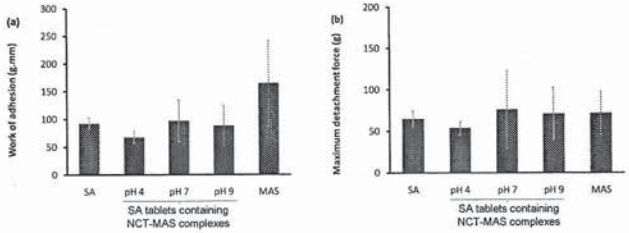

Figure 8
Mucoadhesive properties of SA tablets containing NCT-MAS complexes at various pHs (a) work of adhesion (b) maximum detachment force

Conclusions

The SA tablets containing NCT-MAS complexes showed strong potential for mucosal NCT delivery systems and the highest NCT permeation was obtained when using NCT–MAS complexes prepared at basic condition.

Acknowledgement

This work was supported by the Thailand Research Fund, Bangkok, Thailand (Grant No. RSA5280013). Financial support from Graduate School, Khon Kaen University, Khon Kaen, Thailand, for S. Kanjanabat is gratefully acknowledged.

Tuesday Morning Contributed Papers

Poster Legend M1000 series: Monday afternoon session | **T2000 series: Tuesday morning session** | T3000 series: Tuesday afternoon session
W4000 series: Wednesday morning session | W5000 series: Wednesday afternoon session | R6000 series: Thursday morning session

T2182 Design and Development of Extended Release Tablet Formulation of Guaifenesin Using Co-processed Excipient
V. Kadam, K. Jadhav, A. Patil

T2183 Preparation and Evaluation of Gastro-retentive Tablets Containing Itraconazole
J. Kim, T. Oh, J. Ha, S. Jo, H. Kim, C. Park, Y. Rhee, S. Chi, E. Park

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Propranolol–clay intercalated complex–loaded HPMC matrix tablets: Drug release characteristics and effect of calcium ion

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Purpose.

To characterize drug release of hydroxypropyl methylcellulose (HPMC) matrix tablets containing propranolol–magnesium aluminum silicate (PPN–MAS) intercalated complexes and to investigate effect of calcium ion on PPN release from the tablets.

Methods.

PPN–MAS dispersion in the weight ratio of 0.25:1 was prepared at pH 7, and then the PPN–MAS complexes were collected and dried at 50 °C. The dry complexes were ground using a mortar and pestle. The HPMC tablets containing PPN–MAS complexes that equivalent to 40 mg PPN were prepared using a direct compression method with a hydrostatic press. Moreover, different amounts of calcium acetate were incorporated into the tablets. The drug release of the tablets in 0.1 M HCl and pH 6.8 phosphate buffer was performed using a USP dissolution apparatus I. The drug release data were fitted using power law, Higuchi's equation, and zero order kinetic model. Additionally, the tablets containing pure PPN and PPN–MAS physical mixture were also prepared for drug release comparison.

Results.

The HPMC tablets containing PPN–MAS complexes and pure PPN provided zero order release kinetic of PPN in both 0.1 M HCl and pH 6.8 phosphate buffer. The PPN release rate of the PPN–MAS complex–loaded tablets was lower than that of the PPN–loaded tablets, indicating that the drug release was controlled by the PPN–MAS complexes. In contrast, the drug release of those containing PPN–MAS physical mixture showed good fitting with Higuchi's equation. This suggested that MAS could retard the PPN release via an adsorption process. Furthermore, the PPN release rate increased with increasing amount of calcium ions incorporated in the tablets because calcium ions could induce an ion exchange process with PPN in the silicate layers of MAS.

Conclusion.

The PPN-MAS complexes could be applied as drug carriers for controlling drug release in the polymeric matrix tablets. Moreover, incorporation of calcium ion could modulate drug release of the PPN–MAS complex–loaded matrix tablets.

This work was supported by the Thailand Research Fund, Bangkok, Thailand (Grant No. RSA5280013).

PROPRANOLOL–CLAY INTERCALATED COMPLEX-LOADED HPMC MATRIX TABLETS: DRUG RELEASE CHARACTERISTICS AND EFFECT OF CALCIUM ION

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Objectives

- To characterize drug release of hydroxypropyl methylcellulose (HPMC) matrix tablets containing propranolol-magnesium aluminum silicate (PPN-MAS) intercalated complexes.
- To investigate effect of calcium ion on PPN released from the PPN-MAS complex-loaded HPMC tablets.

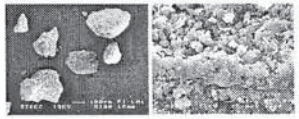
Methods

- PPN–MAS dispersion in the weight ratio of 0.25:1 was prepared at pH 7, and then the PPN–MAS complexes were collected and dried at 50 °C. The dry complexes were ground using a mortar and pestle.
- The HPMC (viscosity grade 15 cp) tablets containing PPN–MAS complexes that equivalent to 40 mg PPN were prepared using a direct compression method with a hydrostatic press at 11 MPa. Additionally, the tablets containing pure PPN and PPN–MAS physical mixture were also prepared for drug release comparison. The drug release of the tablets in 0.1 M HCl or pH 6.8 phosphate buffer was performed using a USP dissolution apparatus I. The drug release data were fitted using Power law, Higuchi's equation, and zero order release kinetic model.
- Different amounts of calcium acetate were incorporated into the HPMC tablets that were compressed at 6.6 MPa. The drug release of the tablets in 0.1 M HCl or pH 6.8 tris buffer with NaCl 8.2 g/L and KCl 0.32 g/L was performed using a USP dissolution apparatus I.

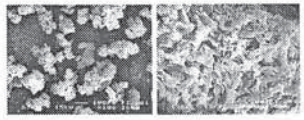
Results

Characteristics of PPN-MAS complexes

- Particle and surface morphology



PPN-MAS complexes



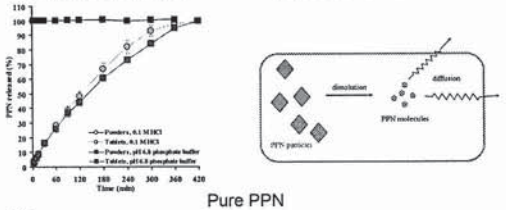
MAS granules

- PPN-MAS complexes contained 20%w/w PPN
- Particle size of the complexes were in the range of 125-180 micron.

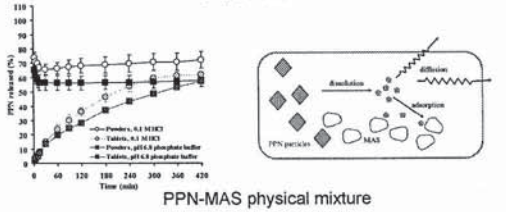
Results

Comparative study of PPN release from the HPMC tablets

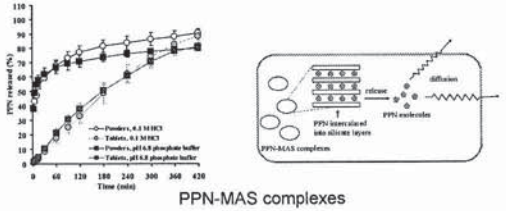
PPN release profile | PPN release mechanism



Pure PPN

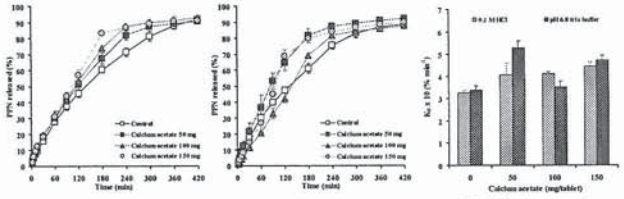


PPN-MAS physical mixture



PPN-MAS complexes

Effect of calcium ion on PPN release



The PPN release rate increased with increasing amount of calcium ions incorporated in the tablets because calcium ions could induce an ion exchange process with PPN in the silicate layers of MAS.

PPN release characteristics from the HPMC tablets

HPMC tablets	Dissolution medium	Release exponent (n)	K_H (% $min^{-0.5}$)	K_0 x 10 (% min^{-1})
Pure PPN	0.1 M HCl	0.75 ± 0.02 (R^2=0.997)	4.91 ± 0.37 (R^2=0.981)	3.90 ± 0.30 (R^2=0.995)
	pH 6.8 PB	0.72 ± 0.04 (R^2=0.987)	4.49 ± 0.30 (R^2=0.983)	3.60 ± 0.20 (R^2=0.991)
PPN-MAS physical mixture	0.1 M HCl	0.64 ± 0.02 (R^2=0.992)	3.76 ± 0.30 (R^2=0.994)	2.20 ± 0.20 (R^2=0.965)
	pH 6.8 PB	0.62 ± 0.03 (R^2=0.992)	2.98 ± 0.05 (R^2=0.998)	1.33 ± 0.01 (R^2=0.951)
PPN-MAS complexes	0.1 M HCl	0.98 ± 0.02 (R^2=0.993)	3.91 ± 0.60 (R^2=0.959)	2.70 ± 0.44 (R^2=0.999)
	pH 6.8 PB	0.89 ± 0.03 (R^2=0.990)	4.28 ± 0.36 (R^2=0.976)	2.90 ± 0.25 (R^2=0.987)

- The HPMC tablets containing PPN-MAS complexes showed zero-order release kinetic with release exponent (n) close to unity.
- The PPN release rate of the PPN-MAS complex-loaded tablets was lower than that of the tablets containing pure PPN, suggesting that the drug release was controlled by the PPN-MAS complex particles.
- The drug release from the tablets containing PPN-MAS physical mixture gave good fitting with Higuchi model. This suggested that MAS could retard the PPN release via an adsorption process.

Conclusion

The PPN-MAS complexes could be applied as drug carriers for controlling drug release in the polymeric matrix tablets. Moreover, incorporation of calcium ion could modulate drug release of the PPN-MAS complex-loaded matrix tablets.

Acknowledgement

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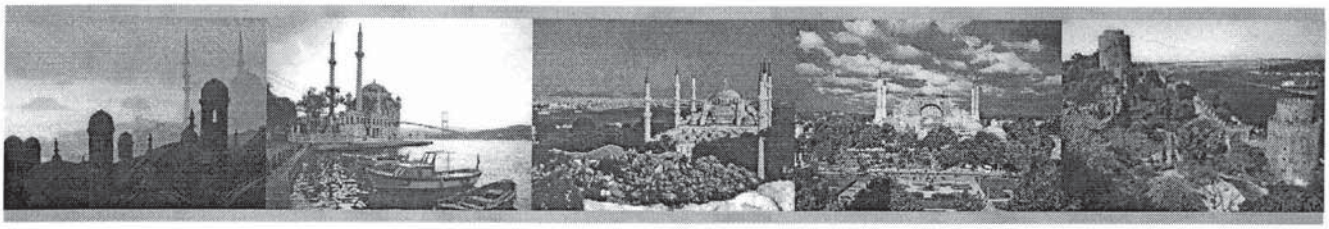

Key Note Speaker

David Tainsh, Senior Vice President & Global Head of Product Development, GlaxoSmithKline, Harlow, UK

Plenary lectures

Patrick Couvreur, Professor of Pharmaceutics and Biopharmaceutics, Université de Paris-Sud, France

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NICOTINE–MAGNESIUM ALUMINUM SILICATE COMPLEX-LOADED HPMC TABLETS: EFFECT OF ACIDIC AND BASIC MODIFYING AGENTS ON UNIDIRECTIONAL RELEASE AND PERMEATION

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INTRODUCTION

Nicotine (NCT) is a volatile and strongly alkaline liquid. It could form diprotonated, monoprotonated and neutral species at acidic, neutral and basic pH levels, respectively [1]. It has been used in smoking cessation therapy for relieving addiction symptoms. NCT is a candidate for mucosal delivery, especially buccal route, due to low bioavailability after oral administration.

NCT could interact with magnesium aluminum silicate (MAS), a mixture of montmorillonite and saponite clays, to form intercalated complexes via electrostatic force and hydrogen bonding. The NCT-MAS complex particles could sustain NCT release after initial burst release in pH 6 phosphate buffer [2]. The use of NCT-MAS complexes as drug reservoirs in matrix tablets was developed and evaluated for buccal delivery of NCT [3]. In this study, the effect of acidic and basic modifying agents, citric acid and magnesium hydroxide, respectively, on unidirectional NCT release and permeation of hydroxypropyl methylcellulose (HPMC) matrix tablets was investigated.

EXPERIMENTAL METHODS

Preparation of NCT-MAS complexes

NCT solution and MAS dispersion were mixed and pH of the mixture was adjusted to 9. To achieve equilibrium of NCT adsorption onto MAS, the dispersions were then incubated with shaking at 37 °C for 24 h. The NCT-MAS complexes were separated from the filtrates by filtration, washed twice using 20 ml of deionized water and dried at 50 °C for 24 h. The dry NCT-MAS complexes were ground using a mortar and pestle.

Preparation of HPMC tablets loaded with NCT-MAS complexes and pH modifying agents

All tablets were prepared using the direct compression method. Each tablet consisted of 120 mg NCT-MAS complexes (equivalent to NCT 15.8 mg), 80 mg HPMC and 2 mg magnesium stearate. Citric acid or magnesium hydroxide was added in the content of 5, 10, or 20 %w/w of the tablet weight. The ingredients were mixed in a rotomixer for 3 min; magnesium stearate was then blended with the mixture for 1 min before tabletting. The mixtures were filled into 10-mm flat-faced punches and dies, then applying 23 MPa with a hydrostatic press without holding time. The tablets obtained were stored in a desiccator until the measurements.

Thickness and hardness of the tablets

The thicknesses of the tablets were measured using a vernier caliper. The hardnesses of the tablets were measured with a Stokes tablet hardness tester.

Unidirectional release and permeation of NCT

Unidirectional release of NCT from the tablets was characterized using a modified USP dissolution apparatus 2 [3]. Briefly, the distance between the paddle and vessel bottom was set to 1 cm, and the dissolution medium used was 300 ml of pH 6 phosphate buffer at 37.0 °C. A cellulose acetate membrane (0.45-μm pore size) which had been hydrated in pH 6 phosphate buffer for overnight was tightly attached at the lowest point of a polypropylene tube (inner diameter=1.8 cm) using a nylon cable tie. This tube was vertically placed in a dissolution vessel and the distance between the tube and the vessel wall was approximately 1.8 cm. The end of the tube was adjusted so that the membrane was wetted and in contact with the medium. The tablets were placed into the tube and wetted using 2 ml of pH 6 phosphate buffer. The rotation speed of the paddle was set to 50 revolutions/min. Samples (7 ml) were collected at various time intervals. The amount of NCT released was quantified with HPLC. In the case of NCT permeation study, porcine esophageal mucosa was used as a mucosal membrane model [4] and the permeation medium was isotonic phosphate buffer at pH 7.4.

RESULTS AND DISCUSSION

The tablet thickness seemed to increase with increasing pH modifier content. Citric acid at the content of 20% caused a decrease in tablet hardness In contrast, a small amount of magnesium hydroxide brought about a remarkable decrease of the tablet hardness. This was due to decrease of interparticle bonding of HPMC when adding citric acid or magnesium hydroxide. However, all tablets were acceptable upon visual inspection and acceptable hardness.

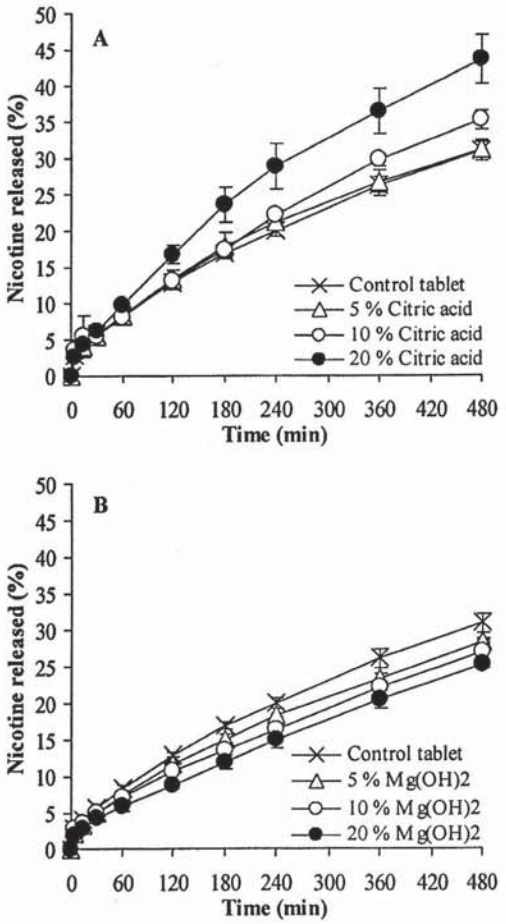

Figure 1. Unidirectional nicotine release of NCT-MAS complex-loaded HPMC tablets adding various contents of citric acid (A) and magnesium hydroxide (B). Each point is mean ± SD, n=3.

The NCT release profiles of the tablets containing citric acid and magnesium hydroxide are present in Figure 1. The NCT release rate calculated using Higuchi' equation is listed in Table 1. Incorporation of magnesium hydroxide caused lower NCT release rate due to the formation of aqueous gel barriers of HPMC with inorganic gel of magnesium hydroxide. On the other hand, citric acid could accelerate NCT release rate because fast dissolution of citric acid could reduce tortuosity of swollen HPMC matrix.

Table 1. NCT release and permeation rate of the tablets.

pH modifying agent	Release rate (% $min^{-0.5}$)	Permeation rate (μg $min^{-0.5}$)
Control tablet	1.51 ± 0.07	117.3 ± 19.4
5% Citric acid	1.56 ± 0.08	19.2 ± 2.0
10% Citric acid	1.78 ± 0.04	24.9 ± 6.0
20% Citric acid	2.24 ± 0.23	8.90 ± 0.7
5% $Mg(OH)_2$	1.39 ± 0.02	227.4 ± 13.4
10% $Mg(OH)_2$	1.28 ± 0.09	277.0 ± 25.7
20% $Mg(OH)_2$	1.23 ± 0.05	235.4 ± 5.9

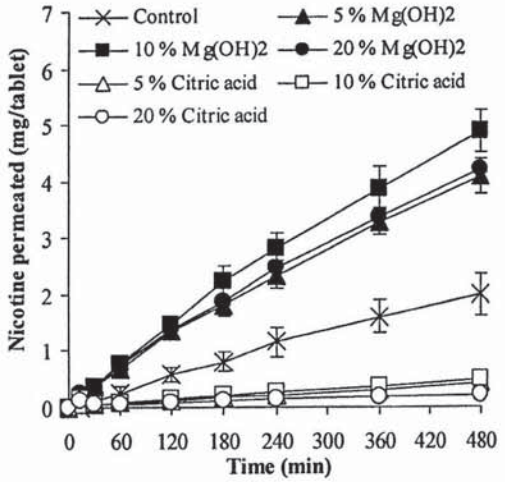

Figure 2. Unidirectional nicotine permeation of NCT-MAS complex-loaded HPMC tablets adding various contents of citric acid and magnesium hydroxide. Each point is mean ± SD, n=3

The NCT permeation across the mucosal membrane is shown in Figure 1. The NCT permeation rate (Table 1), which was computed using Higuchi's equation, of the tablets adding citric acid obviously decreased when compared with the control tablets. This was due to the formation of protonated NCT with low permeability across the mucosal membrane at acidic pH level [1]. Magnesium hydroxide could enhance NCT permeation rate because neutral NCT with high permeability could completely form at basic pH level.

CONCLUSION

Addition of pH modifying agents could change NCT species released from the NCT-MAS complexes, leading to modulation of NCT permeation for buccal delivery.

ACKNOWLEDGEMENTS

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บทคัดย่อ
การเสนอผลงานแบบโปสเตอร์

ทุนเพิ่มขีดความสามารถด้านการวิจัยของอาจารย์รุ่นกลาง ในสถาบันอุดมศึกษา ❁ เมธีวิจัย สกว. ❁ วุฒิเมธีวิจัย สกว. และทุนวิจัยพื้นฐานเชิงยุทธศาสตร์

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Characterization of Calcium Alginate Beads Loading Propranolol-Magnesium Aluminum Silicate Intercalated Complexes as Microreservoirs

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Abstract

Propranolol HCl (PPN), a cationic drug, could interact with magnesium aluminum silicate (MAS), a negatively charged clay, to create small flocculate particles of intercalated complexes. In this study, calcium alginate (CA) beads loaded with PPN-MAS intercalated complexes, which serve as microreservoirs, were prepared using an ionotropic gelation method. The surface and matrix morphology, drug entrapment efficiency, mechanical properties, and drug release behavior of the CA beads were investigated. The results showed that the PPN-MAS complex particles were embedded on the surface and in the matrix of the CA beads, which was examined using scanning electron microscopy with energy dispersive X-ray analysis. The PPN entrapment efficiency of the PPN-MAS complex-loaded CA beads was significantly higher than that of the PPN-loaded CA beads. Increased MAS content brought about an increase in PPN entrapment efficiency and the matrix strength of the CA beads. Moreover, the PPN-MAS complexes in the CA beads could remarkably reduce the initial burst of PPN release as well as its release rate in both 0.1 M HCl and pH 6.8 phosphate buffer, depending on the MAS content added. Additionally, the PPN-MAS complex-loaded CA beads also produced a sustained release pattern of PPN in simulated gastro-intestinal conditions. The findings show that the CA beads containing PPN-MAS intercalated complexes as microreservoirs could enhance drug entrapment efficiency, reduce initial burst release and modulate drug release. Furthermore, these beads represent a promising oral drug delivery system for highly water-soluble cationic drugs.

Keywords: calcium alginate beads, magnesium aluminum silicate, propranolol, intercalated complexes, entrapment efficiency

Outputs

1. Rojtanatanya S, Pongjanyakul T. *Propranolol-magnesium aluminum silicate complex dispersions and particles: Characterization and factors influencing drug release.* International Journal of Pharmaceutics **2010**; 383: 106-115.
2. Pongjanyakul T, Rongthong T. *Enhanced entrapment efficiency and modulated drug release of alginate beads loaded with drug-clay intercalated complexes as microreservoirs.* Carbohydrate Polymers **2010**; 81: 409-419.

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CHARACTERIZATION OF CALCIUM ALGINATE BEADS LOADING PROPRANOLOL-MAGNESIUM ALUMINUM SILICATE INTERCALATED COMPLEXES AS MICRORESERVOIRS

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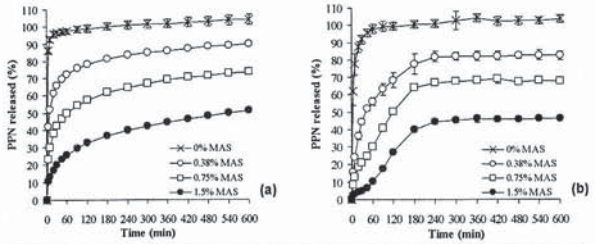
INTRODUCTION

Sodium alginate (SA), a naturally occurring non-toxic polysaccharide found in marine brown algae, is one of the polysaccharides employed to fabricate small beads. Gelation of SA occurs when uronic acids are cross-linked with divalent cations, such as calcium ions[1] . This phenomenon has been applied to the preparation of calcium alginate (CA) beads for use as a drug delivery system, by dropping the drug-containing SA dispersion into a calcium chloride bath[2]. A low entrapment efficiency of water-soluble drugs in the CA beads is a problem for developing CA beads as a drug delivery system[3]. To solve this problem, magnesium aluminum silicate (MAS) was used as an adsorbent for amine drugs to form drug-MAS complexes. A simultaneous formation of small particle drug-MAS complexes occurred when a MAS dispersion and a drug solution were mixed, due to electrostatic interactions between these materials[4,5]. Therefore, the aim of this study was to prepare and investigate CA beads loaded with drug–MAS complexes that serve as microreservoirs. Propranolol HCl (PPN), a cationic drug, was used as a model drug.

EXPERIMENTAL

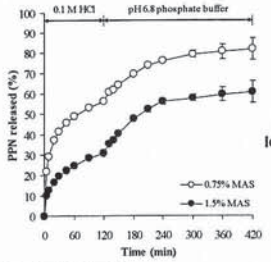
The PPN-MAS complexes in the dispersion were formed before adding SA. The PPN-MAS complex-loaded SA dispersions were dropped through a nozzle (1.2-mm inner diameter) into 2% w/v calcium chloride solution. The gel beads were cured for 30 min, collected and dried at 50°C for 24 h. The surface and internal morphology were investigated using SEM with EDX analysis. The mechanical properties, PPN entrapment efficiency and PPN release were examined.



PPN release profiles of CA beads containing PPN-MAS complexes prepared using different MAS concentrations in 0.1 M HCl (a) and pH 6.8 phosphate buffer (b).

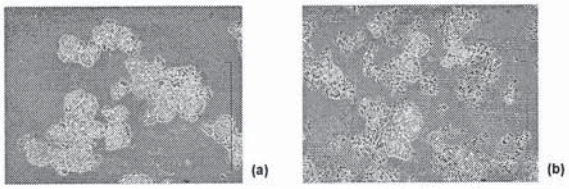
PPN release characteristics of PPN-MAS complex-loaded CA beads.

PPN-loaded CA beads	0.1 M HCl		pH 6.8 phosphate buffer	
	Initial burst release at 5 min (%)	PPN release rate (% $min^{-1/2}$)	Initial burst release at 5 min (%)	PPN release rate (% min^{-1})
0% MAS	86.2 ± 1.9	-	62.2 ± 8.2	-
0.38% MAS	42.2 ± 0.9	14.05 ± 0.05	15.5 ± 1.2	0.77 ± 0.02
0.75% MAS	23.4 ± 1.2	8.64 ± 0.08	8.41 ± 0.07	0.34 ± 0.02
1.5% MAS	10.7 ± 0.7	2.88 ± 0.02	2.65 ± 1.05	0.22 ± 0.01

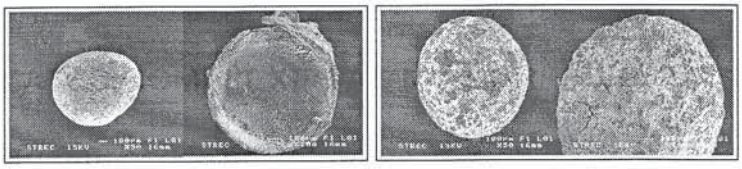


PPN release profiles of PPN-MAS complex-loaded CA beads in simulated gastric-intestinal condition.

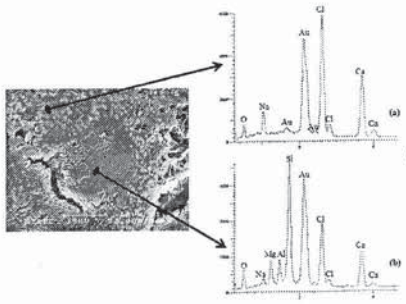
RESULTS



Morphology of PPN-MAS complex particles in the dispersion without (a) and with (b) SA before cross-linking process.

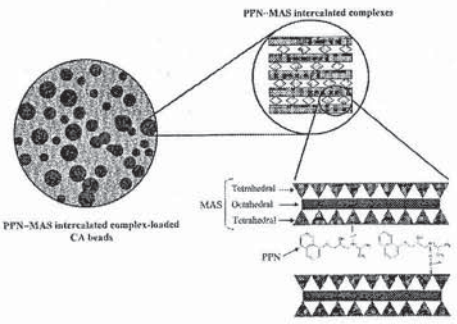


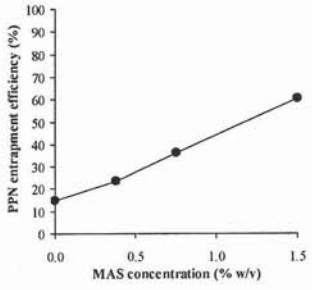
Microscopic morphology and internal structure of PPN-loaded CA beads (a) and PPN-1.5%MAS complex-loaded CA beads (b).



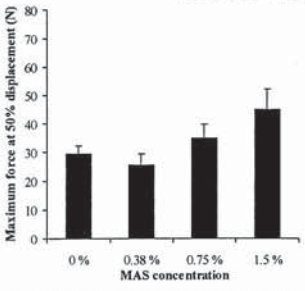
SEM micrograph focused on PPN-MAS complexes in PPN-1.5%MAS complex-loaded CA beads and EDX patterns of CA matrix (a) and PPN-MAS complexes (b).

Schematic presentation of PPN-MAS intercalated complex-loaded CA beads.





Effect of MAS on PPN entrapment efficiency of CA beads.



Effect of MAS on mechanical property of CA beads.

CONCLUSION

The PPN-MAS intercalated complexes formation enhanced PPN entrapment efficiency and strength of CA beads, and modulated PPN release in both acidic medium and pH 6.8 phosphate buffer. The drug-MAS complex-loaded CA beads showed strong potential as an oral drug delivery system for cationic drugs with high water solubility.

ACKNOWLEDGEMENTS

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PUBLICATION

1.Rojtanatanya S, Pongjanyakul T. *Propranolol-magnesium aluminum silicate complex dispersions and particles: Characterization and factors influencing drug release.* International Journal of Pharmaceutics 2010; 383: 106-115.

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Characterization of Nicotine-Magnesium Aluminum Silicate Microparticles for Mucosal Delivery

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Introduction and Objective

Nicotine (NCT), a volatile, strongly alkaline liquid from tobacco plants, has been used for smoking cessation. NCT could interact with magnesium aluminum silicate (MAS), a negatively charged clay, via electrostatic interaction and hydrogen bonding, leading to the formation of NCT-MAS complex flocculates. The aim of this study was to prepare NCT-MAS microparticles by using lyophilization in order to maintain an original morphology of NCT-MAS flocculate particles formed. Effect of preparation pHs and NCT-MAS ratios on characteristics of microparticles were investigated.

Methods

A NCT solution was mixed with a MAS suspension at pH 4 or pH 7 to obtain the mixtures with different NCT-MAS ratios by weight. The NCT-MAS microparticles formed were collected and dried using lyophilization. The Feret diameter and morphology of the microparticles were investigated using an optical microscopy and SEM, respectively. NCT content in the microparticles was determined by acid extraction. The crystallinity and thermal behavior of the microparticles were characterized using PXRD and DSC, respectively. Mucoadhesive properties of the microparticles were also examined. NCT release and permeation across porcine esophageal mucosa were performed by using a modified Franz diffusion cell.

Results

All microparticles had an irregular shape. The size and NCT content of the microparticles tended to increase when increasing NCT concentrations in the preparation. NCT could intercalate into interlayer space of MAS, which was revealed by PXRD. The formation of the NCT-MAS microparticles could enhance thermal stability of NCT. The microparticles gave a sustain release of NCT after an initial burst release. The greater the NCT content of the microparticles, the higher the NCT release rate was found. The microparticles prepared at pH 4 gave lower NCT permeation flux than those prepared at pH 7. This was due to lower permeability of protonated NCT. Additionally, the microparticles obtained also presented mucoadhesive properties with mucosal membrane.

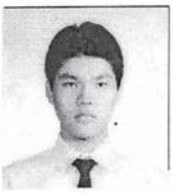
Conclusion

The formation of the NCT-MAS microparticles could improve NCT thermal stability and sustain NCT release. Moreover, the microparticles possessed mucoadhesive properties and NCT released could permeate across mucosal membrane. This finding suggests that the NCT–MAS microparticles have good potential for use as a mucosal delivery system of NCT.

Keywords: Nicotine, Magnesium aluminum silicate, Microparticles, Mucosal delivery

Selected References:

1. Pongjanyakul, T.; Khunawattanakul, W.; Puttipipatkhachorn, S. *Appl Clay Sci*, **2009**, *44*, 242-250.
2. Suksri, H.; Pongjanyakul, T. *Colloids Surf B*, **2008**, *65*, 54-60.
3. Diaz del Consuelo, I.; Jacques, Y.; Pizzolato, G.; Guy, R.H.; Falson, F. *Arch Oral Biol*, **2005**; *50*, 981-987.



Watchara Kanjanakawinkul (วัชระ กาญจนกวินกุล) **RGJ10**
Khon Kaen University, Thailand, Pharmaceutical Sciences, B.Pharm. 2006
Research field: pharmaceutical technology and drug delivery system

Characterization of Nicotine-Magnesium Aluminum Silicate Microparticles for Mucosal Delivery

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Methods

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Results

All microparticles had an irregular shape (Figure 1). The particle size of NCT-MAS microparticles tended to increase when increasing NCT concentration in the preparation (Figure 2).

Figure 1. SEM picture of MAS granules (a), NCT-MAS microparticles prepared at pH 4 (b), and pH 7 (c).

NCT content of the microparticles increased with increasing NCT concentrations in the preparation (Figure 2). In addition, the NCT content of microparticles prepared at pH 4 and pH 7 were comparable.

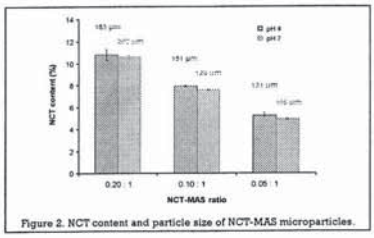

Figure 2. NCT content and particle size of NCT-MAS microparticles.

The shift of basal spacing peak of MAS in NCT-MAS microparticles to lower 2Θ indicated that NCT could intercalate into interlayer space of MAS (Figure 3).

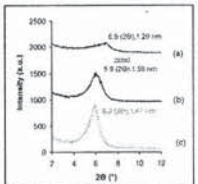

Figure 3. PXRD diffractogram of MAS (a), NCT-MAS microparticles prepared at pH 4 (b), and pH 7 (c).

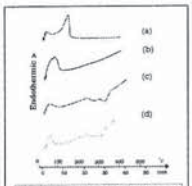

Figure 4. DSC thermogram of NCT (a), MAS (b), NCT-MAS microparticles prepared at pH 4 (c), and pH 7 (d).

The absent of endothermic peak of NCT at 147 °c and the present of exothermic degradation peak of NCT around 300 °c in DSC thermogram of microparticles (Figure 4) indicated the complex formation between NCT and MAS. This resulted in an improvement of NCT thermal stability.

Table 1. Mucoadhesive properties of NCT-MAS microparticle.

		Work of adhesion (mN.mm)	Maximum detachment force (mN)
MAS		490 ± 163	512 ± 316
pH4	0.20 : 1	452 ± 58	243 ± 96
	0.10 : 1	397 ± 75	491 ± 94
	0.05 : 1	404 ± 170	363 ± 176
pH7	0.20 : 1	497 ± 75	311 ± 191
	0.10 : 1	565 ± 158	626 ± 254
	0.05 : 1	561 ± 120	476 ± 244

Additionally, the microparticles obtained also presented mucoadhesive properties with porcine esophageal mucosal membrane (Table 1).

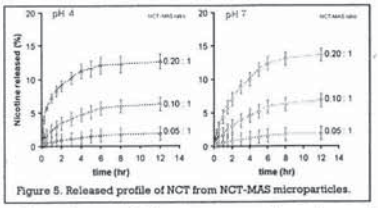

Figure 5. Released profile of NCT from NCT-MAS microparticles.

The microparticles gave a sustain release of NCT after an initial burst release (Figure 5). The greater the NCT content of the micro-particles, the higher the NCT release rate was found.

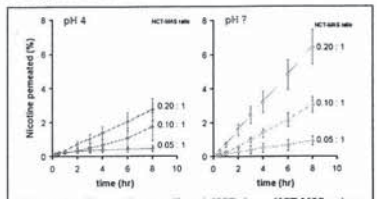

Figure 6. Permeation profile of NCT from NCT-MAS microparticles across porcine esophageal mucus membrane.

The microparticles prepared at pH 4 gave lower NCT permeation flux than those prepared at pH 7 (Figure 6). This was due to lower permeability of protonated NCT of microparticles of pH 4

Conclusion

The formation of the NCT-MAS microparticles could improve NCT thermal stability and sustain NCT release. Moreover, the microparticles possessed mucoadhesive properties and NCT released could permeate across mucosal membrane. This finding suggests that the NCT–MAS microparticles have good potential for use as a mucosal delivery system of NCT.

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Acknowledgement

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การศึกษาคุณลักษณะของยาเม็ดไฮดรอกซีโพรพิลเมทิลเซลลูโลส บรรจุสารประกอบเชิงซ้อนนิโคติน-เคลย์ เพื่อนำส่งทางกระพุ้งแก้ม

CHARACTERIZATION OF HYDROXYPROPYLMETHYLCELLULOSE TABLETS CONTAINING NICOTINE-CLAY COMPLEXES FOR BUCCAL DELIVERY

โสภาพรรณ กาญจนบัตร[1] และ รศ.ดร.ธเนศ พงศ์จรรยากุล[2]

บทคัดย่อ

วัตถุประสงค์ของการศึกษานี้ เพื่อเตรียมและประเมินยาเม็ดไฮดรอกซีโพรพิลเมทิลเซลลูโลสบรรจุสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต ซึ่งทำหน้าที่เป็นแหล่งกักเก็บยาเพื่อนำส่งทางกระพุ้งแก้ม โดยศึกษาผลของปริมาณสารประกอบเชิงซ้อนต่อคุณสมบัติยาเม็ด คือ ความหนา ความแข็ง การปลดปล่อยนิโคติน การซึมผ่านเยื่อเมือกบริเวณหลอดอาหารหมู และความสามารถในการยึดติดทางชีวภาพ ผลการศึกษาพบว่า ยาเม็ดเมทริกซ์ที่ได้มีคุณสมบัติทางกายภาพที่ดี การปลดปล่อยนิโคตินจากยาเม็ดเมทริกซ์ควบคุมโดยกลไกการพองตัวและการกร่อนของพอลิเมอร์ อัตราการปลดปล่อยนิโคติน และอัตราการซึมผ่านเยื่อเมือกของนิโคตินเพิ่มขึ้น เมื่อเพิ่มปริมาณสารประกอบเชิงซ้อนในยาเม็ด นอกจากนี้ยาเม็ดที่เตรียมได้ แสดงคุณสมบัติการยึดติดทางชีวภาพต่อเมมเบรนเยื่อเมือก จากผลการศึกษาสรุปว่า ยาเม็ดไฮดรอกซีโพรพิลเมทิลเซลลูโลสบรรจุสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต มีความเป็นไปได้สำหรับใช้เป็นระบบนำส่งทางกระพุ้งแก้มของนิโคติน

คำสำคัญ : นิโคติน, แมกนีเซียมอะลูมินัมซิลิเคต, ไฮดรอกซีโพรพิลเมทิลเซลลูโลส, ยาเม็ดกระพุ้งแก้ม

ABSTRACT

The purpose of this study was to prepare and evaluate hydroxypropylmethylcellulose (HPMC) tablets containing nicotine-magnesium aluminum silicate (NCT-MAS) complexes as drug reservoirs for buccal delivery. The effect the amounts of complexes on tablet properties, such as hardness, thickness, nicotine release, in vitro permeation across porcine esophageal mucosa and mucoadhesive properties were investigated. The results presented that all tablets gave an acceptable physical properties. The release of nicotine from the tablets could be controlled by polymer swelling and erosion mechanisms. The release and permeation rate of nicotine increased with the increasing of the amount of complexes in the tablets. Moreover, the obtained tablets gave the bioadhesive property for adhesion to the mucosal membrane. These findings suggested that the HPMC tablets containing NCT-MAS complexes showed good potential to be a nicotine buccal delivery system.

KEYWORDS : nicotine, magnesium aluminum silicate, hydroxypropylmethylcellulose, buccal tablets

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[2] อาจารย์ประจำคณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น

1. บทนำ

การบำบัดด้วยนิโคตินทดแทน (nicotine replacement therapy) มีประโยชน์สำหรับผู้ที่ต้องการอดบุหรี่ แต่การบริหารนิโคตินรูปแบบรับประทานให้ค่าชีวประสิทธิผลต่ำ จากการที่นิโคตินถูกทำลายที่ตับ (D'Orlando and Fox, 2004) การนำส่งยาผ่านทางเยื่อเมือกกระพุ้งแก้ม (buccal drug delivery) สามารถเพิ่มประสิทธิภาพการรักษาได้ เนื่องจากหลีกเลี่ยงการที่ตัวยาถูกทำลายที่ตับ ทำให้ความเข้มข้นของยาในเลือดถึงระดับที่ต้องการ (Adrian et al., 2006) ยาเม็ดเมทริกซ์สำหรับติดกระพุ้งแก้มเป็นรูปแบบการนำส่งนิโคตินที่มีการวิจัยและพัฒนา (Ikinci et al., 2004) มีระยะเวลาการออกฤทธิ์นานกว่าหมากฝรั่งเคี้ยวนิโคติน จึงลดความถี่ในการบริหารยาได้ แต่ปัจจัยที่ต้องคำนึงถึงคือ ยาเม็ดต้องติดที่ตำแหน่งเดิมภายในปาก และควบคุมการปลดปล่อยนิโคตินได้ตลอดการบริหารยา (Rossi et al., 2005) นิโคตินเป็นสารประกอบอัลคาลอยด์ เป็นของเหลวใส ไม่มีสี เมื่อสัมผัสกับก๊าซออกซิเจนในอากาศจะเกิดการออกซิเดชัน เปลี่ยนเป็นสีเหลืองหรือสีน้ำตาล (Maryadele, J.O., 2006) นิโคตินรูปเบสอิสระซึมผ่านเยื่อเมือกได้ง่าย แต่เกิดการระเหยและสลายตัวได้ง่าย การนำสารบางชนิด เช่น ไมโครคริสตัลลีนเซลลูโลส มาดูดซับนิโคติน ช่วยป้องกันการระเหยและเพิ่มความคงตัวของนิโคตินได้ (Mihranyan et al., 2004) แมกนีเซียมอะลูมินัมซิลิเคต เป็นเคลย์ในกลุ่มมอนต์โมริลโลไนต์ สามารถดูดซับนิโคตินได้ เกิดเป็นสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต ทำให้ความคงตัวของนิโคตินเพิ่มขึ้น และทำให้นิโคตินปลดปล่อยอย่างช้าๆ (Pongjanyakul et al., 2009) แสดงให้เห็นว่าสารประกอบเชิงซ้อนดังกล่าว มีแนวโน้มสำหรับการนำมาใช้เป็นแหล่งกักเก็บยาในระบบนำส่งยา

การศึกษานี้มีวัตถุประสงค์เพื่อเตรียมยาเม็ดเมทริกซ์ ที่มีสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคตเป็นแหล่งกักเก็บยา และใช้ไฮดรอกซีโพรพิลเมทิลเซลลูโลสเป็นพอลิเมอร์สำหรับยึดติดทางชีวภาพ ในการศึกษานี้จะศึกษาคุณสมบัติต่างๆ ของยาเม็ดเมทริกซ์ เช่น การปลดปล่อยยา ความสามารถในการซึมผ่านเยื่อเมือก และความสามารถในการยึดติดทางชีวภาพ เพื่อนำยาเม็ดชนิดนี้ไปประยุกต์ใช้ในการผลิตยาในขั้นอุตสาหกรรมต่อไป

2. ขั้นตอนการศึกษา / อุปกรณ์และวิธีการวิจัย

2.1 การเตรียมสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต

เตรียมสารกระจายแมกนีเซียมอะลูมินัมซิลิเคตความเข้มข้น 4 %w/v และสารละลายนิโคตินความเข้มข้น 2 %w/v ในน้ำปราศจากไอออน แบ่งสารที่เตรียมอย่างละ 50 มิลลิลิตร ผสมให้เข้ากัน ปรับพีเอช 9 ด้วยสารละลายกรดไฮโดรคลอริกความเข้มข้น 1 M หรือสารละลายโซเดียมไฮดรอกไซด์ความเข้มข้น 1 M นำไปให้ความร้อนในอ่างควบคุมอุณหภูมิที่ 37 องศาเซลเซียส เขย่า 75 ครั้งต่อนาที เป็นเวลา 24 ชั่วโมง กรองสารผสมเพื่อเก็บส่วนตะกอน อบให้แห้งที่อุณหภูมิ 50 องศาเซลเซียส เป็นเวลา 24 ชั่วโมง สารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคตที่ได้ นำมาบดลดขนาดด้วยโกร่งและลูกโกร่ง แร่งผ่านตะแกรงขนาด 180 µm

2.2 การศึกษาการปลดปล่อยนิโคตินจากสารประกอบเชิงซ้อน

เครื่องมือที่ใช้ทดสอบ คือ USP dissolution apparatus II (paddle method) (Vankel VK 200, USA) ตัวกลางการละลาย คือ ฟอสเฟตบัฟเฟอร์พีเอช 6.0 ปริมาตร 500 มิลลิลิตร ควบคุมอุณหภูมิที่ 37 องศาเซลเซียส และกวนด้วยความเร็ว 50 รอบต่อนาที ปริมาณสารประกอบเชิงซ้อนที่ใช้ทดสอบเทียบเท่านิโคติน 15 มิลลิกรัม เก็บสารละลายตัวอย่างที่เวลาต่างๆ และวิเคราะห์หาปริมาณนิโคตินโดยการวัดค่าการดูดกลืนแสงที่ความยาวคลื่น 259 นาโนเมตร ด้วยเครื่อง UV-visible spectrophotometer (Shimadzu UV1201, Japan)

2.3 การเตรียมยาเม็ดเมทริกซ์บรรจุสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต

ยาเม็ดประกอบด้วยสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคตเทียบเท่านิโคติน 5 10 และ 15 มิลลิกรัม ปรับน้ำหนักยาเม็ดเท่ากับ 200 มิลลิกรัม ด้วยไฮดรอกซีโพรพิลเมทิลเซลลูโลสชนิดความหนืด 50 เซนติพอยส์ และเติมแมกนีเซียมสเตียเรตปริมาณ 1 %w/w ของสารผสม ขั้นตอนการเตรียมทำได้โดย ผสมสารประกอบเชิงซ้อน

และไฮดรอกซีโพรพิลเมทิลเซลลูโลส เป็นเวลา 3 นาที ตามด้วยแมกนีเซียมสเตียเรต 1 นาที นำสารผสมที่ได้ไปอัดเม็ดโดยใช้ชุดสากขนาดเส้นผ่านศูนย์กลาง 10 มิลลิเมตร ใช้ความดันในการตอก 23.7 เมกะปาสคาล ด้วยเครื่องตอกไฮโดรลิก

2.4 การประเมินคุณลักษณะยาเม็ดเมทริกซ์

2.4.1 ความแข็งและความหนาของยาเม็ดเมทริกซ์

ทดสอบโดยเครื่อง Monsanto hardness tester และ Vernier caliper ตามลำดับ

2.4.2 การปลดปล่อยนิโคตินจากยาเม็ดเมทริกซ์

เครื่องมือที่ใช้ทดสอบ คือ USP dissolution apparatus I (basket method) (Vankel VK 200, USA) ใช้ฟอสเฟตบัฟเฟอร์พีเอช 6.0 ปริมาตร 500 มิลลิลิตร เป็นตัวกลางการละลาย ควบคุมอุณหภูมิที่ 37 องศาเซลเซียส basket หมุนด้วยความเร็ว 50 รอบต่อนาที เก็บสารละลายตัวอย่างที่เวลาต่างๆ และวิเคราะห์หาปริมาณนิโคตินโดยการวัดค่าการดูดกลืนแสงที่ความยาวคลื่น 259 นาโนเมตร ด้วยเครื่อง UV-visible spectrophotometer

2.4.3 การซึมผ่านเยื่อเมือกของนิโคตินจากยาเม็ดเมทริกซ์

ใช้เยื่อเมือกหลอดอาหารหมูเป็นเมมเบรน (แหล่งที่มา คือ ตลาดบ้านโนนม่วง อ.เมือง จ.ขอนแก่น) เนื่องจากชนิดและปริมาณไขมันที่เป็นส่วนประกอบคล้ายกับเยื่อเมือกกระพุ้งแก้มหมู และคุณสมบัติการยอมให้สารซึมผ่านใกล้เคียงกัน (Diaz del Consuelo et al., 2005) ทำการเตรียมโดยล้างหลอดอาหารหมูด้วยฟอสเฟตบัฟเฟอร์ไอโซโทนิกพีเอช 7.4 ตัดหลอดอาหารหมูยาว 3-4 เซนติเมตร แช่ในสารละลายโซเดียมคลอไรด์ความเข้มข้น 0.9 %w/v ควบคุมอุณหภูมิ 60 องศาเซลเซียส เป็นเวลา 1 นาที จากนั้นแช่ในฟอสเฟตบัฟเฟอร์ ไอโซโทนิกพีเอช 7.4 ที่อุณหภูมิห้อง แยกส่วนที่เป็นกล้ามเนื้อ นำไปเก็บในตู้เย็นควบคุมอุณหภูมิที่ -20 องศาเซลเซียส (Diaz del Consuelo et al., 2007) เมื่อต้องการทดสอบ นำเนื้อเยื่อแช่ในฟอสเฟตบัฟเฟอร์ไอโซโทนิก พีเอช 7.4 ที่อุณหภูมิห้อง เป็นเวลา 15 นาที เครื่องมือที่ใช้ทดสอบ คือ USP dissolution apparatus II (paddle method) ที่นำมาดัดแปลงโดยใช้หลอดพอลิพรอพิลินบรรจุตัวอย่างที่ต้องการทดสอบ ยึดเยื่อเมือกติดกับปลายหลอดพอลิพรอพิลินโดยใช้สายไนลอน ปรับระดับให้ปลายหลอดสัมผัสผิวหน้าตัวกลางการละลาย ตัวกลางที่ใช้คือ ฟอสเฟตบัฟเฟอร์ไอโซโทนิกพีเอช 7.4 ปริมาตร 300 มิลลิลิตร เริ่มทดสอบโดยใส่ยาเม็ดเมทริกซ์ลงในหลอดพอลิพรอพิลิน จากนั้นเติมฟอสเฟตบัฟเฟอร์พีเอช 6.0 ปริมาณ 2 มิลลิลิตรลงในหลอดพอลิพรอพิลิน กวนด้วยความเร็ว 50 รอบต่อนาที เก็บสารละลายตัวอย่างที่เวลาต่างๆ และวิเคราะห์หาปริมาณนิโคตินโดยวิธี HPLC

2.4.4 การยึดติดทางชีวภาพของยาเม็ดเมทริกซ์

ใช้เยื่อเมือกหลอดอาหารหมูในการทดสอบ ล้างหลอดอาหารหมูให้สะอาดด้วยฟอสเฟตบัฟเฟอร์ไอโซโทนิกพีเอช 7.4 ตัดหลอดอาหารหมูขนาด 2 x 2 เซนติเมตร แช่ในฟอสเฟตบัฟเฟอร์ไอโซโทนิก พีเอช 7.4 ควบคุมอุณหภูมิที่ 37 องศาเซลเซียส เป็นเวลา 20 นาที แยกส่วนที่เป็นกล้ามเนื้อออกก่อนการทดสอบ ทำการทดสอบด้วยเครื่อง Texture Analyzer (TA.XT plus, Stable Micro System, UK) load cell ขนาด 50 นิวตัน ยาเม็ดเมทริกซ์ที่ทดสอบยึดติดกับ probe โดยใช้กระดาษกาวสองหน้า ยึดเยื่อเมือกติดกับแท่นทดสอบให้แน่น เติมฟอสเฟตบัฟเฟอร์พีเอช 6.0 ปริมาณ 200 ไมโครลิตร ลงบนเยื่อเมือก ควบคุมให้ยาเม็ดเมทริกซ์สัมผัสผิวเยื่อเมือกด้วยแรงกด 0.50 นิวตัน ระยะเวลา 2 นาที เมื่อเริ่มทดสอบให้ probe เคลื่อนที่ขึ้นด้วยอัตราเร็ว 0.50 มิลลิเมตรต่อวินาที หาความสัมพันธ์ระหว่างแรงที่ใช้กับระยะทาง และคำนวณค่า maximum detachment force

2.4.5 สภาวะของ HPLC เพื่อการวิเคราะห์นิโคติน

ชนิดของคอลัมน์ คือ reversed phase C18 วัฏภาคเคลื่อนที่ (mobile phase) ประกอบด้วย 0.05 โมลต่อลิตรของโซเดียมอะซีเทต เมทานอล และไตรเอทิลเอมีน ในอัตราส่วน 88 ต่อ 12 และ 0.5 ตามลำดับ ปรับ พีเอช

ให้ได้ 4.2 ด้วยกรดอะซิติกเข้มข้น อัตราการไหลของวัฏภาคเคลื่อนที่เท่ากับ 1 มิลลิลิตรต่อนาที วัดปริมาณสารตัวอย่างด้วย UV detector ที่ความยาวคลื่น 259 นาโนเมตร

2.4.6 การศึกษากลไกการปลดปล่อยยา

โมเดลทางคณิตศาสตร์ที่ใช้ศึกษารูปแบบการปลดปล่อยยาของยาเม็ดเมทริกซ์ ประกอบด้วย

(1) Zero order kinetics (Costa and Lobo, 2001)

$$Q = K_0 t \quad \text{..... (1)}$$

เมื่อ Q คือ ปริมาณยา ณ เวลา t และ K_0 คือ อัตราการปลดปล่อยอันดับศูนย์ (zero order release rate)

(2) Korsmeyer-Peppas model (Power law) (Siepmann and Siepmann, 2008)

$$\log \frac{M_t}{M_\infty} = n \log t + \log K \quad \text{..... (2)}$$

เมื่อ M_t คือ ปริมาณยาที่ปลดปล่อยออกมาที่เวลาใดๆ (t) M_∞ คือ ปริมาณยาที่ปลดปล่อยออกมาที่เวลาอนันต์ (∞) K คือ ค่าคงที่ และ n คือ release exponent ที่บอกกลไกการปลดปล่อยยา เมื่อค่า n เท่ากับ 0.5 แสดงว่ากลไกการปลดปล่อยยาเกิดจากการแพร่ (Fickian diffusion) หากค่า n อยู่ระหว่าง 0.5 และ 1 การปลดปล่อยยาเป็นผลจากจากการแพร่ของยา ร่วมกับการพองตัวของพอลิเมอร์ และเมื่อ n มีค่ามากกว่า 1 แสดงว่า การปลดปล่อยยาควบคุมโดยการพองตัวและการกร่อนของพอลิเมอร์

2.4.7 สถิติที่ใช้ในการวิเคราะห์ข้อมูล

การเปรียบเทียบความแตกต่างของข้อมูล วิเคราะห์โดยใช้ One-way analysis of variance (ANOVA) และใช้ Least significant difference (LSD) test ในการเปรียบเทียบความแตกต่างของข้อมูล 2 กลุ่ม โดยใช้โปรแกรม SPSS for MS windows, release 11.5 (SPSS (Thailand) Co. Ltd., Bangkok, Thailand)

3. ผลการวิเคราะห์ / ผลการวิจัยและอภิปรายผล

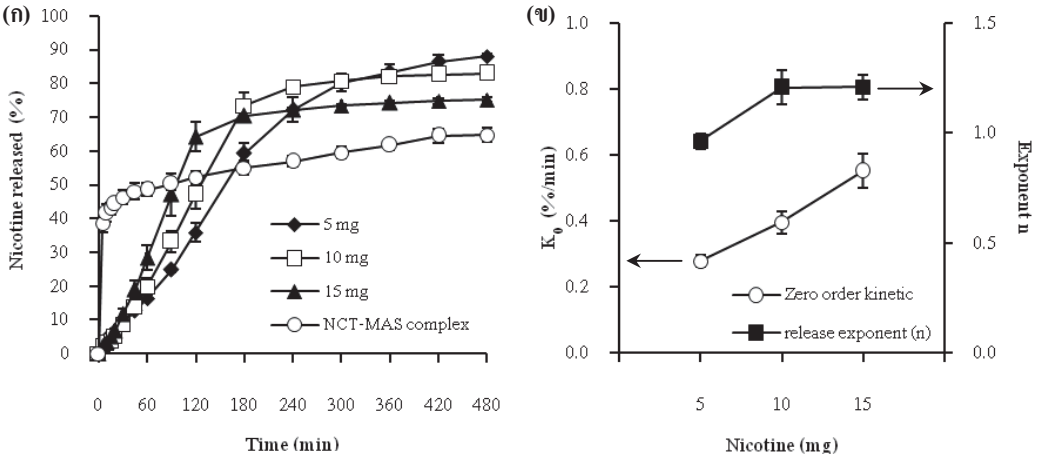
3.1 ความหนาและความแข็งของยาเม็ดเมทริกซ์

ยาเม็ดเมทริกซ์มีความแข็งใกล้เคียงกันทุกตำรับอยู่ในช่วง 100-103 นิวตัน และน้อยกว่าความแข็งของยาเม็ดที่เตรียมจากไฮดรอกซีโพรพิลเมทิลเซลลูโลสเพียงอย่างเดียวที่มีความแข็งเท่ากับ 118 นิวตัน ความหนาของยาเม็ดเมทริกซ์อยู่ระหว่าง 1.82-2.17 มิลลิเมตร ใกล้เคียงกับความหนาของยาเม็ดที่เตรียมจากไฮดรอกซีโพรพิลเมทิลเซลลูโลสเพียงอย่างเดียว ความหนาของยาเม็ดเมทริกซ์ลดลง เมื่อปริมาณของสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเกตในตำรับเพิ่มขึ้น

3.2 การปลดปล่อยนิโคตินจากยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลส

การปลดปล่อยนิโคตินจากสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเกต ที่เตรียมที่พีเอช 9 ในตัวกลางการละลายฟอสเฟตบัฟเฟอร์พีเอช 6.0 (ภาพที่ 1 ก) ในช่วงแรกเกิดการปลดปล่อยยาอย่างรวดเร็วจากกระบวนการแลกเปลี่ยนไอออนบวกระหว่างนิโคตินที่ถูกดูดซับบริเวณผิว และโซเดียมไอออนที่เป็นส่วนประกอบในตัวกลางการละลาย จากนั้นอัตราการปลดปล่อยช้าลง เนื่องจากการแลกเปลี่ยนไอออนเกิดกับนิโคตินที่ถูกดูดซับภายในชั้นของแมกนีเซียมอะลูมินัมซิลิเกต (Pongjanyakul et al., 2009) ยาเม็ดเมทริกซ์สามารถลดการปลดปล่อยนิโคตินในช่วงต้นได้เนื่องจากการพองตัวเป็นชั้นเจลของไฮดรอกซีโพรพิลเมทิลเซลลูโลส เมื่อพิจารณาค่า release exponent (n) จากสมการ Power law (สมการที่ 2) พบว่า ยาเม็ดเมทริกซ์ทุกตำรับ มีค่า n ใกล้เคียง 1 (ภาพที่ 1 ข) แสดงว่า การปลดปล่อยยาจากยาเม็ดเมทริกซ์ควบคุมโดยกลไกการพองตัวและการกร่อนของยาเม็ด ดังนั้นในการคำนวณหาอัตราเร็วในการปลดปล่อยนิโคตินได้ใช้สมการ Zero order (สมการที่ 1) พบว่า ยาเม็ดเมทริกซ์ที่มีปริมาณนิโคตินเพิ่มขึ้น อัตราการปลดปล่อยนิโคตินสูงขึ้นอย่างมีนัยสำคัญ ($p<0.05$) (ภาพที่ 1 ข) เป็นผลจากยาเม็ดเมทริกซ์มีเกรเดียนต์ความเข้มข้น

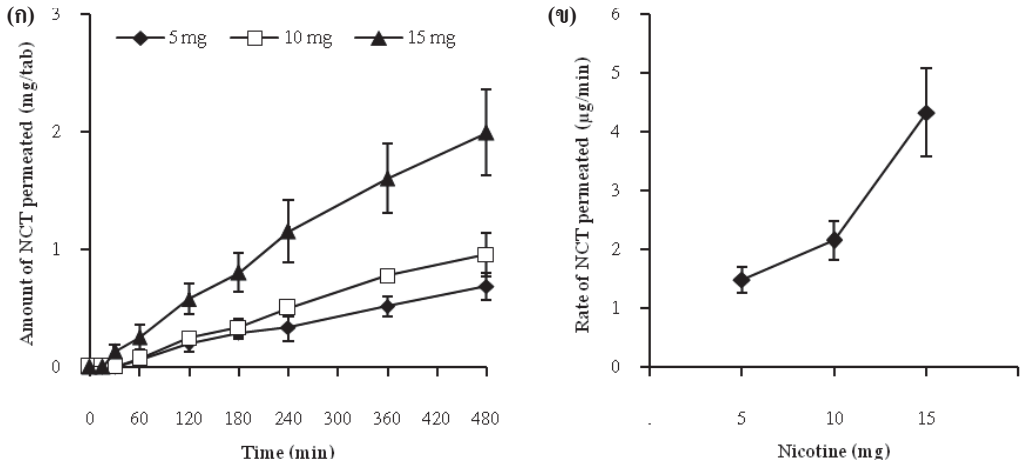
ของตัวยาสูงขึ้น และเนื่องจากตำรับที่มีนิโคตินปริมาณมาก ต้องใช้สารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคตมาก ทำให้ปริมาณไฮดรอกซีโพรพิลเมทิลเซลลูโลสลดลง มีผลต่อการก่อตัวเป็นชั้นเจล จากคุณสมบัติของยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลส เมื่อยาเม็ดสัมผัสตัวกลางการละลาย พอลิเมอร์ดูดน้ำเข้าสู่ภายในยาเม็ด เกิดการพองตัวและก่อตัวเป็นชั้นเจลบริเวณรอบ ยาเม็ด ทำหน้าที่เป็นสิ่งกั้นการซึมผ่านของยาออกสู่ตัวกลางการละลาย (Sung et al., 1996) ตำรับที่มีพอลิเมอร์ปริมาณมาก ก่อให้เกิดชั้นเจลหนาและมีความหนืดมาก มีผลต้านการแพร่ของยาและอัตราการปลดปล่อยยาลดลง (Cao et al., 2005; Narendra et al., 2005; Velasco et al., 1999)



ภาพที่ 1 รูปแบบการปลดปล่อยนิโคติน **(ก)** และค่า release exponent และอัตราการปลดปล่อยนิโคติน **(ข)** ของยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลสที่มีปริมาณนิโคติน 5 10 และ 15 มิลลิกรัมต่อเม็ด ในฟอสเฟตบัฟเฟอร์พีเอช 6.0 แต่ละค่าแสดงในรูปของค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน ค่าละ 3 ตัวอย่าง

3.3 การซึมผ่านเยื่อเมือกของนิโคตินจากยาเม็ดเมทริกซ์

การซึมผ่านเยื่อเมือกของนิโคตินจากยาเม็ดเมทริกซ์แสดงดังภาพที่ 2 ก เมื่อปริมาณนิโคตินในตำรับสูงขึ้น การซึมผ่านของนิโคตินเพิ่มขึ้น อัตราการซึมผ่านเยื่อเมือกของยาเม็ดเมทริกซ์ตำรับที่มีปริมาณนิโคติน 15 มิลลิกรัมต่อเม็ด เพิ่มขึ้นอย่างมีนัยสำคัญ ($p<0.05$) และมีค่ามากที่สุดเท่ากับ 4.33 ± 0.75 µg/min (ภาพที่ 2 ข)



ภาพที่ 2 รูปแบบการซึมผ่านเยื่อเมือก **(ก)** และอัตราการซึมผ่านเยื่อเมือก **(ข)** ของนิโคตินจากยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลสบรรจุสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัมซิลิเคต ที่มีนิโคติน 5 10 และ 15 มิลลิกรัมต่อเม็ด แต่ละค่าแสดงในรูปของค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน ค่าละ 3 ตัวอย่าง

3.4 การยึดติดทางชีวภาพของยาเม็ดเมทริกซ์

ยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลสที่มีปริมาณนิโคติน 5 10 และ 15 มิลลิกรัมต่อเม็ด มีค่า maximun detachment force เท่ากับ 990.0 ± 425.4 505.5 ± 145.0 และ 486.7 ± 122.3 มิลลินิวตัน แสดงให้เห็นว่า ยาเม็ดเมทริกซ์ที่เตรียมขึ้น มีคุณสมบัติการยึดติดทางชีวภาพต่อเมมเบรนเยื่อเมือก

4. บทสรุป / สรุปผลการวิจัย

ยาเม็ดเมทริกซ์ไฮดรอกซีโพรพิลเมทิลเซลลูโลสบรรจุสารประกอบเชิงซ้อนนิโคติน-แมกนีเซียมอะลูมินัม ซิลิเคตที่เป็นแหล่งกักเก็บยา สามารถควบคุมการปลดปล่อยยานิโคติน และนิโคตินสามารถซึมผ่านเยื่อเมือกจำลองได้ โดยขึ้นอยู่กับปริมาณนิโคตินที่บรรจุในยาเม็ด นอกจากนี้ยาเม็ดเมทริกซ์ยังคงให้คุณสมบัติการยึดติดเยื่อเมือก ดังนั้น ยาเม็ดเมทริกซ์นี้สามารถนำมาประยุกต์ใช้เป็นระบบนำส่งนิโคตินทางเยื่อเมือกกระพุ้งแก้มได้ และมีความเป็นไปได้ในการพัฒนาในระดับอุตสาหกรรมต่อไป

5. กิตติกรรมประกาศ

คณะผู้วิจัยขอขอบคุณบัณฑิตวิทยาลัย มหาวิทยาลัยขอนแก่น ในการสนับสนุนทุนวิจัยสำหรับคณาจารย์บัณฑิตศึกษา เพื่อให้สามารถรับนักศึกษาที่มีความสามารถและศักยภาพสูง เข้าศึกษาในหลักสูตรและทำวิจัยในสาขาที่อาจารย์มีความเชี่ยวชาญ ประจำปีการศึกษา 2552 และขอขอบคุณสำนักงานกองทุนสนับสนุนการวิจัย ที่สนับสนุนทุนพัฒนานักวิจัย ประจำปี 2552 (RSA 5280013)

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บทคัดย่อ
การเสนอผลงานแบบโปสเตอร์

การประชุมนักวิจัยรุ่นใหม่ พบ เมธีวิจัยอาวุโส สกว. ครั้งที่ 11

วันที่ 19-21 ตุลาคม 2554
โรงแรมฮอลิเดย์อินน์ รีสอร์ท รีเจนท์ บีช ชะอำ
จังหวัดเพชรบุรี

สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) สำนักงานคณะกรรมการการอุดมศึกษา (สกอ.)

Application of Nicotine-Magnesium Aluminum Silicate Complexes as Drug Carriers in Alginate Matrix Buccal Tablets: Effect of Complex/Alginate Ratio

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Abstract

Nicotine (NCT) buccal tablets consisting of sodium alginate (SA) and nicotine-magnesium aluminum silicate (NCT-MAS) complexes prepared at pH 9 acting as drug carriers were produced using the direct compression method. The effect of the complex/SA ratios on NCT release, permeation across mucosa and mucoadhesive properties of the tablets was examined. The NCT-MAS complex-loaded SA tablets had good physical properties. The complex-loaded SA tablets tested using the whole tablets showed zero-order release kinetics of NCT, which indicate a swelling/erosion controlled release mechanism. Measurement of unidirectional NCT release and permeation across porcine esophageal mucosa using a modified USP dissolution apparatus 2 showed that the higher the SA content in the tablets, the lower the NCT release and permeation rates were found. The complex-loaded SA tablets provided similar NCT release and permeation rates at the same complex/SA ratio, suggesting that the delivery of NCT across the mucosal membrane was mainly controlled by the swollen matrix tablets. Additionally, the tablets possessed a bioadhesive property for adhesion to the mucosal membrane. These findings suggest that the SA matrix tablets loaded with the pH 9 NCT-MAS complexes as drug carriers present strong potential for use as a buccal delivery system for NCT.

Keywords: nicotine, magnesium aluminum silicate, sodium alginate, buccal tablets, release and permeation

Outputs

1. Rojtanatanya S, Pongjanyakul T. *Propranolol-magnesium aluminum silicate complex dispersions and particles: Characterization and factors influencing drug release*. International Journal of Pharmaceutics **2010**; 383: 106-115.
2. Pongjanyakul T, Rongthong T. *Enhanced entrapment efficiency and modulated drug release of alginate beads loaded with drug-clay intercalated complexes as microreservoirs*. Carbohydrate Polymers **2010**; 81: 409-419.
3. Kanjanabat S, Pongjanyakul T. *Preparation and characterization of nicotine-magnesium aluminum silicate complex-loaded sodium alginate matrix tablets for buccal delivery*. AAPS PharmSciTech **2011** (DOI: 10.1208/s12249-011-9633-y).

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APPLICATION OF NICOTINE–MAGNESIUM ALUMINUM SILICATE COMPLEXES AS DRUG CARRIERS IN ALGINATE MATRIX BUCCAL TABLETS: EFFECT OF COMPLEX/ALGINATE RATIO

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INTRODUCTION

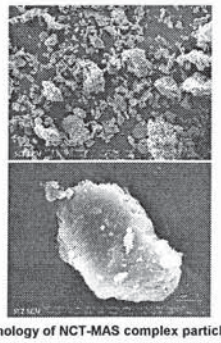
Nicotine (NCT), obtained from tobacco plants, is a volatile and strongly alkaline liquid. It has been widely used in smoking cessation therapy. NCT is absorbed through skin and mucosal membrane, such as buccal and nasal membranes[1]. Due to a poor stability of NCT, adsorbing materials were used for reduction of evaporation and oxidative degradation of NCT. Magnesium aluminum silicate (MAS), a mixture of montmorillonite and saponite clays, could interact with NCT to form an intercalated complexes. The complex particles were shown to sustain NCT release in distilled water and pH 6 phosphate buffer[2]. Sodium alginate (SA), a naturally occurring non-toxic polysaccharide found in marine brown algae, has been used as a bioadhesive material and drug release modifier for intraoral drug delivery dosage forms[3]. Thus, the aim of this study was to prepare and investigate SA tablets loaded with NCT-MAS complex particles as microreservoirs for buccal delivery of NCT. The effect of complex/SA ratios in the tablets on NCT release and permeation and mucoadhesive properties was examined.

EXPERIMENTAL

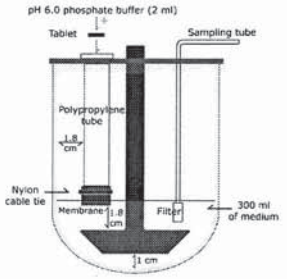
The NCT-MAS complexes were prepared using an adsorption process at pH 9[2]. The mixtures of the dried complex particles and SA powder were compressed using a hydrostatic press at 23 MPa pressure. The NCT release from the whole tablets was studied using a USP dissolution apparatus 1 (basket method). A modified USP dissolution apparatus 2 was employed for characterizing unidirectional release and permeation of NCT that cellulose acetate membrane and porcine esophageal membrane[4,5] were used as model membranes, respectively. The NCT concentration was analyzed using HPLC. The mucoadhesive properties of the tablets on porcine esophageal mucosa were determined using a texture analyzer.

Component of NCT-MAS complex-loaded SA tablets using different complex/SA ratios.

Component (mg)	Complex-SA ratio			
	1 : 4	1 : 1.5	1 : 0.67	1 : 0
NCT-MAS complexes	40.0	80.0	120.0	200.0
SA	160.0	120.0	80.0	0.0
Magnesium stearate	2.0	2.0	2.0	2.0
Amount of NCT (mg/tablet)	5 mg	10 mg	15 mg	26.3 mg

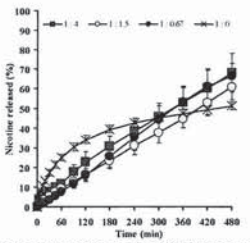


Morphology of NCT-MAS complex particles.



A modified USP dissolution apparatus 2 for characterizing unidirectional NCT release and permeation of the tablets.

RESULTS



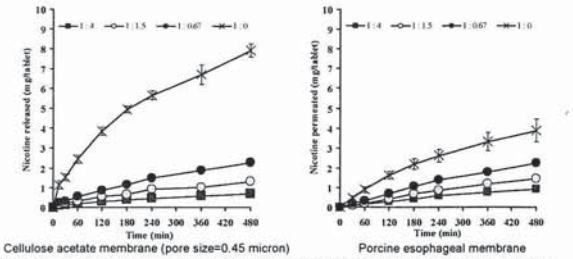
NCT release profiles of the NCT-MAS complex-loaded SA tablets.

Physical properties and NCT release parameters of the whole tablets.

Complex-SA ratio	Thickness (mm)	Hardness (N)	NCT release (Whole tablet)	
			Release exponent, n	Release rate (% min^{-1})
1 : 4	1.71 ± 0.02	48.8 ± 3.2	0.77 ± 0.03 (R^2=0.992)	0.14 ± 0.02 (R^2=0.996)
1 : 1.5	1.69 ± 0.02	39.2 ± 0.1	0.85 ± 0.04 (R^2=0.992)	0.12 ± 0.01 (R^2=0.999)
1 : 0.67	1.61 ± 0.01	60.8 ± 2.7	0.98 ± 0.07 (R^2=0.992)	0.15 ± 0.03 (R^2=0.997)
1 : 0	1.42 ± 0.01	68.6 ± 0.1	0.46 ± 0.01 (R^2=0.972)	3.20 ± 0.08 * (R^2=0.988)

Data are mean ± S.D., n=3

* calculated from Higuchi model and the unit is % min$^{-1/2}$.



Cellulose acetate membrane (pore size=0.45 micron) Porcine esophageal membrane

Unidirectional release (a) and permeation (b) of NCT from the NCT-MAS complex-loaded SA tablets.

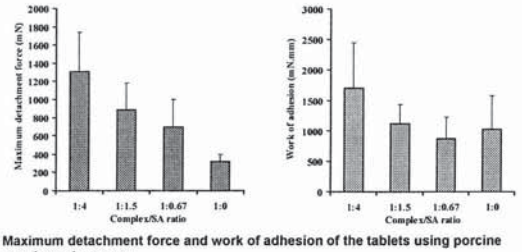
Unidirectional NCT release and permeation parameters of the tablets.

Complex-SA ratio	Release exponent, n	NCT release rate[a]		NCT permeation rate[b]	
		K_0 (μg min^{-1})	K_H (μg min$^{-1/2}$)	K_0 (μg min^{-1})	K_H (μg min$^{-1/2}$)
1 : 4	0.58 ± 0.04 (R^2=0.989)	1.30 ± 0.07 (R^2=0.992)	32.7 ± 1.7 (R^2=0.989)	1.90 ± 0.24 (R^2=0.982)	52.5 ± 6.6 (R^2=0.989)
1 : 1.5	0.63 ± 0.05 (R^2=0.991)	2.49 ± 0.23 (R^2=0.966)	62.3 ± 5.5 (R^2=0.981)	3.11 ± 0.23 (R^2=0.986)	85.7 ± 5.8 (R^2=0.990)
1 : 0.67	0.66 ± 0.04 (R^2=0.993)	4.51 ± 0.23 (R^2=0.979)	109.8 ± 5.2 (R^2=0.986)	4.88 ± 0.30 (R^2=0.980)	131.6 ± 7.4 (R^2=0.993)
1 : 0	0.58 ± 0.03 (R^2=0.991)	15.27 ± 0.66 (R^2=0.937)	382.3 ± 15.8 (R^2=0.995)	7.90 ± 1.30 (R^2=0.955)	208.9 ± 32.6 (R^2=0.996)

Data are mean ± S.D., n=3

[a] NCT release using cellulose acetate membrane.

[b] NCT permeation using porcine esophageal membrane.



Maximum detachment force and work of adhesion of the tablets using porcine esophageal mucosa.

CONCLUSION

The NCT-MAS complex-loaded SA tablets could be prepared using the direct compression method. The NCT release from the tablets were controlled by drug diffusion and swelling of SA tablets. The NCT release and permeation rate increased with increasing amount of NCT-MAS complexes in the tablets. The tablets gave mucoadhesive properties on porcine esophageal mucosa. This study suggests that the NCT-MAS complex-loaded SA tablets show strong potential for use as a buccal delivery system for NCT.

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