CHAPTER III

RESULTS AND DISCUSSION

1. Evaluation of Propranolol HCl Core Tablets

The physical appearance of the propranolol HCl core tablets was white with rather smooth surface. It was dependent mainly on the natural of the raw material and their color.

Sodium chloride was used as an osmotic agent within tablet. NaCl particles had an obvious clear cubic crystal habit. The tablets were also smooth and its surface appeared as layer structure of NaCl. The physical properties of propranolol HCl core tablets containing different amount of sodium chloride are presented in Table 4. The average weight, friability, diameter, thickness, disintegration time of all core tablet formulations were within the limit of standard official USP XXVI.

When sodium chloride was used as an osmotic agent in tablet, the tablet diameter, thickness and disintegration time tended to decrease with increasing amount of NaCl especially the tablet hardness, although the value of the maximal deformation hardness of NaCl was more than lactose (Leuenberger, H. 1982). The final hardness of tablets was often considered to be the result of the bonding between particles, which was the building blocks of tablets (Veen, B.V. et al., 2002). Strength reduction could be considered as the result of reduction in interparticle bonding. The decreased hardness of tablets compressed from the addition of NaCl indicated that the adhesive forces between NaCl particles were smaller than that of lactose. Additionally, the high yield pressure of NaCl illustrated its difficult densification. A similar effect was found by Veen et al (2000) for a blend of NaCl and pregelatinised starch. This was also the reason for the increasing of % friability when increasing the amount of NaCl.

The values of bulk density and tapped density of NaCl were more than lactose (Arthur, 2000). Hence, the volume of NaCl under pressure was less than lactose. It was a reason that increasing the amount of NaCl tended to decrease the thickness and

diameter of tablet. The decrease of disintegration time when increasing the amount of NaCl was caused from its solubility. The solubility of NaCl in water (1 in 2.8 at 25°C) was higher than lactose (1 in 4.63 at 25°C) at the same temperature (Arthur, 2000).

Table 4 The physical properties of propranolol HCl core tablets containing different amount of sodium chloride

Properties	Mean (SD)				
	Core 1	Core 2	Core 3	Core 4	Core 5
1.Weight (mg)	301.97(4.08)	296.81(8.43)	303.85(6.32)	302.03(5.49)	302.33(4.04)
2.Friability (%)	0.33	0.47	0.46	0.45	0.86
3.Diameter (mm)	9.53(0.02)	9.54(0.01)	9.53(0.02)	9.52(0.02)	9.51(0.02)
4.Thickness (mm)	3.97(0.09)	3.54(0.05)	3.53(0.07)	3.34(0.07)	3.17(0.07)
5.Hardness (kp)	11.41(0.94)	9.13(0.75)	8.36(0.10)	6.33(0.35)	3.56(0.57)
6.Disintegration time (min)	9.70(0.47)	8.53(0.67)	8.29(0.19)	7.70(0.38)	8.1(0.39)
7.Uniformity of Dosage units (%)	102.52(2.63)	100.07(1.06)	100.65(0.96)	101.02(5.33)	96.36(1.42)
8. Label Content (%)	102.44(0.26)	96.65(1.44)	97.57(2.94)	96.12(3.10)	98.31(3.14)

The uniformity of dosage units and the percent of labeled content of every formulation were within the range of 90-110%, which followed the USP standard.

2. Evaluation of Osmotic pump Tablets

The coated tablets exhibited smooth and uniform colored film. Color migration did not occurred on surface of coated tablets. This came from the partial ionic bond between chitosan and dye (Phaechamud et al., 2000).

Moist heat treatment at 60°C enhanced color intensity of tablets coated with chitosan acetate film. The increase in time of moist heat treatment, the increase in the color intensity visually observed. The coloration of coated tablets was intensified might be the result of the Maillard reaction between NH_2 and OH groups. Srinivasa et al (2004) found a similar effect for drying chitosan cast film by conventional oven and radiative infrared.

2.1 Average Weight and Weight Variation

The weight variation of coated tablet is presented in Figure 7 and Table 5. Weight variation values of coated tablets were all within the limit of USP standard (% CV < 7.5).

After exposure to accelerated condition, the weight of coated tablet in which core tablets containing NaCl of more than 33.33%w/w (Core 3, 4, 5) was increased, probably due to water absorption of NaCl, a high solubility material (1 in 2.8 at 25°C), thus subsequently led to weight raise. The coated tablets with a less amount of NaCl, less than 16.67%w/w, (Core 1 and 2) tended to decrease in weight after exposure to accelerated condition. This was due to the decrease of highly soluble material and the increase of less soluble one. The more amount of lactose, the adsorption of water was unaffected. Moreover, the moisture content of coated tablets might be decreased due to higher temperature during exposure to accelerated condition.

Table 5 The physical properties of propranolol HCl tablets (Core 1-5) coated with different chitosan film (A, B, C) freshly prepared and after exposure to accelerate condition for 1 to 24 hours.

Formulation	Mean (SD)				
	Weight (mg)	Hardness (kp)	Diameter (mm)	Thickness (mm)	Disintegration time (min)
A1	361.77(8.26)	> 20	9.89(0.02)	4.36(0.06)	> 30
B1	371.49(4.50)	> 20	9.91(0.02)	4.41(0.05)	> 30
C1	352.55(8.59)	> 20	9.89(0.01)	4.33(0.09)	> 30
A1:24	359.20(8.50)	> 20	9.88(0.01)	4.38(0.01)	> 30
B1:24	363.62(4.38)	> 20	9.81(0.03)	4.32(0.08)	> 30
C1:24	353.10(8.60)	> 20	9.87(0.01)	4.35(0.06)	> 30
B1:1	362.18(9.08)	> 20	9.89(0.02)	4.30(0.03)	> 30
B1:3	364.16(7.42)	> 20	9.89(0.02)	4.28(0.05)	> 30
B1:4	366.26(5.64)	> 20	9.89(0.03)	4.30(0.09)	> 30
B1:5	362.85(9.45)	> 20	9.86(0.03)	4.30(0.07)	> 30
B1:6	366.66(6.63)	> 20	9.84(0.03)	4.26(0.08)	> 30
B1:12	364.91(7.14)	> 20	9.82(0.02)	4.30(0.12)	> 30
B1:24	363.62(4.38)	> 20	9.81(0.03)	4.32(0.08)	> 30
B2	374.01(11.94)	13.86(0.95)	10.04(0.01)	4.29(0.09)	> 30
B3	376.48(6.75)	14.95(1.16)	10.02(0.02)	4.19(0.06)	> 30
B4	371.99(5.06)	14.53(0.84)	9.98(0.02)	4.00(0.09)	> 30
B5	368.72(4.39)	15.53(0.80)	9.94(0.02)	3.81(0.10)	> 30
B1:5	362.85(9.45)	> 20	9.86(0.03)	4.30(0.07)	> 30
B2:5	372.57(8.73)	11.27(0.69)	9.98(0.02)	4.46(0.10)	> 30
B3:5	383.68(7.74)	10.91(0.59)	9.99(0.02)	4.38(0.09)	> 30
B4:5	376.41(6.47)	11.24(0.58)	9.95(0.01)	4.08(0.08)	> 30
B5:5	369.39(6.24)	11.22(0.68)	9.97(0.02)	3.919(0.05)	> 30

B1:24 mean that coated tablets used chitosan *B* as film former for coated core tablet *1* and after exposure to accelerate condition for *24* hours.

2.2 Friability

Most coated tablets were not friable. Their weight was slightly changed during friability test (< 0.01 %). The friability was also negligible in case of coated tablets after exposure to accelerated condition. The minute friability of coated tablets was due to the ability of film to protect the core from abrasion during friability test.

2.3 Diameter and Thickness

The diameter and thickness are presented in Table 5. The diameter and thickness of most coated tablets changed according to their core tablet. NaCl had tapped density value more than lactose (Arthur, 2000), thereby the volume of NaCl under pressure was less than that of lactose. When the amount of NaCl in coated tablets was increased thus decreased that of lactose, the decreased of thickness was obtained.

2.4 Hardness

Tablet hardness is presented in Figure 8 and Table 5. The hardness of coated tablets was notably higher than that of core tablets. Due to higher strength and toughness of chitosan acetate film, mean and standard deviation of the tablet hardness of some formulations could not obtained because some values exceeded 20 kp, that was the maximum limit of the apparatus. NaCl particles had adhesive force lower than lactose. Incorporation of NaCl and decrease amount of lactose affected the hardness of core and coated tablets. Addition of NaCl, the lower hardness was obtained. However, the amount of NaCl was less influenced in coated tablets due to the higher ability of film to influence on hardness. The exposure to the accelerated condition would reduce the hardness of coated tablet with NaCl. When tablets were exposed to atmospheres with high relative humidity, multimolecular adsorption of water could occur followed by condensation of water in the pore of the tablets. It has been suggested by Ahleck and Alderborn (1989) that the presence of condensed water in the pores of a tablet will reduce the bonding forces, between particles in the tablet and thus decrease the tablet strength. A less pronounced effect was obtained from saccharose. An increase in %RH during storage resulted in an increase in tensile

strength up to a certain level. This was probably a result of a rearrangement of molecules at the particle surfaces by the action of adsorbed water leading to a formation of solid bridges. Whereas no such effect was obtained for calcium hydrogen phosphate.

2.5 Disintegration Time

The disintegration time of coated tablets in deionized water is shown in Table 5. The coated tablets exhibited apparently higher disintegration time than core tablets. Because of the gel forming property of chitosan film, the greater amount of film would provide the thicker gel layer around core tablet before its dissolution and this was resulted in longer disintegration time in deionized water. The chitosan-coated films were changed to insoluble form after heat treatment thus the disintegration time of treated film coated tablets was mostly prolonged.

2.6 Labeled Content

From the determination of percentages of drug content, it revealed that propranolol HCl content in coated tablets was in the range of 90-110% as shown in Table 6. All of them were also conformed to the monograph in USP 26.

2.7 Drug Release Study

Owing to acid soluble property of chitosan film, incorporation of magnesium stearate could prolong drug release. The electrostatic charge interactions between protonated amino groups on chitosan and stearate molecules from magnesium stearate resulted in retardation of dissolution of film coat that contained magnesium stearate.

Typical calibration curve for propranolol HCl data as determined by using linear regression is shown in Table 1A to 7A and Figures 1A to 7A (Appendix A) The dissolution data and profiles were demonstrated in five categories: firstly, showing the effect of molecular weight of chitosan; secondly, showing the effect of moist heat treatment; thirdly, showing the effect of passageway; fourthly, showing the effect of osmolality of dissolution medium and finally, showing the effect of osmotic agent.

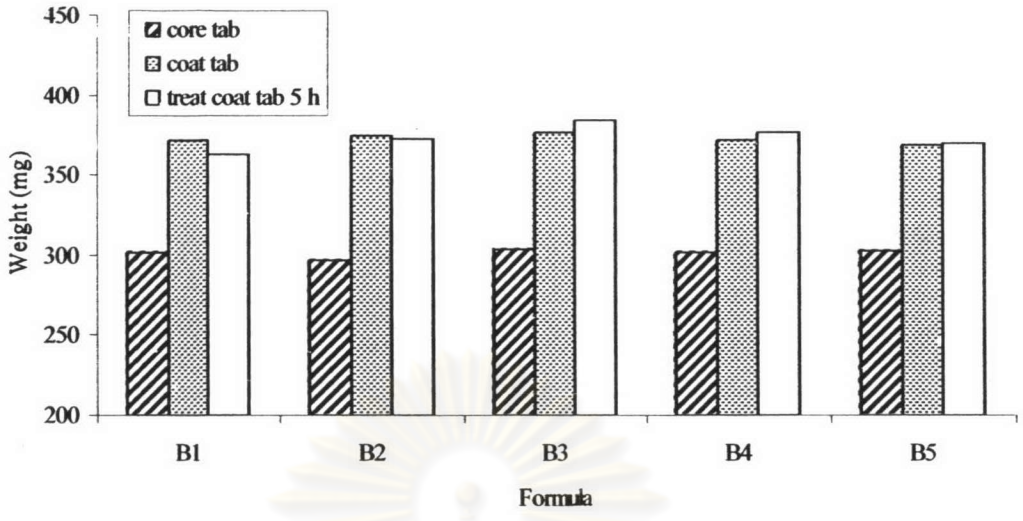


Figure 7 Weight of core tablet with different amount of NaCl and tablet coated with chitosan B freshly prepared and after exposure to accelerate condition for 5 hours.

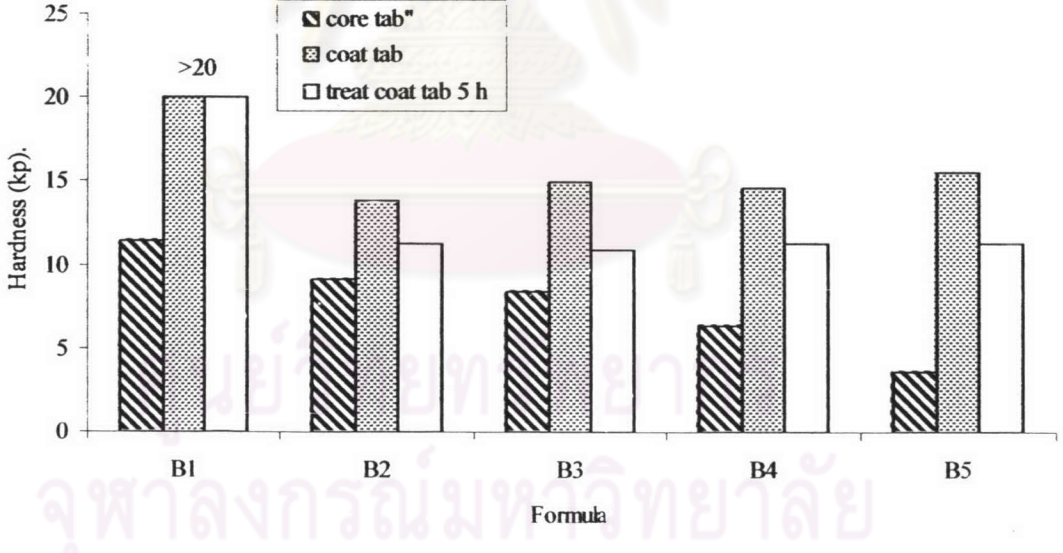


Figure 8 Hardness of core tablet with different amount of NaCl and tablet coated with chitosan B freshly prepared and after exposure to accelerate condition for 5 hours.

Table 6 The average of percent label amount of propranolol HCl coated tablets with core tablets containing different amount of sodium chloride (Core 1-5) coated with chitosan film (B)

Formula	%Label amount	SD	%CV
B1	95.30	0.55	0.58
B2	96.62	1.67	1.72
B3	97.23	1.88	1.93
B4	94.49	2.91	3.08
B5	94.58	0.50	0.53

2.7.1 The Effect of Molecular Weight of Chitosan

Propranolol HCl film coated tablets were prepared from three grades of chitosan and other additives (magnesium stearate, castor oil and brilliant blue). Three grades of chitosan which used in this study are shown in Table 3. The formulation A, B and C were the coated tablet formulation, which used chitosan A, B and C as a polymer.

The drug release profiles of propranolol HCl from A, B, C and core tablet are depicted in Figure 9. Drug liberation from all coated tablets was slower than that from core tablet. Core tablet exhibited the highest drug release at each time interval. Formulation A and C had similar pattern of dissolution profile and amount of drug released. For formulation B, the percentage of drug dissolved was lower than those of A and C. Generally, the permeability of membranes prepared from high molecular weight chitosan was lower than that from those of low molecular weight. The permeability increased with the increasing swelling index of the membranes. Swelling index was proportional to the amorphous region. Crystallinity increased with the increasing molecular weight of chitosan (Huei and Hwa, 1996). However, this lower

drug release from B could be caused by the lower molecular weight of the polymer. Tsaih and Chen (1997) attributed that larger molecular weight chitosan should have a larger degree of polymerization, therefore the molecular entangle easier than smaller molecular weight ones; in turn larger molecular weight chitosans should have more intra-molecular hydrogen bonding and/ or more even charge distribution. As the molecular weight decreased, more amino groups might become available for ionic interaction with the oppositely charged ions (Rege et al., 1999). Additionally, the chain flexibility of higher molecular weight chitosan were higher than those of lower molecular weight ones. Thus, the stiffness of small molecular weight chitosan was more than that of higher molecular weight ones (Tsaih and Chen, 1997). More stiffness and ionic interaction between chitosan with acetic acid and magnesium stearate with chitosan acetate could cause the most sustained release of formulation B. Therefore, the lower molecular weight chitosan (chitosan B) was selected to apply as coating material for the further study.

The release profile of these coated tablets after exposure to accelerated condition at 60°C 75%RH for 24 h is presented in Figure 10. The more apparent retardation of drug release after exposure to accelerated condition was greater than that of freshly prepared. Meanwhile, tablets coated with film formulation B after exposure to accelerated condition exhibited the slower drug release than the others. RDT values of dissolution profiles were tested with ANOVA revealed that tablets coated with film formulation A were not-significantly different ($P > 0.05$) from those of C, whereas tablets coated with film formuiation B were significantly different from those of A and C both freshly prepared and after moist heat treatment for 24 h.

2.7.2 The Effect of Moist Heat Treatment on Drug Release

Heat treatment could prolong drug release. It enhanced to a greater extent the water resistance of chitosan film (Lim and Wan, 1995). The effect of moist heat treatment was more dominant as presented in Figure 11. Moist heat at 75% RH 60°C could promote sustainable release. The capability to sustain drug release also depended on the treatment period. The longer period of treatment, the more prolonged drug release was obtained. The long lag time was more prominent in release profile of coated tablets especially at high treatment period. The drug release from coated

tablets after exposure to accelerated condition for 1 h was conformed to the monograph in USP 26 that not more than 30% of drug dissolved in 90 minutes. In addition, after exposure to accelerated condition for more than 4 h, the release pattern of these treated coated tablets were close to linear. Therefore, the treatment period for 5 h was chosen to apply for the later study.

Longer or higher temperature and %RH of moist heat treatment could greater prolong drug release due to the water-soluble solid comprised of ionic complex between chitosan and acetic acid was converted into chitin. The thermally-induced conversion of a water-soluble chitosonium acetate in film form into a water-insoluble chitin film was concluded by Toffey et al. (1996) Phaechamud (1999) and Nunthanid et al. (2004). Phaechamud (1999) also proposed the mechanism of amide formation between chitosan and carboxylic acid. The protonated amino group and carboxylate ion could bind at elevated temperature. As the catalyst, water in atmosphere of 75% RH promoted extensive ionization of amino groups and carboxylic groups to readily react with each other. During drying the progressive regeneration of the linkage was formed and water molecule was eliminated as by product. The decrease of hydrophilic group after amidation led to the decrease in dissolution of treated film and related to the alteration to insoluble form of chitosan films. This mechanism was

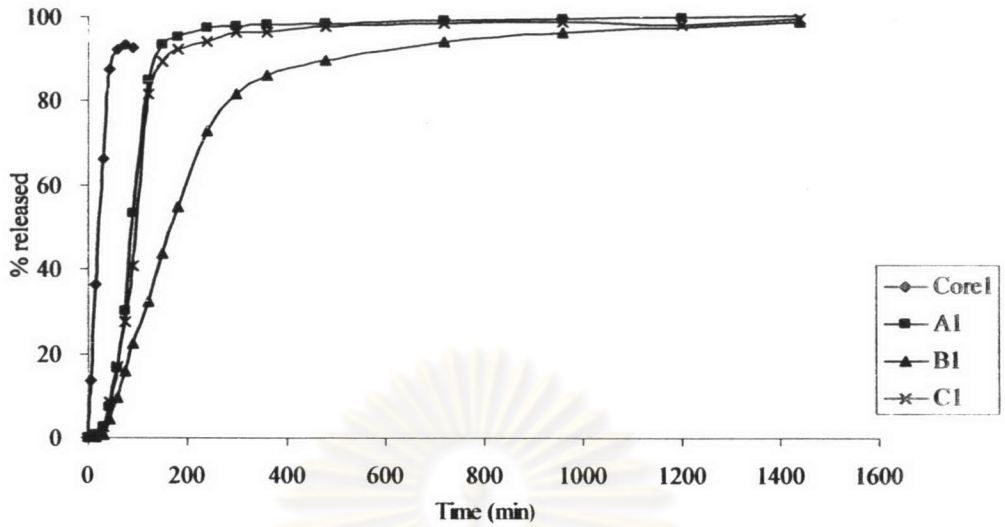


Figure 9 The dissolution profiles of propranolol HCl from core tablet and tablets coated with different grade of chitosan in pH change system

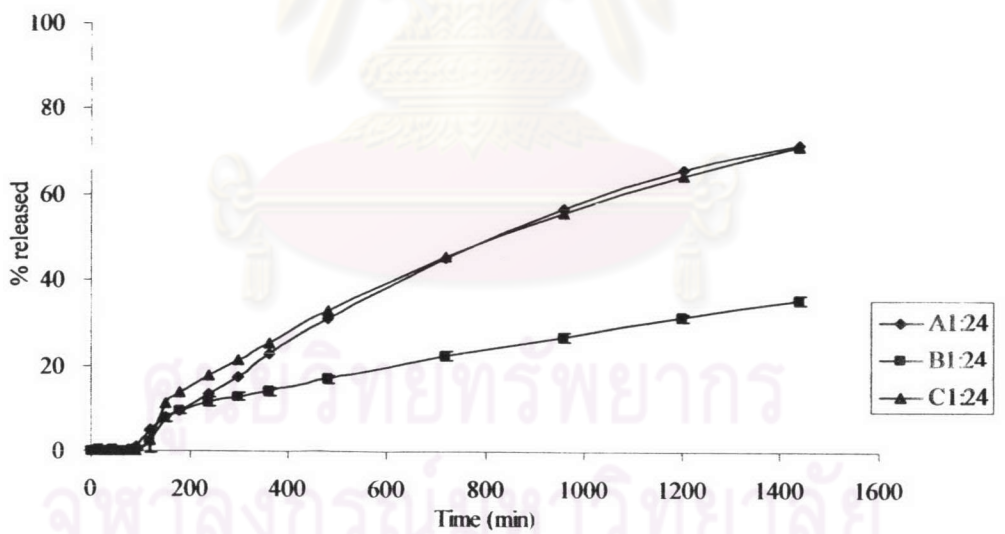
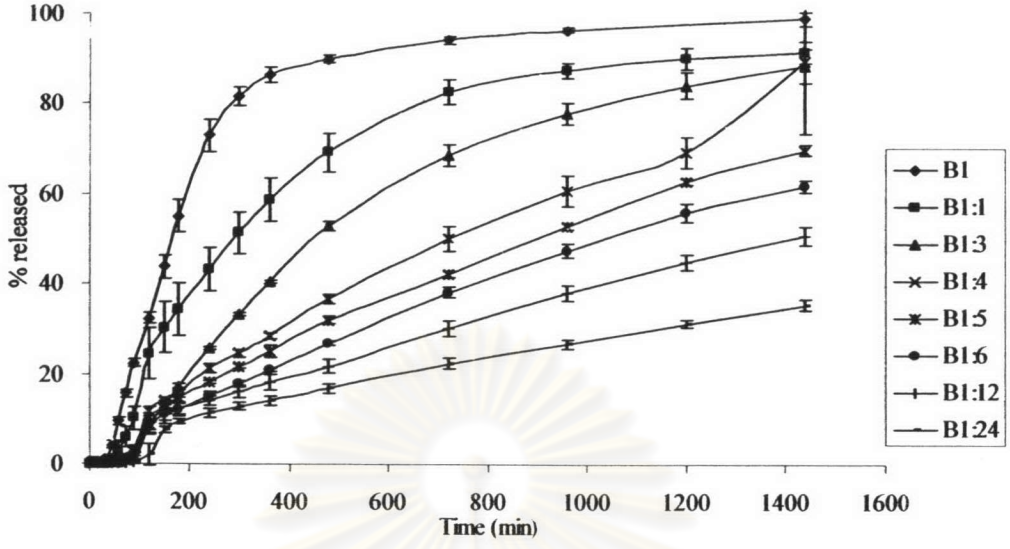


Figure 10 The dissolution profiles of propranolol HCl from tablets coated with different grade of chitosan after moist heat treatment at 60°C in pH change system

a)



b)

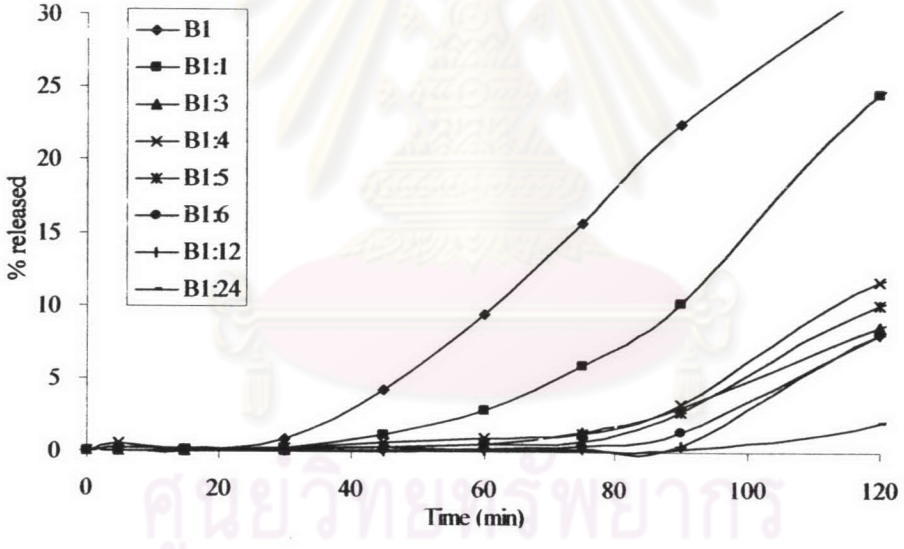


Figure 11 The dissolution profiles of propranolol HCl from tablets (Core 1) coated with chitosan B after moist heat treatment for different time interval in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

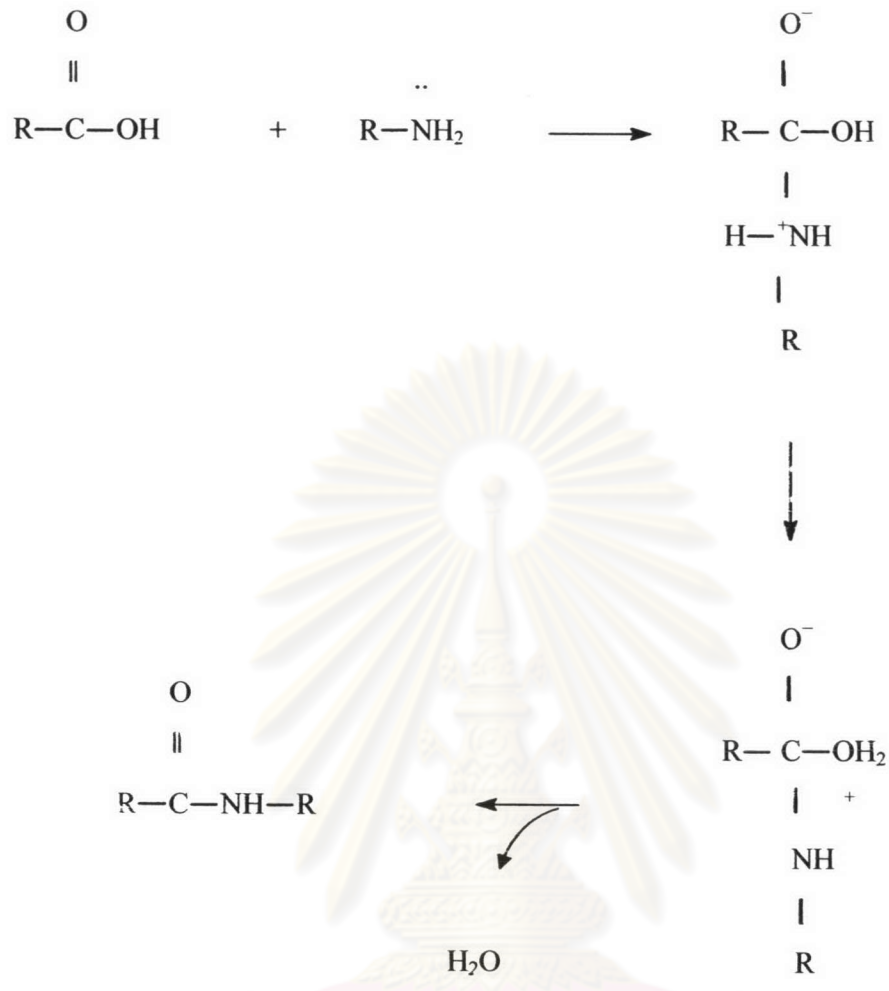


Figure 12 shows the relationship between the relative dissolution time (RDT value) and the time interval of moist heat treatment at 60°C of propranolol HCl coated tablets in pH change system. The longer period of treatment had the higher RDT value, which indicated the slower drug release. The RDT values between the first 5 h of moist heat treatment were increased rapidly, whereas after more than 5 h, the RDT values were minimally raised. The effect of moist heat treatment was dominant to decrease release rate especially during the initial 5 h. This could be explained by the influence of the ionic interaction. Within 5 h, more amino groups might be free to become available for ionic interaction with the oppositely charged ion. More ionic interaction between chitosan with acetic acid and magnesium stearate could occurred. Therefore, the remained free amino groups was lower, the release rate were minimally decreased afterward.

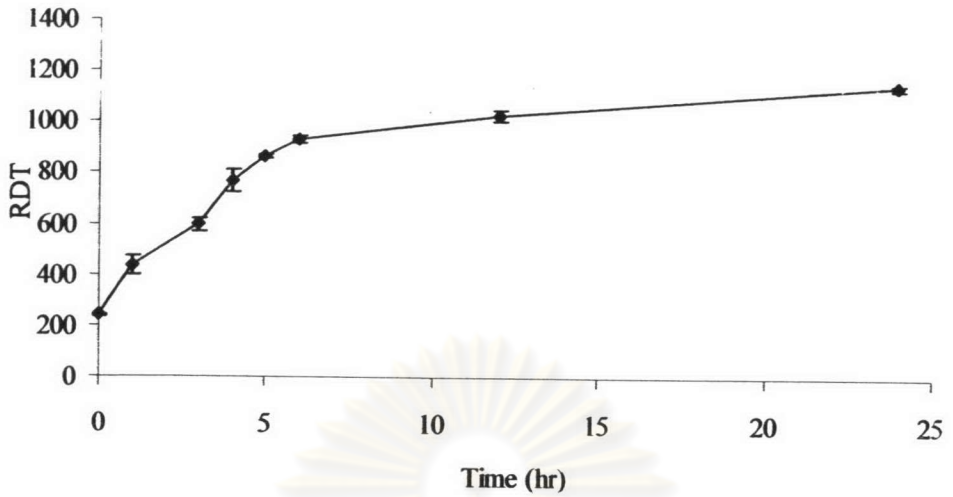


Figure 12 The relationship between the relative dissolution time (RDT value) and the time interval of moist heat treatment at 60°C of propranolol HCl coated tablets in pH change system

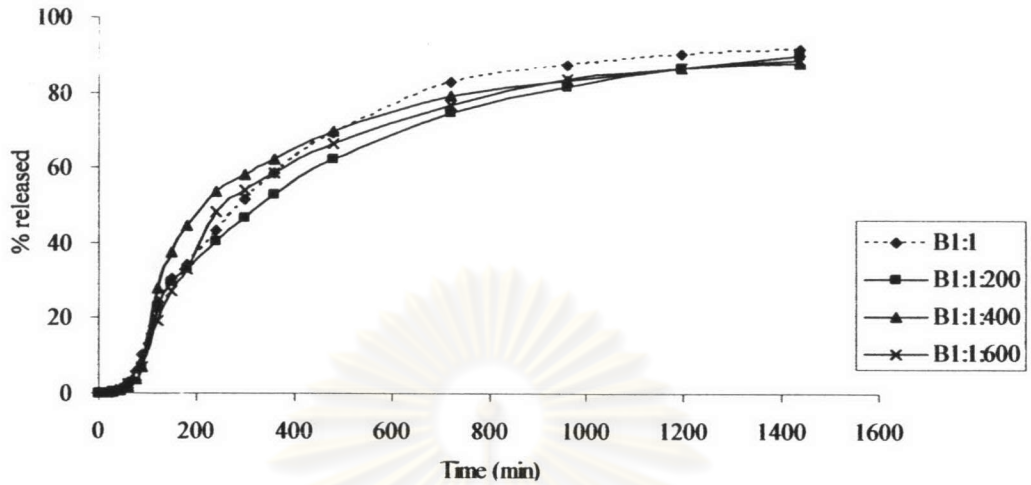
2.7.3 The Effect of Passageway

The film coated tablets that contained 200, 400 and 600 μm of passageway at various interval of moist heat treatment was used in this study. The comparison of release profiles of osmotic pump tablets using three sizes of passageway is represented in Figure 13-19. An enhancement of passageway had a tendency to increase drug release. The orifice could increase the water intake and outflow rate through the membrane. Most osmotic devices with a passageway had the drug release higher than those without a passageway especially after treatment for more than 4 h.

Drug release from 1 h treated coat tablet showed that the apparent retardation of drug release from coated tablet with orifice was greater than that from without orifice. This same characteristic was also observed in 3 h treated tablets after testing interval of 5 h. In consideration of RDT value, the drug release rate with passageway was slower than those without passageway in treated tablet for 1 and 3 h as shown in Figure 20. This could be explained by the completion of ionic interaction within film formulation. Thus, the lower period of treatment, the less completion of reaction and less enduring membrane was obtained. In this situation, continuous water influx into the system without orifice increased the volume of drug solution inside the system, which would generate hydrostatic pressure that could deform and expand the film. At the critical point, the continuous water influx into the system could be equilibrated with the water outflow. Thus, the lower unexpected release profile of coated tablet without orifice was exhibited. On the other hand, for the system with passageway, orifice could decrease pressure from influx water. Therefore, membrane with less pressure would be more persisted and endured.

The release of coated tablets with passageways after treatment for more than 4 h was higher than that without passageway. Moist heat treatment for more than 5 h (6, 12 and 24 h), the one-way ANOVA showed statistically significant difference ($P < 0.05$) between coated tablet with and without orifice. This result indicated that for long treatment interval on coated tablets, the orifice had more effect on drug release. It might be due to more integrity coated film and less membrane relaxation after treatment. Thus, long treatment period, drug diffusion through the membrane was

a)



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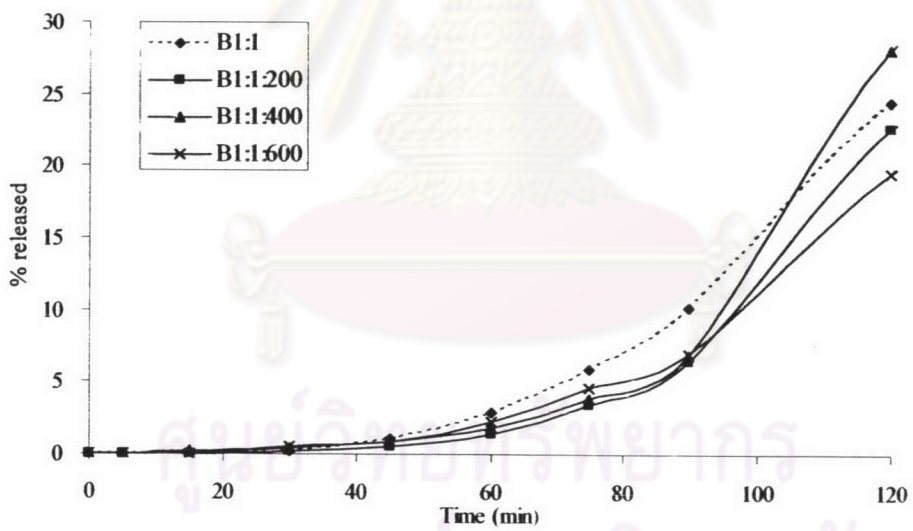
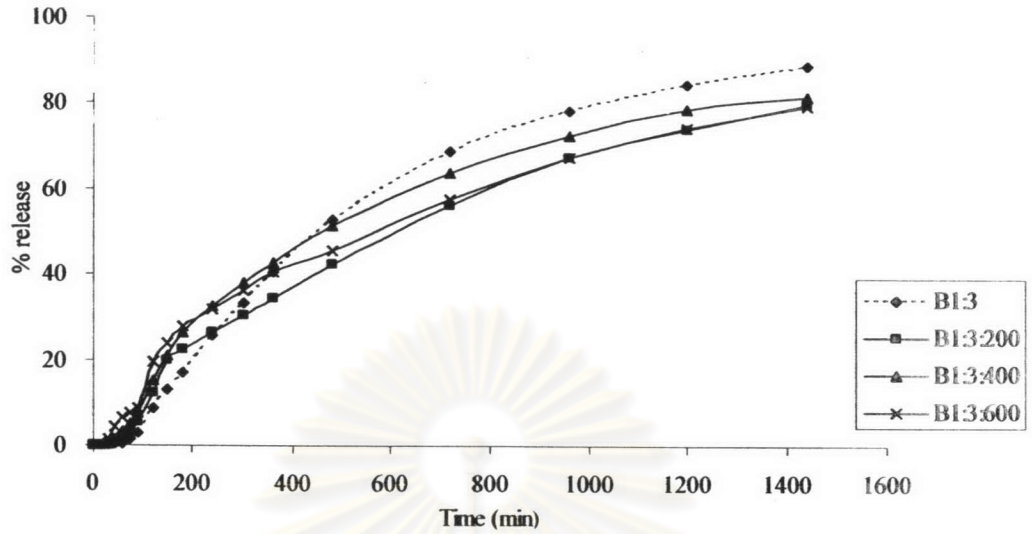


Figure 13 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 1 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

a)



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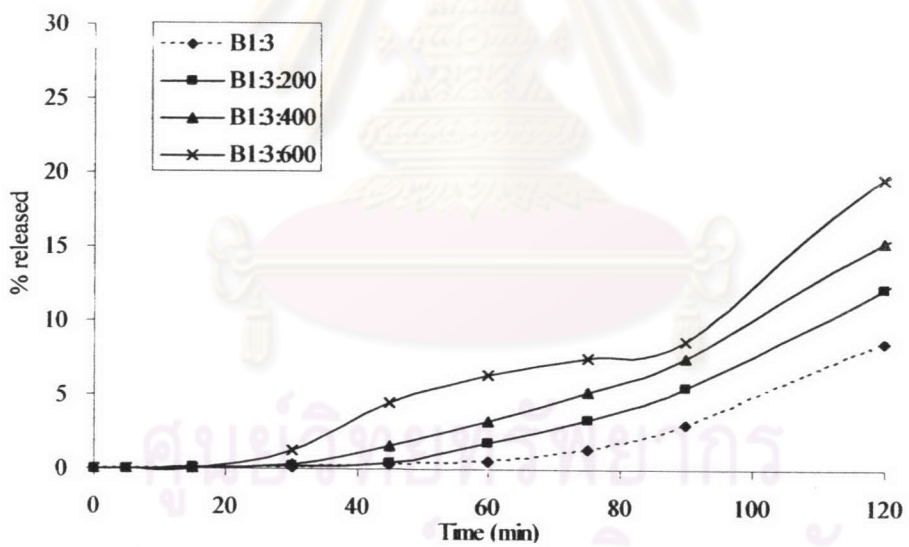


Figure 14 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 3 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

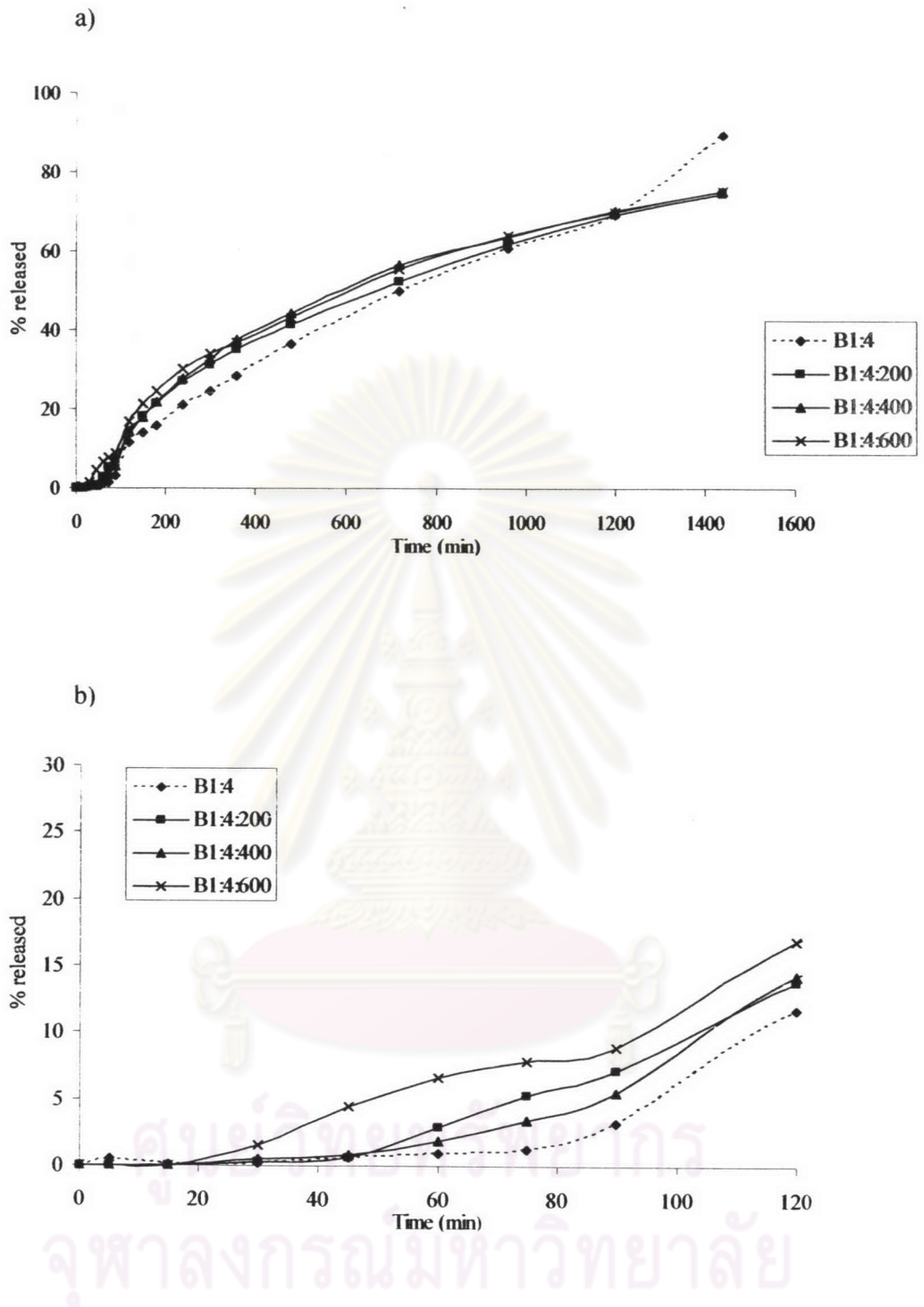
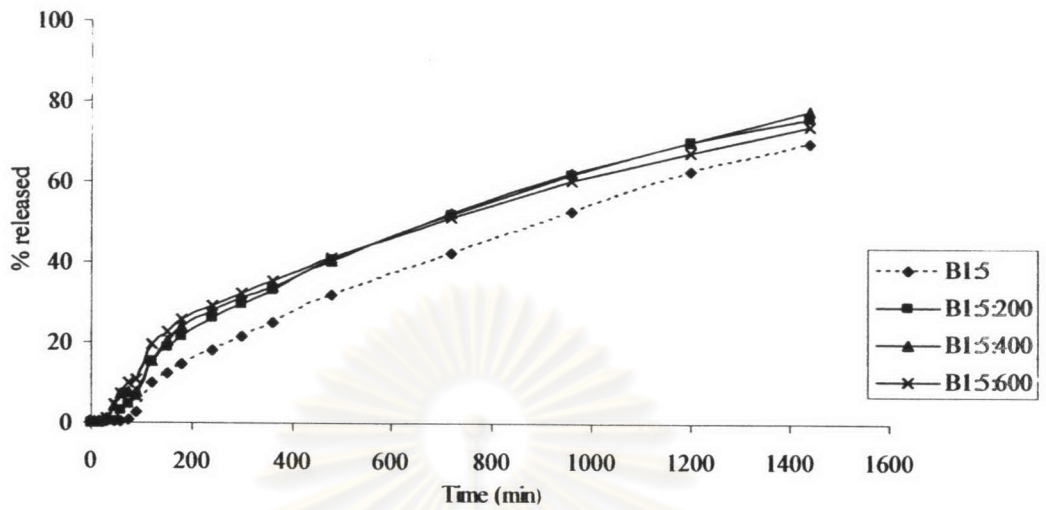


Figure 15 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 4 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

a)



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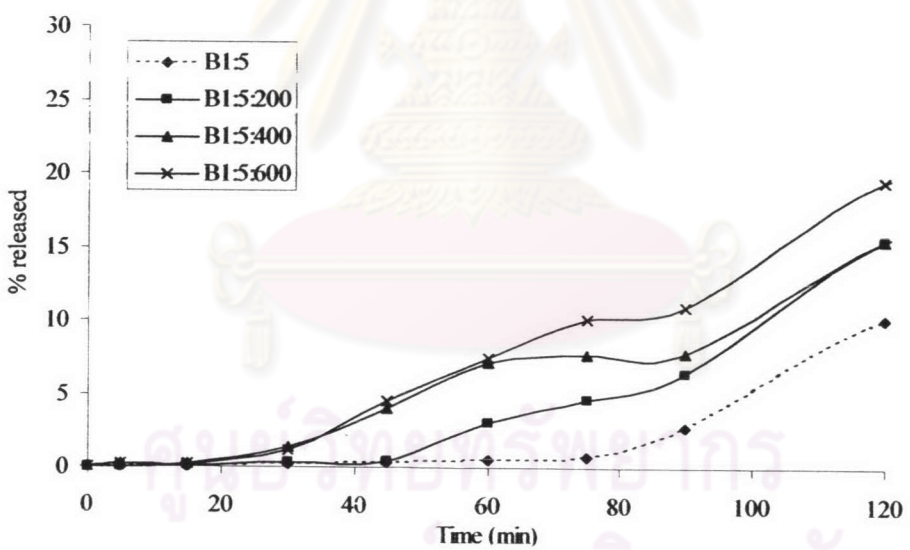
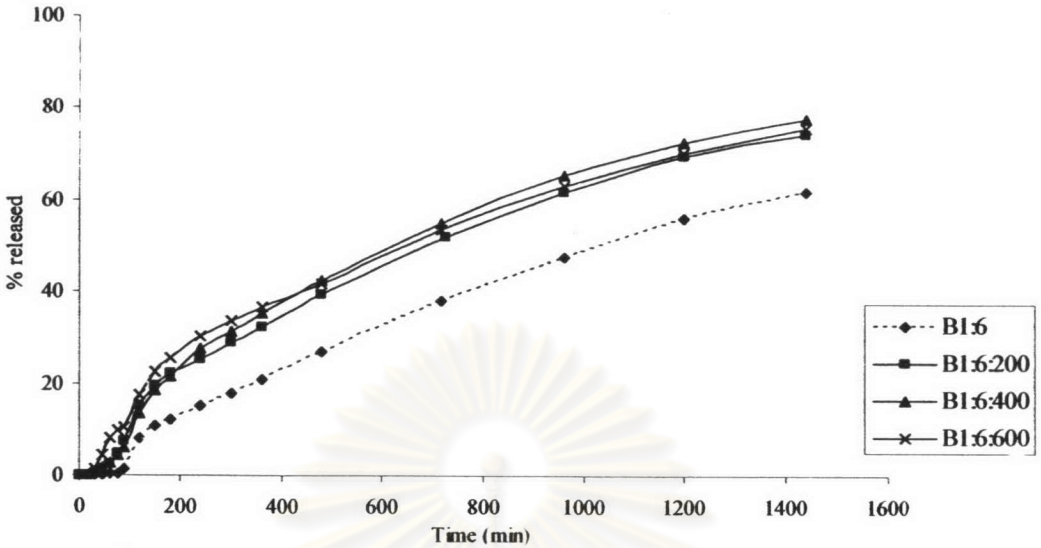


Figure 16 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 5 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

a)



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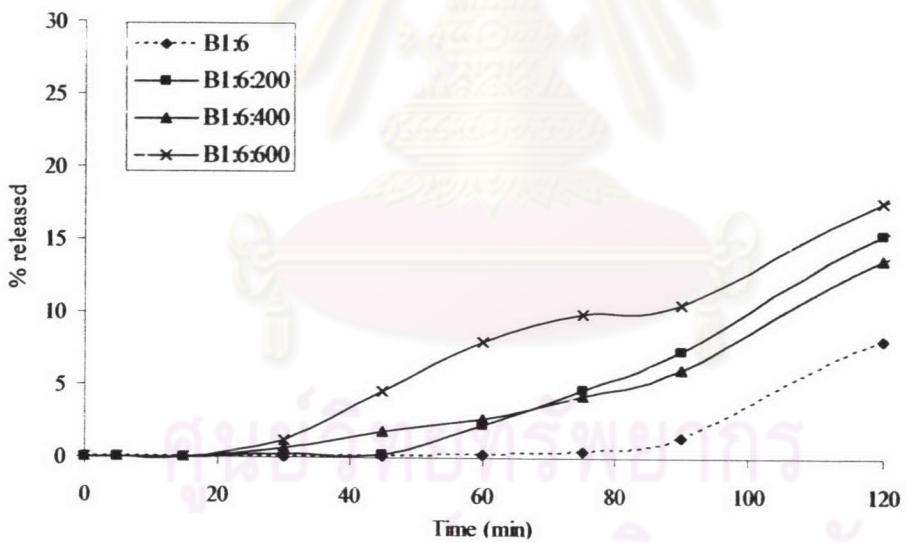
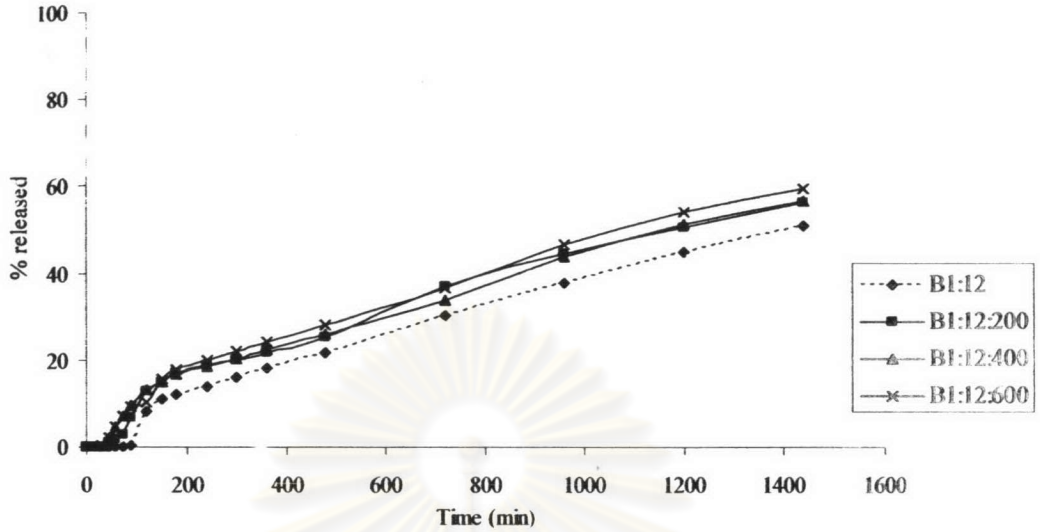


Figure 17 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 6 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

a)



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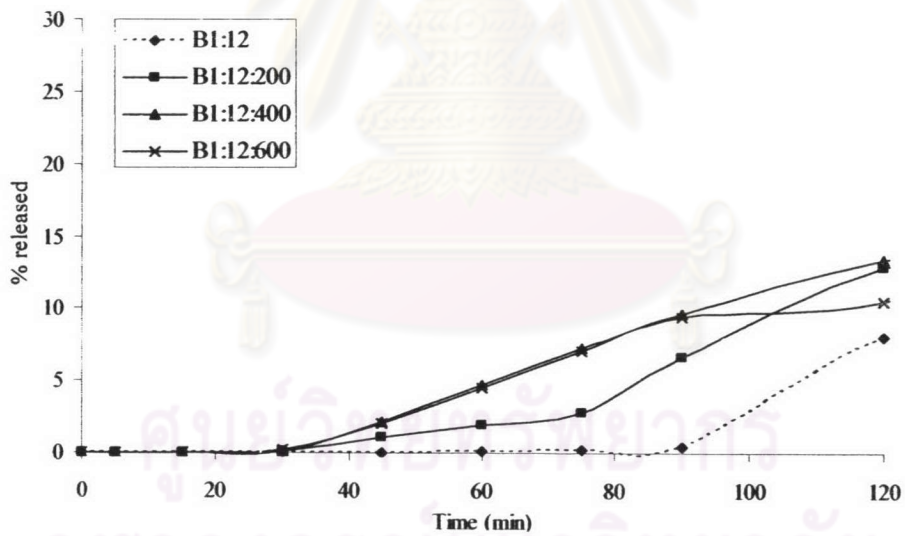
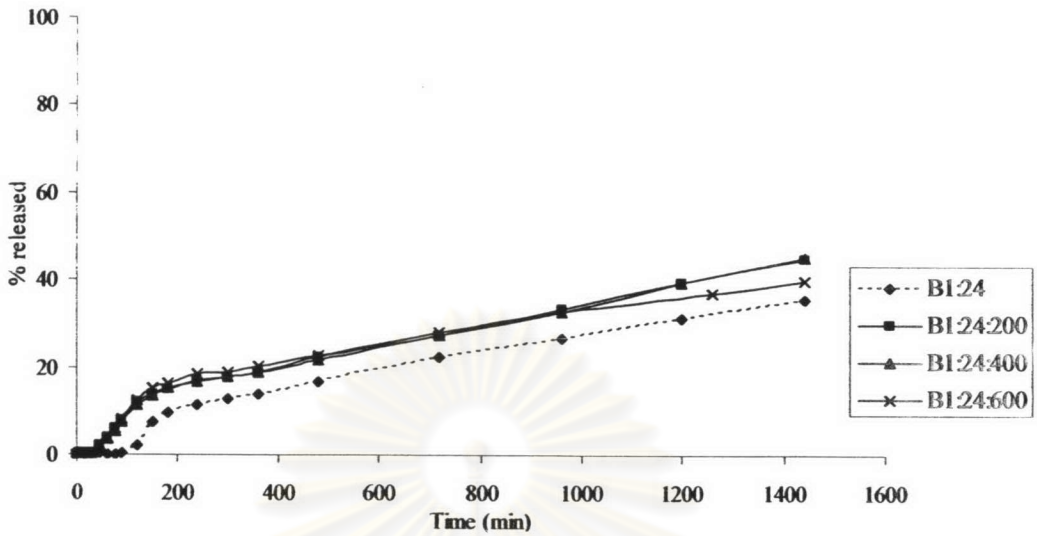


Figure 18 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 12 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

a)



b)

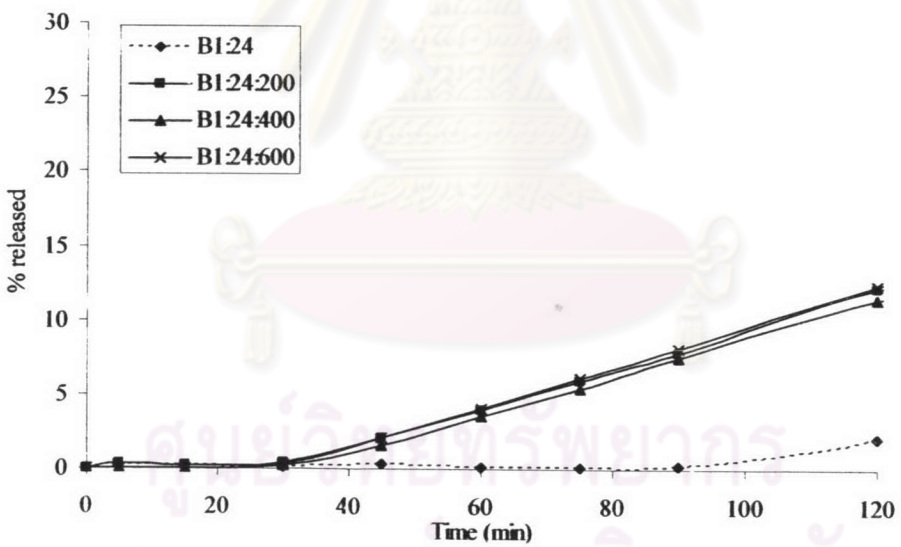


Figure 19 The dissolution profiles of propranolol HCl coated tablets after moist heat treatment for 24 hr with different size of passageway in pH change system a) during 0 to 1440 min and b) 0 to 120 min of testing interval

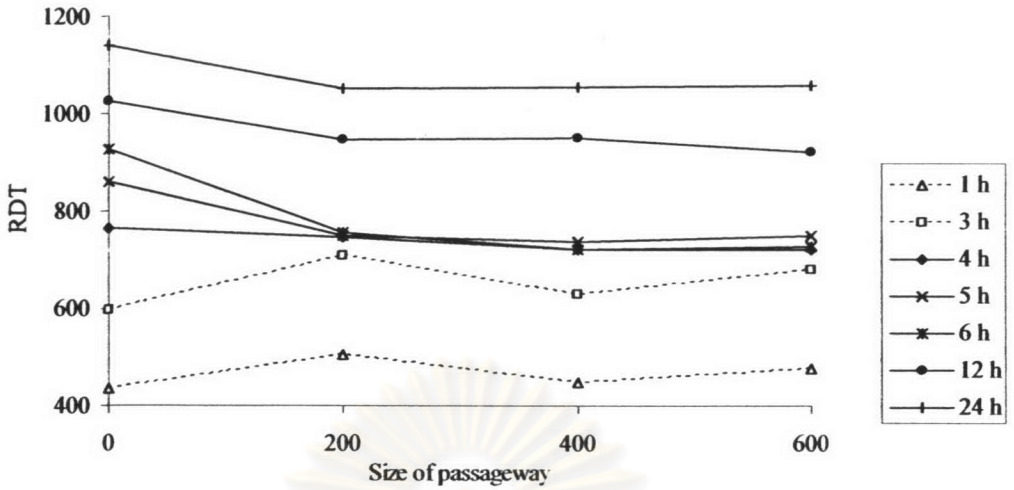


Figure 20 The relationship between the relative dissolution time (RDT value) and the size of passageway of propranolol HCl coated tablets after moist heat treatment between 1-24 hr in pH change system

decreased, whereas the osmotic system with orifice was more influenced. For this reason, the orifice of long period treated coat tablet had more affected on drug release.

The passageway promoted the drug release and minimized lag effect. The lag time of tablet was occurred from diffusion of solvent into the tablet. The water penetrated through chitosan membrane into the core tablet and dissolved active material. Moist heat treatment could promote the lag time before drug delivery began as previously mentioned.

The lag times of film coated tablet after treatment for 5 h (L_5) were decreased from about 75 to 45, 15 and 15 minutes when the orifice size were 200, 400 and 600 μm, respectively, whereas the drug release were increased from 2.73 to 6.38, 7.78, and 10.90 % at acid stage (after 90 minutes of testing interval). The difference of release profile at the initial period from coated tablet with difference size of orifice was clearly observed with treatment period of less than 24 h. Most small size of orifice had longer lag effect and lower drug profile during the initial period than the large one.

For the coated tablet after treatment for 24 h, the lag times (L_{24}) were decreased from 90 to 30 minutes in all sizes of passageway, whereas the drug release were increased from 0.23 to 7.82, 7.46 and 8.12 % at acid stage with the orifice of 200, 400 and 600 μm, respectively. Different orifice size from 200 to 600 μm had little effect both on lag time and % increased drug release at acid stage. The result was related to coated film properties. The short period of treatment, the conversion of a water-soluble film form into a water-insoluble chitin form was not complete. The polymer relaxation of coated film could occur. Thus, swelling and diffusion was main mechanism to control drug release. Size of orifice had influence to increase the water intake. Larger orifice had water intake and outflow more than smaller one, hence polymer relaxation of tablet with large orifice was faster than that with small one. Consequently, the low treatment tablet with larger orifice had smaller lag time and more initially drug release.

For long period of treatment, completed membrane could obtain. Therefore, swelling and diffusion mechanism was small affected the drug released. Osmotic system could be the major mechanism governing drug release characteristic. Drug release from osmotic system was not affected by the size of the delivery orifice within certain limits (Verma et al., 2002). This could explain the initial release profile and lag effect of 24 h treated tablet that was not affected by the size of the delivery orifice. Moreover, the difference of the entire testing interval released profile from different size of orifice tended to lower after long period of treatment, these was also explained by this reason.

However, in the test under the statistic ANOVA method, the results showed non-significant difference ($P > 0.05$) of the various passageway sizes in every period of treatment. The next step, passageway 400 μm was choosen for future study.

2.7.4 The Effect of Osmolality of Dissolution Medium

The dissolution study were conducted on propranolol HCl coated tablets after moist heat treatment at 60°C for 5 hr with 400 μm of passageway in water or in glucose aqueous solution with different concentrations to vary osmotic pressure as

represented in Figure 21. Assessment of drug release pattern in dissolution fluids which were different in osmotic pressure was the convenient method to evaluate the release mechanism (Narisawa et al., 1997). Figure 22 clearly demonstrated that the osmotic pressure difference across the film was reduced by increasing the glucose concentration in the test fluid while the lag time was prolonged and the drug release rate was decreased. This evident could be explained that the increase in osmotic pressure of dissolution medium could decrease in osmotic water influx. Therefore, rate of solvent to dissolve the core component was decreased. The formation of inside osmotic pressure was slower. Thus, the lag time was prolonged. In addition, the decrease of amount of outer water would penetrate through the film coat with increase in osmolality of dissolution fluid. This situation also decreased the drug released rate.

There have been several reports described that the osmotic pressure difference across the membrane played an important role in drug release behavior (Zhang, et al., 2003; Narisawa et al., 1997; Lindstedt et al., 1989). Theroretically represented the drug release rate from such devices under the condition of zero hydrostatic pressure (Zhang et al., 2003):

$$\frac{dM}{dt} = \frac{AC_S}{h}.\left(L_P\sigma\Delta\pi + P\right)$$

where *dM/dt* was the steady-state release rate, *A* was membrane surface area; C_s was the drug solubility; *h* was the membrane thickness; $\Delta\pi$ was the osmotic pressure difference across the membrane; L_p was the mechanical permeability which should be reflected in the total membrane surface area per unit weight; σ was the reflection coefficient; *P* was the permeability coefficient of the drug through coating film and $L_p\sigma$ was permeability coefficient of water.

For equation, it was evident that the release rate of drug (*dM/dt)* was directly proportional to the osmotic pressure difference across the membrane ($\Delta\pi$). A lower osmotic pressure difference across the membrane ($\Delta\pi$) would give a lower osmotic flux, as this would reduce the release rate by diffusion through the membrane. For controlling the drug release from this system, it was important to optimize the osmotic pressure gradient between inside compartment and the external environment.

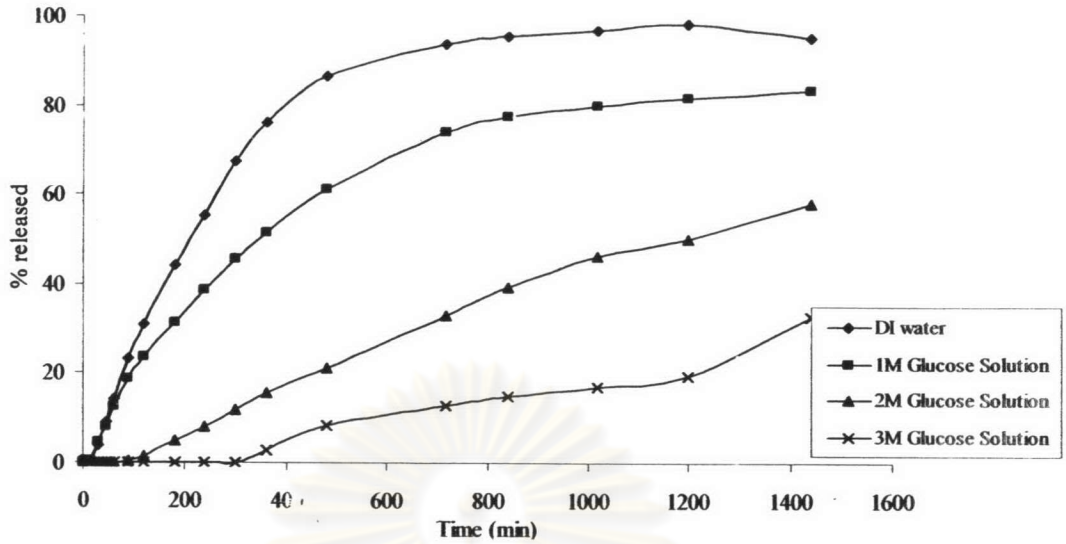


Figure 21 The dissolution profiles of propranolol HCl from tablets (core 1) coated with chitosan B after moist heat treatment for 5 hr with 400 μm of passageway in deionized water and glucose solutions with different osmolality

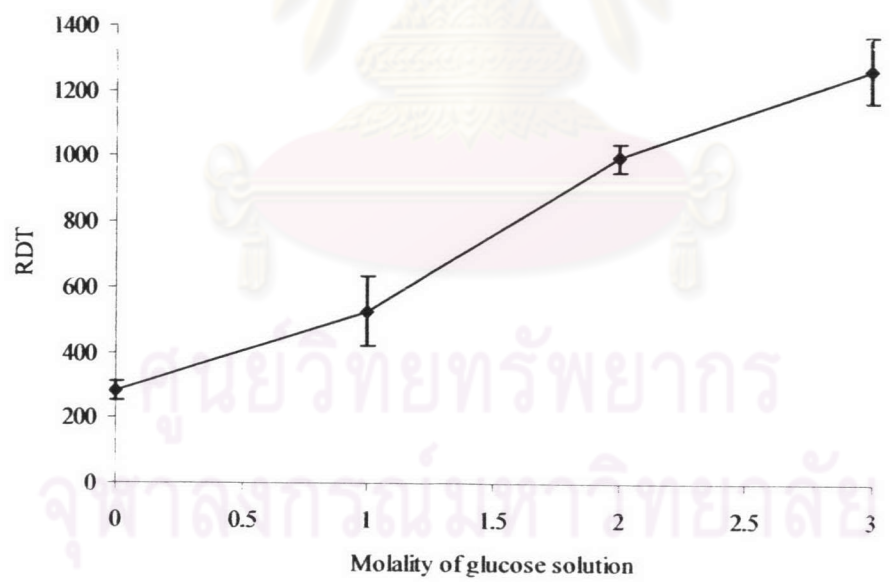


Figure 22 The relationship between the relative dissolution time (RDT value) and the molality of glucose solution medium from propranolol HCl coated tablets after moist heat treatment at 60°C for 5 hr with 400 μm of passageway

However, drug solubility was also decreased as the osmolality of glucose solution was increased (Phaechamud, 1999). It might be due to water being solvent that dissolved both glucose and propranolol HCl. The increase of osmolality of glucose solution by increasing glucose concentration in solution might mean that the solvent which was to dissolve glucose was increased. Therefore, the dissolved solvent for propranolol HCl was decreased. The increase of osmolality of glucose solution was result in decrease propranolol HCl solubility.

It could be concluded that the decrease in drug release rate might be from two factors: a decrease in the osmotic pressure difference across the film, and a decrease in propranolol HCl solubility in glucose solutions.

2.7.5 The Effect of osmotic agent

The release profiles of osmotic devices with passageway 400 μm after treatment for 5 h that using osmotic agent in deionized water are represented in Figure 23. Osmotically active agent, sodium chloride (NaCl), was added to the core tablets in different concentrations. The increase in osmogent content was affect tablet crushing strength and disintegration time of core tablet. The physical properties of core tablet are shown in Table 4. It could be clearly seen that tablets containing NaCl could prolong lag time and their release rate was decreased as shown in Figure 23 and 24. These indicated that the release rate might be governed by the change of chitosan membrane that related to osmogent. The membrane could decrease the water influx to the system to produce a lag time and decrease the release rate

The osmotic devices with NaCl at concentration 16.67, 33.33 and 50 %w/w (B2:5:400, B3:5:400 and B4:5:400) had the same release profile. The more increased amount of NaCl provided the greater drug release. In high ionic strength solution, the concentration of Cl^- was raised by adding NaCl which screens the protonated amino group. The bond joining together the water molecules bonded to chitosan which caused polymer relaxation and swelling became split. The counter ion increased the distances among chitosan and water molecules. In this situation, the lower swelling could occur and caused to decrease permeability of membrane. Tsaih and Chen (1997) also reported that in high ionic strength solution, the conformation of chitosan

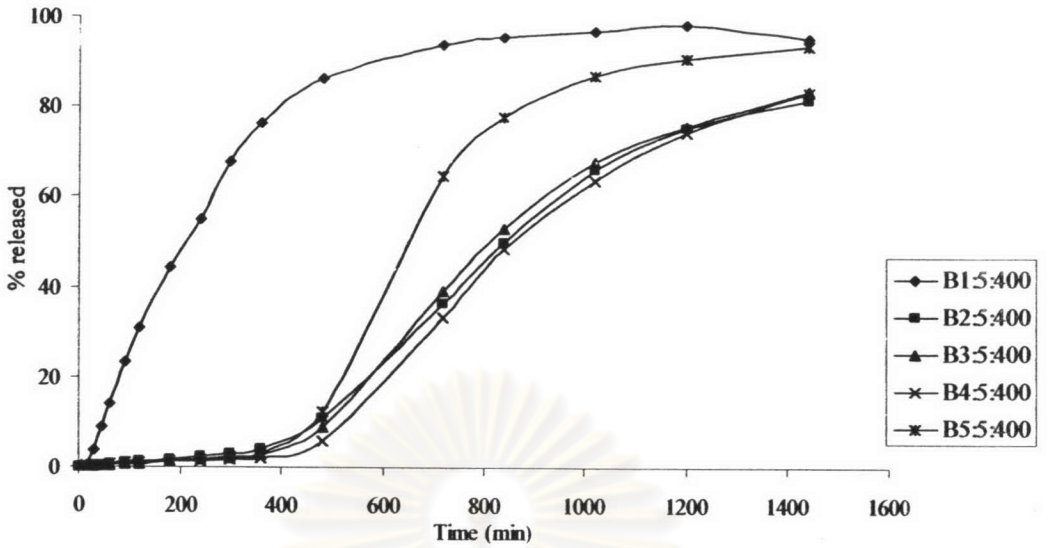


Figure 23 The dissolution profiles of propranolol HCl from core tablets containing different amount of sodium chloride coated with chitosan after moist heat treatment for 5 hr with 400 μm of passageway in deionized water

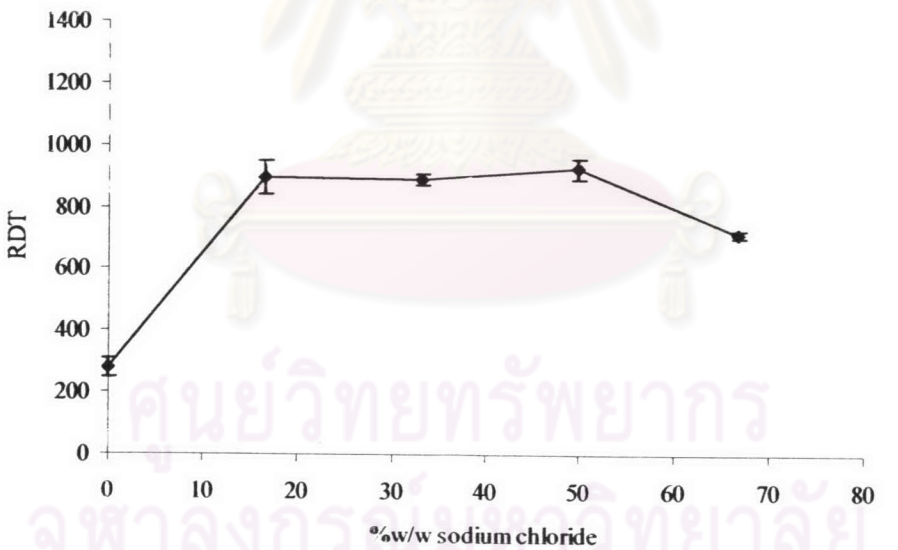


Figure 24 The relationship between the relative dissolution time (RDT value) and the percentage of sodium chloride in core tablet of propranolol HCl coated tablets after moist heat treatment for 5 hr with 400 μm of passageway in deionized water

became contracted. Comparison to the coat tablet without NaCl (B1:5:400), showed that those with NaCl (B2:5:400, B3:5:400 and B4:5:400) had slower release rate and prolonged lag time. When ionic strength was increased to infinity, the protonated amine group was totally neutralized resulting in no electrostatic repulsion forces. The intra-molecular hydrogen bonds were destroyed. Chitosan conformation became extended (Tsaih and Chen, 1997). With this reason, the polymer relaxation of film would increase and, as a consequence, could increase the permeability of membrane. These results provided greater drug release of coat tablet with NaCl 66.67 %w/w (B5:5:400) than those with lesser amount of NaCl.

2.8 The evaluation of drug release kinetics

The determination of the suitable mathematical model was required to explain the drug release characteristics; therefore, an analysis of dissolution profiles was performed to elucidate the best fitted model for the experimental release data. The determination values from curve fitting with zero order, first order, Higuchi's and Weibull model were obtained. The equations for the drug release model are shown in Table 7.

Table 7 The release kinetic model

Model	Equation
Zero order	$Q_t = Q_o + kt$
First order	$\mathrm{Ln}Q_t = \mathrm{In}Q_o + kt$
Higuchi	$Q_t = kt^{1/2}$
Weibull	$\mathrm{Log}[-\ln(1-Q_t/Q_a) = b \times \log t - \log a$
Power law expression	$Q_t/Q_a = kt^n$ $\mathrm{In}\ Q_t/Q_a = \mathrm{In}\ k + n\ \mathrm{In}\ t$

Q_t was the amount of drug released in time t, Q_o was the initial amount of drug in the solution (most times, Q_o= 0), Q_α was the amount of drug released at infinite time.

The drug releases were analyzed during 20-80% of drug release. The highest coefficient of determination (R^2) was accepted as the model for drug release. The values of coefficient of determination from curve fitting with different equation of core and coated tablets are shown in Table 8 and 9.

In case of tablets coated with chitosan acetate film, correlation coefficients (R^2) of kinetic model could not solely determine the suitability of models. However, the most suitable mathematic model for describing the experimental data was first order. This linear relationship indicated that the drug release properties of the film coated tablets were in good agreement with diffusion model. Diffusion was caused by the initial hydration of polymeric coating in the dissolution medium, followed by chain relaxation which led to the formation of channels or pores which drug molecules could pass through.

The release mechanism of this study might combine with another mechanism due to low correlation of determination of some systems (r^2 = 0.9055-0.9997). The assessment of drug release pattern in dissolution fluids which was different in osmotic pressure was the convenient method to evaluate the release mechanism (Narisawa et al., 1997). From the study of the effect of osmolality of dissolution fluids on drug release behavior demonstrated that the drug release was decreased as the osmotic pressure of dissolution medium was increased. The similar effect with beads containing propranolol HCl coated with aqueous polymeric dispersion was found by Rekhi et al. (1995). The release of propranolol HCl from these coated tablets appeared to be diffusion controlled accompanied by osmotic effect. Both drug diffusion and osmotic pumping had been reported that they possible enabled drug transfer through a very low osmotic permeable membrane such as ethyl cellulose (Lindstedt et al., 1989; Ozturk et al., 1990).

The release mechanism of film coated tablet was investigated by fitting the dissolution data into the power law expression as shown in Table 8 and 10, when

Q_t / Q_a was the fraction of drug release (0.0-0.6), t was the release time, k was a kinetic constant incorporating structural and geometric characteristics of the release device and n was the release exponent indicative of the mechanism of drug release. In case of swelled tablet, n = 0.45 for Case I or Fickian diffusion, n=0.89 for Case II transport, 0.45 ‹ n ‹ 0.89 for anomalous or non-Fickian transport and n › 0.89 for super Case II transport.

The comparisons of the values of release exponent (n) revealed that anomalous transport was most applicable for drug release data of treated tablets coated with chitosan film. This indicated that the drug release mechanisms were a combination of diffusion and polymer relaxation. However, the drug release pattern in various osmolality dissolution fluids indicated that osmotic pressure had an effect to control the release pattern.

The drug release mechanism of propranolol HCl film coated tablet was investigated. The effect of moist heat treatment, passageway, osmolality of dissolution medium and osmotic agent on drug release mechanism were discussed.

2.8.1 The effect of moist heat treatment on drug release mechanism

As shown in Table 8, the values of release exponent (n) of three types of chitosan untreated tablets were in the range of 1.2605-3.1271, indicating the mechanism of supercase II transport. This result pointed out that the untreated tablets released the drug in pH change system via the polymer relaxation acted as dominant mechanism in drug release from the tablets. The reason for this finding might be due to the remained charge groups in cationic network were ionized under acid condition and resulting repulsion between groups caused the network to expand and thus its permeability was enhanced (Berger et al., 2004). However, the similar mechanism was also responsible for drug permeation through most of the swollen hydrogel membranes (Frohoff-Hulsmann, Schmitz and Lippold, 1999; Sujja-areevath et al., 1996).

Table 8 The coefficient of determination and release rate from curve fitting of drug release from tablets coated with different chitosan film freshly prepare and after moist heat treatment at 60° C for 24 hour in pH change system

Formula	Zero order		First order		Higuchi model		Weibull model	Power law expression model		
	R^2	k	R^2	k	R^2	k	R^2	R^2	n	k
Core1	0.9904	1.7117	0.9840	0.0237	0.9995	18.1428	0.9960	0.9999	0.8807	0.0334
A1	0.9962	1.3955	0.9953	0.0132	0.9986	26.4092	0.9964	0.9980	3.1271	4.127
B1	0.9895	0.3184	0.9919	0.0031	0.9950	8.3032	0.9972	0.9945	1.2605	0.0008
C1	0.9523	1.4675	0.9055	0.0135	0.9415	27.5794	0.9586	0.9999	2.1927	2.1229
A1:24	0.9773	0.0466	0.9982	0.0004	0.9953	2.6561	0.9982	0.9956	0.9296	0.0010
B1:24	0.9979	0.0186	0.9983	0.0001	0.9967	1.2023	0.9962	0.9969	0.6810	0.0025
C1:24	0.9849	0.0438	0.9991	0.0004	0.9989	2.4294	0.9995	0.9948	0.7962	0.0024

Table 9 The coefficient of determination and release rate from curve fitting of drug release from tablets coated with chitosan film after moist heat treatment at 60°C between 1-24 hours in pH change system and different equations

Formula	Zero order		First order		Higuchi model		Weibull model
	R^2	*k*	R^2	*k*	R^2	*k*	R^2
B1:1	0.9753	0.1125	0.9995	0.0011	0.9969	3.9745	0.9991
B1:1:200	0.9508	0.0778	0.9961	0.0008	0.9904	3.1346	0.9978
B1:1:400	0.8794	0.0789	0.9689	0.0009	0.9439	3.0488	0.9697
B1:1:600	0.8699	0.0764	0.9677	0.0008	0.9376	3.1990	0.9630
B1:3	0.9591	0.0770	0.9974	0.0008	0.9884	3.5434	0.9945
B1:3:200	0.9717	0.0485	0.9988	0.0005	0.9957	2.4783	0.9968
B1:3:400	0.9536	0.0533	0.9963	0.0005	0.9909	2.5479	0.9971
B1:3:600	0.9683	0.0448	0.9989	0.0004	0.9975	2.2034	0.9963
B1:4	0.9874	0.0517	0.9995	0.0004	0.9986	2.5943	0.9988
B1:4:200	0.9741	0.0430	0.9989	0.0004	0.9980	2.1958	0.9986
B1:4:400	0.9518	0.0432	0.9939	0.0004	0.9909	2.2232	0.9984
B1:4:600	0.9686	0.0424	0.9982	0.0004	0.9971	2.1271	0.9980
B1:5	0.9941	0.0427	0.9957	0.0004	0.9978	2.3479	0.9965
B1:5:200	0.9816	0.0449	0.9996	0.0004	0.9992	2.2828	0.9973
B1:5:400	0.9872	0.0447	0.9968	0.0004	0.9982	2.2190	0.9911
B1:5:600	0.9845	0.0407	0.9987	0.0004	0.9990	1.9869	0.9922
B1:6	0.9880	0.0389	0.9996	0.0003	0.9992	2.2070	0.9998
B1:6:200	0.9792	0.0444	0.9987	0.0004	0.9970	2.2590	0.9951
B1:6:400	0.9731	0.0461	0.9991	0.0004	0.9972	2.3529	0.9980
B1:6:600	0.9764	0.0429	0.9987	0.0004	0.9980	2.1017	0.9941
B1:12	0.9952	0.0307	0.9997	0.0002	0.9992	1.8393	0.9996
B1:12:200	0.9817	0.0333	0.9961	0.0002	0.9964	1.8898	0.9966
B1:12:400	0.9942	0.0337	0.9947	0.0002	0.9883	1.7623	0.9850
B1:12:600	0.9941	0.0346	0.9964	0.0003	0.9924	1.8516	0.9888
B1:24	0.9979	0.0186	0.9983	0.0001	0.9967	1.2023	0.9962
B1:24:200	0.9988	0.0236	0.9956	0.0002	0.9895	1.3644	0.9883
B1:24:400	0.9991	0.0245	0.9943	0.0002	0.9881	1.4145	0.9878
B1:24:600*	0.9900	0.0186	0.9943	0.0001	0.9958	1.0512	0.9946

***B1:24:600** mean that coated tablets used chitosan *B* as film former for coated core tablet *1* after exposure to accelerate condition for *24* hours and containing *600* µm of passageway.

For the release of treated tablet at difference time interval, the mechanism of drug release was anomalous transport as shown in Figure 25 and Table 10. This indicated that the drug release mechanisms were a combination of diffusion and polymer relaxation. The alteration from polymer relaxation to combination of diffusion and polymer relaxation after moist heat treatment was noted. Usually, hydrophobic film coat was more effective than the hydrophilic film coat to retard the penetration of permeating solvent. Therefore the more hydrophobic nature by greater extensive amide linkage formation of the treated chitosan film, the slower was the penetration of permeating solvent and thereafter the inside viscosity and drug diffusivity were increased and decreased, respectively. Such diffusion mechanism was typically observed in the transport of diffusion through hydrophobic membrane materials (Sutinen et al., 1990).

2.8.2 The effect of passageway

For both with and without orifice on treated film coated tablet, the mechanism of drug release in pH change system was anomalous transport which the combination of diffusion and polymer relaxation mechanism controlled the drug release from tablets. The addition of orifice led to the decrease of release exponent (n) as shown in Figure 26 and Table 10. It might be regarded to reduce the swelling effect. Adding orifice could inhibit the expansion of chitosan film coated tablets, which was affected from the osmotic pressure inside the core tablets The osmotic pressure could induce the expansion of the coated tablets and result in further pore formation and/ or pore enlargement in the hydrated film coating. This suggestion had been mentioned by Li and Pack (1989). Orifice also potentially enhanced the absorption of water, water penetrated into core and drive off water. Therefore, the influence of orifice on release profile was clearly.

Table 10 The values of release exponent (n), coefficient of determination (r^2) and kinetic constant (k) of drug release from tablets coated with chitosan film after moist heat treatment at 60° C between 1-24 hours in pH change system

Formula	Power law expression model		
	R^2	*n*	*k*
B1:1	0.9980	0.7814	0.0059
B1:1:200	0.9888	0.7092	0.0081
B1:1:400	0.9611	0.7755	0.0074
B1:1:600	0.9667	0.9703	0.0021
B1:3	0.9958	1.0852	0.0007
B1:3:200	0.9986	0.6711	0.0067
B1:3:400	0.9826	0.6994	0.0069
B1:3:600	0.9927	0.5563	0.0149
B1:4	0.9983	0.8039	0.0025
B1:4:200	0.9969	0.6176	0.0091
B1:4:400	0.9942	0.6801	0.0066
B1:4:600	0.9969	0.5747	0.0125
B:5	0.9987	0.7525	0.0030
B1:5:200	0.9994	0.6336	0.0080
B1:5:400	0.9957	0.5771	0.0116
B1:5:600	0.9984	0.5114	0.0176
B1:6	0.9987	0.8198	0.0017
B1:6:200	0.9971	0.6295	0.0081
B1:6:400	0.9967	0.6473	0.0078
B1:6:600	0.9930	0.5472	0.0146
B1:12	0.9991	0.7840	0.0017
B1:12:200	0.9935	0.7144	0.0032
B1:12:400	0.9930	0.6867	0.0039
B1:12:600	0.9943	0.6466	0.0054
B1:24	0.9969	0.6810	0.0025
B1:24:200	0.9929	0.6242	0.0046
B1:24:400	0.9929	0.6503	0.0039
B1:24:600*	0.9961	0.4968	0.0107

***B1:24:600** mean that coated tablets used chitosan *B* as film former for coated core tablet *1* after exposure to accelerate condition for *24* hours and containing *600* μm of passageway.

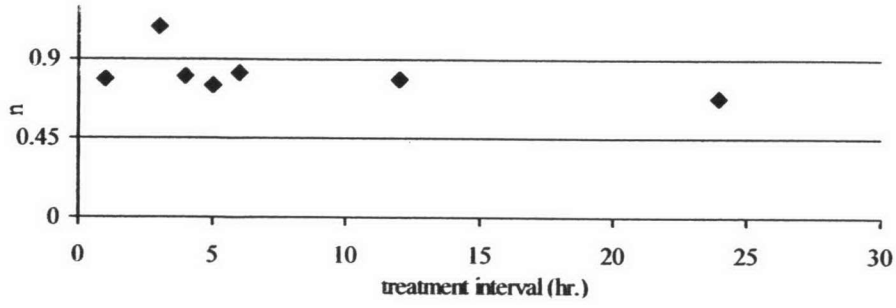


Figure 25 The relationship between the release component (n) and treatment interval of tabiets coated with chitosan B in pH system.

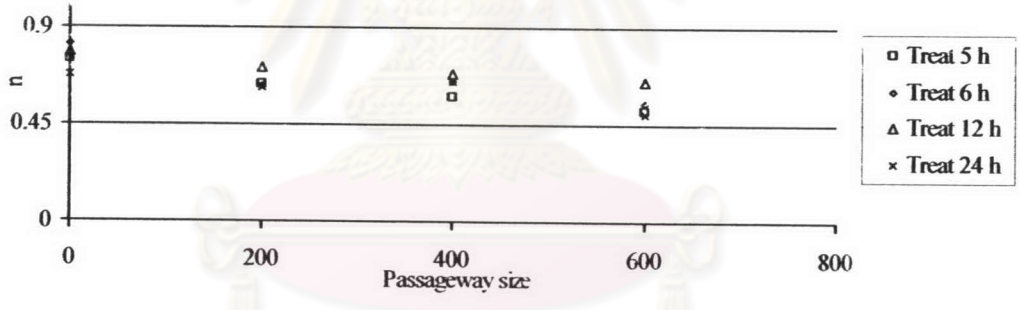


Figure 26 The relationship between the release component (n) and the size of passageway of propranolol HCl coated tablets after moist heat treatment between 5-24 hr in pH system.

The decrease of lag time by passageway was the primary drug release of tablet with orifice. The initial drug release of tablet with orifice during lag times of those without passageway, the influence on drug release was mainly from passageway. Later, drug release was influenced by several factors such as pore that was generated from polymer chain relaxation, passageway from drilling and changed of permeability of hydrated membrane from polymer relaxation. The effect of passageway on the initial drug release of film coated tablets after treatment for 6-24 h was evaluated as shown in Table 11. The lower interval of treatment (0-5 h), the lower lag time was obtained that resulted not enough data to determine. It revealed that the release kinetic of propranolol HCl from film coated tablets with passageway was a function of interval of moist heat treatment. Correlation coefficients (R^2) of kinetic model could not solely determine the suitability of models. The result of this study showed that when the interval of treatment was increased, the release mechanism was changed, toward making having zero order release with 24 h treatment. Increase of treatment period was concerned the integrity and lower permeability of chitosan film. It might decrease of diffusion mechanism, whereas osmotic effect was more dominant that might be the reason to have zero order release. The results obtained in this study confirmed that the property of membrane changed by moist heat treatment and influence of passageway had a great effect on the mechanism of drug release.

2.8.3 The effect of osmolality of dissolution medium

The dissolution profiles of treated tablet with 400 μm of passageway in 3 M glucose solution were not evaluated because the drug release from these less than 35% of released drug. The values of release exponent (n) of treated tablet with 400 μm of passageway in dissolution treated media with various osmolality are presented in Figure 27 and Table 12. The obtained values were anomalous transport and altered to supercase II after dissolution medium was 2 M. The similar effect was found by Narisawa et al (1997).

This finding demonstrated that the release mechanism was controlled by a combination of both diffusion and polymer relaxation.

Table 11 The coefficient of determination and release rate from curve fitting of initial drug release from tablets coated with chitosan film after moist heat treatment at 60°C between 6-24 hours in pH change system and different equations

Formula	Initial release time (min)	Zero order		First order		Higuchi model		Weibull model
		R^2	*k*	R^2	*k*	R^2	*k*	R^2
B1:6:400	45-75*	0.9766	0.0842	0.9755	0.0004	0.9643	1.2851	0.9891
B1:6:600	30-75	0.9847	0.1970	0.9869	0.0009	0.9940	2.7980	0.9553
B1:12:200	45-90	0.8512	0.1170	0.8466	0.0005	0.8173	1.8562	0.9966
B1:12:400	45-90	0.9998	0.1664	1.0000	0.00077	0.9986	2.6925	0.9861
B1:12:600	45-90	0.9996	0.1653	0.9998	0.0008	0.9985	2.6762	0.9850
B1:24:200	45-90	0.9999	0.1274	0.9998	0.0006	0.9969	1.3644	0.9941
B1:24:400	45-90	0.9994	0.1304	0.9989	0.0006	0.9948	2.1077	0.9887
B1:24:600	45-90	0.9999	0.13406	0.9997	0.0006	0.9966	2.1674	0.9935

B1:24:600 mean that coated tablets used chitosan *B* as film former for coated core tablet *1* after exposure to accelerate condition for *24* hours and containing *600* µm of passageway.

***45-75** *45* minutes was the primary time that coated tablet with orifice had drug release more than 1 %
75 minutes was the lag time of coated tablet without passageway

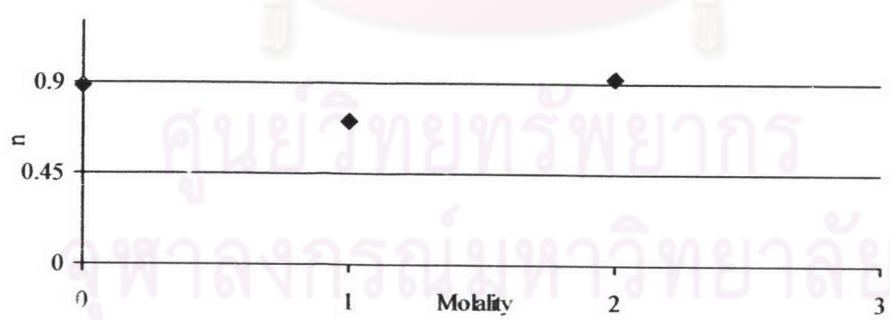


Figure 27 The relationship between the release component (n) and the molality of glucose solution medium from propranolol HCl coated tablets after moist heat treatment for 5 hr with 400 µm of passageway.

Table 12 The coefficient of determination and release rate from curve fitting of drug release from core tablets 1 coated with chitosan film after moist heat treatment at 60° C for 5 hour with 0.4 mm passageway in different medium

Formula	Zero order		First order		Higuchi model		Weibull model	Power law expression model		
	R^2	k	R^2	k	R^2	k	R^2	R^2	n	k
DI	0.9945	0.1958	0.9909	0.0019	0.9986	5.6252	0.9973	0.9962	0.8833	0.0044
1 M	0.9593	0.0770	0.9962	0.0008	0.9921	3.1287	0.9989	0.9995	0.7069	0.0080
2 M	0.9814	0.0381	0.9956	0.0003	0.9950	2.3057	0.9942	0.9863	0.9154	0.0008
3 M	0.8674	0.0294	0.8521	0.0002	0.8400	1.9388	0.8661	-	-	-

When osmotic pressure of dissolution fluid was increased, it would be concluded that the diffusion mechanism was decreased. The capacity of permeating medium to penetrate through the film coat to dissolve the encapsulated core component was dependent on the film component and film property after moist heat treatment which affected to the viscosity of surrounding environment of remained core tablet. The permeating solvent entered the polymer, dissolved the drug and enabled the drug in solution out of the coated tablet. The diffusivity of drug was strongly affected by the concentration of the liquid and naturally it increased largely when the concentration of liquid was increased. An increase in osmolality of dissolution fluid also decreased the amount of outer water would penetrate through the film coat, thus this situation also decreased the drug diffusivity. The transfer of both dissolved drug and permeating were controlled by transient diffusion.

The longer lag time was found as the osmotic pressure of dissolution medium increased as previously shown in Figure 21. This demonstrated that osmotic pressure of medium obviously affected the lag time. The lag time was the initial phase where coated tablet was introduced into dissolution fluid, permeating fluid penetrated through the film coat, dissolved the encapsulated drug and built up osmotic pressure inside tablets. The decreasing in osmotic water influx by increasing the osmotic pressure of dissolution medium could obtain. The rate of solvent to dissolve the core component and the formation of inside osmotic pressure was slower, thus the lag time was prolonged.

2.8.4 The effect of osmotic agent

After moist heat treatment for 5 h, the values of release exponent (n) of chitosan film coated tablets containing various amount of NaCl with 400 μm of passageway are shown in Figure 28 and Table 13. The drug release mechanism of propranolol HCl treated tablet without osmotic agent in deionized water was anomalous transport An increase in osmotic agent content caused an increase in release exponent (n). This result presented that the release mechanism was supercase

Table 13 The coefficient of determination and release rate from curve fitting of drug release from different core tablets coated with chitosan film after moist heat treatment at 60° C for 5 hour with 0.4 mm passageway in deionized water

Formula	Zero order		First order		Higuchi model		Weibull model	Power law expression model		
	R^2	k	R^2	k	R^2	k	R^2	R^2	n	k
B1:5:400	0.9945	0.1958	0.9909	0.0019	0.9986	5.6252	0.9973	0.9962	0.8833	0.0044
B2:5:400	0.9782	0.0883	0.9980	0.0008	0.9897	5.2675	0.9869	0.9963	2.3196	8.3571
B3:5:400	0.9622	0.0874	0.9974	0.0008	0.9788	5.2281	0.9732	0.9893	2.4698	3.2550
B4:5:400	0.9777	0.0839	0.9997	0.0009	0.9870	5.1856	0.9865	0.9888	2.3817	5.2444
B5:5:400	0.9795	0.1428	0.9998	0.0017	0.9858	7.6563	0.9904	0.9470	2.2055	3.2282

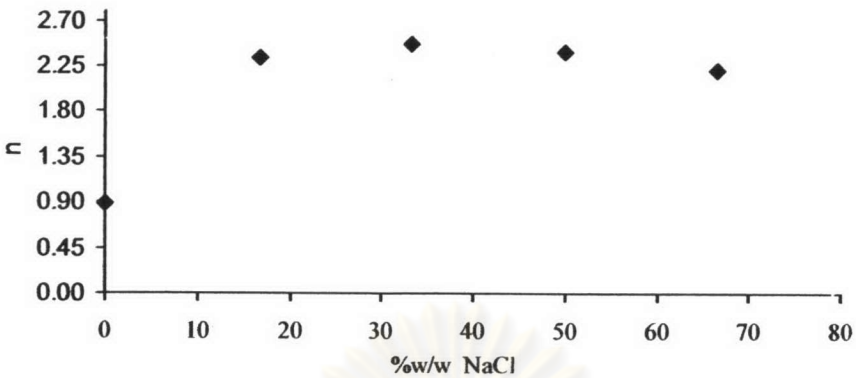


Figure 28 The relationship between the release component (n) and percentage of sodium chloride in core tablet of propranolol HCl coated tablets after moist heat treatment for 5 hr with 400 μm of passageway in deionized water

II. Incorporation of NaCl increased the osmotic pressure inside coated tablet. However, the release rate was decreased due to the influence of the prolonged lag time as shown in Figure 24. When disregarding the lag time, the release mechanism of coated tablet with NaCl was supercase II. This result confirmed that the osmotic pressure influenced on the mechanism of drug release, beside diffusion and polymer relaxation mechanism.

The retardation of drug release due to longer lag period was obviously evident after incorporation of NaCl into the core tablets. This evidence was attributed to the change of chitosan conformation by ionic strength effect. Incorporation of NaCl, led to increase in the ionic strength and osmotic pressure inside coated tablet. In high ionic strength concentration (core 2, 3, 4), the conformation of chitosan became contracted. The related effect with small molecular weight chitosan in solution with ionic strength between 0.01-0.3 M was reported (Tsaih and Chen, 1997). This result could indicate the decrease of permeating medium to penetrate through the film coat. When amount of NaCl was more increased, the ionic strength and osmotic pressure inside coated tablet was also increased. When ionic strength increased to infinity (core

5), the protonated amine group was neutralized. Chitosan conformation became extended. The increase of ionic strength with increased osmotic agent of more than 66.67 %w/w would raise the release rate. The increase of osmotic pressure and change of chain conformation provided the greater drug release than those with lesser amount of NaCl. This demonstrated that osmotic mechanism and ionic strength affected the drug release profile.

2.9 Surface Topography

Scanning electron micrographs showing the surface topography of coated tablets are illustrated in Figure 29. The coated film was rough and homogeneous. However, several reports showed that the membrane prepared from chitosan was transparent, integral, homogeneous and dense (Shu and Zhu, 2002; Lim and Wan, 1995; Qurashi, Blair and Allen, 1992). The introduction of magnesium stearate to film-coating formulation produced rough with solid particles dispersed in the film texture (Ritthidej, et al., 2000) After moist heat treatment at 60°C for 5 h, smoothner film could be observed, as seen in Figure 29 B1 and B2.

The cross-section topography of coated tablets which core tablets containing different amount of sodium chloride between 0 to 66.67 % (core 1-5) are displayed in Figure 30. The scanning electron photomicrograph showed that the film was rather loosely adhered to the core tablet surface. There were void spaces as boundary layer between core surface and film coat. An addition of NaCl into core tablets resulted in thickener film. NaCl had tapped density value more than lactose (Arthur, 2000). Thus, the volume of NaCl under pressure was less than lactose. NaCl incorporation in core tablets would decrease the thickness and surface area of core tablets. As the volume of film solution to surface area ratio was increased, thickener coated film was resulted. In addition, the process of coating was concerned. Higher amount of NaCl would diminish the void spaces in the cross-section especially coated tablets which containing NaCl 66.67 % (core 5). It might be due to the lower strength of coated tablets. NaCl particles had lower adhesive force than lactose. Adding NaCl led to a decrease in the amount of lactose that affected the hardness of core and coated tablets. Weak tablet would have low resistance to pressure from cross-section method. The

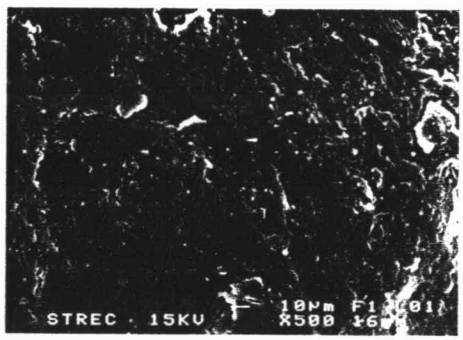
lower void space in the cross-section while increasing amount of NaCl was obtained. The inferior void space of NaCl containing coated tablets after moist heat treatment had the same reason which concerned hardness of tablets. After treatment, the tablet strength was lower. When tablets were exposed to atmospheres with high relative humidity, multimolecular adsorption of water could occur followed by condensation of water in the pore of tablet. Ahleck and Alderborn (1989) suggested that the presence of condensed water in the pore of tablet would reduce the bonding force between particles in the tablet and thus decrease the tablet strength. Moreover, the cross-sectioned clue on film and smoother core tablet content in cross-sectioned area were clearly observed on weak tablets after treatment as shown in Figure 31 B, C, D and E. It might be due to the low strength of tablet. The pressure from cross-sectioned method produced the core composition to fuse together. The smooth core tablet content in cross-sectioned area was exhibited.

In case of passageway, scanning electron micrographs showed the surface and shape of 400 μm orifice that was performed by high speed drilling machine. The round shape and untrimmed passageway edge were obtained. There was only minute dissimilarity on two individual samples, as displayed in Figure 32 A and B which indicated the reproducibility of the drilling process. It could be suggested that the drilling was suitable method to provided orifice.

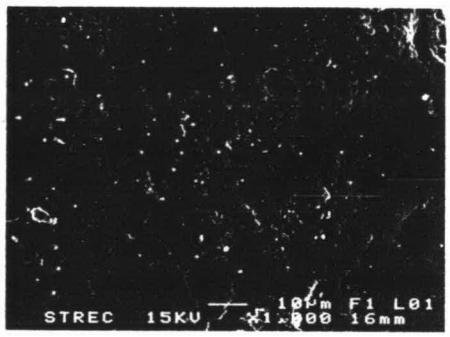
2.10 Physicochemical Properties

2.10.1 Powder X-ray Diffraction

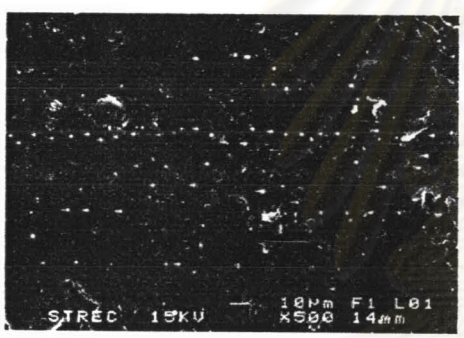
The powder X-ray diffractograms of chitosan powder, chitosan acetate cast film, film peeled off from coated tablet and after exposure to moist heat are depicted in Figure 33. The diffraction characteristic of chitosan powder was composed of a large reflection at 20°2θ and a minor reflection at 10.6°2θ, respectively. Ogawa (1991) had proposed chitosan into three forms: non-crystalline, hydrated crystalline and anhydrous crystalline. The hydrated crystalline structure showed one of reflection at 10.4°2θ and anhydrous crystalline showed one of reflection at 15°2θ.



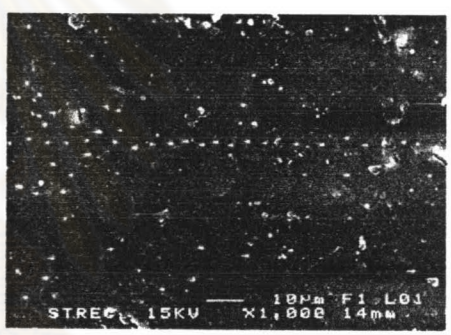
A1



A2



B 1



B 2

Figure 29 Surface morphology of tablets coated with chitosan acetate film: freshly prepared (A) and after exposure to moist heat at 60°C for 5 h (B) (1: surface area x 500; 2: surface area x 1000)

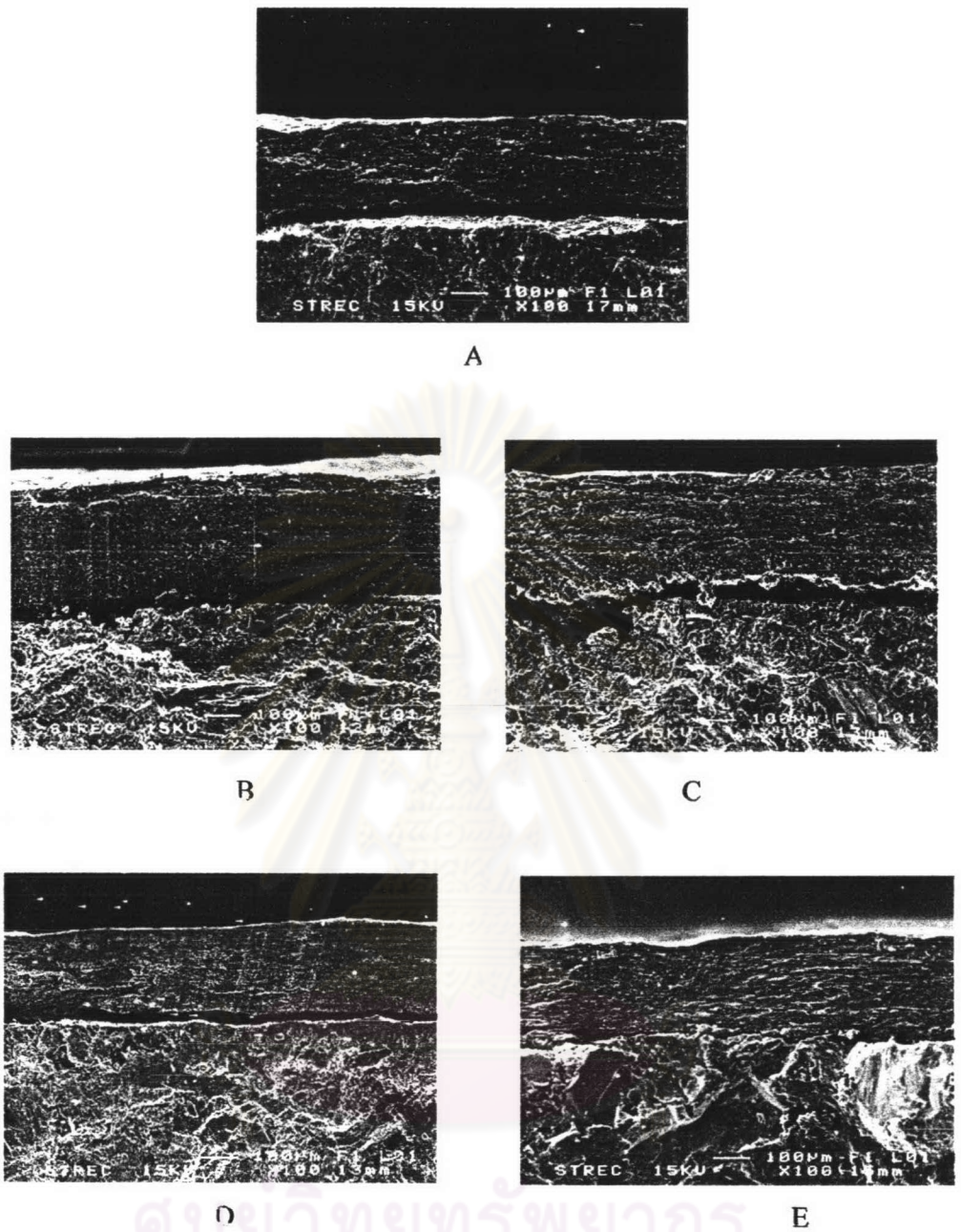
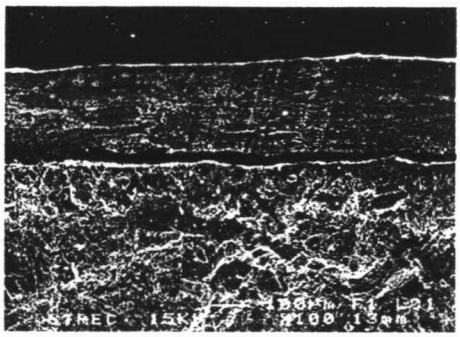
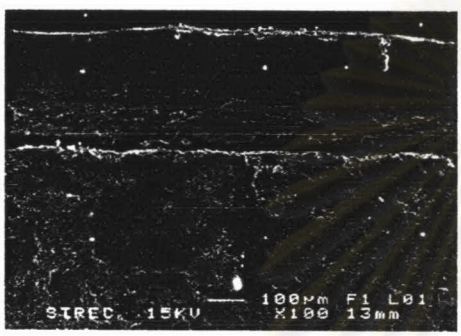


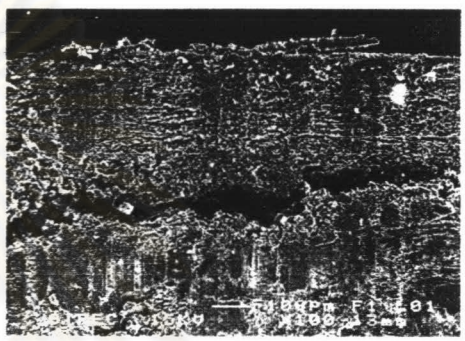
Figure 30 Scanning electron photomicrographs of the cross section of coated tablets that core tablets containing sodium chloride 0% (A) 16.67% (B) 33.33% (C) 50% (D) and 66.67% (E) w/w (cross section x 100)



A

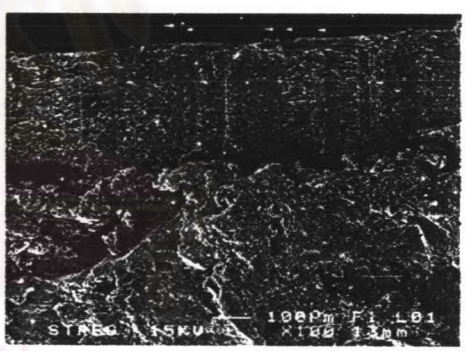


B



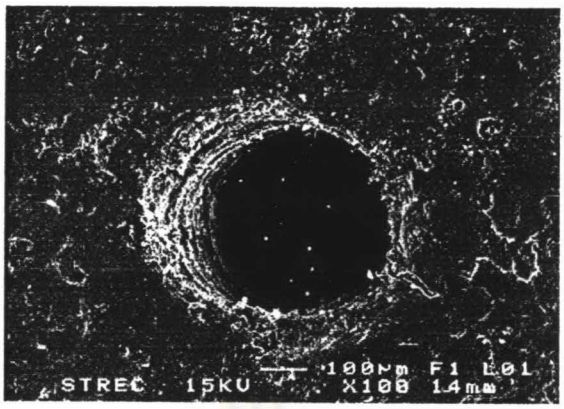
C

D

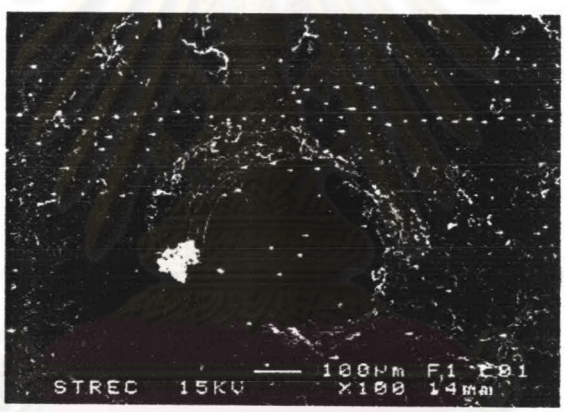


E

Figure 31 Scanning electron photomicrographs of the cross section of coated tablets after exposure moist heat at 60°C for 5 h that core tablets containing sodium chloride 0% (A) 16.67% (B) 33.33% (C) 50% (D) and 66.67% (E) w/w (cross section x 100)



A



B

Figure 32 Surface morphology of passageway of tablets coated with chitosan acetate after exposure to moist heat at 60°C for 5 h (passageway size 400µm x 100)

Since the diffraction pattern of chitosan powder exhibited reflection at 10.6°2θ, the chitosan used this study was hydrate form. In addition, Yui et al. (1994) and Ogawa et al. (2004) claimed that anhydrous crystalline became insoluble in acidic solvents which involved the noncrystalline region whereas hydrated crystals were easily dissolved in acidic medium. Hence, it was strongly evident of the existence of hydrated crystalline form of chitosan in this experiment.

By comparison, the crystallinity of salt form of chitosan was less than neutral from. The diffraction of chitosan acetate film exhibited small peaks around 15°, which had been attributed to the anhydrous crystal lattice (Srinivasa et al., 2004). Moreover, reflection at 9.5° and 21.5° was observed, indicating that occurrence of small amounts of hydrate crystals.

The powder x-ray diffraction pattern of magnesium stearate, stearic acid and brilliant blue are displayed in Figure 34. The dominant peaks of magnesium stearate were detected at 5.4, 21.3, and 21.7°2θ. Magnesium stearate utilized in this study exhibited the diffraction pattern of anhydrate form which characteristic was described by Ertel and Cartensen (1988). Of particular interest was the region near 2θ = 21°. The diffractogram of the dihydrate or trihydrate magnesium stearate exhibited several distinct peaks while in the case of the anhydrate, there was mainly single broad peak. This type of peak was indicative of a structure in which the magnesium atoms of magnesium stearate were arranged in irregularly spaced parallel planes. (Ertel and Cartensen, 1988). It was observed that the intensities of diffraction peak of chitosan acetate film after incorporation of additive (magnesium stearate, castor oil and brilliant blue) which was peeled off from coated tablets were stronger than that of chitosan acetate cast film and exhibited some new peaks that were different from cast film peak. This result indicated that peeled off film from coated tablets comprised of main characteristics peak of each substance in the film. The major reflection of peeled off film chitosan were corresponded to stearic acid peak characteristic (at about 9.5, 21.5 and 28.66°2θ) which resulted from the transformation of magnesium stearate to stearic acid under acidic condition. However, the reflection at 5.32°2θ still presented in the diffraction of coated film which indicated the existence of magnesium stearate. After moist heat treatment for 5 h, it was found that there was no change in X-ray

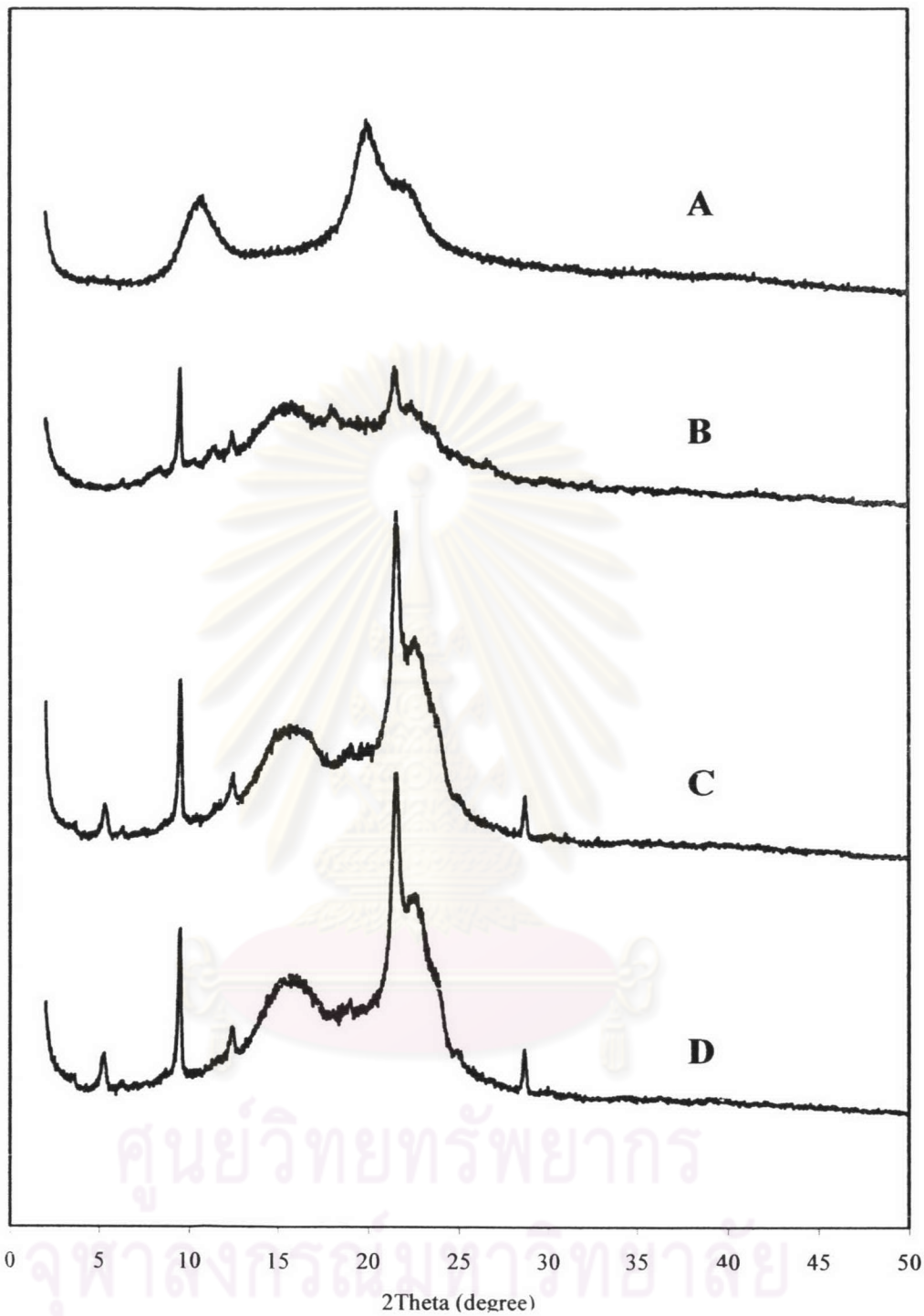


Figure 33 X-ray diffractograms of (A) chitosan powder; (B) chitosan acetate cast film; (C) film peeled off from coated tablet; and (D) film peeled off from coated tablet after exposure to moist heat at 60°C for 5 hrs.

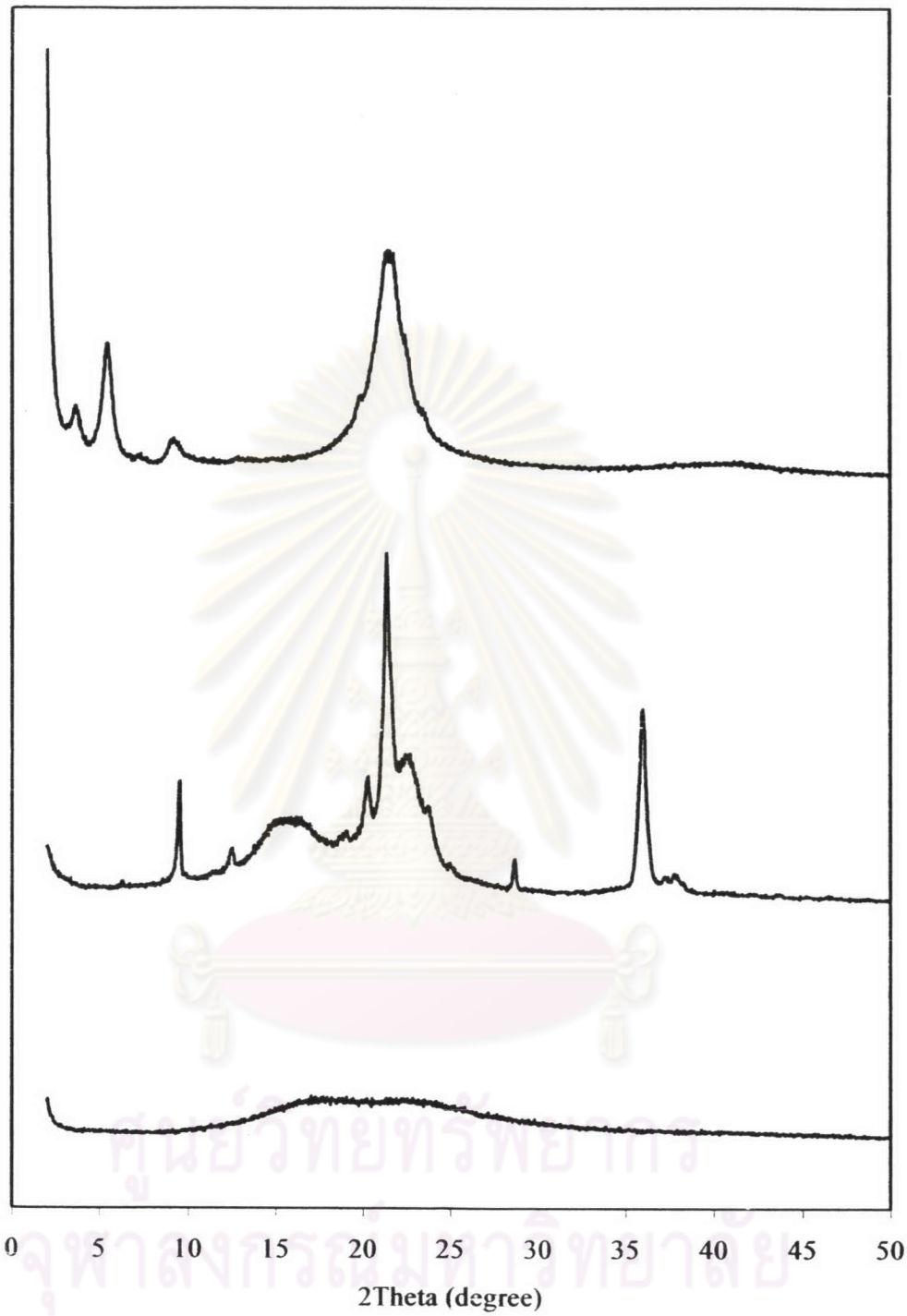


Figure 34 X-ray diffractograms of (A) magnesium stearate; (B) stearic acid and (C) brilliant blue

diffraction pattern. It could be concluded that moist heat treatment did not affect the structural arrangement of coated film.

2.10.2 Fourier Transform Infrared (FT-IR) studies

The IR spectra of chitosan powder, chitosan acetate cast film, film peeled off from coated tablets and after exposure to moist heat treatment are illustrated in Figure 35. In the infrared spectrum of chitosan powder, sharp bands were observed at 1595.9, 1670, 2990 and 3436.8 cm^{-1} in the region 1600-3500 cm^{-1}. The NH_2 deformation at 1595.9 cm^{-1} representing the glucosamine function group and the C=O stretching (amide I) peak was observed at 1670 cm^{-1} representing the structure of N-acetylglucosamine The broad band centered at 3436.8 cm^{-1} was assigned O–H stretching indicating of intermolecular hydrogen bonding and the peak nearly to 2990 cm^{-1} was C–H stretching band. The same appearance was reported by Nunthanid et al (2004) and Imai et al (1991).

The evidence from FT-IR spectra of chitosan acetate cast film exhibited the peak at 1566.1 cm^{-1} which were indicated to $-NH_3^+$ band (Osman and Arof, 2003) but the band at 1595.9 cm^{-1} indicating of $-NH_2$ deformation was disappeared. Additionally, the weak absorption at near 1710 cm^{-1} due to C=O stretching vibration of free carbonic acid (Yamamoto et al., 1997) was found. The disappearance of NH_2 deformation in the chitosan acetate film was probably due to interaction between NH_3^+ of chitosan and –COO– of acetic acid molecules to form the amide linkage (C=O–NHR).

The FT-IR spectra of chitosan acetate film containing additive (magnesium stearate, castor oil and brilliant blue) that peeled off from coated tablets appeared shoulder peak at 1746 cm^{-1} indicating of the carbonyl of esters which were the component of castor oil. The dominant peaks of coating film at wavelengths of 2919.77 and 2852.21 cm^{-1} were from C-H symmetric and symmetric stretching of hydrocarbon chains in stearic molecule of magnesium stearate. The shift of peaks to the lower wavelength from 1566.1 to 1544.1 cm^{-1} after incorporation of several additives in chitosan acetate film was observed. This evidence might be the ionic

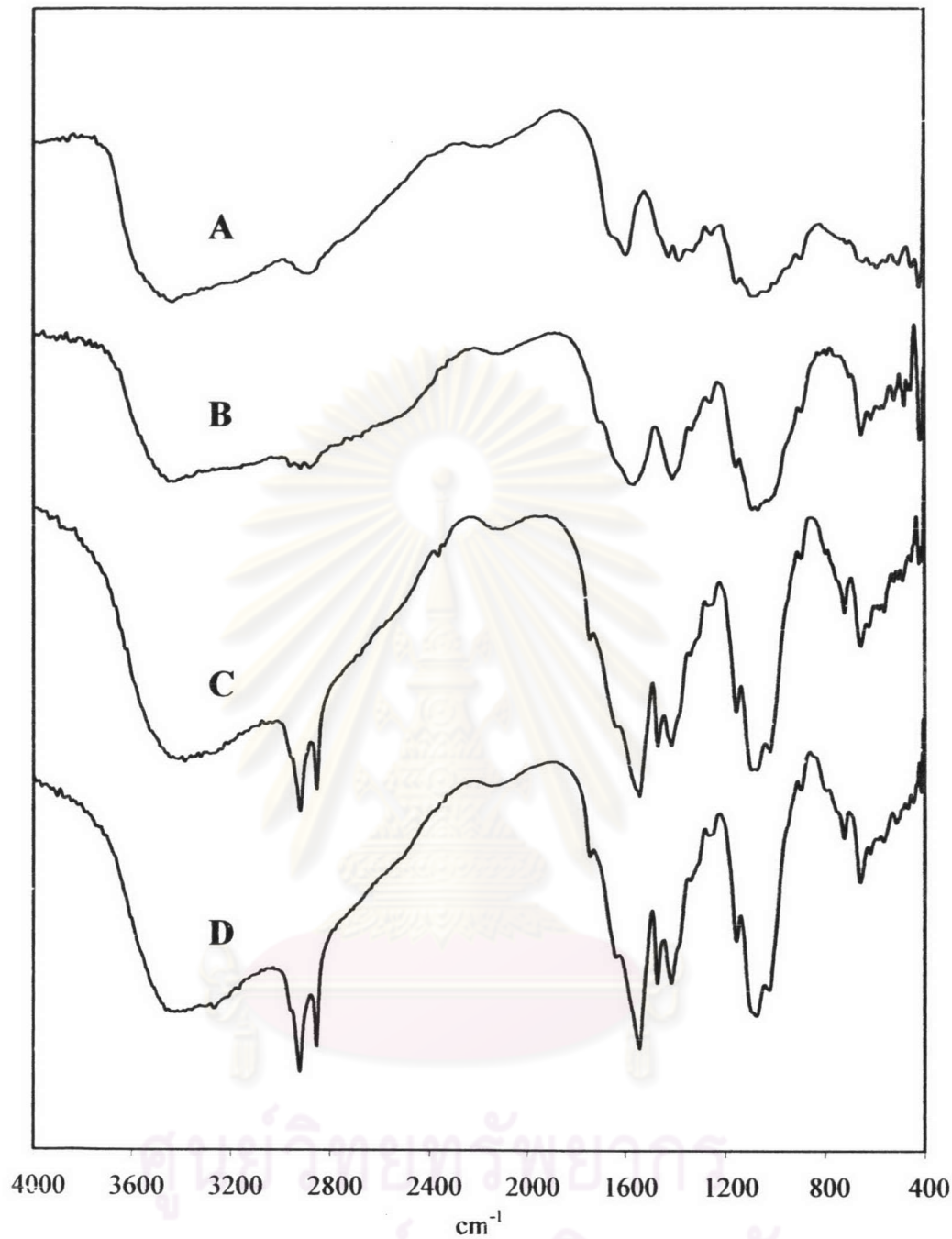


Figure 35 FT-IR spectra of (A) chitosan powder; (B) chitosan acetate cast film; (C) film peeled off from coated tablet and (D) film peeled off from coated tablet after expose to moist heat at 60°C for 5 hrs.

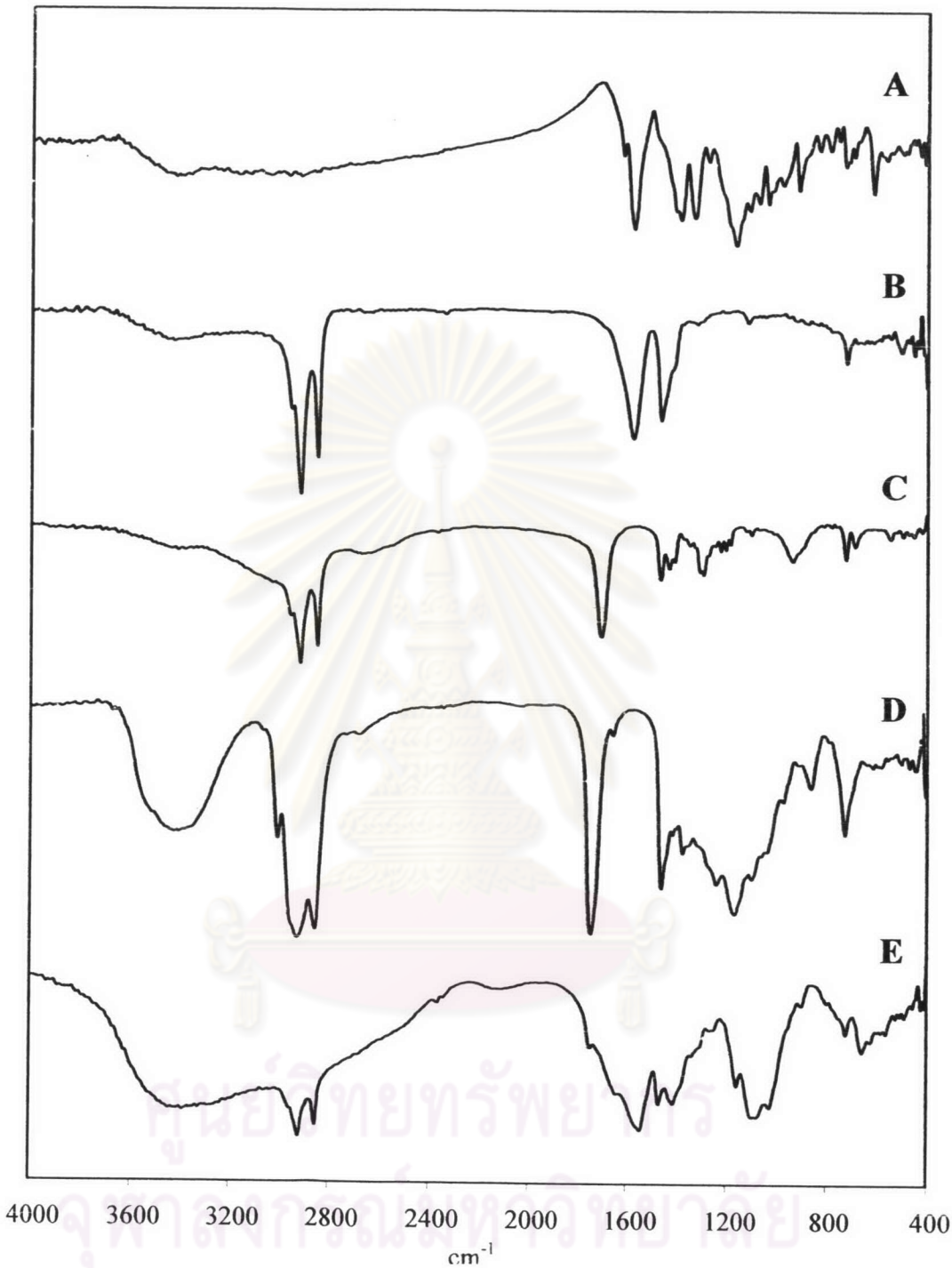
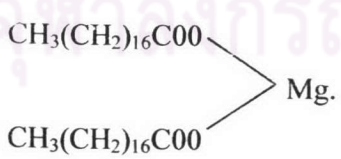


Figure 36 FT-IR spectra of (A) brilliant blue; (B) magnesium stearate; (C) stearic acid; (D) castor oil and (E) film peeled off from coated table

interaction between protonated amino groups on chitosan and carbonyl group of stearic acid liberated from magnesium stearate molecule. This was the suggestion by Phaechamud (1999). While the longer duration of moist heat treatment, the sharper of peak of C=O stretching (1655 cm^{-1}) was found in coating film. This evidence indicated to the amide formation. Ritthidej (2002) suggested that moist heat treatment at the temperature of 60°C and 75 %RH could change ionic interaction to rather homogeneous amide formation in chitosan film. In other words, the sharper peak of C=O stretching represented the structure of N-acetylglucosamine of chitin, while the strong peak at 1550-1600 cm^{-1} region indicated the acetate salt form were absent. The incidence of the conversion of chitosan acetate film to chitin was also reported by Nunthanid, et al. (2004) and Toffey et al. (1996).

The FT-IR spectra of magnesium stearate and stearic acid are displayed in Figure 36. **The dominant peaks occurred at 2920.2 and 2851.7 cm^{-1} in FT-IR spectra** of magnesium stearate and stearic acid were the C-H symmetric and symmetric stretching of hydrocarbon chains in stearic molecule. The broad peak around 3100-3600 cm^{-1} was the peak representing the water crystallization in magnesium stearate. This characteristic was also detected in FT-IR spectrum of stearic acid. The small peak at about 1467 cm^{-1} was the CH_2 stretching found both in spectra of magnesium stearate and stearic acid. The peak appeared at 1577.6 cm^{-1} in FT-IR spectra of magnesium stearate was the COO^- asymmetric stretching which indicated that the carbonyl group was in an ionized state. In other words, this broad band at 1577.6 cm^{-1} was assigned to the asymmetric metal carboxylate stretching vibration. These peak characteristics of metal stearate were identified by Antony et al (1999). The C=O stretching of stearic acid was appeared at 1704.6 cm^{-1}. Thus, the magnesium salt of stearic acid was formed at the carbonyl end of the molecules as illustrated.



The differences between the infrared absorption spectra of stearic acid and magnesium stearate are mainly due to change in absorption bonds association with the carbonyl group. The peak shift of magnesium stearate from 1577.6 to 1704.6.6 cm^{-1}

of stearic acid indicated that the carbonyl groups had changed from an ionized to an unionized state in forming stearic acid. The stearate chain could liberate from magnesium salt in dilute acetic acid, as confirmed by Ritthidej et al, 2000. The breakdown product of magnesium stearate molecule, stearic acid that containing carbonyl group in its structure could interact with protonated amino group on chitosan by electrostatic charge. The peak at 1544.1 of coated film was CO_2 symmetrical stretching. This might be the result of partial ionic interaction between protonated amino groups on chitosan and carbonyl group of stearates in stearic acid and magnesium stearate molecule.

2.10.3 Differential Scanning Calorimetry (DSC) studies

The DSC thermograms of chitosan powder, chitosan acetate cast film, film peeled off from coated tablet and after exposure to moist heat treatment are shown in Figure 37. The endotherm with peak temperature near 100°C, attributable to water loss, represented the energy required to vaporize water that present in the chitosan acetate cast film (Lim and Wan, 1995; Kittur et al., 2002; Nunthanid et al., 2004). Chitosan molecules had a strong affinity for water molecules. Chitosan acetate films had a higher affinity for water compared with powder, probably because the chitosan molecule in the films was protonated, rendering the film more hydrophilic than the powder (Cervera et al., 2004). Hence, chitosan acetate film still exhibited the endotherm near 100°C.

The endothermic peak of magnesium stearate appeared at 110.2°C as showed in Figure 38. Ertel and Cartensen (1988) reported that the thermogram obtained from the anhydrous form of magnesium stearate exhibited a single endothermic transition that associated with the melting of the crystals. Therefore, magnesium stearate in this study was anhydrous form which corresponding to the result in power x-ray diffractogram. DSC analyses of chitosan acetate coating film that containing additives showed that there was no endothermic peak of magnesium stearate and/ or stearic acid but the new endothermic peak was appeared at 87.1°C. This endothermic peak should be the characteristic of hydrate form of magnesium stearate since the anhydrous form of magnesium stearate changed to trihydrate form during coating process. When the relative humidity exceeded 50% the anhydrate rehydrated to form a trihydrate as

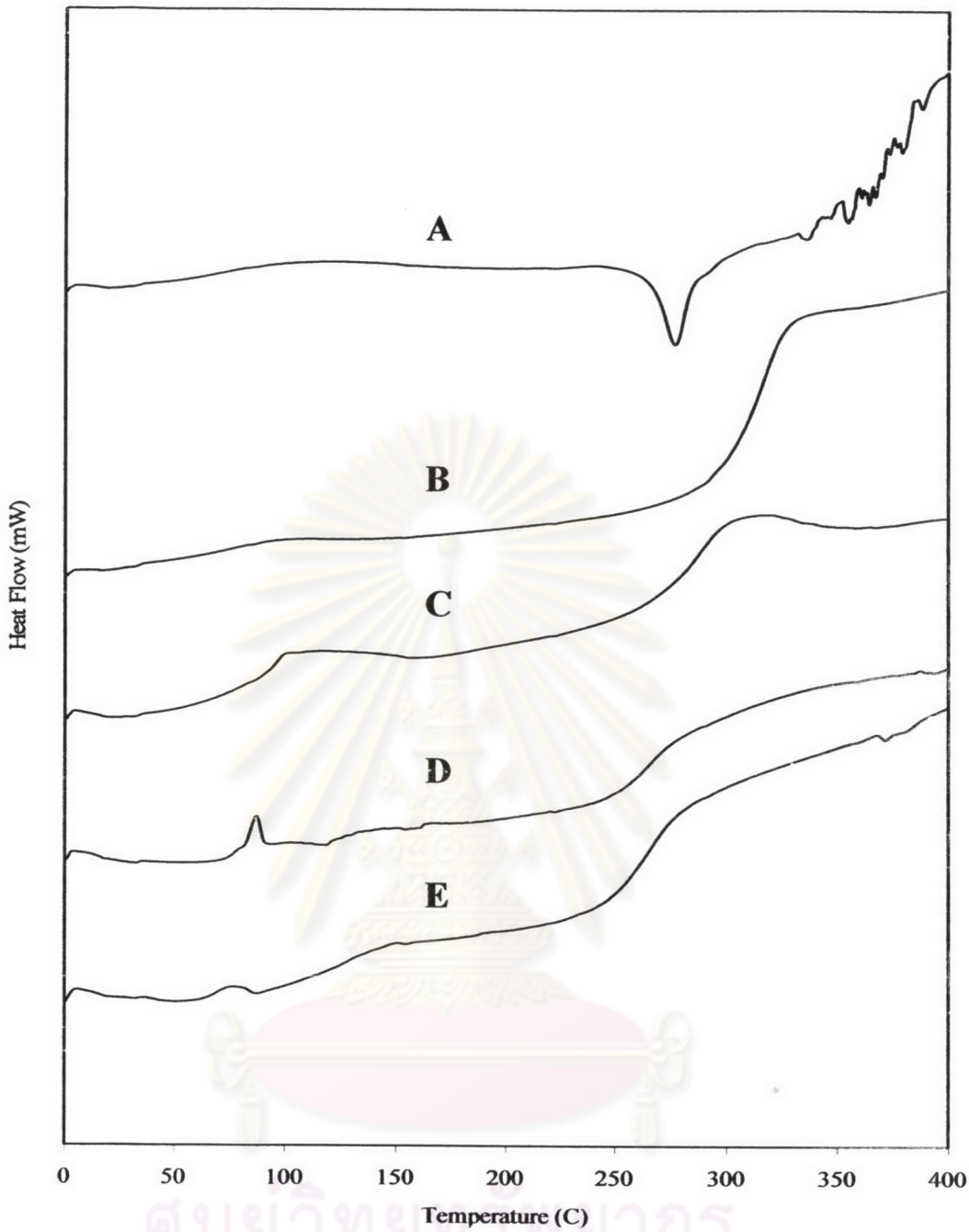


Figure 37 DSC thermogram of (A) brilliant blue; (B) chitosan powder; (C) chitosan acetate cast film; (D) film peeled off from coated tablet; and (E) after expose to moist heat at 60°C for 5 hrs.

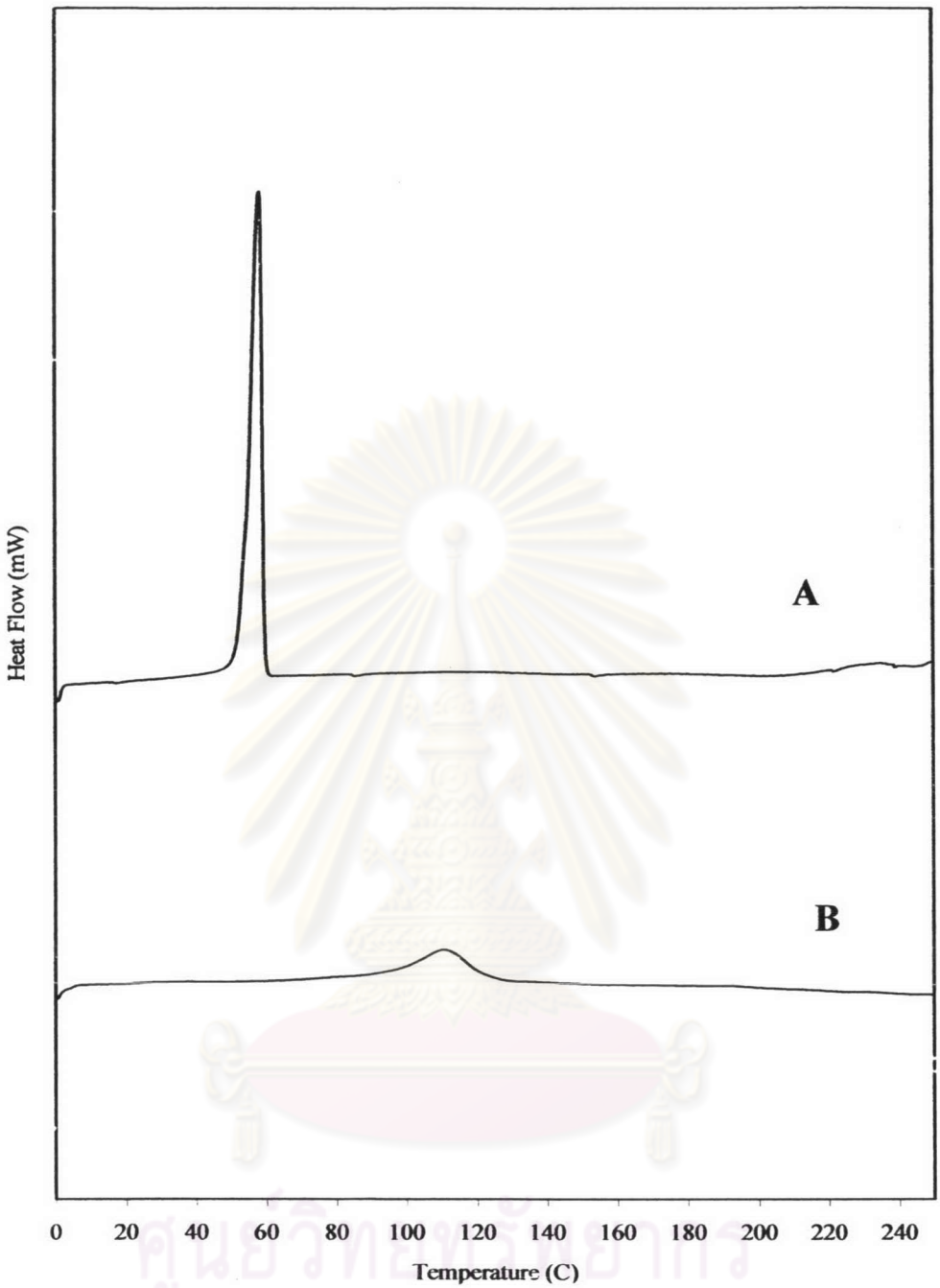


Figure 38 DSC thermogram of (A) stearic acid and (B) magnesium stearate

reported by Ertel and Cartensen (1988). Moreover the endothermic peak represented the loss of water from dihydrate and trihydrate magnesium stearate at about 100.1°C and 82.9°C respectively (Ertel and Cartensen, 1988). For coated film after moist heat treat for 5 h, the lower endotherm peak at 87°C was noticed. The lower endotherm peak that represented the loss of water from hydrate form might be caused by the lower quantity of hydrate form of magnesium stearate. This finding might be attributed to the generation of anhydrate by moist heat treatment. Ertel and Cartensen (1988) revealed that the anhydrate could be regenerated by drying the trihydrate at 105°C. Thereby after treatment, the lower endotherm peak at 87°C was shown.

2.11 The Tablet Swelling and Change of Passageway Size

As previously mentioned, the release profile was controlled by diffusion and osmotic mechanism. Therefore, the membrane permeability and the nature of the polymer membrane were important. The tablet swelling and change of passageway size might be the useful clues to explain the difference in drug release rate of the film coat under the different experimental conditions.

Propranolol HCl film coated tablets containing various amount of NaCl with 400 μm of passageway after moist heat treatment at 60°C for 5 hours were chosen for investigated in deionized water. The percent swelling of all treated tablets between swelling tests was more than those before experiment as represented in Figure 39. During the first 6 h, the maximum percentage of tablet swelling was from those without NaCl. The decrease of tablet swelling was clearly observed when NaCl was incorporated into the core tablets especially core tablet contained NaCl of 16.67-50 %w/w (core 2, 3 and 4). This evidence was attributed to the change of chitosan conformation by ionic strength effect. Adding NaCl provided ionic strength increased. In high ionic strength, the conformation of chitosan become contracted (Tsaih and Chen, 1997). Hence, chitosan film coated tablet with NaCl 16.67-50 %w/w (B2:5:400, B3:5:400 and B4:5:400) was less swelling than those without NaCl (B1:5:400). This result was corresponding to the prolonged time lag and decrease the drug release when NaCl was incorporated into the coated tablets. However, while the amount of NaCl was sufficiently increased (B5:5:400), the tablet swelling was also

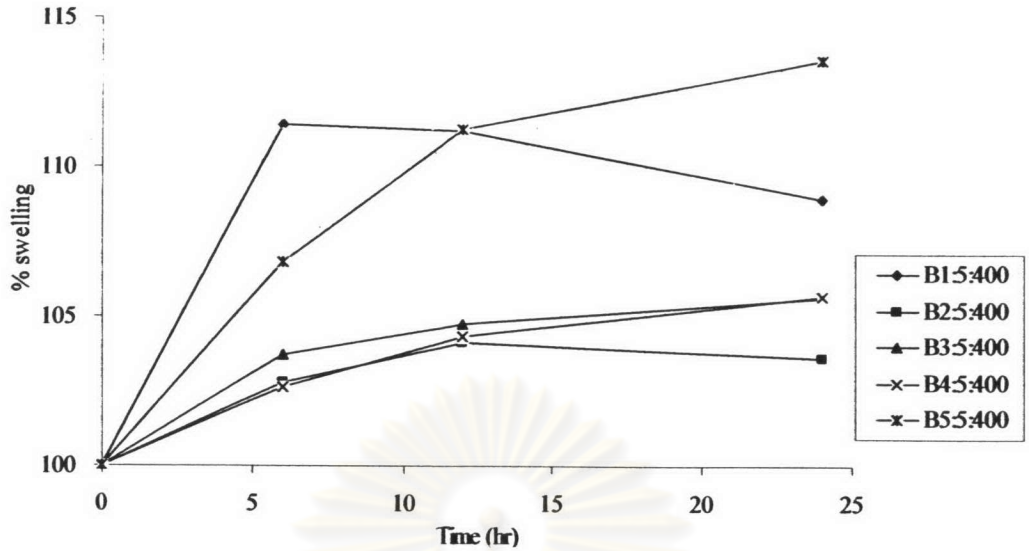


Figure 39 The percent swelling of propranolol HCl film coated tablets containing different amount of sodium chloride after moist heat treatment at 60°C for 5 h in deionized water

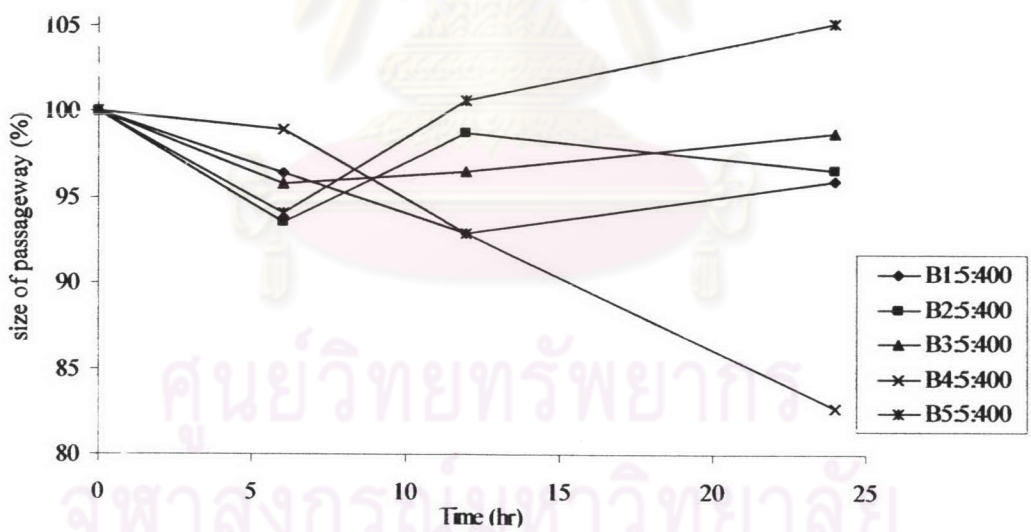


Figure 40 The size change of passageway of propranolol HCl film coated tablets containing different amount of sodium chloride after moist heat treatment at 60°C for 5 h in deionized water

increased. It was obvious that coated tablet with NaCl 66.67 %w/w (B5:5:400) was more swelling than those with lower amount of NaCl (B2:5:400, B3:5:400 and B4:5:400) and also more than those without NaCl (B1:5:400) after 12 hours. This characteristic was also affected by the ionic strength. While ionic strength increased to infinity, the protonated amino group was totally neutralized. The destruction of intra-molecular hydrogen bonds was occurred. The conformation of chitosan would dilate (Tsaih and Chan, 1997), thus high swelling of tablets with NaCl 66.67 % (B5:5:400) was obtained. Moreover, the increase of NaCl amount was also increased osmotic pressure inside coated tablets. Osmotic pressure would be another important factor that affected to increase the swelling of high amount NaCl tablets. The percent swelling of coated tablet with lowest amount and without NaCl was decreased after 6 h. The increase of osmotic pressure with the increasing osmotic agent of more than 33.33 %w/w (B3:5:400 and B4:5:400), increased the swelling until 24 h. Furthermore, coated tablet containing NaCl of more than 66.67 % (B5:5:400), exhibited different of swelling. This evidence was explained that osmotic pressure had influence on the tablet swelling in addition to the effect of ionic strength.

The change of passageway size of treated tablets containing various amount of NaCl was evaluated, as represented in Figure 40. The change of passageway size was not clearly distinguished in some cases probably due to the small amount of sample and other factor such as unsmooth edge of the orifice from the drilling, the swelling of polymer and the measurement by photography. The changes of passageway size of treated tablets within 24 h in deionized water were less than 30%. During first 6 h, all treated tablets showed increased tablet swelling and the smaller size of passageway were noticed. It could be explained by the hydration and swelling of coated film. The polymeric coating was hydrated in the beginning with the dissolution medium, following by chain relaxation which led to increase membrane swelling. The expansion of coating film from membrane swelling behavior possible caused smaller size of passageway. This step could also prolong the lag time in drug release characteristic. Therefore. the membrane swelling could affect the alteration of passageway size.

During 6-12 h, the passageway size of treated coat tablets containing NaCl tended to increase, whereas those without NaCl had decreased size of passageway.

Adding NaCl led to increase osmotic pressure inside tablets. The increase of osmotic pressure inside tablet provided the increase of water intake and driven off which might influence the passageway size. Thus, osmotic pressure would affect the change of passageway between dissolution tests. However, the decreased size of passageway from coated tablets without NaCl might be caused by the higher swelling behavior during this period. After 12 h, most coated tablets with NaCl had larger size of passageway than these without NaCl. Moreover, coated tablet with lower amount of NaCl (B2:5:400 and B3:5:400) exhibited slight alteration of passageway size, whereas B5:5:400 showed an increased in passageway size until 24 h. The coated tablets with highest NaCl quantity (B5:5:400), the osmotic pressure could cause erosion of weak membrane around orifice by increase of water intake and driven off. It could be explained that osmotic pressure by NaCl was important factor influenced the change of passageway. This study was concluded that the osmotic pressure inside tablets together with membrane swelling affected to change of passageway size.