Original Article

Effect of Particle Size of Chitosan on Drug Release from Layered Matrix System Comprising Chitosan and Xanthan Gum

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ABSTRACT

Biopolymers such as chitosan and xanthan gum were applied as matrix component for fabrication into tablet using a direct compression technique to control the release of propranolol HCl. Covering both planar surfaces of middle tablet with polymeric mixture containing chitosan-xanthan gum-lactose could modulate the release of propranolol HCl. Increased amount of lactose enhanced the drug release and diminished the pH sensitive drug release of tablet containing chitosan and xanthan gum. However, the drug release from the three layer tablets comprising this system was pH dependent. Particle size of chitosan did not significantly affect the drug release from the three layer tablets comprising this system. The drug release behaviour from the developed tablets was characterized with the curve fitting with different mathematical equations and the water & erosion studies.

Key words: chitosan, drug release layered matrix, particle size, xanthan gum

Thai Pharm Health Sci J 2008;3(1):1-11[§]

Introduction

Matrix diffusion seems to be a suitable system in producing oral sustained release dosage form, especially tablet, in term of the economic and scale-up process. It can be achieved by using appropriate type and concentration of a matrix substance, followed by a general tablet manufacturing such as compression. Matrix system comprising chitosan and xanthan gum was claimed to sustain the release of water soluble drug. FT-IR and DSC studies exhibited the charge interaction between NH_3^+ of chitosan molecule and COO^- of acetate or pyruvate groups of xanthan gum molecule of this matrix system.[1]

Three-layer matrix tablets have been investigated on different core or barrier composition. Linear release profiles could be obtained by applying hydrophilic barrier layers on both faces of the hydrophobic matrix tablet, or by applying a hydrophilic barrier layer on one face and a hydrophobic barrier layer on the other face of the matrix tablet.[2-4] Increasing the amount of matrix in barrier or in middle layer of the three layer tablet containing chitosan and xanthan gum resulted in prolongation of drug release.[1] Furthermore, the investigation of drug release from one planar surface demonstrated that the lag time for drug release through barrier layer was apparently longer as the amount of barrier was enhanced.[1] Except for the amount of polymer used, the particle sizes of polymer was also a decisive factors in controlling release rates of drug from matrix tablet.[5] Some investigation revealed that the coarse fractions of hydroxypropyl methyl cellulose (HPMC) hydrated too slowly to allow sustained release.[6] As the content proportion of HPMC was higher, the effect of the particle size was less important on the release of propranolol hydrochloride, while the effect of this variable was more important when

[§] 13th year of Srinakharinwirot Journal of Pharmaceutical Science

the content of this polymer was low,. However HPMC particles in certain areas of the matrices containing low levels of HPMC led to burst release.[7] The behaviour and function of the particle size of HPMC have also been explained by its fibre content and the resultant problems encountered in sieving fibre-like materials.[8] Thus, the different particle size ranges may not only differ in their size but also in the shape or morphology of the particles.[9] The guaifenesin release rate was dependent upon the particle size of ethyl cellulose and the processing conditions employed to prepare the tablets. The guaifenesin release rate was slower in tablets prepared with the "fine" ethyl cellulose particle size fraction due to the presence of fewer soluble drug clusters within the matrix. Tablets prepared by direct compression using "coarse" ethyl cellulose were found to release guaifenesin by both diffusion and erosion.[10]

Although considerable research has been done on such above mentioned manner, the investigation of the effect of particle size of chitosan on the drug release from layered matrix containing two polymers which could form the polyelectrolyte complex such as chitosan and xanthan gum has not been addressed. Additionally, the effect of an incorporation of lactose on drug release and effect of pH of dissolution medium on the matrix system comprising chitosan and xanthan gum should be investigated. Therefore, the current investigation dealt with the evaluation the effect of lactose and particle size of chitosan on physical properties and release of propranolol HCl from three-layer tablet comprising chitosan and xanthan gum.

Material and Methods

Materials

Chitosan (Aqua Premier, Chonburi, Thailand) having a degree of deacetylation of 99.3% and molecular weight of 137 kDa with different particle sizes were prepared by grinding chitosan powder with Fitz mill (Kan Seng Lee Factory Ltd., Bangkok, Thailand) and then were separated using sieve shaker. The chitosan powder passing through sieve No. 40, 60, 80, 100 and 200 meshes were used to prepare the tablets. Xanthan gum (Xantural 75, CP Kelco U.S., Inc. Chicago, USA) was used as received. Propranolol hydrochloride (Batch No. 941002) was purchased from China National Chemical Imp. & Exp., Shanghai, China. Lactose was purchased from Wyndale, Hawera, New Zealand. Magnesium stearate (Lot No. MAF 07, P. C. Drug Center Co.) was passed through sieve No. 80 mesh before used. Sodium chloride (Lot k20420804, Merk, E Merck, Darmstadt, Germany) was used as received. All other reagents were of AR grade.

Preparation of matrix tablets

The 400-mg tablets containing propranolol HCl were prepared by direct compression method. The tablets containing chitosan and xanthan gum in the ratio of 1:1 with various amount of lactose were prepared according to the composition in Table 1. The amount of lactose was varied from 25 to 75 % of the matrix component excluding the amount of drug and magnesium stearate. The concentration of drug was kept constantly at 20% by weight (80 mg/tablet). To make the powder mixture, the drug, polymers and lactose were mixed with magnesium stearate for 5 minutes with mortar and pestle. Then the blended drug powder of 400 mg was compressed into a tablet at a compression force of two tons using 13 mm round, flat and plain punches on a hydraulic press (Carver Press, WI). The percent compositions of barrier for the layered matrix tablets are shown in Table 2.

Table 1 Percent composition of different single layer formulations containing lactose with different concentrations*

Substances	Formulation (% w/w)		
	L25	L50	L75
Propranolol HCl	20.00	20.00	20.00
Chitosan	29.25	19.50	9.75
Xanthan gum	29.25	19.50	9.75
Lactose	19.50	39.00	58.50
Magnesium stearate	2.00	2.00	2.00

* L25, L50 and L75 = formulations containing lactose of 25%, 50% and 75% of the matrix component respectively.

Table 2 Percent composition of barrier.

Substance	Formulations (%,w/w)
Chitosan	12.25
Xanthan gum	12.25
Lactose	73.5
Magnesium stearate	2

Layered matrix tablets were prepared by adding 100 mg of the powder mixture without drug in the die cavity and slightly compressed for uniform spreading. The 400 mg of the powder mixture with drug was placed over the first layer and again slightly compressed for uniform spreading. Another 100 mg of the powder mixture without drug was subsequently placed and compressed with a two tons force using a hydraulic press to obtain the three-layer tablet. The dwell time after target pressure achieved was 10 sec.

Evaluation of matrix tablets

The hardness of tablets was determined using a hardness tester (Pharmatest, USA). The tablet thickness and diameter were measured using a thickness tester (Teclock, Japan). The friability was determined as the percent weight loss of 20 tablets. Twenty tablets were weighed and rotated for 100 revolutions in 4 min in a friabilator (Yieheng Engineering, Bangkok, Thailand). The tablets were then weighed again and the percentage friability was calculated. A test of drug release was undertaken using a dissolution apparatus (Prolabo, France) with the basket method at 100 rpm. A volume of 900 mL of HCl buffer pH 1.2 equilibrated at 37 ^{o}C was utilized as dissolution fluid. Samples were collected at specific time intervals and assayed by a UV-Vis spectrophotometer (Perkin-Elmer, Germany) at a wavelength of 320 nm. To study the effect of the dissolution fluid on release behavior, the drug release tests in distilled water, phosphate buffer pH 6.8 and pH change were also undertaken. For the dissolution test with pH change, the drug released in HCl buffer pH 1.2 was conducted for one and a half hour. Then the pH was raised to 6.8 by adding 4.6 g sodium hydroxide, 3.06 g monobasic potassium phosphate and 4.005 g dibasic sodium phosphate. The operation was continued for 12 hours. During the drug release studies, the tablets were observed for physical integrity.

Dissolution profile fitting

Least square fitting the experimental dissolution data (cumulative drug release > 10% and up to 80%) to the mathematical equations (power law, first order, Higuchi's and zero order) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (MSC)[11], given below.

$$MSC = \ln\left\{\frac{\sum_{i=1}^{n} w_i \left(Y_{obs\,i} - \bar{Y}_{obs}\right)^2}{\sum_{i=1}^{n} w_i \left(Y_{obs\,i} - Y_{cal_i}\right)^2}\right\} - \frac{2p}{n}$$

Where Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is the weight that applies to the i-th point, n is number of points and p is number of parameters.

Water uptake study and erosion study

The tablet water uptake and erosion studies were done using the same condition of dissolution study. The weight of tablet (W_0) was determined before tested. At selected time intervals, the tablets were withdrawn, blotted to remove excess water, weighed for wet weight (W_1), then was taken place into the hot air oven at 80 ^{o}C until the tablet weight did not change and weighed for dry weight (W_2). Swelling and erosion characteristics of the tablets were expressed in terms of water uptake (%) and mass loss (%) as following.[12]

$$\text{Water uptake (\%)} = \frac{(W_1 - W_2)}{W_2} \times 100$$

$$\text{Mass loss (\%)} = \frac{(W_0 - W_2)}{W_0} \times 100$$

Results and Discussions

Physical properties of matrix tablets

The data on weight, thickness, friability and hardness of the single and the three-layered tablets are presented in Table 3. The hardness of tablet decreased as the amount of lactose was increased. The hardness of layered tablet increased as the smaller chitosan powder was utilized since the distance between particles was less than that using the larger chitosan powder. The friability of tablets tended to decrease as the smaller chitosan powder was utilized. Friability values of all formulations were less than 1% except the tablet containing lactose 50%.

Table 3 Physical properties of prepared tablets

Formulation§	Weight (mg)* (n = 20)	Thickness(mm)* (n = 10)	Friability (%) (n = 20)	Hardness (Newton)* (n = 10)
L25	401.60 ± 8.10	2.34 ± 0.08	0.73	60.56 ± 8.19
L50	402.56 ± 10.12	2.24 ± 0.03	1.08	36.03 ± 4.58
L75	402.83 ± 7.82	2.25 ± 0.02	0.92	33.39 + 5.37
L75, 3-layer, 40 mesh	596.42 ± 4.82	3.51 ± 0.09	0.65	31.88 ± 1.38
L75, 3-layer, 60 mesh	590.72 ± 2.91	3.49 ± 0.09	0.71	32.66 ± 2.42
L75, 3-layer, 80 mesh	598.14 ± 8.53	3.40 ± 0.04	0.62	33.06 ± 3.69
L75, 3-layer, 100 mesh	596.29 ± 6.82	3.51 ± 0.04	0.45	37.18 ± 3.49
L75, 3-layer, 200 mesh	595.02 ± 4.83	3.48 ± 0.02	0.31	39.41 ± 4.61

* Presented as mean ± S.D,

§ L25, L50 and L75 = formulations containing lactose of 25%, 50% and 75% of the matrix component respectively.

In Vitro Drug Release

Increasing the amount of lactose in 400-mg tablet containing 1:1 chitosan:xanthan gum led to faster drug release as presented in Figure 1. The effect of pharmaceutical diluents on drug release from matrix devices was claimed to be mainly due to a change in hydrophilic gel expansion.[13] These findings were in good agreement of results obtained with diphenhydramine HCl released from polyvinylacetate/polyvinylpyrrolidone matrix containing lactose or maize starch.[14] Lactose, by its water soluble and hydrophilic nature, facilitated gel formation; hence, the time taken for the dissolution medium to permeate to the core was shorter as the amount of this soluble substance was increased. Moreover, soluble substance acted as a channeling agent, by rapidly dissolving and easily diffusing outward, therefore allowed a decrease in tortuosity and/or an increase in the matrix porosity.[15-17] However, the sustainable drug release could be obtained for the matrix containing chitosan and xanthan gum. Ionic interaction between chitosan and xanthan gum decreased the rate of polymer dissolution and the rate of solvent penetration, therefore the drug diffusion into dissolution medium was diminished.

Curve upward of dissolution profile appeared during pH change as shown in Figure 1. The pH dependence of drug release was decreased as the amount of lactose was increased. Moreover, the dissolution profile in HCl buffer pH 1.2 was closer to that in pH change media as the amount of lactose was increased. The difference was apparently minimized in case of the tablet containing 75% lactose. Therefore, lactose could adjust a pH sensitive property of polymeric matrix containing chitosan and xanthan gum due to the reduced amount of chitosan-xanthan gum in the tablet, since the amount of chitosan-xanthan gum played important role in liquid uptake, erosion and swelling of compact matrix.

However, one of the popular methods to obtain the pH independent drug release was the adjustment of the environmental pH in dosage forms. Dissolution profile of drug from alginate matrices was different upon increase of pH. In order to obtain pH-independent drug release, usually pH-modifier agent such as organic acids was used for matrix containing weak basic drugs to keep the pH in the intestinal pH range low and thus the drug solubility was high.[14,18]

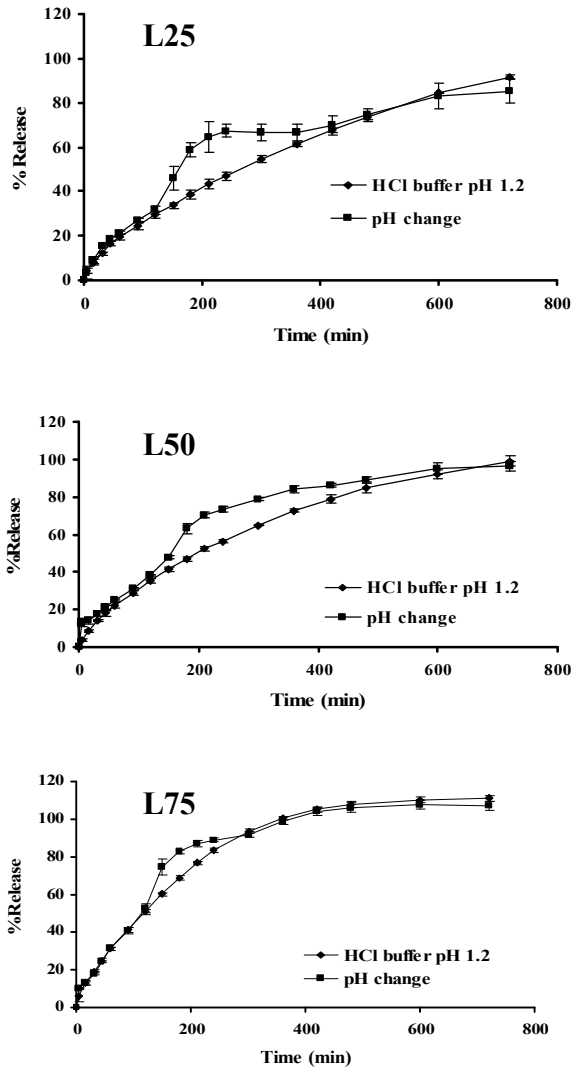


Figure 1 Dissolution profiles of propranolol HCl from single layer tablets containing 1:1 chitosan: xanthan gum and lactose of 25% (L25), 50% (L50) and 75% (L75) in different dissolution fluids. Each point represents the mean ± S.D., n = 3.

Effect of polymeric layering on drug release was illustrated in Figure 2. The drug release from three-layer tablet was obviously slower than that of single layer tablet. Drug release from the middle layer could be modified by the delayed diffusion from the two coated surfaces as a result of simple diffusion. The compression with polymeric layers on both sides of tablet could prolong and modify the drug release to achieve a constant release rate. Zero-order release could be qualitatively explained by assuming that the decreasing release rate from the lateral surface of the middle layer was balanced by delayed diffusion through the two laminated faces as a result of increasing polymer hydration/dissolution over time. The early drug release was the diffusion of dissolved drug molecules through cylindrical side surface of the tablet. The coated layers were designed to initially delay the hydration rate of the middle layer. The external layers would disappear gradually at disproportionate rates, creating more surface area for drug diffusion, thus counterbalancing the reduction of diffusing surface area due to the erosion as well as the increase in diffusional path-length due to continuous system swelling.[19]

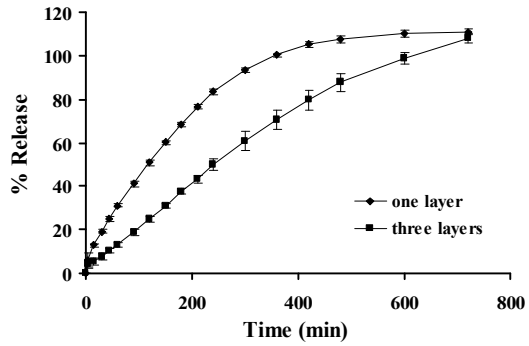


Figure 2 Dissolution profiles of propranolol HCl from single layer (L75) and three layer (L75 3L) tablets containing 1:1 chitosan:xanthan gum and lactose 75% in HCl buffer pH 1.2. Each point represents the mean ± S.D., n = 3.

Particle size of chitosan did not significantly affect the drug release of three layer tablet (Figure 3). Since the polymeric matrix could hydrate and form gel rapidly to

modulate the drug release, the difference of distance between particles of polymers could not affect significantly to the drug diffusion. Additionally, porosity of the hydrated matrix was independent of the initial porosity, the difference of particle size posed to have little influence on drug release.[9] Some studies demonstrated that the guaifenesin release rate was dependent upon the particle size of ethyl cellulose employed to prepare the tablets. The guaifenesin release rate was slower in tablets prepared with the "fine" ethyl cellulose particle size fraction due to the presence of fewer soluble drug clusters within the matrix. Tablets prepared by direct compression using "coarse" ethyl cellulose were found to release guaifenesin by both diffusion and erosion.[10] Alderman (1984)[6] stated that coarse fractions of HPMC hydrate too slowly to allow sustained release. Later, Mitchell et al. (1993)[7] indicated that, when the content of HPMC is higher, the effect of the particle size is less important on the release of propranolol hydrochloride, while the effect of this variable was more important when the content of this polymer was low.

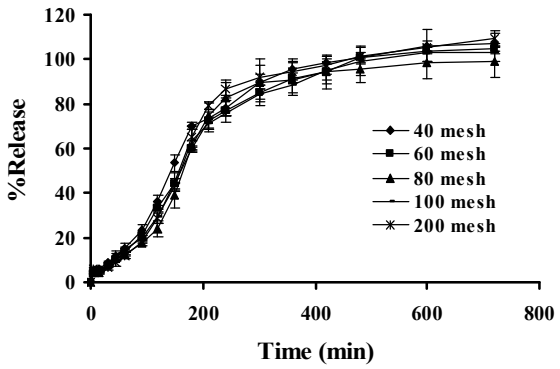
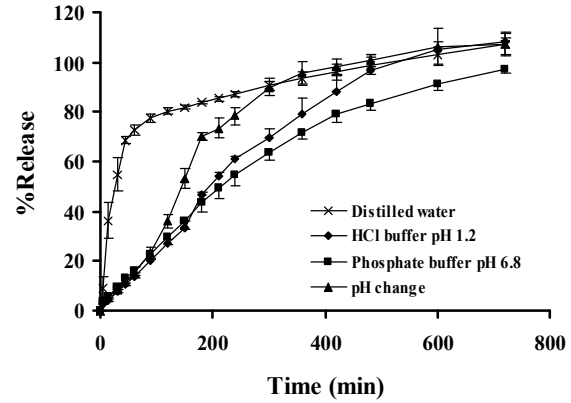


Figure 3 Effect of particle size of chitosan on dissolution profiles of propranolol HCl from three-layer tablets containing the 400 mg middle layer of 1:1 chitosan:xanthan gum and 75% lactose with the 100-mg upper and 100-mg lower barriers in pH change media. Each point represents the mean ± S.D., n = 3.

By comparison, the drug release from the three-layer tablets prepared from 40 mesh chitosan in distilled water was faster than that in pH change, HCl buffer pH 1.2 and phosphate buffer pH 6.8, respectively (Figure 4A). While the drug release from the three-layer tablets prepared from 200 mesh into HCL buffer 1.2 was rather slower than the others as shown in Figure 4B. This indicated that this drug release was pH dependent. Propranolol HCl, an anionic basic drug with a pKa of 9.45, should be more soluble in acidic environment than in neutral and alkaline environment, respectively. However this anticipation was not found as the drug solubility in deionized water was greater than that in acid and basic dissolution fluids respectively. The decline of solubility in HCl buffer pH 1.2 was attributed to the common-ion (chloride) effect, which provided an unexpected trend in solubility of this medicament in the presence of chloride ion in this acidic medium. Therefore, the release of propranolol in HCl buffer pH 1.2 was slower than that in distilled water. This evidence was also noted by Rekhi et al. (1989)[20] and Takka et al. (2001).[21] In addition, the pH dependence on dissolution of this drug from matrices containing HPMC and carbopol was reported.[18] This can be explained by the difference of charge balance inside the gel immersed in different dissolution fluids. The degree of interaction between the two polymers was modified by the environmental pH; thereafter the swelling of the complex was changed.[22] Polyacid of xanthan gum was neutralized in acidic medium due to free ammonium groups of chitosan; therefore, the positive charges appeared dominantly inside the gel. The mutual repulsion and the entry of water together with counterions to neutralize these charges caused matrix swelling. In neutral or basic medium, the mechanism is the same but the swelling was performed by the free negative charges of xanthan gum. In pH change system, rate of drug release apparently increased after adding buffering agents since the rapid pH alteration during pH change process induced the adjustment of matrix charge density which influenced the drug release. Normally, the small particle chitosan (200 mesh) could protonate and form sticky gel than the large particle chitosan (40 mesh) in

acid environment. Therefore the drug release from the three-layer tablets prepared from 200 mesh into HCL buffer 1.2 was rather slower than the others.



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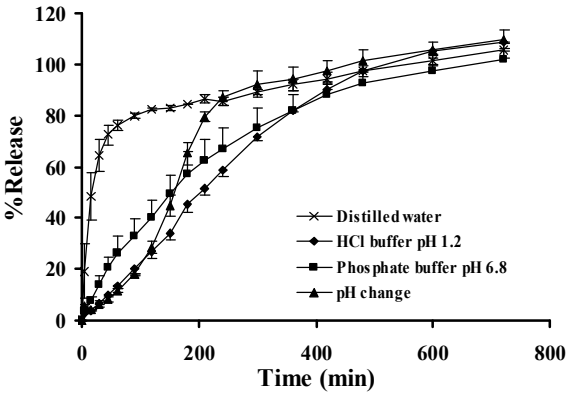


(B)

Figure 4 Effect of dissolution medium on release of propranolol HCl from three-layer tablets containing the 400 mg middle layer of 1:1 chitosan:xanthan gum and 75% lactose with the 100-mg upper and 100-mg lower barrier using chitosan 40 mesh passed (A) and 200 mesh passed (B). Each point represents the mean ± S.D., n = 3.

Dissolution profile fitting

The kinetics of propranolol HCl release from the developed matrices was analyzed using the power law expression. This equation (an empirical equation) gained popularity for analysis of release data.[23] The n value from power law is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms are classified based on the value that n assumes. For a cylinder, the mechanism of drug transport is described by Fickian diffusion when n = 0.45. When 0.45 < n < 0.89, it indicates anomalous (non-Fickian) transport and for values of n = 0.89, Case II or zero order release kinetics is indicated.[24] Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms; the coupling of drug diffusion and polymer relaxation.[23,25]

The large value of coefficient of determination (r^2) or model selection criteria (MSC) indicated a superiority of the dissolution profile fitting to mathematical equations. The r^2 and MSC from curve fitting to power law, first order, Higuchi's and zero order equations are shown in Table 4. The estimated parameters from curve fitting to power law equation are presented in Table 5. Fitting experimental drug dissolution profiles to power law equation provided high r^2 (a range of 0.9767 - 0.9999) and high MSC (a range of 3.26 - 8.87), indicating a superiority of this model. However, these values were rather low in the case of the drug release from single layer tablet containing 1:1 chitosan:xanthan gum and lactose 25% (L25) in pH change (r^2 = 0.9420, MSC = 2.45).

There was a tendency of the shift of drug release both in HCl buffer pH 1.2 and pH change to zero order kinetic as the amount of lactose was increased. Addition of lactose could diminish the pH dependent release of this drug from chitosan-xanthan gum matrix tablets. Release profiles and swelling rates of hydrophilic matrix were found to be highly influenced by the type and amount of pharmaceutical excipients incorporated which changed the hydrophilic gel expansion and the interactions between the drug and polymer.[13]

By comparison, the dissolution profiles of three-layer tablets in HCl buffer pH 1.2 could better fit to zero order kinetic than first order and Higuchi's equation, respectively. The curve fitting to zero order kinetic gave the large values of r^2 (0.9972) and MSC (5.51) (Table 4). It is suggested from these data that the developed three-

layer tablets showed zero-order or Case II release. The values of the kinetic constant (k) were in accordance with the values of n, the diffusional exponent, with k having lower values when the transport mechanism was Case II and higher values for formulations that released the drug by Fickian diffusion. The alteration of these estimated parameters as mentioned above was previously reported.[23,25] The relationship characteristics of these two estimated parameters are shown in Table 5. However, the dissolution profiles of some three-layer tablets in other dissolution fluids could be best fitted with first order equation (Table 4). Therefore the drug release characteristic was pH dependent. Difference of gel forming and erosion of tablets in different dissolution fluids could change the drug diffusion from these controlled release devices. The rate of drug release into distilled water was higher than that into HCl buffer pH 1.2, pH change and phosphate buffer pH 6.8, respectively (Figures 4).

Table 4 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution in HCl buffer pH 1.2 to different release models*

Tablet	Power law		First order		Higuchi's		Zero order	
	r^2	MSC	r^2	MSC	r^2	MSC	r^2	MSC
L25	0.9998	7.99	0.9976	5.73	0.9870	4.03	0.9874	4.07
L50	0.9994	6.85	0.9981	5.95	0.9917	4.45	0.9798	3.57
L75	0.9999	8.87	0.9919	4.37	0.9736	3.19	0.9958	5.02
L25[a]	0.9420	2.45	0.9557	2.85	0.9355	2.48	0.8808	1.86
L50[a]	0.9767	3.26	0.9627	2.96	0.9226	2.23	0.9746	3.34
L75[a]	0.9980	5.36	0.9385	2.29	0.8718	1.55	0.9814	3.49
L75 3-layer	0.9989	6.24	0.9806	3.58	0.8886	1.83	0.9972	5.51
L75 3-layerL[a]	0.9978	5.64	0.9959	5.18	0.9972	5.58	0.9588	2.88
L75 3-layer[b]	0.9991	6.49	0.9993	6.95	0.9845	3.80	0.9859	3.90
L75 3-layer[c]	0.9884	4.02	0.9683	3.17	0.9883	4.17	0.9278	2.34

* The dissolution test performed in [a]pH change, [b]phosphate buffer pH 6.8 and [c]distilled water.

Owing to pH dependent solubility of this drug as described above, the drug release from this three-layer tablet in phosphate buffer pH 6.8 and pH change system was rather far from zero order kinetic release. Sustained release tablet prepared by hot-melt extrusion containing chitosan and xanthan gum was reported in terms of the influence of pH and ionic strength on the release of chlorpheniramine maleate.[26] These pH and buffer species independent releases were attributable to the combination of the property of slow media uptake speed into a tablet due to the melt state of hot-melt extrusion process and inter- and intra-molecular hydrogelation of chitosan and xanthan gum.

Table 5 Estimated parameters from curve fitting of drug dissolution in HCl buffer pH 1.2 to power law expression*

Tablet	K (mean ± S.D. x10^{-3})	n (mean ± S.D.)
L25	12.4560 ± 0.6852	0.6607 ± 0.0088
L50	19.8030 ± 1.6500	0.6136 ± 0.0139
L75	12.615 ± 0.6522	0.7648 ± 0.0093
L25[a]	29.5860 ± 13.3520	0.5317 ± 0.0766
L50[a]	5.8822 ± 5.3428	0.8602 ± 0.1523
L75[a]	2.8974 ± 1.7028	1.0463 ± 0.1086
L75 3L	4.2688 ± 0.8770	0.8709 ± 0.0330
L75 3L[a]	26.297 ± 2.7126	0.5239 ± 0.0163
L75 3L[b]	9.6947 ± 1.2644	0.6580 ± 0.0199
L75 3L[c]	27.1211 ± 5.5262	0.5013 ± 0.0327

* The dissolution test performed in [a]pH change, [b]phosphate buffer pH 6.8 and [c]distilled water.

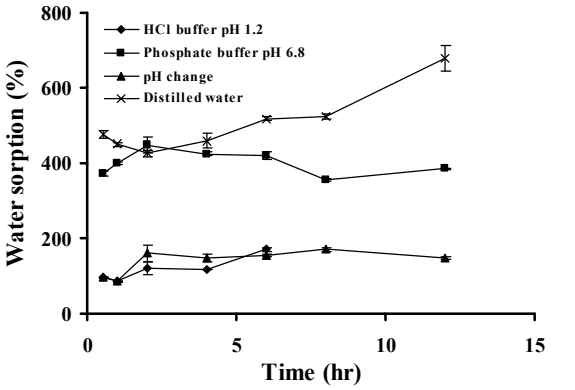
Water uptake study and erosion study

The water sorption of chitosan tablet in HCl buffer pH 1.2 was rather lower than that in other dissolution fluids and the moderate erosion of tablet was found and it was complete at 8 hrs as presented in Figure 5. Protonation of chitosan in acid environment promoted the gradual hydration and erosion of the tablet. The water sorption and erosion values of chitosan tablet seemed stable after pH changed to 6.8 owing to the alteration from protonated form to unprotonated form. The water sorption in distilled water and phosphate buffer were high (Figure 5) since the hydrophilic groups of chitosan structure could absorb the water but could not dissolve. The high erosion of tablet in distilled water was due to the partial tablet disintegration. Apparently, the water sorption and erosion of xanthan gum were greater than those in other dissolution fluids as shown in Figure 6. Absence or lower levels of ions in distilled water promoted the xanthan hydration ability whereas those ions in other dissolution fluids diminished the ability of this polymer.

The values in Table 6 were the water sorption and erosion of different tablets from dissolution test at 12 hrs. The erosion of single layer tablet was enhanced as the amount of lactose was increased both in HCl buffer pH 1.2 and pH change. The higher erosion and water sorption were found in the case of using HCl buffer pH 1.2 comparing to those in pH change. Three layer tablet was completely eroded at 12 hrs and the erosion in pH change was higher than that in distilled water and phosphate buffer pH 6.8, respectively. By observation, the water absorption and erosion of three layer tablet in distilled water and phosphate buffer were similar. Since chitosan could not protonate in these fluids and xanthan gum might form complex with propranolol, the hydration of this matrix in these fluid could be limited. COO^- of acetate or pyruvate groups of xanthan gum molecule[27,28] could form complex with amine group in propranolol structure contributing to the prevention of over-swelling to sustain the drug release.

Conclusions

Covering both planar surfaces of middle tablet with polymeric mixture containing chitosan-xanthan gum-lactose could modulate the release of propranolol HCl. Increased amount of lactose enhanced the drug release and diminished the pH sensitive drug release of tablet containing chitosan and xanthan gum. However, the drug release from the three layer tablets comprising this system was pH dependent. Particle size of chitosan did not significantly affect the drug release from the three layer tablets comprising this system.



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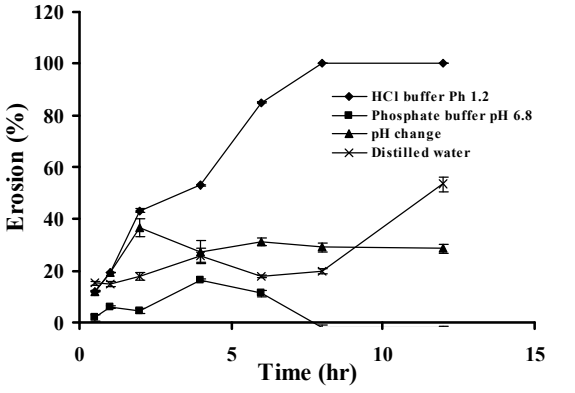
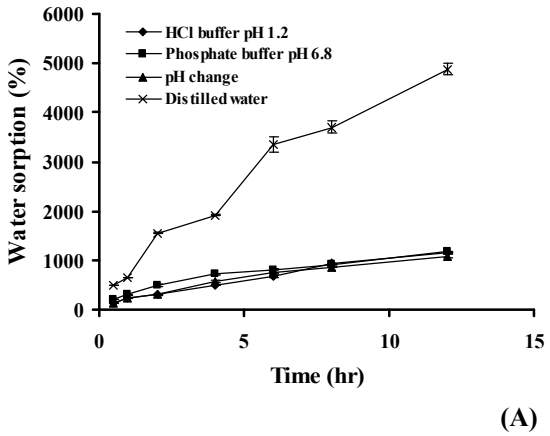


(B)

Figure 5 Water sorption (A) and erosion (B) of tablet containing 400 mg chitosan in different dissolution fluids.



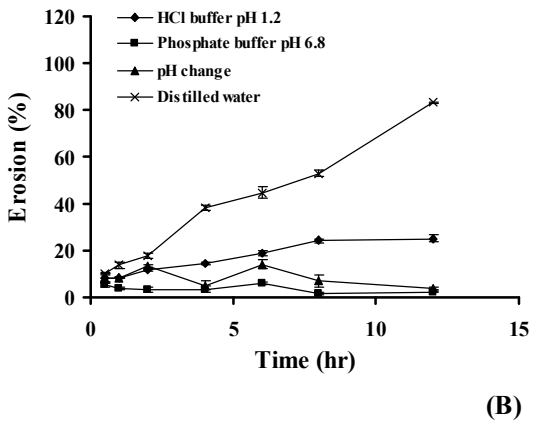


Figure 6 Water sorption (A) and erosion (B) of tablet containing 400 mg xanthan gum in different dissolution fluids.

Table 6 Water sorption and erosion of tablets*

Tablet	Water	Mass
L25	1977.21±69.02	63.90±1.78
L50	2675.76±107.94	79.01±0.80
L75	n/d	100.00±0.00
L25[a]	628.30±49.09	42.28±0.48
L50[a]	814.85±22.72	63.33±0.42
L75[a]	1099.36±31.58	83.49±0.14
L75 3L	n/d	100.00±0.00
L75 3L[a]	1108.92±42.21	82.22±0.22
L75 3L[b]	846.30±65.79	64.50±0.68
L75 3L[c]	800.18±20.57	76.03±0.29

n/d = not determined

* The dissolution test performed in [a]pH change, [b]phosphate buffer pH 6.8 and [c]distilled water.

Acknowledgements

The work was supported by Thailand Research Fund (Grant no. MRG4780076). This research work was kindly supported by the Faculty of Pharmacy, Silpakorn University. I appreciate Prof. Dr. Garnpimol C. Ritthidej for her valuable comments during the preparation of the manuscript.

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