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Sustained-release from Layered Matrix System Comprising Chitosan and Xanthan Gum

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ABSTRACT Sustained-release tablets of propranolol HCl were prepared by direct compression using chitosan and xanthan gum as matrix materials. The effective prolongation of drug release in acidic environment was achieved for matrix containing chitosan together with xanthan gum which prolonged the drug release more extensive than that containing single polymer. Increasing lactose into matrix could adjust the drug release characteristic by enhancing the drug released. Component containing chitosan and xanthan gum at ratio 1:1 and lactose 75% w/w was selected for preparing the layered matrix by tabletting. Increasing the amount of matrix in barrier or in middle layer resulted in prolongation of drug release. From the investigation of drug release from one planar surface, the lag time for drug release through barrier layer was apparently longer as the amount of barrier was enhanced. Least square fitting the experimental dissolution data to the mathematical expressions (power law, first order, Higuchi's and zero order) was performed to study the drug release mechanism. Layering with polymeric matrix could prolong the drug release and could shift the release pattern approach to zero order. The drug release from chitosan-xanthan gum three-layer tablet was pH dependent due to the difference in charge density in different environmental pH. FT-IR and DSC studies exhibited the charge interaction between of NH_3^+ of chitosan molecule and COO^- of acetate or pyruvate groups of xanthan gum molecule. The SEM images revealed the formation of the loose membranous but porous film that was due to the gel layer formed by the polymer relaxation upon absorption of dissolution medium. The decreased rate of polymer dissolution resulting from the decreased rate of solvent penetration was accompanied by a decrease in drug diffusion due to ionic interaction between chitosan and xanthan gum. This was suggested that the utilization of chitosan and xanthan gum could give rise to layered matrix tablet exhibiting sustained drug release.

KEYWORDS Layered matrix, Chitosan, Xanthan gum, Drug release

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INTRODUCTION

A layered tablet according to the present research belonged to the group of tablets which have an active substance-containing, layered matrix (active core)

and a cover layer lying on said matrix and controlling the active substance release. The middle layer shielded by external layers on one side or both sides is the drug deposit core (Conte et al., 1993; Conte & Maggi, 1996; Yang & Fassihi, 1997; Chidambaram et al., 1998; Conte & Maggi, 2000). Many barrier compositions were tested and reported, using different type of polymer, and their technological behavior and modulation efficiency were investigated (Conte et al., 1993; Chidambaram et al., 1998). The utilization of guar gum as the matrix material in three-layer tablet was claimed that it was suitable for controlling the release of highly water soluble drug such as metoprolol tartrate (Krishnaiah et al., 2002). The linear release kinetic of some drugs was achievable for the three layered tablets containing poly(ethylene oxide) and hydroxypropylmethyl cellulose as the major polymeric constituents (Yang & Fassihi, 1997).

In recent years, applied researchers have become increasingly interested in utilization of biopolymers in controlled-release dosage forms. The sustained release tablet prepared by hot-melt extrusion containing chitosan and xanthan gum was investigated in terms of influence of pH and ionic strength on the release of chlorpheniramine maleate. This drug release from hot-melt matrix tablet exhibited pH and buffer species independent 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 (Fukuda et al., 2006).

The main driving force in the advanced investigation and application of chitosan comes from the actuality that this biopolymer is not only naturally abundant, but also satisfactorily biocompatible, biodegradable and nontoxic. A flurry of applications has been focused on chitosan since its structure is cellulose-like, and the free amino groups on this polymeric chain contribute the reactive and polycationic nature that exhibit complexation properties. The potential applications of chitosan as an excipient in oral formulation and other delivery systems are reported (Felt et al., 1998; Berger et al., 2004). The utilization of chitosan was claimed as diluents for chewable, sublingual or oral mucosal tablets prepared by direct compression (Sawayanagi, 1982a).

Xanthan gum is an anionic linear heteropolysaccharide gum produced commercially by a pure culture fermentation of a carbohydrate with the bacterium *Xanthomonas campestris*. (El-Gazayerly, 2003; Giannouli & Morris, 2003). Its main chain consists of β-D-glucose units linked at the 1 and 4 positions. Trisaccharide side chains contain one D-glucose acid unit between two D-mannose units linked at the O-3 position of every other glucose residue in the main chain. Approximately one-half of the terminal D-mannose contains a pyruvic acid residue linked to the main chain contains an acetyl group at position O-6. The presence of acetic and pyruvic acids produces an anionic polysaccharide type (Garcia-Ochoa et al., 2000). Xanthan gum has been widely used in oral and topical formulations, cosmetics and food as thickening agent. Xanthan gum has been also used as an effective excipient for sustained release formulations; it not only retards drug release, but also provides time-dependent release kinetics (El-Gazayerly, 2003). Since it is suggested that polyion complexation occurs between cationic and anionic polymers, the combination of chitosan and xanthan gum may be used in the preparation of sustained-release devices.

The present study addresses the application of chitosan and xanthan gum by layering with tabletting to develop a prolonged release tablet of propranolol hydrochloride. Propranolol hydrochloride, a beta-blocker used for treatment of hypertension, classified as a water-soluble medicament. It was used as the model drug for this study. The effects of the diluents, the amount of layers and the pH of the dissolution fluid on drug release from matrix tablets were investigated. An attempt was subsequently made to describe in vitro release profiles by fitting the release profiles to mathematical release models. Additionally, the retardation of drug release mechanism was also characterized.

MATERIALS AND METHODS

Materials

Chitosan (Aqua premier, Chonburi, Thailand) having degree of deacetylation 99.3% and molecular weight 70 kDa was sieved through sieve No. 80 mesh before used. Xanthan gum (Xantural 75, CP Kelco U.S., Inc. Chicago) 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.

Preparation of Matrix Tablets

The 400-mg tablets containing propranolol hydrochloride and other additives (Table 1) were prepared by direct compression. The concentration of drug was kept constantly at 20% by weight (80 mg/tablet). The polymeric materials were chitosan and xanthan gum at different ratio. To make the powder mixture, the drug and polymer were mixed with magnesium stearate of 2% w/w for 5 min using mortar and pestle. Then the drug blend powder of 400 mg was compressed into a tablet at a compression force of two tons using 13 mm round, flat and plain punches using a hydraulic press (Carver Press, WI). The tablets containing chitosan and xanthan gum in ratio of 1:1 with various amount of lactose were prepared according to the composition in Table 2. The amount of lactose was varied from 25 to 75% of the matrix component that not included the amount of drug and magnesium stearate. The concentration of drug was kept constantly at 20% by weight (80 mg/tablet) as the previous described method. The percent compositions of barrier for the layered matrix tablets are shown in Table 3. Layered matrix tablets were prepared by adding the preweighed amount of the powder mixture without drug in the die cavity and slightly compressed for uniform spreading. The preweighed amount of the powder mixture with drug of formulation A75 was placed over the first layer and again slightly compressed for uniform spreading. The other preweighed amount of the powder mixture was subsequently placed and compressed with a 2-tons force using a hydraulic press to obtain the three-layer tablet. The dwell time after target pressure achieved was 10 s.

TABLE 1 Percent Composition of Different Single Layer Formulations

	Formulations (%, w/w)				
Substance	OC	X	OC:X 1:2	OC:X 1:1	OC:X 2:1
Propranolol HCl	20	20	20	20	20
Chitosan	78	—	26	39	52
Xanthan gum	—	78	52	39	26
Magnesium stearate	2	2	2	2	2

TABLE 2 Percent Composition of Different Single Layer Formulations Containing Lactose

	Formulation (%, w/w)				
Substances	A0	A25	A50	A75	A100
Propranolol HCl	20	20	20	20	20
Chitosan	39	29.25	19.5	9.75	–
Xanthan gum	39	29.25	19.5	9.75	–
Lactose	–	19.50	39	58.5	78
Magnesium stearate	2	2	2	2	2

TABLE 3 Percent Composition of Barrier

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

The Evaluation of Matrix Tablets

The hardness of the tablets was determined using a hardness tester (Pharmatest). The tablet thickness was measured using a thickness tester (Teclock, Japan). 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 HCl buffer pH 1.2 equilibrated at 37°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 both distilled water and phosphate buffer pH 6.8 were also undertaken. For the dissolution test with pH change, the drug released in HCl buffer of pH 1.2 was conducted for one and half hour. Then the pH was increased 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 until completing 12 hr. During the drug release studies, the tablets were observed for physical integrity.

Drug Release from One Planar Surface of Three-layer Tablet

The three-layer tablets with different amount of barrier (50, 100, 150, and 200 mg for each side of barrier) were prepared using the formulation of A75 of 200 mg as the middle layer. These tablets except only upper flat planar of tablet were imbedded into

melt hard paraffin, which was placed in plastic cylinder. After solidification of hard paraffin, the prepared devices containing single planar area of barrier layer were introduced into the basket of the dissolution apparatus for exposure to the dissolution fluids and tested for 12 hr as the same condition of pH change.

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 performed using a nonlinear computer program, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT). 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) (MicroMath Scientist Handbook, 1995), given below.

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

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

Fourier Transform Infrared (FT-IR)

The physicochemical properties of chitosan, xanthan gum, tablet of these two polymers at ratio of 1:1 (without drug) before and after immersion in HCl buffer pH 1.2 for 1 and 4 hr were characterized using the FT-IR spectroscopy. These tablets were removed from HCl buffer pH 1.2, washed twice using the dissolution fluid, freeze-dried using a freeze dryer (type 77560–01, Labconco, Missouri) and ground with a mortar and a pestle. The FT-IR spectra were recorded using an IR spectrometer (Magna-IR system 750, Nicolet Biomedical, Madison, WI) by KBr disc method. Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of above specimens were analyzed by a differential thermal analyzer (DSC 7, Perkin Elmer). The samples of 5–7 mg were accurately weighed into aluminum pans and sealed. The rate of heat was 10°C/min under nitrogen purge at the temperature of 30–300°C.

Scanning Electron Microscopy (SEM)

At that specified time intervals (1 and 4 hr after dissolution testing), the tablets were moved from dissolution fluid and then were freeze-dried using a freeze dryer (type 77560–01, Labconco, Missouri). The surface and cross sectional topography of the tablets was characterized under a scanning electron microscope (Maxim2005, Cam scan).

RESULTS AND DISCUSSION

The Physical Properties of Matrix Tablets

The data on weight, hardness and thickness of the core and the layered tablets are presented in Table 4. For the last six formulations, the number of the first term of formula represents the number of layer of tablet; and the first and third number in the second term multiply with 100 represents the amount (mg) of each barrier layer and the second number in the second term multiply with 100 represents the amount (mg) of core tablet. The powder mixture with drug of formulation A75 was used as the core tablet. The hardness of the core tablets was obviously less than that of the layered tablets. An increase in the amount of the coating layer clearly enhanced the hardness. The friability of tablets tended to increase as the hardness was decreased. Friability value of all formulations were less than 1% except the tablet containing lactose 100% as the excipient (A100) and 200-mg tablet containing chitosan and xanthan gum 1:1 and lactose 75% (A75 200 mg). The high friability of A100 was due to the low compressibility of lactose whereas the later formulation (A75 200 mg) was too thin to resist the impact during a friability test.

TABLE 4 **Physical Properties of Prepared Tablets**

Formulation	Weight ± SD (mg)	Diameter ± SD (mm)	Thickness ± SD (mm)	Friability (%)	Hardness ± SD (N)
OC	402.05 ± 6.68	13.27 ± 0.03	2.53 ± 0.05	0.86	40.30 ± 5.16
X	392.31 ± 7.29	13.28 ± 0.03	2.31 ± 0.05	0.90	34.08 ± 5.26
OC:X 1:2	402.67 ± 6.33	13.27 ± 0.03	2.34 ± 0.04	0.73	54.10 ± 5.99
OC:X 1:1	400.49 ± 8.08	13.21 ± 0.04	2.12 ± 0.66	0.60	59.81 ± 3.84
OC:X 2:1	399.12 ± 6.77	13.26 ± 0.03	2.52 ± 0.05	0.73	44.18 ± 4.62
A25	400.25 ± 7.97	13.30 ± 0.04	2.45 ± 0.11	0.72	51.47 ± 4.64
A50	398.42 ± 9.80	13.28 ± 0.04	2.36 ± 0.07	0.67	40.01 ± 3.92
A75 200 mg	190.94 ± 7.04	12.03 ± 0.54	1.31 ± 0.01	2.14	9.72 ± 0.86
A75 400 mg	396.48 ± 8.04	13.33 ± 0.13	2.37 ± 0.14	0.82	36.48 ± 4.93
A75 600 mg	595.38 ± 8.45	13.24 ± 0.23	3.48 ± 0.20	0.62	49.62 ± 2.11
A100	383.04 ± 6.46	12.56 ± 0.30	2.47 ± 0.14	1.00	17.22 ± 5.16
2L 1/2	300.65 ± 7.13	12.72 ± 0.01	2.06 ± 0.32	0.82	17.34 ± 4.08
3L 1/2/1	396.53 ± 7.96	13.39 ± 0.08	2.42 ± 1.69	0.67	24.43 ± 1.69
3L 1/4/1	597.19 ± 7.95	13.27 ± 0.04	3.55 ± 0.11	0.86	40.12 ± 2.85
3L 1/6/1	795.07 ± 9.70	12.72 ± 0.01	5.42 ± 0.03	0.69	20.61 ± 2.96
3L 2/2/2	595.34 ± 9.58	13.28 ± 0.06	4.77 ± 0.06	0.41	39.41 ± 4.61

In Vitro Drug Release Studies

Drug Release from Single Layer Tablet

The drug dissolution profiles of tablets containing chitosan or xanthan gum in HCl buffer pH 1.2 are illustrated in Fig. 1. The rapid drug release from chitosan tablets was observed after 90 min whereas the prolonged drug release was found for the xanthan gum tablet. Some investigators noted that at least 80% of chitosan was needed to achieve proper sustained release tablets (Sawayanagi et al., 1982b). The use of pure chitosan formulation in oral administration was limited owing to its fast dissolution in acidic environment of the stomach (de la Torre et al., 2003); therefore the combination of chitosan and xanthan gum was used in this study. The drug release from tablets containing chitosan and xanthan gum at any ratio was slower than that of tablets containing the single polymer as presented in Fig. 1. There was very similar drug dissolution rate of tablets containing different ratio of two polymers, however, the drug release from tablet at ratio of chitosan and xanthan gum at ratio 1:1 was slightly slower than that at ratio of 1:2 and 2:1. A general characteristic that occurred during dissolution testing of these tablets was the rapid surface hydration of the matrix, which resulted in the swelling, and the formation of gel layer around the tablets. Simultaneous surface erosion could have also promoted in controlling this drug release process.

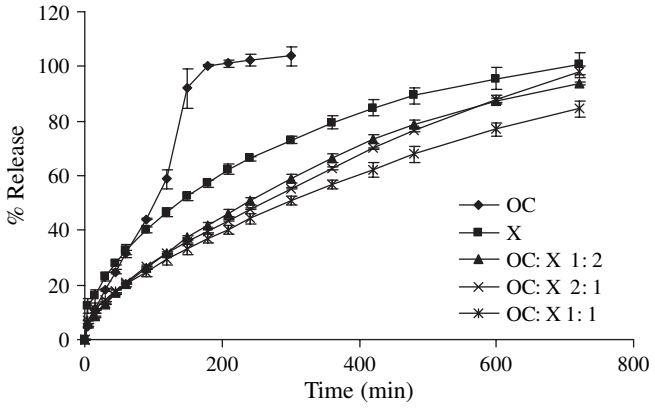

FIGURE 1 **Dissolution profiles of propranolol HCl from tablets containing chitosan (OC); xanthan gum (X) and chitosan and xanthan gum at different ratio in HCl buffer pH 1.2 (Apparatus 1, 100 rpm). Each point represents the mean ± SD, *n* = 3.**

Usually, the incorporation of coexcipients such as lactose is necessary to obtain tablets with desirable technological properties. However, this material may affect to the drug release from the developed dosage forms. Increasing the amount of lactose in 400-mg tablet containing chitosan and xanthan gum at ratio of 1:1 led to faster drug release as presented in Fig. 2. Lactose, by its water soluble and hydrophilic nature, facilitated gel formation and 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

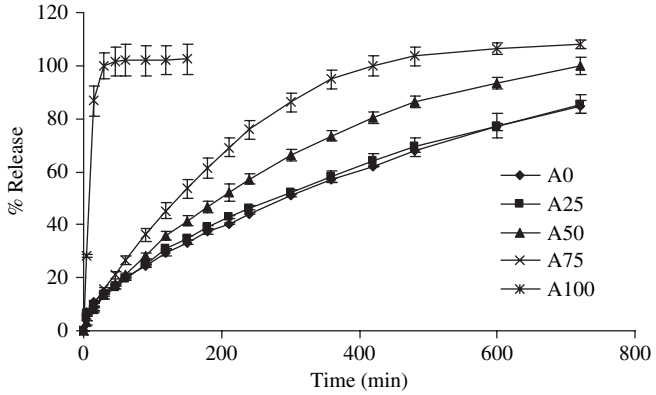

FIGURE 2 **Dissolution profiles of propranolol HCl from tablets containing chitosan and xanthan gum in ratio of 1:1 with different amount of lactose in HCl buffer pH 1.2 (Apparatus 1, 100 rpm). Each point represents the mean ± SD, *n* = 3.**

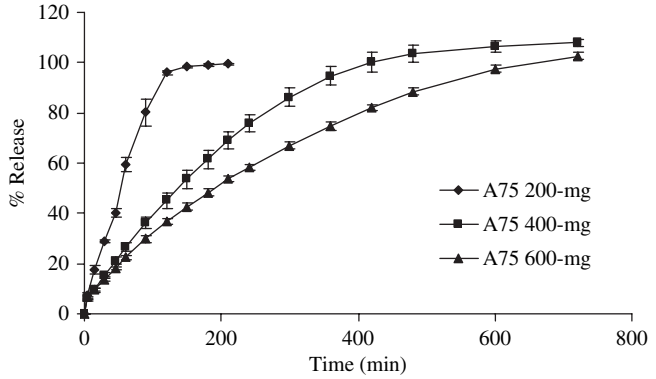

FIGURE 3 **Dissolution profiles of propranolol HCl from tablets containing chitosan and xanthan gum in ratio of 1:1 with lactose of 75% (A75) at different amount of matrix in HCl buffer pH 1.2 (Apparatus 1, 100 rpm). Each point represents the mean ± SD, *n* = 3.**

channeling agent, by rapidly dissolving and easily diffusing outward, therefore allowed a decrease in tortuosity and/or an increase in the matrix porosity (Xu, 1995; Gao et al., 1996; Williams et al., 2002). All these tablets released the drug apparently slower than the tablet using lactose as the only excipient (A100). An increase amount of matrix component resulted in a slower rate of drug release of tablets containing chitosan and xanthan gum at ratio 1:1 and lactose 75% w/w as illustrated in Fig. 3. This might be from the enhancement of continuous viscoelastic gel matrix, which resulted in the reduction of penetration of dissolution medium and drug diffusion.

Drug Release from Multiple Layers Tablet

Effect of polymeric layering on drug release was illustrated in Fig. 4. These dissolution profiles were

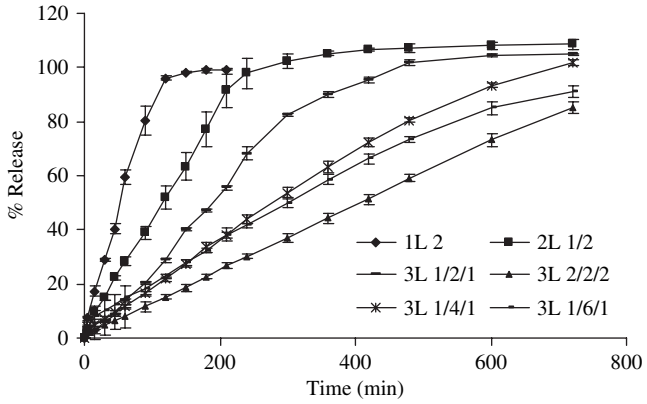

FIGURE 4 **Dissolution profiles of propranolol HCl from layered tablets which the core containing different amount of chitosan and xanthan gum in ratio of 1:1 with lactose of 75% (A75) and different amount of barrier in HCl buffer pH 1.2 (Apparatus 1, 100 rpm). Each point represents the mean ± SD, *n* = 3.**

obtained from the tablets coated by compression on the single or both planar surfaces. The 200 mg single layer tablet containing chitosan and xanthan gum 1:1 and lactose 75% (A75 200 mg) was symbolized as 1L 2 in this figure. The drug release from three-layer tablet was obviously slower than that of two-layer tablet and single layer tablet, respectively. The drug dissolution was prolonged as the amount of core or polymeric layer was increased. Therefore, the release rate greatly depended on the amount of matrix component in the formulation. Increasing the amount of matrix component in the formulation resulted in slower rate and extent release of the drug from the tablet. The release of pentoxifylline from xanthan gum matrix was prolonged as the amount of matrix was increased (El-Gazayerly, 2003). The increase amount of barrier apparently retarded the drug release. 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 drug release and modify the drug release to achieve 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 (Yang & Fassihi, 1997).

By comparison, the drug release from the three-layer tablets containing chitosan and xanthan gum at ratio 1:1 and lactose 75% w/w (3L 1/4/1) in HCl buffer pH 1.2 was faster than that in pH change, distilled water and phosphate buffer pH 6.8, respectively, as shown in Fig. 5. This matrix tablet exhibited pH-sensitive drug release. 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 (Nge et al., 2002). 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 basic medium, the mechanism is the same but the swelling was performed by the free negative charges of xanthan gum.

Drug Release from One Planar Surface of Three-layer Tablet

There was no lag time in the drug release from single planar area of tablet without barrier layer, whereas the apparent lag time was observed of drug release of three-layer tablets. The lag time of drug release trended to prolong as the amount of barrier was increased as shown in Fig. 6. This result suggested that the barrier layer played a significant role in modifying the lag time and the drug release. The increase in matrix quantity of barrier resulted to a substantial increase of the lag time. Therefore, the apparent release rate was determined by the summation of release rates from the lateral surface and from two coated surfaces, which would vary, depending on the formulation variables of the barrier layer including thickness.

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 (Ritger & Peppas, 1987). 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 drug transport mechanism is by Fickian diffusion when n=0.45, if $0.45 < n < 0.89$, it indicates anomalous (non-Fickian) transport and for values of n=0.89, Case II or zero order release kinetics is indicated (Peppas, 1985). Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms; the coupling of drug diffusion and polymer relaxation (Ritger & Peppas, 1987; Nerurkar et al., 2005).

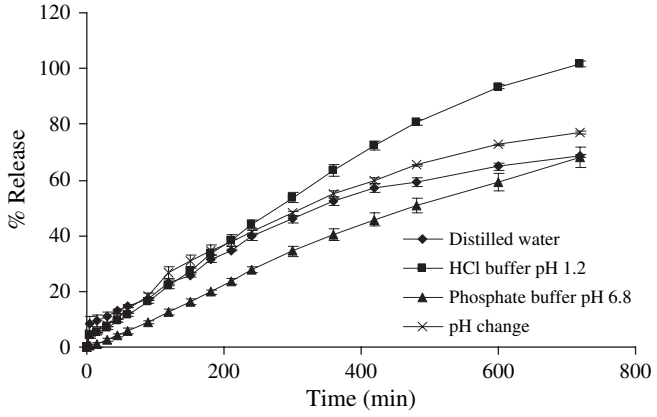

FIGURE 5 **Dissolution profiles of propranolol HCl from three-layer tablets containing the middle layer of 400 mg comprising of chitosan and xanthan gum in ratio of 1:1 and lactose of 75% with the 100 mg upper and 100 mg lower barriers (3L 1/4/1) in different dissolution fluids (Apparatus 1, 100 rpm). Each point represents the mean ± SD, n = 3.**

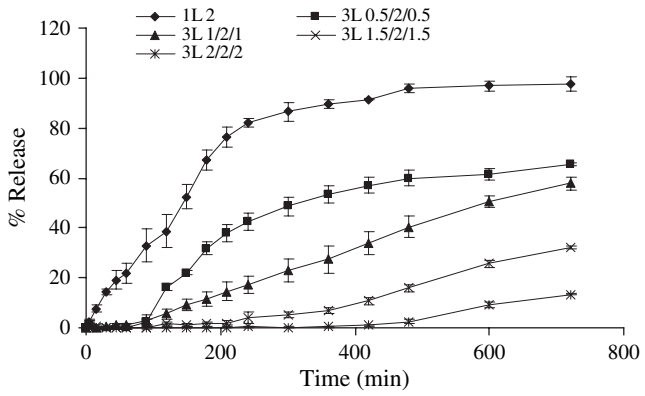

FIGURE 6 **Dissolution profiles of propranolol HCl from one planar of three-layer tablet containing the middle layer of 200 mg comprising of chitosan and xanthan gum in ratio of 1:1 and lactose of 75% with different amount of barrier in pH change (Apparatus 1, 100 rpm). Each point represents the mean ± SD, n = 3.**

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 5. The estimate parameters from curve fitting to power law equation are presented in Table 6. Fitting experimental drug dissolution profiles to power law equation provided high R^2 (in range of 0.9727–0.9999) and MSC (in range of 3.10–8.87), indicating a superiority of this model.

The R^2 and MSC from fitting drug dissolution profile of tablet containing xanthan gum to Higuchi's equation were larger than those from fitting to first order and zero order equations, respectively. Additionally, the n value from curve fitting dissolution profile was near to 0.45 (0.5093 ± 0.0116), suggesting that the drug release from xanthan gum matrices followed Fickian diffusion. This simple matrix system could be incapable of attained zero-order release due to the inherent limitations that the area of diffusing surfaces decreased and diffusion path length increased as time progressed (Lee, 1980).

The coefficients of determination obtained with tablet containing chitosan and xanthan gum at different ratio and that containing lactose of 25% and 50% for first order kinetic were found obviously higher (R^2=0.9944–0.9990 and MSC=4.90–6.62) comparing to those of zero order and Higuchi's kinetics. The n values from fitting of drug dissolution of tablets in HCl buffer pH 1.2 to power law equation were in range of 0.5658 ± 0.0098 to 0.6711 ± 0.0139. This indicated that the release of propranolol HCl from the majority of these tablets in HCl buffer pH 1.2 was by anomalous (non-Fickian) mechanisms with an initially high release rate followed by a rapidly declining rate.

The n values from curve fitting all dissolution profiles of three-layer tablets to power law equation were in range of 0.8793 ± 0.0296 to 0.9818 ± 0.0231 with close to 1 (Table 6), and zero order gave the largest R^2 and MSC (Table 5). It is evident 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 reported previously by Nerurkar et al. (2005). However, the drug releases from three-layer tablets containing chitosan and xanthan gum at ratio 1:1 and lactose 75% w/w (3L 1/4/1) in phosphate buffer pH 6.8 and pH change were an anomalous as

TABLE 5 **Comparison of Degree of Goodness-of-Fit From Curve Fitting of Drug Dissolution in HCl Buffer pH 1.2 to Different Release Models**

	Power law		First order		Higuchi's		Zero	
Tablet	cd	MSC	cd	MSC	cd	MSC	cd	MSC
OC	0.9996	6.78	0.9866	3.65	0.8845	1.49	0.9995	6.94
X	0.9989	6.32	0.9978	5.8	0.9988	6.40	0.9536	2.76
OC:X 1:2	0.9998	8.01	0.9962	5.25	0.9870	4.03	0.9862	3.97
OC:X 1:1	0.9998	8.05	0.9982	6.03	0.9884	4.19	0.9822	3.76
OC:X 2:1	0.9993	6.88	0.9944	4.90	0.9854	3.92	0.9871	4.06
A25	0.9994	7.05	0.9990	6.62	0.9963	5.32	0.9709	3.25
A50	0.9996	7.28	0.9983	5.99	0.9876	4.03	0.9853	3.85
A75 400 mg	0.9999	8.87	0.9932	4.54	0.9826	3.61	0.9953	4.92
A75 200 mg	0.9958	3.97	0.9510	2.02	0.9187	1.51	0.9820	3.02
A75 600 mg	0.9997	7.74	0.9968	5.42	0.9917	4.45	0.9798	3.57
2L 1/2	0.9991	6.19	0.9745	3.10	0.9549	2.53	0.9990	6.34
3L 1/2/1	0.9961	4.79	0.9567	2.64	0.6796	0.64	0.9960	5.02
3L 2/2/2	0.9997	7.71	0.9807	3.58	0.9152	2.10	0.9997	7.82
3L 1/4/1	0.9994	6.75	0.9863	3.89	0.9246	2.18	0.9982	5.91
3L 1/6/1	0.9990	6.45	0.9859	3.93	0.9514	2.69	0.9980	5.89
3L 1/4/1[a]	0.9853	3.79	0.9744	3.38	0.9839	3.85	0.9374	2.49
3L 1/4/1[b]	0.9980	5.70	0.9984	6.11	0.9505	2.67	0.9855	3.90
3L 1/4/1[c]	0.9727	3.10	0.9840	3.80	0.9472	2.61	0.9065	2.04

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

TABLE 6 **Estimate Parameters From Curve Fitting of Drug Dissolution in HCl Buffer pH 1.2 to Power Law Expression**

Tablet	K + SD *10^{-3}	*n* + SD
OC	3.5639 + 1.1178	1.0430 + 0.0586
X	40.0000 + 2.6240	0.5093 + 0.0116
OC:X 1:2	13.4000 + 0.5947	0.6615 + 0.0072
OC:X 1:1	13.1166 + 0.5855	0.6352 + 0.0070
OC:X 2:1	11.9400 + 1.0300	0.6711 + 0.0139
A25	21.0820 + 1.2986	0.5658 + 0.0098
A50	19.0240 + 1.2682	0.5833 + 0.0110
A75 400 mg	13.4090 + 0.7371	0.7386 + 0.0096
A75 200 mg	0.0615 + 0.4960	2.0000 + 1.5023
A75 600 mg	20.4958 + 1.0662	0.6141 + 0.0087
2L 1/2	2.8247 + 1.3751	1.0638 + 0.0848
3L 1/2/1	2.2990 + 1.6655	1.0411 + 0.1194
3L 2/2/2	1.3659 + 0.2128	0.9818 + 0.0231
3L 1/4/1	3.6824 + 0.6861	0.8793 + 0.0296
3L 1/6/1	3.0906 + 0.6760	0.8823 + 0.0336
3L 1/4/1[a]	21.8206 + 5.888	0.5355 + 0.0426
3L 1/4/1[b]	7.6979 + 1.4014	0.6970 + 0.0279
3L 1/4/1[c]	27.5422 + 8.9623	0.5275 + 0.0532

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

first order kinetic because the *n* values were of 0.6970 ± 0.0279 and 0.5275 ± 0.0532, respectively. The drug release of this tablet in distilled water was diffusion control since the *n* value was 0.5355 ± 0.0426. The increase in the value of *n* to 2.00 of A75 200-mg tablet might be due to a change of matrix characteristics or matrix disintegration of this thin tablet during dissolution test.

FTIR Spectroscopy

The FT-IR spectrum of chitosan powder as shown in Fig. 7 exhibited the NH_2 deformation peak at 1588 cm^{-1} overlapped with the amide II band at 1558 cm^{-1}. The peak at the wavelength of 1140–1170 cm^{-1} indicated the ether linkage of glucosamine unit, while that in range of 3480–3400 cm^{-1} indicated the hydroxyl group. The C=O stretching (amide I) peak near 1655 cm^{-1} representing the structure of N-acetylglucosamine as well as the NH_2 stretching peak at 1600 cm^{-1} representing the glucosamine functional group was exhibited in the spectrum of chitosan powder. The vibration peak of –OH and the C–H stretching of xanthan gum powder were exhibited at 3464.7 and 2929.4 cm^{-1}, respectively. The vibration peak of the acetal was found at 1049.1 cm^{-1}. The C=O stretching peak was found at 1738.3 and 1671.4 cm^{-1}, representing the structure of acetate and pyruvate in xanthan gum molecule. There was the new peak occurred at 1527.7 cm^{-1} in FT-IR spectrum of the component containing chitosan and xanthan gum 1:1 after dissolution in HCl buffer pH 1.2 for 1 and 4 hr. This evidence was assigned to the absorption band of carboxylate groups that form the ionic bonds with protonated amino groups. Therefore, it was possible to have the charge interaction of NH_3^+ in chitosan molecule and COO^- of acetate or pyruvate groups of xanthan gum molecule. The polyion complex formation in gel layer of chitosan and xanthan gum contributed to prevent over-swelling and strengthen the wet matrices and to sustain the drug release. The occurrence of strong band at 1560 and 1580 cm^{-1} of the interpolyelectrolyte complexs of Eudragit E100 with Eudragit L100 and Eudragit E100 with sodium alginate, respectively, was reported by Moustafine et al., 2005a,b. Polyelectrolyte complex of chitosan-poly (acrylic aid) exhibited new absorption band near 1555 cm^{-1} assigned to asymmetric deformation of COO^- (Nge et al., 2002; de la Torre et al., 2003). From FT-IR spectra, it could be suggested that both polymers were ionized at pH 1.2 and the electrosmotic flux produced by the mixtures and complex of chitosan-xanthan gum might be higher than chitosan alone, consequently, the degree of swelling and rate of swelling of the chitosan-xanthan gum system would be higher than chitosan. This mentioned characteristic was found on polyelectrolyte complexs and mixtures of chitosan-carragenan which were used as prolonged diltiazem chorhydrate release systems (Tapia et al., 2004).

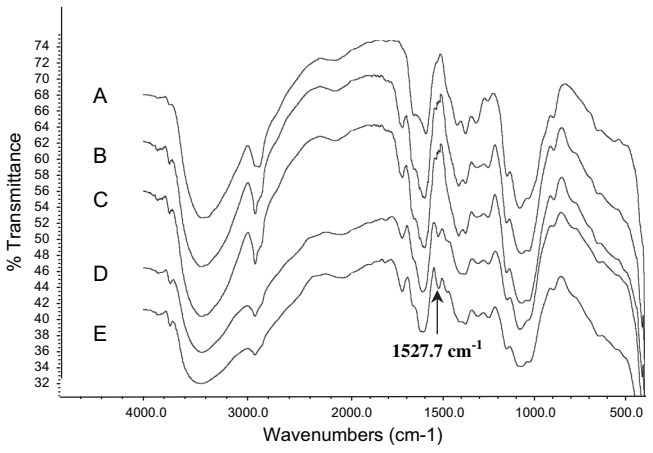

FIGURE 7 **FT-IR spectra of (A) chitosan; (B) xanthan gum; (C) physical mixture of chitosan and xanthan gum in a ratio 1:1; tablet containing chitosan and xanthan gum in a ratio 1:1 after immersion in HCl buffer pH 1.2 for (D) 1 hr and (E) 4 hr.**

DSC Studies

The first endothermic peak, appearing nearly to 100°C, of chitosan, xanthan gum, physical mixture of these two polymers and tablets without drug after dissolution for 1 and 4 hr corresponded to the evaporation of water (Fig. 8). The second endothermic peak was evident at 225.1°C only for the tablets after dissolution for 4 hr. This evidence might be associated with the interpolyelectrolyte complexs of chitosan and xanthan gum that promoted the new crystalline region in the matrix after freeze-drying.

Surface and Cross Sectional Morphologies

The SEM images of the xanthan gum and chitosan particles indicated a fibrous nature of these materials (data not shown). The SEM images of the dry tablet surfaces show a degree of mechanical interlocking of the polymers and drug as shown in Fig. 9. The surface topography and the cross-sectional SEM images of the hydrated tablets after freeze-drying are shown in Fig. 9. The surface of tablets was apparently swollen during the dissolution test. The surface of the tablets after 1 hr dissolution showed the formation of the loose membranous but porous film that was due to the gel layer formed by the polymer relaxation upon absorption of water. The gel layer on surface of tablet after dissolution for 4 hr was denser than that of tablet after 1 hr dissolution. This indicated that the gel mass was

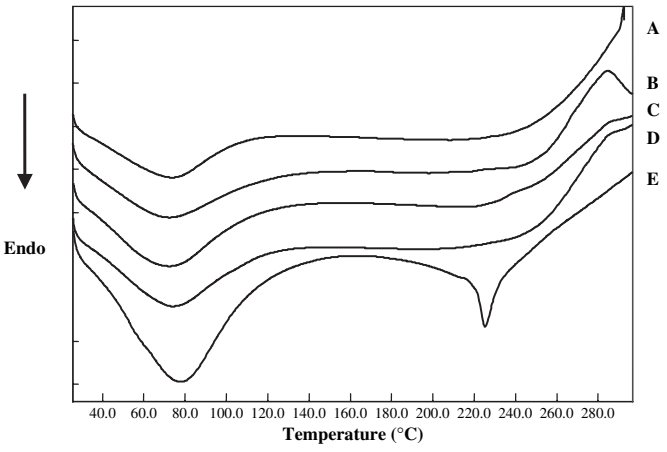

FIGURE 8 DSC thermograms of chitosan (A); xanthan gum (B); tablet containing chitosan:xanthan gum 1:1 before (C) and after dissolution for 1 hr (D) and 4 hr (E) using HCl buffer pH 1.2 as dissolution medium.

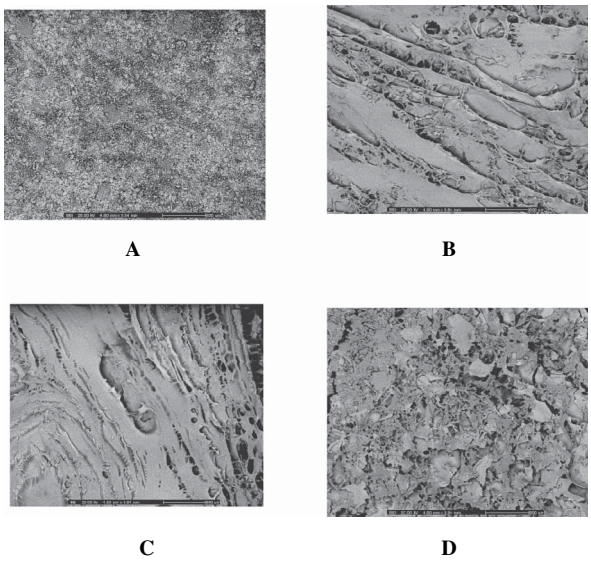

FIGURE 9 Surface topography of tablet containing chitosan and xanthan gum in a ratio 1:1 before dissolution (A) and after dissolution 1 hr (B) and 4 hr (C) using HCl buffer pH 1.2 as dissolution medium and cross section (D) of tablet after dissolution 4 hr using HCl buffer pH 1.2 as dissolution medium at magnification of 25.

increased with time during dissolution test and covered the core surface. The dissolved drug molecules were allowed to diffuse out from the core through the polymer network of gel layer containing the porous structure. The cross-sectional SEM image, which was the area under the gel layer, indicated a highly porous structure containing the polymer particles that readily formed the gel structure after contact with the penetrating dissolution medium. Subsequently, the generated gel layer could sustain the drug release after the outer gel was dissolved and eroded. As the particles of these polymers began to hydrate, a gelatinous layer of partially hydrated gum formed rapidly on the outside of the particle and the charge interaction was occurred. Therefore, the dissolved molecule of gum could not leave the particle surface easily and this prevented the penetration of the dissolution medium to complete hydration and form dissolving the particle. The electrostatic attraction between the cationic amino groups of chitosan and the anionic groups of xanthan gum was the main interaction leading to the formation of the gel to sustain the drug release. The decreased rate of polymer dissolution resulting from the decreased rate of solvent penetration was accompanied by a decrease in drug diffusion due to ionic interaction between chitosan and xanthan gum.

CONCLUSION

The present study was performed to develop controlled-release tablet using chitosan and xanthan gum as a matrix component by direct compression method. Chitosan together with xanthan gum could prolong the release of propranolol HCl in HCl buffer pH 1.2 more extensive than single polymer. Incorporation of lactose in the developed tablet facilitated the medium penetration, decreased matrix tortuosity and enhanced the drug release. The drug release was prolonged apparently as the amount of these matrix components was increased. Layering with polymeric matrix could prolong the drug release in HCl buffer pH 1.2 and shift the release pattern approach to zero order as described from the least square curve fitting. In addition, increasing the amount of matrix component in coating layer or in core tablet could apparently prolong the drug release. FT-IR and DSC studies revealed the charge interaction between of NH_3^+ in chitosan molecule and COO^- of acetate or pyruvate groups of xanthan gum molecule. This interpolyelectrolyte complex could sustain the drug release with pH dependent owing to the charge density in different environmental pH.

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