ผลของพอลิเมอร์ธรรมชาติสามชนิดต่อจลนศาสตร์การละลายของพรอพรานอลลอลไฮโดรคลอไรด์จากเมทริกซ์พองตัวที่ชอบน้ำ I: เมทริกซ์ที่มีไมโครคริสตอลลีนเซลลูโลส

Effect of Three Natural Polymers on the Release Kinetics of Propranolol HCl from Hydrophilic Swellable Matrices I: Matrices Containing Microcrystalline Cellulose

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: กลไกการปลดปล่อยยาถูกควบคุม โดยการพองตัวและการกร่อนของพอลิเมอร์ และการละลาย/การแพร่ของยา การศึกษาวิจัยนี้มีจุดประสงค์ เพื่อตรวจหาผลของพอลิเมอร์ธรรมชาติ 3 ชนิด ได้แก่ แซนแธนกัม (XG) เปคติน (P) และเมือกกระเจี๊ยบเขียว (OM) ที่มีต่อจลนศาสตร์การปลดปล่อยพรอพรานอลลอลไฮโดรคลอไรด์ (PRH) ในฟอสเฟสบัฟเฟอร์ pH 6.8 จากเมทริกซ์ชอบน้ำ **วิธีการศึกษา:** แต่ละตำรับarfarinมี PRH 80 mg ที่แมสแฟรคชั่น (mf) เท่ากับ 0.22 สำหรับตำรับที่ใช้ P หรือ OM แต่ละพอลิเมอร์จะถูกใช้ที่ mf = 0.30, 0.45, 0.60 และ 0.75 ส่วนตำรับที่ใช้ XG จะถูกใช้ที่ mf = 0.15, 0.30, 0.45 and 0.60 เติมไมโครคริสตอลลีน เซลลูโลส (MCC) เพื่อให้ได้น้ำหนักยาเม็ดคงที่ที่ 360 mg เตรียมยาเม็ดโดยวิธีตอกอัดโดยตรง ใช้เครื่องทดสอบการละลาย แบบ I ของ USP ศึกษาการปลดปล่อยตัวยา ในฟอสเฟสบัฟเฟอร์ pH 6.8 จากเมทริกซ์แต่ละตำรับ ภายใน 24 ชั่วโมง **ผลการศึกษา:** พบว่าตัวยาที่ปลดปล่อยของพอลิเมอร์ใดๆ ขึ้นกับรากที่สองของเวลา โดยเป็นไปตามสมการของฮิกูชิ จากสมการดังกล่าว การออกฤทธิ์นานของตัวยาจากพอลิเมอร์ใดๆ ขึ้นกับความสามารถในการลดค่าคงที่ความเร็วจลนศาสตร์ (k) และการพาธรรมชาติ (Q_0) นำการวิเคราะห์ความแปรปรวนเพื่อทดสอบนัยสำคัญของ k และ Q_0 ของการปลดปล่อยแต่ละตำรับ สำหรับ k พบว่า (i) เมื่อใช้ XG ที่ mf = 0.15 - 0.60 และ P ที่ mf = 0.30 - 0.75 การเพิ่ม mf ของพอลิเมอร์ จะลดค่า k อย่างมีนัยสำคัญ (ii) เมื่อใช้ OM ที่ mf = 0.30 - 0.75 การเพิ่ม mf ของพอลิเมอร์ สามารถลด Q_0 ได้อย่างเป็นที่น่าสังเกต แต่ไม่สามารถลดค่า k ได้อย่างมีนัยสำคัญ สำหรับ Q_0 ผลการทดลองสามารถจัดอันดับการลดค่าดังกล่าว คือค่าของ XG > OM >> P เมื่อนับทั้งการลด k และ Q_0 ขีดการออกฤทธิ์นานของพอลิเมอร์ของ XG > OM >> P **สรุป**: มีการประยุกต์ใช้แม่แบบการปลดปล่อยตัวยากับข้อมูลการปลดปล่อยตัวยา เพื่ออธิบายกลไกและจลนศาสตร์การปลดปล่อยพรอพรานอลลอลไฮโดรคลอไรด์

คำสำคัญ: เมทริกซ์พองตัวที่ชอบน้ำ, เมือกกระเจี๊ยบเขียว, พรอพรานอลลอลไฮโดรคลอไรด์, เปคติน, แซนแธนกัม

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Abstract

Objective: The mechanism of drug release is controlled by polymer swelling and erosion, and drug dissolution/diffusion. This study aimed to examine the effects of 3 natural polymers, i.e., xanthan gum (XG), pectin (P), and okra mucilage (OM) on the release kinetics of propranolol hydrochloride (PRH) in pH 6.8 phosphate buffer from hydrophilic matrices. **Methods:** Each formulations contained 80 mg PRH at a mass fraction (mf) of 0.22. For formulas using P or OM, each polymer was used at the mf of 0.30, 0.45, 0.60 and 0.75; while those using XG, at the mf of 0.15, 0.30, 0.45 and 0.60. Microcrystalline cellulose (MCC) was added to make the the constant tablet weight of 360 mg. All tablets were prepared by direct compaction, and USP dissolution apparatus I was used to study the drug release in pH 6.8 phosphate buffer from matrices within 24 h. **Results:** According to Higuchi equation, the results showed that the amount of drug released from matrices of all formulas depended upon the square root of time. From Higuchi equation, a retardability for drug release of any polymers depended on an ability to decrease both the kinetic rate constant (k), and natural convection (Q_0). An analysis of variance (ANOVA, P-value < 0.01) was performed for various k and Q_0. For k, the results showed that: (i) when XG with mf of 0.15 - 0.60 and P with mf of 0.30 - 0.75 were used, the increased mf of polymer could decrease k significantly, and (ii) when OM with mf of 0.30 - 0.75 were used, the increased mf could only decrease Q_0 remarkably, but could not significantly decrease k. For Q_0, the results indicated that the efficacy to lower Q_0 could be ranked as that of XG > OM >> P. Based on the ability to lower k and Q_0, the sustainability of polymers for drug release could be ranked as that of XG > OM >> P. **Conclusion:** Various drug release models were applied to drug release data in order to explain the release mechanisms and kinetics of propranolol hydrochloride.

Keywords: hydrophilic swellable matrix, okra mucilage, propranolol hydrochloride, pectin, xanthan gum

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Introduction

Propranolol hydrochloride (PRH) is a nonselective beta-adrenergic blocker which has been used to treat hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmia, and to prevent migraine.[1] PRH with a molecular weight (MW)

of 295.80 and pK_a of 9.05 is readily soluble in water.[2, 3] The first pass metabolism could affect PRH's half-life to be shorter than 6 h[4], and the patient would take it more frequently. The controlled release drug delivery was developed to improve the compliant problems via reducing the systemic side effect, the total amount of drug used, the fluctuation of drug in blood level, and the dosing interval that improved the patient compliance[5], along with a high drug loading, and cost effectiveness.[6]

Xanthan gum is a polysaccharide produced by fermentation of gram negative *Xanthomonas campestris*.[7] Xanthan gum has a MW of 2×10^6 daltons, with the trisaccharide side chains aligned with the backbone.[8] Talukdar et al. indicated that xanthan gum possessed a higher drug retardability than hydroxypropyl methylcellulose (HPMC) did.[10,11] Pectin is a water soluble polymer produced from apples, citrus and beet plant. Its MW is 100,000 ± 50,000 daltons. Sriamornsak et al. studied the drug release, swelling and erosion behaviors of matrices with different pectin types.[12]

Okra is the common name of *Abelmosc esculentus* (L.) Moench. MW of okra mucilage from okra fruit is 170,000 daltons.[13] It was used as a diuretic agent, and for treating peptic ulcer, diarrhea, and dental disease.[14] Baddam et al. showed that increase in polymer concentration (conc.) could retard drug release rate.[15]

Mechanism of drug release from matrix is due to polymer swelling and erosion, and drug dissolution/ diffusion. In swelling step, after oral uptake and exposure to gastrointestinal fluid, the polymer in hydrophilic matrix is hydrated, forms a gel layer, and increases in volume. In the next step, due to the time progress and more water content, molecular chain of polymer is progressively uncoiled and the outermost becomes weakening. Finally, the entire polymeric molecule is uncoiled, referred to as relaxation, and it disentangles from the surface of the matrix, referred to as erosion/dissolution.[16,17] Higuchi described that the cumulative amount of drug released depended on the square root of time in the early time.[18,19] Besides, Shah et al. developed a model to predict drug released from matrices with different HPMC conc. and an insoluble filler.[20] Krosmeyer-Peppas equation was used to describe the mechanism of drug release from matrix.[21-23]

The objective of this study was to investigate the effect of xanthan gum, pectin and okra mucilage on the release rates of PRH from hydrophilic swellable matrices with microcrystalline cellulose (MCC) as insoluble direct compression filler. PRH is selected to study the release kinetics because its high solubility in water and short elimination half-life.[4, 24] The findings could be useful in selecting appropriate natural polymer to prepare once-daily dose PRH controlled release tablets.

Methods

Chemicals

PRH was purchased from Zhejiang Medicine and Health, China. MCC (Avicel® PH 102) was purchased from Asahikasei Chemical Corp., Japan). Ethanol, 95% v/v was purchased from Liquor Distillery Organization, Thailand. Potassium dihydrogen phosphate, sodium hydroxide, and potassium chloride were purchased from Merck KGaA, Darmstadt, Germany; Carlo Erba Reactifs, France; and Ajax Finechem, Australia, respectively.

Preparation of polymers

Xanthan gum and pectin were purchased from Jungbunzlauer, Austria and Sigma Aldrich, Switzerland, respectively. Okra mucilage was prepared from fresh okra fruits obtained from the local market at Lat Lum Kaeo, Patumthani, Thailand. The fruits were authenticated by the authors using the monograph in Indian Medicinal Plants.[25] A voucher specimen (MPPYMU-OK02) of the fruit was preserved in the herbarium of our department for future reference. Collected okra fruits were washed with distilled water and seeds were removed. The fruits were cut into small pieces and homogenized using a mechanical blender. The resultant was stirred in 1.5 L distilled water and was boiled for 45 min and then filtrated using muslin cloth. The solution was then mixed with 95% ethanol at ratio of 1:4 w/w, the okra mucilage was then precipitated[26], and was dried at 45 °C for 6 h in a hot air dryer. Hard mucilage was ground, sieved through 80-mesh sieve, and stored as yield powders of 9.54% w/w in a desiccator.

Preliminary confirmative tests for dried okra mucilage

The preliminary confirmative tests for dried mucilage was performed as follows: (i) Molisch's test[27-29], (ii) Ruthenium test, (iii) iodine test for the presence of carbohydrates, mucilage, and polysaccharides without starch[28,29], respectively. Furthermore, (iv) enzyme test was conducted to

show the absence of enzyme which is the distinction between dried mucilage and acacia.[28,29]

Loss on drying (LOD) of Natural Polymers

The %LOD of 2.5 g of each polymer was determined using a moisture analyzer (HB43-S model, Mettler Toledo, Fisher Scientific UK, England).

pH of 1.0% w/v natural polymers

The suspension of 1.0% w/v of each polymer with 1.0% w/v KCl was determined for its pH using a pH meter (pH Basic Entry Level Bench top, Sartorius, Germany) at 25 ± 1 ºC.

Viscosity of 1.0% w/v natural polymers

According to the monograph of xanthan gum[30], the suspension of 1.0% w/v of each polymer was prepared and a viscosity measurement was conducted at 25 ± 1 ºC at 60 rpm using a viscometer (HaakeRotoVisco1 equipped with cup ZD34, Themo Scientific, Germany). The limit of detections (LODs), pHs and viscosities were determined in triplicate, and corresponding means with standard deviations were calculated.

Preparation of matrices

Twelve formulas were prepared with a batch size of 100 tablets (Table 1). Each formula possessed the weight of 360 mg tablet, and contained 80 mg PRH at a mass fraction (mf) of 0.22. For formulas using pectin or okra mucilage, each polymer was used at the mf of 0.30, 0.45, 0.60 and 0.75. For those using xanthan gum, the polymer was used at the mf of 0.15, 0.30, 0.45 and 0.60. MCC was added to make a tablet weight of 360 mg. All materials were blended by a motar and a pestle for 15 min and matrices were made by compaction of the 360 mg mixture at a force of 1500 kg in a hydraulic press (model C, Fred S. Carver, USA) equipped with a 12.5-mm round flat-face tooling.

Calibration curve of propranolol hydrochloride (PRH)

The absorbance (A) at the wave length of 319.7 nm of standard PRH in pH 6.8 phosphate buffer solution using double beam UV/Visible spectrophotometer (UV-1601-Shimadzu Japan) at its various concentrations (C) were performed. C was obtained as (A – 0.0047) / 6.9182 by using a linear regression analysis with the R^2 of 0.9999.

Drug content assay

Ten tablets were finely powdered and an amount equivalent to 80 mg of propranolol hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask and extracted with pH 6.8phosphate buffer. The mixture was then filtered to remove the un-dissolved particle and 1 ml of the filtrate was suitably diluted and analyzed for propranolol hydrochloride content at 319.7 nm using the UV/Visible spectrophotometer. This method was validated for linearity, precision and accuracy. Table 1 summarized the data of drug content.

***In vitro* drug release study**

The release of PRH from matrix was detected in a 900 ml of pH 6.8 phosphate buffer at 37 ºC ± 0.5 ºC using basket apparatus (Hanson Virtual Instruments, model SR8Plus, USA) at a speed of 100 rpm. Filtered samples were drawn and assayed within 24 h using the UV spectrophotometer (model UV-1601, Shimadzu, Japan) at 319.7 nm. % drug release was calculated compared with 80 mg PRH. Six replicates were done for each formula, and mean with SD was calculated.

Table 1 Various PRH tablet formulas using various polymers and MCC as filler along with their drug contents as mean with standard deviation.

	Weight (mg) by formula number											
	1	2	3	4	5	6	7	8	9	10	11	12
PRH	80	80	80	80	80	80	80	80	80	80	80	80
MCC	226	172	118	64	172	118	64	10	172	118	64	10
XG	54	108	162	216	-	-	-	-	-	-	-	-
P	-	-	-	-	108	162	216	270	-	-	-	-
OM	-	-	-	-	-	-	-	-	108	162	216	270
Total	360	360	360	360	360	360	360	360	360	360	360	360
% mean drug content (SD)	101.25 (1.43)	100.32 (0.95)	99.86 (1.53)	99.28 (1.95)	100.56 (1.22)	99.95 (2.04)	101.34 (1.82)	99.73 (1.98)	99.62 (0.89)	99.33 (1.36)	99.47 (1.37)	100.84 (1.25)

Note: PRH = propranolol hydrochloride; MCC = microcrystalline cellulose; XG = xanthan gum; P = pectin; OM = okra mucilage.

Theoretical consideration

Higuchi explained that a drug diffusion through the gel layer depended on the square root of time as

$$Q = K_H \times t^{1/2} \quad (1)$$

where, Q is the amount of drug released in time t, and K_H is the Higuchi dissolution constant. In Higuchi model, a few assumptions are made as follows: (i) the initial drug concentration in the system is much higher than that in the matrix solubility, (ii) perfect sink conditions are maintained, (iii) he diffusivity of the drug is constant, and (iv) the swelling of the polymer is negligible. The sink conditions are achieved by ensuring the concentration of the released drug in the release medium never reaches more than 10% of its saturation solubility.

Shah et al. modified Higuchi equation and proposed a model of diffusion[20] as

$$Q = K_H \times t^{1/2} = K' \times (D_a \times t)^{1/2} \quad (2)$$

where t is the time, D_a as detailed in equation 3, is the apparent diffusivity of drug through the rubbery region[20], and K' and K are kinetic constants.

The apparent diffusivity is the function of a porosity (ε) and a tortuosity of the matrix (τ) as in the following equation.

$$D_a = \varepsilon / \tau \quad (3)$$

Shah et al. explained drug release rate from matrices with insoluble filler by using 4 assumptions as follows.[20] First, the drug release can be approximately modeled using the square root of time relation. Second, the apparent diffusion coefficient (D_a) of a drug in the rubbery region is related to the porosity (ε) and the tortuosity (τ) of the swelling layer. Third, the porosity is only directly proportional to the volume fraction of a soluble drug in matrix, and then depends upon the mass fraction of the (f) divided by the density of solid compact and is assumed to be constant as in equation 4. Fourth, the tortuosity, of the swelling layer depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration, C_p, as a mass fraction (mf) of polymer in the matrix as in Eq (5). D_a is then derived. The drug released at time t is then obtained, namely Shah *et al*. equation as in Eq (7).

$$\varepsilon = \delta f / \rho_a \quad (4)$$

$$\tau = \psi C_p \quad (5)$$

$$D_a = \gamma / C_p \quad (6)$$

$$Q = \sigma \times (t / C_p)^{1/2} \quad (7)$$

where δ, ψ, γ and σ are kinetic constants.

From Eq (6), Q is the function of C_p and can be expressed as

$$Q = \alpha + \beta (1/C_p)^{1/2} \quad (8)$$

where α and β are kinetic constants.

The regression equation for the amount of drug released at 1, 2, 3, …., i h (Q_1, Q_2, Q_3, …, Q_i) in relation of polymer concentration is

$$Q_i = a_i + b_i (1/C_p)^{1/2} \quad (9)$$

A plot of the amount (Q_i) versus $(1/C_p)^{1/2}$ will give a_i and b_i. It is possible that both a_i and b_i are a function of the square root of time, therefore

$$a_i = c + K_a t^{1/2} \quad (10)$$

$$b_i = d + K_b t^{1/2} \quad (11)$$

where c, d, K_a and K_b are the regression constants.

Equation (12) is further derived to obtain the working equation for prediction of drug release from a hydrophilic swellable matrix.

$$Q_i = (c + K_a t^{1/2}) + (d + K_b t^{1/2}) (1/C_p)^{1/2} \quad (12)$$

$$Q_i = (c + d (1/C_p)^{1/2} + (K_a + K_b (1/C_p)^{1/2} t^{1/2} \quad (13)$$

To understand the dissolution mechanisms from the matrix, the release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas.[20-22] They put forth a simple relationship which described the drug release from a polymeric system follow which type of dissolution and they represented an equation as:

$$M_t/M_\alpha = K_{kp} t^n \quad (14)$$

where M_t/M_α is a fraction of drug released at time t. Then take logarithm both side to achieve the following equation.

$$\log M_t/M_\alpha = \log K_{kp} + n \log t \quad (15)$$

where M_t is the amount of drug released in time t, M_α is the amount of drug released after time α, n is the diffusional exponent or drug release exponent, and K_{kp} is the Korsmeyer release rate constant. To study release kinetics, a graph is plotted between log cummulative % drug release vs. log time, i.e., log (M_t/M_α) vs. (log t).

Hence, n value is used to characterize different release mechanisms as given here for cylindrical shaped matrices which is the main assumption of the model. Value of $n < 0.45$ indicates Quasi-Fickian diffusion, $n = 0.45$ indicates case I or Fickian diffusion, while $0.45 < n < 0.89$ for non-Fickian transport, $n = 0.89$ for zero-order transport of case II transport, and $n > 0.89$ indicates super case II transport.[21-23]

Analysis of Variance (ANOVA Test)

The single one-way ANOVA was detected for its pooled variance, s^2 by an Xlstat Designer ver. 2018.1® statistic program to detect significant differences in PRH release data among various formulas at *P*-value < 0.01.

Multiple comparison by least significant difference (LSD) procedure

The mean parameters among various groups were significantly ranked by the LSD procedure at 1.0% allowance, two-tailed (α = 0.01, 2-tailed) as follows.[32]

1.0% allowance = $t_\alpha [s^2(1/n_i + 1/n_j)]^{1/2}$ (16)

where t is a critical value at α of 0.01 (depending on degree of freedom within group), s^2 is the pooled variance detected from ANOVA test, and n_i and n_j are number of members between groups.

Results

Preliminary confirmative tests for dried okra mucilage

The results of preliminary confirmative tests for dried okra mucilage were depicted in table 2.

Physical characteristics of natural polymers

Some physical characteristics of natural polymers showing mean (SD) of % LOD of dried powders, pH and viscosity of 1.0% of each polymer are depicted in Table 3.

Higuchi equation

All formulas provided the high R^2 of > 0.99 from regression analysis of % PRH release *vs.* $\sqrt{t}$. This indicated that the release of PRH diffusing across swelling layer of matrices depended on $\sqrt{t}$. The parameters obtained are depicted in Table 4.

Table 2 Preliminary confirmative test for dried mucilage.[28,29]

Sample Test Number	Method	Observation	Inference
1. Molisch's test	100 mg dried mucilage powder + Molisch's reagent + conc. H_2SO_4 on the side of a test tube.	Violet green color observed at the junction of the two layers.	Carbohydrate presented.
2. Ruthenium test	Took a small quantity of dried mucilage powder, mount it on a slide with ruthenium red solution, and observe it under microscope.	Pink color developed.	Mucilage presented.
3. Iodine test	100mg dried mucilage powder + 1 ml 0.2 N iodine solution.	No color observed in solution.	Polysaccharides presented (starch is absent).
4. Enzyme test	Dissolved 100 mg dried mucilage powder in 20 ml distilled water; add 0.5 ml of benzidine in alcohol (90%). Shake and allow to stand for few min.	No blue color produced.	Enzyme absent (distinction between dried mucilage and acacia).

Table 3 % LOD, pH and viscosity of 1.0% of natural polymers showing mean and SD.

Natural polymer	% LOD	pH	Viscosity (mPa.sec)
Xanthan gum	9.53 (0.39)	7.05 (0.10)	616.00 (6.63)
Pectin	9.04 (0.25)	6.75 (0.05)	10.90 (0.96)
Okra mucilage	9.92 (0.32)	6.09 (0.02)	42.23 (0.80)

Table 4 Kinetic *k* (slope), natural convection, Q_0 (y-intercept) of 12 formulas.

Mass fraction (mf) of polymer	Xanthan gum			Pectin			Okra mucilage		
	Formula	*K*	Q_0	Formula	*K*	Q_0	Formula	*K*	Q_0
0.15	F1	24.98	13.11	-	-	-	-	-	-
0.30	F2	23.73	-5.87	F5	51.57	17.56	F9	28.05	-0.13
0.45	F3	19.32	-7.20	F6	48.41	4.76	F10	28.25	**-6.10**
0.60	F4	18.57	-10.48	F7	46.90	-4.95	F11	28.36	**-9.66**
0.75	-	-	-	F8	46.82	-13.68	F12	28.47	-11.92

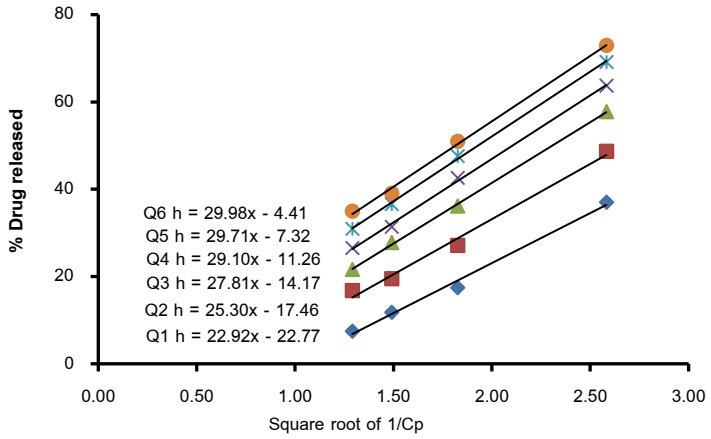

Figure 1 Regression analysis of percentage PRH released (Q) from matrices using MCC and square root of 1/*Cp* of xanthan gum at different given times in h. **Note:** ● = 6 h; ∗ = 5 h; ×= 4 h; ▲ = 3 h; ■ = 2 h; and ◆ =1 h.

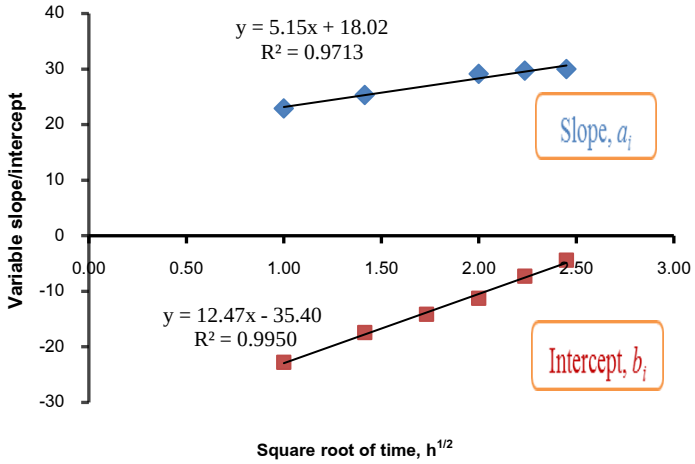

Figure 2 Regression analysis of variable slope a_i & intercept b_i with $t^{1/2}$ of xanthan gum.

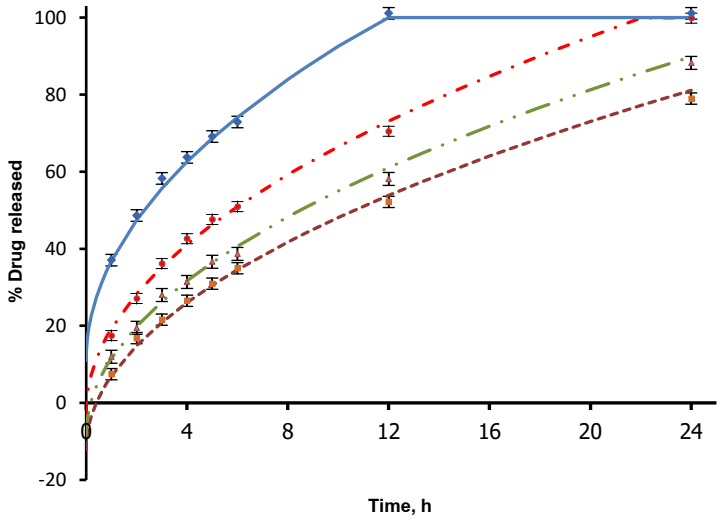

Figure 3 Theoretical predicted release profiles versus experimental data with their standard deviations (SD) for matrices using MCC at various mass fractions of **xanthan gum**. **Note:** Mass fraction: (1) theoretical: - - - - - = 0.60; - . . - . . - = 0.45; - . - . - = 0.30; and —— = 0.15. (2) experimental: ■ = 0.60; ▲ = 0.45; ● = 0.30; and ◆ = 0.15.

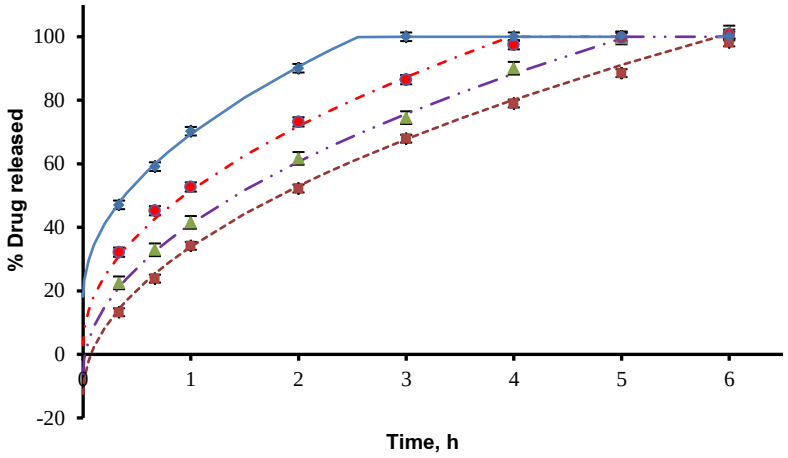

Figure 4 Theoretical predicted release profiles versus experimental data with their SD for matrices using MCC at various mass fractions of **pectin**. **Note:** Mass fraction: (1) theoretical: - - - - - = 0.75; - . . - . . - = 0.60; - . - . - = 0.45; and —— = 0.30. (2) experimental: ■ = 0.75; ▲ = 0.60; ● = 0.45; and ◆ = 0.30.

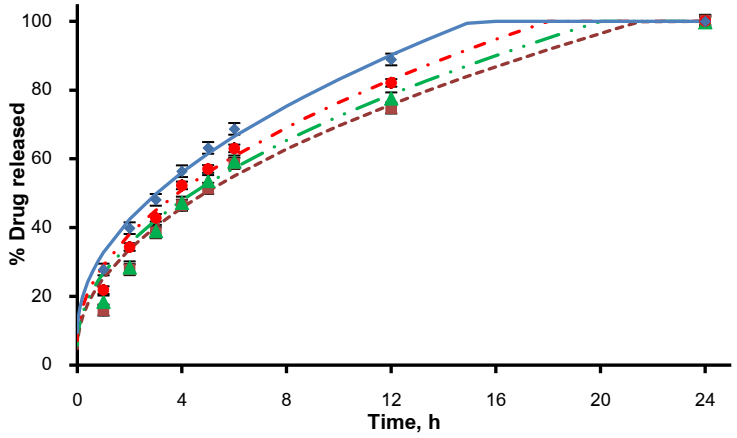

Figure 5 Theoretical predicted release profiles versus experimental data with their SD for matrices using MCC at various mass fractions of **okra mucilage**. **Note:** Mass fraction: (1) theoretical: - - - - - = 0.75; - . . - . . - = 0.60; - . - . - = 0.45; and —— = 0.30. (2) experimental: ■ = 0.75; ▲ = 0.60; ● = 0.45; and ◆ = 0.30.

Shah et al. model of diffusion

From the regression analyses of Eq (10) and (11) as shown in Figures 1 and 2 for xanthan gum, the kinetic constants c, K_a, d, and K_b, were obtained as depicted in Table 5. Eq (13) was further substituted with such various parameters to obtain the working Eq (17) for predicting drug release from swellable MCC matrices using xanthan gum.

$$Q = (-35.40 + 18.02x) + (12.45 + 5.15)\, t^{1/2} \quad \text{for xanthan gum} \quad (17)$$

Similarly, we obtained working Eq (18) and (19) for pectin and okra mucilage, respectively as follows:

$$Q = (-65.00 + 45.57x) + (37.79 + 7.34)\, t^{1/2} \quad \text{for pectin} \quad (18)$$

$$Q = (-3.09 + 6.87x) + (15.65 + 4.19)\, t^{1/2} \quad \text{for okra mucilage} \quad (19)$$

where $x = (1/Cp)^{1/2}$.

Table 5 Kinetic constants c and K_a, d and K_b due to Eq (9) and Eq (10) with high R^2.

Polymer	c	K_a	R^2	d	K_b	R^2
Xanthan gum	-35.40	12.47	0.9950	18.02	5.15	0.9713
Pectin	-65.00	37.79	0.9916	45.57	7.34	0.9724
Okra mucilage	-3.09	15.65	0.9917	6.87	4.19	0.9740

Krosmeyer-Peppas model of diffusion

Parameters to explain the mechanism of drug transport in each mf of each polymer are shown in Table 6.

Table 6 Characterization of release mechanism by n value for all matrices.

Polymer	Formula	Mass fraction	Release exponent (*n*)	R^2	Drug transport mechanism*
Xanthan gum	F1	0.15	0.3825	0.9982	QFT
	F2	0.30	0.5671	0.9887	NFT
	F3	0.45	0.6422	0.9888	NFT
	F4	0.60	0.6392	0.9981	NFT
Pectin	F5	0.30	0.3270	0.9830	QFT
	F6	0.45	0.4336	0.9968	QFT
	F7	0.60	0.5489	0.9993	NFT
	F8	0.75	0.7361	0.9934	NFT
Okra mucilage	F9	0.30	0.4746	0.9953	NFT
	F10	0.45	0.5398	0.9884	NFT
	F11	0.60	0.5888	0.9799	NFT
	F12	0.75	0.6298	0.9712	NFT

* QFT: Quasi-Fickian diffusion, NFT: Non-Fickian transport.

ANNOVA and multiple comparisons

From ANOVA and LSD, with α of 0.01 (2-tailed), the *k* of PRH could be significantly decreased by the increased mf of xanthan gum and pectin. However, for matrices with okra mucilage, the *k* could not be significantly affected by the okra mucilage mf. For *k* from matrices using the same polymer mf of 0.30 - 0.60, the release rate of PRH could be significantly ranked as follows: *k* of xanthan gum < okra mucilage << pectin. At mf of 0.75, the *k* of PRH could be ranked as *k* of okra mucilage << pectin.

For Q_0, they could be significantly decreased by the increased mf of each polymer. At the mf of 0.30 - 0.60, Q_0 were from -6% to -14.5% for xanthan gum, 17.6% to -5% for pectin, and 0% to -9.7% for okra mucilage (Table 1).

Discussions and Conclusion

Preliminary confirmative test for dried okra mucilage

The preliminary confirmative tests for dried okra mucilage were (i) Molisch's test, (ii) Ruthenium test, (iii) iodine test for the presence of carbohydrates, mucilage, and the polysaccharides without starch, respectively. Furthermore, enzyme test showed the absence of enzyme which is the distinction between dried mucilage and acacia.[28,29] The yield of mucilage was 9.54% w/w. The sample contained carbohydrates. Confirmation of mucilage was done and it gave negative test for tannins, alkaloids and proteins. This can be considered as proof for purity of the isolated.

Physical characteristics of natural polymers

Natural polymers possessed high LOD of 9-10%., because of their high hygroscopicity. The USP %LOD limits for XG and P, were 15%[30] and 10%[33], respectively. These polymers must be kept from moisture in a well-closed container.

For the pH of 1.0%, pectin and okra mucilage provided a weak acid nature, whereas xanthan gum provided a neutral one. These results provided no disadvantage to the *in vitro* release test of PRH in pH 6.8 phosphate buffer, since each pH of polymers used was closely near to pH 6.8.

For the viscosity of 1.0%, pectin and okra mucilage provided low values of 10.90 and 42.23 cps, respectively, whereas xanthan gum provided a higher value of 616 cps above the limit of 600.[30] From the results, the viscosity might be ranked as those of xanthan gum >> okra mucilage > pectin. The higher viscosity retarded the drug release from hydrophilic swellable matrices better than did the lower one. This might be caused by more viscous gel layer that could retard the water uptake and the drug release.[34]

Higuchi equation

From Table 4, it showed the good fitness to Higuchi equation. It meant that the release of PRH by diffusing across swelling layer of a matrix, depending upon $t^{1/2}$.

Shah *et al*. model of diffusion

Figures 3 - 5 suggested that the experimental data for MCC matrices using xanthan gum, pectin and okra mucilage closely fitted the theoretical release profiles determined from the working equation (17), (18), and (19), respectively.

Shah et al. model of diffusion could be used to construct the working equations to predict drug release from matrices with natural polymers because one of assumptions of Shah et al. model was based on Higuchi equation. Higuchi and Shah et al. models were appropriate for an initial period of constant matrix pore size.

Korsmeyer-Peppas model of diffusion

Most of the formulations possessed non-Fickian transport characteristics of which the drug was released by diffusion and erosion process. It was because polymeric molecule was uncoiled, namely, relaxation, and disentangled from the surface of the matrix, namely, erosion or dissolution.[17-19] For quasi-Fickian diffusion, the drug diffusing through gelling layer did not follow Higuchi model.

ANOVA and LSD

Increasing the mf of xanthan gum and pectin could significantly lower the rate of drug release. This was because higher polymer concentration could cause the gel formation with longer diffusion path length (Figure 6). But for matrix with okra mucilage, the increased mf could not decrease the *k* significantly (Figure 6), but could only lower Q_0 remarkably (Figure 7).

For comparing the data of *k* from matrices using each polymer at the identical mf of 0.30 - 0.60, the release rate of PRH could be ranked as follows: *k* of xanthan gum < okra mucilage << pectin.

For Q_0, the mf of each polymer could significantly decrease Q_0 (Figure 7). Each polymer provided Q_0 of around -6% to -14.5% for xanthan gum, 0% to -9.7% for okra mucilage, and 17.6% to -5% for pectin. According to the retardability to decrease the natural convection, for Q_0 at the polymer mf of 0.30 - 0.60, xanthan gum and okra mucilage had the same ability to decrease Q_0 to negative values and to be lower than those of pectin. However, at the mf of 0.30, xanthan gum could retard Q_0 better than okra mucilage significantly.

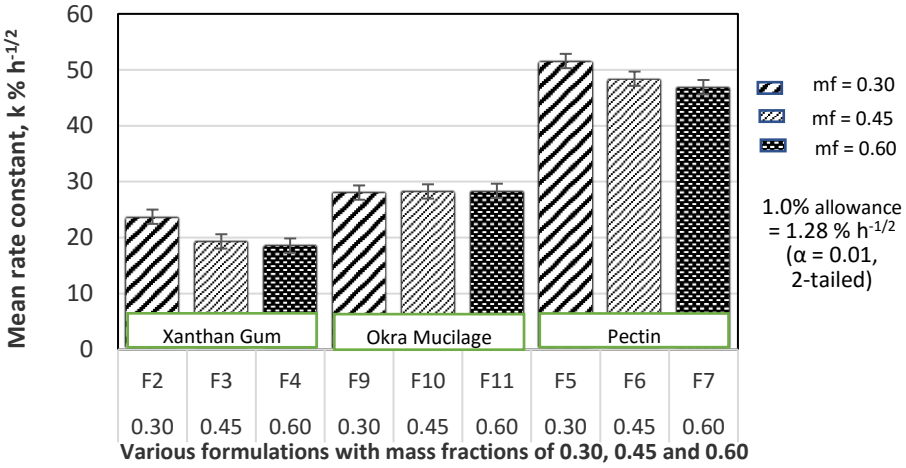

Figure 6 Statistical comparisons on mean rate constants of various formulations with mass fractions.

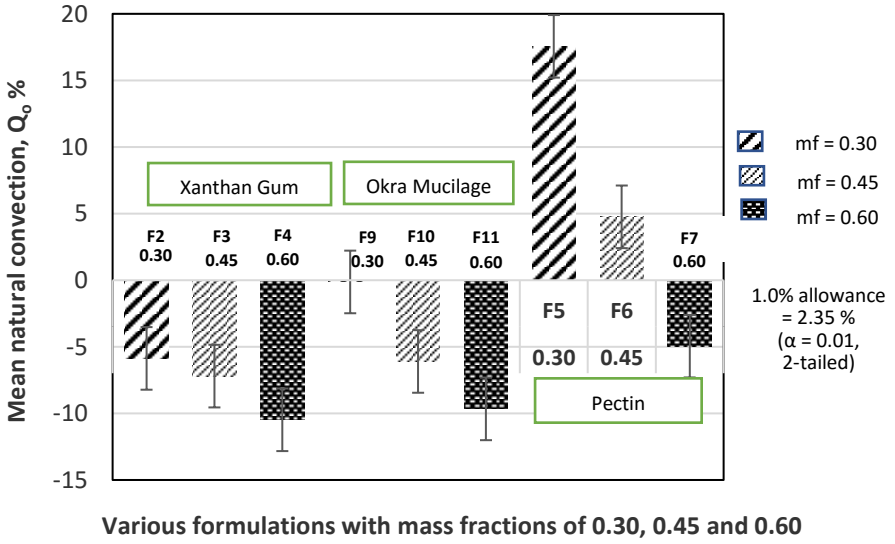

Figure 7 Statistical comparison on mean natural convections of various formulations with mass fractions.

Conclusion

According to ability to decrease *k* of propranolol hydrochloride at the polymer mf of 0.30 to 0.60, the sustainability of polymer for PRH release rate might be ranked as that of XG > OM >> P. The efficiency in lowering Q_0, could be ranked as that of XG > OM >> P. In terms of efficacy in retarding both release rate of propranolol hydrochloride and natural convection, xanthan gum provided the highest retardability for propranolol hydrochloride release from matrices. This study indicated that the drug released from

matrices with MCC could be optimized to prepare the once-daily dose of propranolol hydrochloride using xanthan gum as the polymer.

References

1. Facts and Comparisons. Drug facts and comparison 2012 edition. The United States of America. Wolters Kluwer Health, 2012: pp. 839-841.
2. Lund W. The Pharmaceutical Codex. London. The Pharmaceutical Press, 1994: pp. 1025-1029.
3. Vogelpoel H, Welink J, Amidon GL, et al. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. *J Pharm Sci* 2004; 93(8): 1945-1956.
4. Nies AS, Shand DG. Clinical pharmacology of propranolol. *Circulation* 1975; 52: 6-15.
5. Jayanthi B, Manna PK, Madhusudhan S, *et al*. Per oral extended release products - An overview. *J Appl Pharm Sci* 2011; 1(2): 50-55.
6. Hiremath PV, Saha RN. Oral matrix tablet formulations for concomitant controlled release of anti- tubercular drugs: Design and in vitro evaluations. *Inter J Pharm* 2008; 362: 118-125.
7. Rosalam S, England R. Review of xanthan gum production from unmodified starches by *Xanthomonas comprestris* sp. *Enz Microbiol Technol* 2006; 39: 197-207.
8. Braun DB, Rosen MR. Rheology modifiers handbook: Practical use and application. Braun Norwich, NY. William Andrew Publishing, 1999.
9. Kadaji VG, Betageri GV. Water soluble polymers for pharmaceutical applications. *Polymers* 2011; 3: 1972-2009.
10. Talukdar MM, Michoel A, Rombaut P, Kinget R. Comparative study on xanthan gum and hydroxypropyl methylcellulose as matrices for controlled-release drug delivery I. Compaction and *in vitro* drug release behavior. *Inter J Pharm* 1996; 129: 233-241.
11. Talukdar MM, Kinget R. Comparative study on xanthan gum and hydroxypropyl- methylcellulose as matrices for controlled- release drug delivery. II. Drug diffusion in hydrated matrices. *Inter J Pharm* 1997; 151: 99-107.
12. Sriamornsak P, Thirawong N, Weerapol Y, et al. Swelling and erosion of pectin matrix tablets and their impact on drug release behavior. *Eu J Pharm Biopharm* 2007; 67:211-219.
13. Siemonsma JS, Kouamé C. Abelmoschus esculentus (L.). In: Grubben GJH, Denton OA (eds.). Record from PROTA4U. PROTA (Plant Resources of Tropical Africa/ Ressources végétales de l' Afrique tropicale). Wageningen, Netherlands. 2004. (Accessed on Dec. 15, 2018, at http://www.prota4u.org/search.asp)
14. Sengkhamparn N, Verhoel, Schols HA, et al. Characterization of cell wall polysaccharides from okra [*Abelmoschus esculentus* (L.) Moench]. *Carbohyd Res* 2009; 344:1824-1832.
15. Baddam M, Bandela S. Formulation and evaluation of albendazole sustained release matrix tablets using okra gum. *Inter J Res Pharm Biomed Sci* 2013; 4(4): 1344-1353.
16. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. *J Control Release* 2011; 154(1): 2-19.
17. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Inter J Pharm 2008; 364: 328-343.
18. Siepmann J, Peppas NA. Higuchi equation: Derivation, applications, use and misuse. *Inter J Pharm* 2011; 418: 6-12.
19. Lamberti G, Galdi I, Barba AA. Controlled release from hydrogel-based solid matrices. A model accounting for water up- take, swelling and erosion. *Inter J Pharm* 2011; 407: 78-86.
20. Shah N, Zhang G, Apelian V, Zeng F, Infeld MH, Malick AW. Prediction of drug release from hydroxypropylmethylcellulose (HPMC) matrices: effect of polymer concentration. *Pharm Res* 1993; 10(11): 1963-1965.
21. Moharram A, Khan, Shefeeq T. Role of mathematical modeling in controlled drug delivery. *J Sci Res* 2009; 1(3): 539-550.
22. Shoaib MH, Tureen J, Merchant HA, et al. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pakistan J Pharm Sci* 2006; 19(2): 119-124.
23. Prasanthi NL, Manikiran SS, Rao NR. Effect of solubility of the drug on the release kinetics from hydrophilic matrices. *Inter J Pharm Tech Res* 2010; 2(4): 2506-2511.
24. Chidsey CA, Morselli P, Bianchetti G, Morganti A, Leonetti G, Zanchetti A. Studies of the absorption and removal of propranolol in hypertensive patients during therapy. *Circulation* 1975; 52(2): 313-318.
25. Basu BD. Indian medicinal plants plates part I: plate 1-267. Allahabad. The Indian Press, 1975. plate No. 132.
26. Patipatpaopong T. Extraction and characterization of okra, *Abelmoschus esculentus* mucilage. M. Sc. Thesis. Bangkok. Chulalongkorn University, 2007.
27. Devor AW. Carbohydrate tests using sulfonated α-naphthol. *J Am Chem Soc* 1950; 72(5): 2008–2012.
28. Bhosale RR, Ali R, Osmani M and Moin A: Natural gums and mucilages: a review on multifaceted excipients in pharmaceutical science and research. *Inter J Pharmacog Phytochem Res* 2014-15; 6(4): 901-912.
29. Mahammed N, Deshpande RD and Gowda DV: Modified polysaccharides as drug delivery: Review. *Inter J Pharm Sci Rev Res* 2011; 11(1): 42-47.
30. The United States Pharmacopeia Conventions. Xanthan gum. In: United States Pharmacopeia 37/National Formulary 32. Baltimore MD. United Book Press, Inc., 2013: pp.1443-1444.
31. Barba AA, Amore MD, Chirico S, Lamberti G, Titomanlio G. A general code to predict the drug release kinetics from different shaped matrices. *Eu J Pharm Sci* 2009; 36: 359-368.

32. Bolton S. Statistics: Multiple comparison in ANOVA. In: Troy DB (ed.). Remington: The science and practice of pharmacy. 22nd ed. London. Pharmaceutical Press, 2012: pp.508-517.
33. Pectin. The United States Pharmacopeia Conventions. United States Pharmacopeia 29 / National Formulary 24. Baltimore MD: United Book Press, Inc.; 2005: 1647.
34. Paud el P, Noori HM, Poudel BK, Shakya S, Bhatta P, Lamichhane S. Influence of different grades and concentrations of hydroxypropylmethylcellulose on the release of metformin hydrochloride. *World J Pharm Sci* 2014; 2(9): 966-980.