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Sustained Release of Propranolol HCl Using Matrix Granule Comprising Wax and Polymers

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ABSTRACT

Typically, propranolol HCl was fast release from matrix granules filled into capsule therefore the effect of the preparation technique and matrix component on the modulation of the release of propranolol HCl was performed for producing the sustainable release of this model drug. Propranolol HCl granules containing different component prepared with different techniques were tested for the drug dissolution using dissolution apparatus. The effect of dissolution medium type and rotation speed on drug release was conducted. Preparation of matrix granule by mixing propranolol HCl dispersed in melted phytowax with HPMC and xanthan gum and subsequently wetting with the granulating liquid could provide slower drug release. The mechanism of the drug release was found to be matrix diffusion control. The release of propranolol HCl from matrix granules displayed similar behavior in water, HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change. Higher rotation speed enhanced the release of drug from matrix capsule.

Keywords: Matrix granule, Wax, Polymer, Sustained release

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INTRODUCTION

Multiple-unit dosage forms could be prepared in form of pellet, granule, multi-particulate and mini-tablet. Granule could be produced by wet and dry granulation techniques. Addition of hydrophilic polymer as matrix component might prolong the drug release from the granule. Typically, capsule is one of the most popular pharmaceutical dosage forms. Many antibiotic drugs and other drugs are usually filled into the hard gelatin capsules. The production of pharmaceutical products in form of capsule is the cost and process effectiveness. The utilization of capsule as the controlled drug delivery device is also interesting. After oral administration, the water soluble capsule dissolved in the gastric juices and the hydrogel plug swelled. Additionally, type of swellable hyprophilic agent (hydroxypropyl methylcellulose (HPMC) or guar gum) and molecular weight of HPMC affected the drug release [1]. Hydrophilic matrix has become extremely popular in controlling the drug release rate from solid dosage forms. Hydroxypropyl methylcellulose (HPMC) and xanthan gum have been employed extensively as matrix former in the oral controlled-release dosage forms. Type of solvent and amount of water played an important role for physical properties of HPMC in the formation of the matrix granule due to the hydrophilicity and gel formation of this polymer. The use of isopropyl alcohol as granulating liquid and subsequently adding with water was a suitable process in producing the matrix granules consisting of HPMC [2]. In this study, the effect of the preparation technique and matrix component on the modulation of the release of propranolol HCl was performed for producing the sustainable release of propranolol HCl granules as multiple-unit dosage form filled in hard HPMC capsule.

MATERIALS AND METHODS

Materials

Propranolol HCl (Batch No. 941002) was purchased from China National Chemical Imp. & Exp., Shanghai, China. HPMC (Methocel® K 15M, lot no. NH 16012N11) was purchased from Colorcon Asia Pracific Pte., Ltd. Phytowax L48® (Sophim, Parc dela Cassine, France), eudragit L 100® (lot no. 1200403005, Rohm GmbH Chemische Fabrick, Germany), lactose (lot no. 080200 A9249, Auckland, New Zealand) and xanthan gum (Xantural 75®, CP Kelco U.S., Inc. USA.) were used as received. Ethylcellulose was supplied by The Dow Chemical Company, Michigan, USA. HCl solution (lot no. A01025, BAKER ANALYZED® A.C.S. Reagent, USA), monobasic potassium phosphate (lot no. 45-2, P.C. Drug Center Co., Ltd., Thailand), sodium hydroxide pellet (lot no. 03/07/157A), corn starch and sodium chloride (lot no. 1149, P.C. Drug Center Co., Ltd., Thailand) were purchased from P.C. Drug Center Co., Ltd., Thailand. HPMC capsules No.1 and NP™caps No.1 (Capsugel, Thailand) were kindly supported from Capsugel, Pranakorn Sriauthuthaya, Thailand and used as received.

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Preparation of Matrix Granules

Table 1 Composition of propranolol HCl matrices granules containing different diluents

Formula	Drug (mg)	Excipients (%w/v)							
		HPMC K15M	Phytowax	Xanthan	Avicel PH 101	Ethocel	Eudragit L100	Corn starch	Lactose
F1	40	25	-	-	-	-	-	-	75
F2	40	100	-	-	-	-	-	-	-
F3	40	-	100	-	-	-	-	-	-
F4	40	25	75	-	-	-	-	-	-
F5	40	25	-	75	-	-	-	-	-
F6	40	25	-	-	75	-	-	-	-
F7	40	25	-	-	-	-	-	75	-
F8	40	25	-	-	50	25	-	-	-
F9	40	25	-	50	-	-	25	-	-
F10	40	25	25	50	-	-	-	-	-

Different matrix granules were prepared by wet granulation method with the components as shown in Table 1. All materials were mixed in a porcelain mortar by geometric dilution and then wetted with isopropyl alcohol in quantity sufficient to achieve the funicular state of agglomeration before passing through the sieve No. 20 mesh and drying in a hot air oven at 40°C for 4 hours. The dried granules were rescreened through the sieve No. 20 mesh. The prepared granule was filled into NP™caps No.1 using capsule filling machine No.1 (S.T.P No.1 B.M., Thailand) which one capsule contained 40-mg propranolol HCl and other diluents as presented in Table 1. Capsule size No.1 with volume of 0.49±0.01 mL was used to be filled with the drug and matrix component. However, hydrophobic wax granules (formulation F4 and F10) were prepared by melting phytowax, and then propranolol HCl was dispersed in molten phytowax. The mass was passed through a sieve No. 20 mesh to obtain the hydrophobic wax granules. These granules were mixed with HPMC and other diluents in a porcelain mortar by geometric dilution and then wetted with granulating liquid in quantity sufficient to achieve the funicular state of agglomeration. The wet mass was passed through a sieve No. 20 mesh and dried in a hot air oven at 40°C for 4 hours, then left to cool down to room temperature. The dried granules were rescreened through the sieve No. 20 mesh before filling into NP™caps No.1.

Evaluation of Matrix Granules

The dissolution of propranolol HCl was performed with the basket method using a dissolution apparatus (type 1) (Prolabo, France). The dissolution fluid was 900 mL HCl buffer pH 1.2. The speed of basket rotation was 100 rpm maintained at 37°C. The samples were withdrawn at predetermined time intervals. The amount of drug released was measured using UV spectrophotometer (Perkin-Elmer, Germany) at 320 nm. The drug release from conventional HPMC capsule was also compared with that of the systems using NP™caps. To study the effect of the dissolution fluid on release behavior, the drug release tests in distilled

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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 a period of one and a half hours. 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 8 hours. To study the effect of hydrodynamic force on drug release, the tablets were tested for dissolution at different paddle rotational speed of 25, 50, 100 and 150 rpm. Least square fitting the experimental dissolution data to the mathematical equations [3] 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) and model selection criteria (msc) were used to indicate the degree of curve fitting.

RESULTS AND DISCUSSION

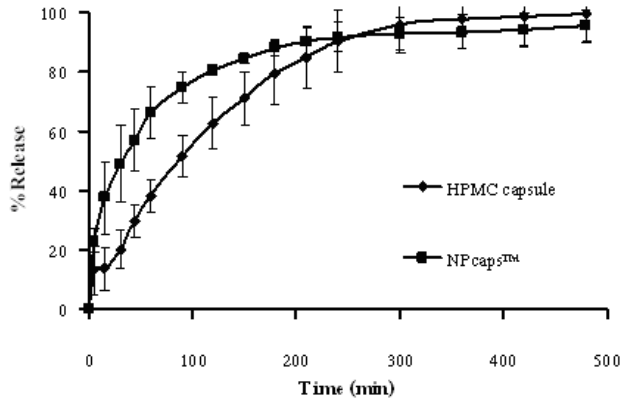

Figure 1 Dissolution profiles of propranolol HCl released from HPMC matrix granules containing 75% lactose in HCl buffer pH 1.2 using basket method

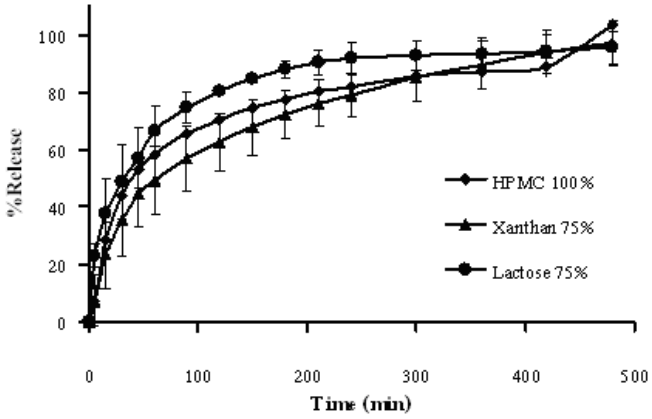

Figure 2 Dissolution profiles of propranolol HCl released from capsule filled with various hydrophilic components in HCl buffer pH 1.2 using basket method

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The 20 mesh propranolol HCl matrix granule containing HPMC-based was developed as multiple-unit dosage form. Different excipients were used to achieve the sustained drug release. To minimize the effect of charge interaction especially the positive charge of propranolol and negative charge of gelatin therefore HPMC capsule was used in this study. The prepared granules filled into NP cap™ capsule which made from HPMC since this capsule has been designed to disintegrate quickly than that of conventional HPMC capsule after contact to the dissolution medium. Therefore the drug release from NP cap™ capsule was faster than that of conventional HPMC capsule as shown in Fig. 1. The drug release from the granule containing 75% lactose (F1) or 75% xanthan gum (F5) was more than 50% within 1 h (Fig. 2) using basket method because the granule comprised the more porous surface and the presence of water-soluble filler. The release of propranolol HCl still was rapid in case of the formulation containing 100% HPMC (F2) (Fig. 2). This formulation limited amount of water used in wet granulation due to hydrophilicity of HPMC, therefore the granules were the quite loose compact powders and contained more porous surface. It could confirm by the values of bulk density and tapped density which it had the lowest bulk density and tapped density (data not shown).

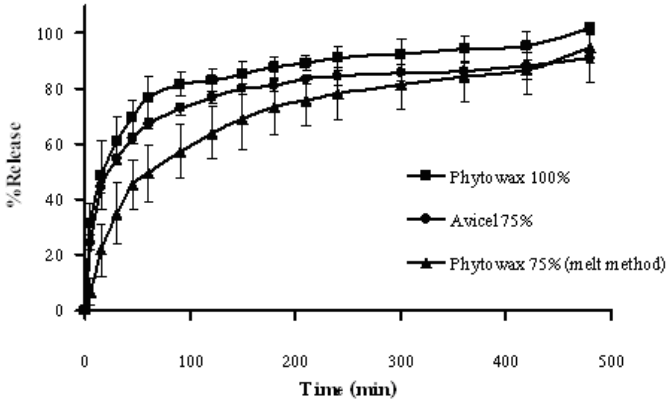

Figure 3 Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing various hydrophobic components in HCl buffer pH 1.2 using basket method

The dispersion of propranolol HCl in 100% phytowax (F3) by melt granulation did not decrease the drug release (Fig. 3) because hydrophilic propranolol HCl did not dissolve in phytowax. It deposited on the surface of the granule, thus the drug dissolved and diffused from the surface of the granules. There was a decrease in drug release from the formulation containing 75% phytowax (F4) prepared by melt granulation since propranolol HCl and HPMC were dispersed in melted wax. HPMC in the formulation still could swell form gel when the granules were hydrated therefore the drug released from surface of the granule and hydrated gel of HPMC. The formulation containing 75% avicel (F6) (Fig. 3) showed similar release profile to the formulation containing 100% phytowax. This could result from the disintegration property of avicel [4]. When HPMC contacted with the dissolution medium, it swelled and became the hydrated gel and also avicel had disintegration properties therefore it could promote the disintegration of the granule.

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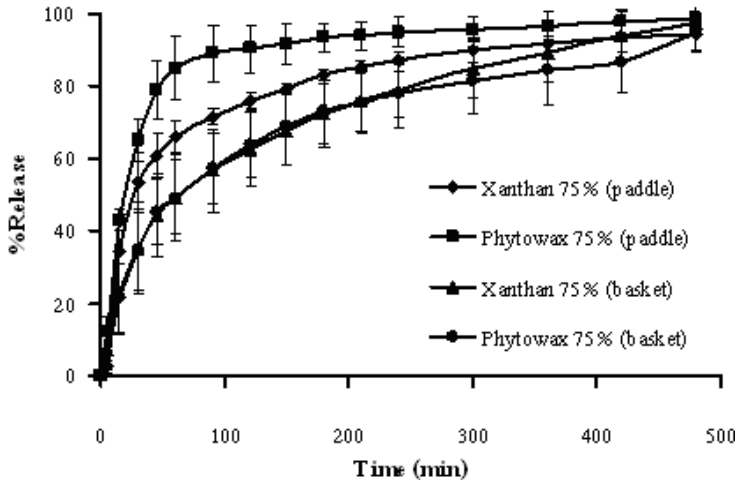

Figure 4 Dissolution profiles of propranolol HCl granules released from capsule filled with HPMC matrix granule tested with basket method and paddle method in HCl buffer pH 1.2

The granule formulation containing 75% xanthan gum (F5) exhibited similar release profile to the formulation that containing 75% phytowax (F4) that prepared by melt granulation (Fig. 4). The dissolution of propranolol HCl from matrix granules examined using basket method might able to increase the tendency of hydrated granule to adhere to one another of granule due to the limited dispersion of granules in basket. Therefore, the dissolution of propranolol HCl from matrix granules was examined using paddle method. Granules from F4 and F5 prepared by melt granulation exhibited faster drug release than that examined using basket method. The drug release was increased because a dispersion area of the granules was increased and a surface area of the granules contacting with dissolution medium was increased

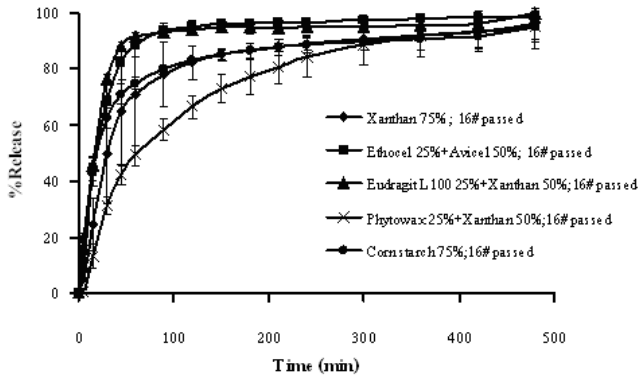

Figure 5 Dissolution profiles of propranolol HCl granules released from capsule filled with HPMC matrix granule containing various amounts and types of diluents in HCl buffer pH 1.2 using paddle method

Table 2 Estimate parameters from curve fitting of dissolution profile of propranolol HCl granules released from F10 in HCl buffer pH 1.2 to power law expression.

Power law		First order		Higuchi's		Zero order	
r^2	msc	r^2	msc	r^2	msc	r^2	msc
0.9982	5.48	0.8729	1.49	0.9863	3.73	0.9606	2.66

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The matrix granules (F5, F7, F8, F9 and F10) were attempted to produce into the larger size to decrease the surface area of granule, by passing the wet mass through the sieve no.16 mesh. Various excipients were used in this preparation. Most of dissolution profiles exhibited fast release even they contained a hydrophobic polymer or a pH-dependent polymer in the formulations (Fig. 5). Because the drug deposited at surface area of granule was dissolved and diffused out from matrix, the percentage of drug release was more than 60% within 1 h.

Table 3 Estimate parameters from curve fitting of dissolution profile of propranolol HCl granules released from F10 in HCl buffer pH 1.2 to power law expression to power law expression.

r^2	k ± sd^10^{-1}	tl ± sd (hr)	n ± sd
0.9982	0.5713 ± 0.0172	0.38 ± 0.08	0.31 ± 0.02

However, the prolongation of drug release could be obtained by dispersion of propranolol HCl in molten phytowax (25%) and passing through the sieve no.20 mesh and thereafter the drug granules were mixed with 25% HPMC and 50% xanthan gum to produce matrix granule size 16 mesh by wet granulation (F10). This granule formulation exhibited the percentage of drug release of 50% within 1 hour and following sustained drug release, since propranolol HCl entrapped in phytowax was gradually dissolved and diffused through strong gel matrix. The increasing of the viscous of gel layer around matrix core attributed to the intermolecular hydrogen-bonding between HPMC and xanthan gum. This synergistic of gel structure could decrease the amount of drug release. The percentage of drug release from formulation F10 was less than 50% at the first 1 h and could reach to 80% within 5 h. The maximum percentage of drug release from this formulation was 95.50% at 8 hours whereas the percentage of drug release from other formula showed a fast drug release at the first 1 h. The dissolution data of this formulation was fitted to Higuchi's model (Table 2). The release exponent (n) of this formulation was 0.31 which was less than 0.45, indicating the release mechanisms was close to Fickian transport (Table 3).

Effect of pH of Dissolution Medium on Drug Release

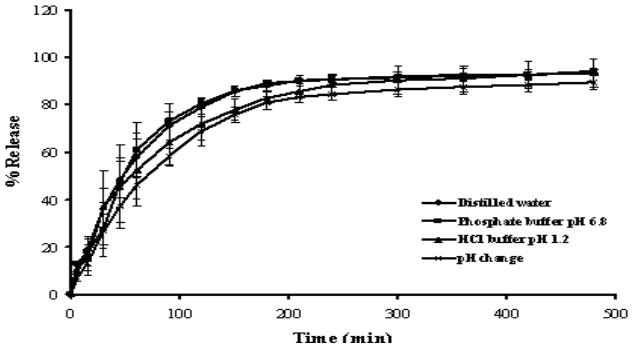

Figure 6 Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing 75% lactose in the different pH of dissolution medium using paddle method

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The effect of pH of dissolution medium on the release of propranolol HCl from capsules was investigated to simulate the environment of the gastrointestinal tract. The matrix granule containing 75% lactose (F1) was chosen for investigating the influence of pH of dissolution medium on the propranolol HCl release (Fig. 6). The dissolution of propranolol HCl was studied using paddle method. The dissolution profile of propranolol HCl release in water was similar to that in buffer pH 6.8. Whereas, the dissolution profile of propranolol HCl release in HCl buffer pH 1.2 was similar to the release profile in pH change. HPMC polymers are non-ionic and therefore the solubility and swelling behavior were not influenced by pH [5]. Hydrogel based on high-viscosity HPMC was known to deliver the drug at a constant rate independent of the hydration, gel viscosity and relative permeability of dosage form. Typically, the rate of drug release was related directly to the solubility of the drug [6, 7]. Propranolol HCl is a weakly basic drug. Therefore, it gave pH-dependent release from HPMC-based matrix formulations due to its pH-dependent solubility. The solubility was found to be 225 mg/ml at pH 1.2, 130 mg/ml at pH 6.8 and 360 mg/ml in water. The release of propranolol HCl was faster in water and 0.1 N HCl compared to that in a phosphate buffer [7]. However, in this study propranolol HCl did not show apparently the pH-dependent solubility from HPMC matrix granule filled into capsule.

Effect of Rotation Speed of Paddle on Drug Release

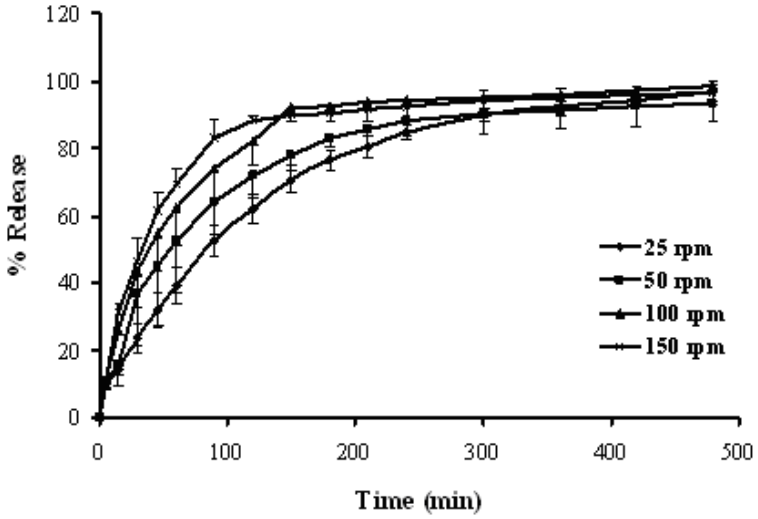

Figure 7 Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing 75% lactose with different rotational speed of paddle in HCl buffer pH 1.2 using paddle method

The release rate of drug increased when the rotation speed of paddle was increased (Fig. 7). The release rate of propranolol HCl increased when the rotation speed of paddle was increased. There was more rapid erosion of matrix at higher stirring rates because the increased rate of detachment of polymer chains away from the matrix surface. This led to the thinner layer of gel forming at surface of the dosage form at higher agitation rate [2]. There were more rapid erosion of matrix at higher stirring rates because the increased rate of detachment of polymer chains away from the matrix surface. This led to the thinner layer of

gel forming at surface of the dosage form at higher agitation rates [8]. This demonstrated that the drug release could change easily due to physical agitation and probably peristaltic movement in the gastrointestinal tract.

CONCLUSION

Most dissolution profiles of propranolol HCl from matrix granules filled into capsule were fast release. The granule formulation containing 25% phytowax, 50% xanthan gum and 25% HPMC (propranolol HCl dispersed in melted phytowax before mixed with HPMC and xanthan gum) exhibited the 80% drug released within 5 hours whereas the other granule formulations showed fast release. The drug release kinetics of this propranolol HCl matrix granule was fitted well with the Higuchi's model. The release of propranolol HCl from matrix granules displayed similar release behavior in water, HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change. However, the paddle rotation speed affected the drug release.

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