Saudi Pharmaceutical Journal (2016) **24**, 627–634

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Drug release behavior of polymeric matrix filled in capsule

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Received 7 April 2015; accepted 27 April 2015
Available online 2 May 2015

KEYWORDS

Matrix capsule;
Drug release;
Hydroxypropyl methylcellulose

Abstract A single unit sustainable drug release system was developed using hydroxypropyl methylcellulose (HPMC)-based matrices filled in capsule as the drug delivery device. Release behavior of propranolol HCl from these capsules was investigated and least square fitting was performed for the dissolution data with the different mathematical expressions. Effect of diluent, polymer, pH and hydrodynamic force on the drug release from the developed systems was investigated. The utilization of HPMC as a matrix former extended the drug release longer than 8 h. HPMC viscosity grades affected the drug release, that is, increasing the amount of fillers such as lactose and dibasic calcium phosphate enhanced the drug release rate of HPMC matrices. The hydrodynamic force, type and amount of incorporated polymer apparently influenced the drug release. The physiochemical properties of polymers and interaction between HPMC and other polymers were important factors for prolongation of the drug release. The release mechanism from HPMC-based matrices in capsules was the non-Fickian transport in which the sustainable drug release of HPMC capsules could be achieved by the addition of polymeric matrix.

1. Introduction

Typically, hard gelatin capsule is commonly used for filling large number of drugs including antibiotics. The production of pharmaceutical products in the form of capsules is both cost- and process-effective. The utilization of capsules as a controlled drug delivery device is also interesting. The lipid system in a molten state can be directly filled into hard gelatin capsules to control the drug release. A diffusion-controlled system was obtained with Gelucire® containing lithium sulfate, which remained inert in the aqueous environment at 37 °C. On the contrary, the erosion was proved to control the release of indomethacin when the dispersible Gelucire® was added to the non-dispersible Gelucire® (Vial-Bernasconi et al., 1995). Some retardation in urinary excretion was obtained for total salicylate when administering capsules of aspirin mixed with Gelucire® 50/13 (Djimbo et al., 1984). For colon drug delivery with a chitosan capsule, an additional outer enteric coating prevented the drug release in the stomach owing to the solubility of chitosan under acidic conditions. Resultant enteric-coated chitosan dispersed system capsules reached the large

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.jsps.2015.04.003

intestine within 1–3 h after oral administration and they gradually degraded in the colon (Shimono et al., 2002). Pulsatile drug delivery system has been developed using a water insoluble capsule body and a hydrophilic plug (HPMC or guar gum). The body portion was cross-linked by formaldehyde and heat treatment which the drug was liberated from a limited surface area of the open end of this hard gelatin capsule. This design was similar to the Pulsincap™ system which had an insoluble capsule body (Gothoskar et al., 2004). In addition, the type of hydrophilic agent (HPMC or guar gum) and the molecular weight of HPMC affected the drug release (Mukesh and Sumitra, 2002).

Propranolol HCl (PPH) is widely used in therapeutics for its antihypertensive and antiarrhythmic actions. It has a short plasma half-life of about 2–6 h. Consequently, it has to be frequently taken in order to maintain the plasma concentration in the therapeutic range. The main purpose of the extended release product is to reduce side effects and prolong the drug intake interval and, thus, it is also convenient for drug administration. Furthermore, being highly water soluble drug (Lund, 1994) it is suitable to be used as model drug for this study to assess the efficacy of the developed system for prolongation of its release.

HPMC capsules do not become brittle when exposed to low humidity and they are chemically stable. In addition, the slower drug release from HPMC capsule than that from gelatin capsules has been reported (Cole et al., 2004). HPMC capsules were used in this study to minimize the effect of charge interaction, especially the positive charge of propranolol and the negative charge of gelatin. HPMC has been employed extensively as a hydrophilic matrix former in oral controlled-release dosage forms for various drugs. This popularity can be attributed to its non-toxic nature, its capability to accommodate high levels of drug loading in matrix and a small influence of processing variables on drug release (Ganga et al., 1992; Taylan et al., 1996; Chattaraj and Das, 1996). There are many disadvantages for manufacturing matrix tablet including the longer period and higher energy-consuming process. In addition, some polymer using as matrix former renders the granules elastic and the elastic deformation during the compression leads to soft tablets with not adequate hardness. For matrix filled in capsule, the cost of production will be minimized because of the lesser production steps and excipients in formula. Although the single-unit matrices of PPH sustained release tablets have been widely developed, in order to reduce the frequency of dosing and to produce steady pharmacological effects, the development of this drug into single HPMC matrix filling into capsules has not been reported. The purpose of this study was to develop PPH sustained release capsules using different polymers as a matrix former and to investigate the factors affecting the drug release from the prepared capsules , which is the simplest way to make prolonged release formulations. Authors need to highlight draw backs of matrix tablets such as.

2. Materials and methods

2.1. Materials

PPH was purchased from China National Chemical Imp. & Exp., Shanghai, China. HPMCs (Methocel® K 4M, Methocel® K 15M, Methocel® K 100M and Methocel® E 15LV were purchased from Colorcon Asia Pacific Pvt., Ltd., Bangkok, Thailand. Chitosan (Aqua premier, Chonburi, Thailand) with a degree of deacetylation of 99.3% and a molecular weight of 70 kDa was passed through sieve No. 80 mesh before being used. Dibasic calcium phosphate (DPC) (Sudeep Pharma Ltd., India), HCl (Baker Analyzed, A.C.S. Reagent, USA), and xanthan gum (Xantural 75®, CP Kelco U.S., Inc. USA.) were used as received. Monobasic potassium phosphate, sodium hydroxide pellets, sodium bicarbonate and sodium chloride were purchased from P.C. Drug Center Co., Ltd., Thailand. HPMC capsules size No.1 were kindly supplied by Capsugel, Pranakorn Sriauthuthaya, Thailand and used as received.

2.2. Formulation and preparation of single-unit controlled release capsules

Hard HPMC capsules (size No. 1 with a volume of 0.49 ± 0.01 mL) were filled with the drug and matrix component. The amount of PPH per capsule was 40 mg. Different viscosity grades of HPMC, i.e. Methocel® type K4M, K15M, K100M and E15LV, were utilized as a matrix former to investigate the effect of viscosity grade of HPMC on the drug release. A study was also performed for the effect of types and amounts of diluents (lactose, dibasic calcium phosphate (DPC) and sodium bicarbonate ($NaHCO_3$)) and polymers (chitosan and xanthan gum) on the drug release from HPMC matrices. The tapped density of the excipients (Table 1) was used to determine the amount to fill into capsules. The capsule formula presenting the excipient composition is shown in Table 2. The powders were mixed manually with a mortar and pestle for 5 min to obtain the homogeneous powder mix and filled in capsules using a capsule filling machine No. 1 (S.T.P No.1 B.M., Bangkok, Thailand).

2.3. Evaluation of physical properties of capsule

Weight variation of capsules was determined by using an analytical balance. Twenty capsules were individually weighed. The contents of each capsule were removed by using a suitable means. The empty shells were individually accurately weighed and calculated for the net weight of its contents by subtracting the weight of the shell from the respective gross weight.

Table 1 Tapped density of drug and materials (mean ± SD, $n = 3$).

Materials	Tapped density (g/mL)
PPH	0.42 ± 0.00
Chitosan (180 mesh passed)	0.32 ± 0.01
Dibasic calcium phosphate	0.86 ± 0.01
Ethyl cellulose	0.32 ± 0.00
HPMC K15M	0.46 ± 0.01
HPMC K4M	0.49 ± 0.00
HPMC K100M	0.48 ± 0.01
HPMC E15LV	0.51 ± 0.01
Lactose	0.67 ± 0.00
Sodium bicarbonate	0.67 ± 0.00
Xanthan gum	0.69 ± 0.02

Table 2 Composition formula of PPH matrix capsules containing different diluents.

Formula	Excipients (%w/v)								
	HPMC K4M	HPMC K15M	HPMC K100M	HPMC E15LV	Lactose	DCP	Xanthan gum	Chitosan	$NaHCO_3$
F1	100	–	–	–					
F2	–	100	–	–					
F3	–	–	100	–					
F4	–	–	–	100					
F5				–	100	–	–	–	–
F6				25	75	–	–	–	–
F7				50	50	–	–	–	–
F8				75	25	–	–	–	–
F9				–	–	100	–	–	–
F10				25	–	75	–	–	–
F11				50	–	50	–	–	–
F12				75	–	25	–	–	–
F13				–	–	–	100	–	–
F14				25	–	–	75	–	–
F15				50	–	–	50	–	–
F16				75	–	–	25	–	–
F17				–	–	–	–	100	–
F18				25	–	–	–	75	–
F19				50	–	–	–	50	–
F20				75	–	–	–	25	–
F21				40	–	–	–	–	60
F22				60	–	–	–	–	40
F23				80	–	–	–	–	20

2.4. Study of drug release

The dissolution of PPH was performed with the basket method using a dissolution apparatus (type 1) (Prolabo, France). The dissolution fluid was 900 mL pH 1.2 buffer solution maintained at 37 °C and the basket rotational speed was 100 rpm. To study the effect of the dissolution fluid on release behavior, 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 release in PH 1.2 buffer solution was conducted for a period of one and a half hours. Then the pH was increased to 6.8 by adding 4.6 g of sodium hydroxide, 3.06 g of monobasic potassium phosphate and 4.005 g of dibasic sodium phosphate. An aliquot of 5 mL sample was withdrawn and replaced with another 5 mL of fresh dissolution medium at various time intervals. The drug content in the samples was determined by measuring the absorbance at 323 nm ($n = 3$) in a UV–Vis spectrophotometer (Perkin–Elmer, Germany). During the drug release studies, the matrices were observed for physical integrity. To study the effect of hydrodynamic force on drug release, the capsules were tested for dissolution at different basket rotational speeds of 25, 50, 100 and 150 rpm.

2.5. Dissolution profile fitting

A least square fitting the experimental dissolution data (cumulative drug release $>10\%$ and up to 80%) to the mathematical equations (power law and zero order) was carried out using a nonlinear computer program, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). A coefficient of determination (r^2) was used to indicate the degree of curve fitting (MicroMath, 1995). Goodness-of-fit was also evaluated using Model Selection Criterion (MSC), given below.

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

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

3. Results and discussion

The tapped density values of PPH, diluents and other excipients are presented in Table 1. The tapped density of these materials depended on the specific characteristic of individual materials. The lowest tapped density was found in the case of chitosan while the tapped density of different grades of HPMC was in the range of 0.46–0.51 g/mL. There were the factors affecting drug release of single-unit controlled release capsules as following.

3.1. Influence of viscosity grade of matrix former on drug release

The dissolution profiles of PPH released from the matrix system in HPMC capsules containing different viscosity grades of HPMC (Methocel®K4M, K15M, K100M and low viscosity grade, E 15LV) powder are shown in Fig. 1. The drug release from capsules containing HPMC E 15LV was faster than those containing K4M, K15M and K100M, which showed similar release profiles. The drug release profile from the HPMC K100M matrix was slightly lower than that containing HPMC type K4M and K15M. The results demonstrated that HPMC apparently extended the release time of drug for longer

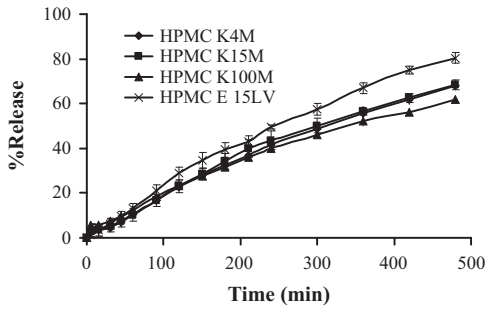

Figure 1 Dissolution profiles of PPH released from the matrix containing a different viscosity grade HPMC in pH 1.2 buffer solution (mean ± SD, $n = 3$).

than 8 h. The dissolutions data of capsules containing HPMC K4M, K15M and K100M followed the first order equation whereas the dissolution data of capsules containing HPMC E 15LV fitted well with the zero order equation, as presented in Table 3.

The utilization of HPMC as a matrix former extended the drug release owing to the hydrophilic nature of HPMC. It swelled on contact with water thereafter the medium diffused into the device. Generally, the thickness of the swollen layer formed around the matrix core was greater in matrices containing HPMC with higher viscosity grades (Gao et al., 1996). Increasing the molecular weight of the HPMC powder from K4M grade to K15M grade had no influence on the drug release. A possible explanation was the existence of a limiting HPMC viscosity, when no further decrease in drug release was observed, probably due to the time necessary to form the release-limiting gel barrier (Sung et al., 1996; Krogel and Bodmeier, 1999). However, the matrix tablets comprising propranolol hydrochloride (26–64% of HPMC), aminophylline (16–54% of HPMC) and promethazine hydrochloride (55–86% of HPMC) have not shown significantly different release profiles with viscosity grades of HPMC of 850 CP and above (12,450 and 93,000 cps) (Ford et al., 1985a,b). Higher HPMC ratios (20% and 30%) in metronidazole matrix tablet showed no difference on drug release rate when the viscosity of HPMC was changed (Campos-Aldrete and Villafuerte-Robles, 1997). Therefore the high amount of HPMC loading could effectively modulate the drug release which related to the increased tortuosity and apparently influenced greater than the porosity. In addition, the effect of HPMC concentration on swelling rates was less marked at higher polymer content (Wan et al., 1995). A saturation state was attained beyond 40% HPMC content of these matrices. The release of repaglinide from microsphere fabricated from HMPC 5 cps and 100 cps was similar but the latter was slightly slower (Sharma et al., 2015). While the drug release profile from the HPMC K100M matrix was slightly lower than those of the previous two viscosity grades, the increased viscosity grade of HPMC enhanced the thickness of the gel layer and the tortuosity of the drug diffusion path was increased. In addition, the HPMC particles of the increased viscosity grades swelled more slowly and produced swollen particles of smaller volumes. As a result, matrices made of particles of HPMC with higher viscosity grades showed slower drug release rates than those prepared from HPMC particles with lower viscosity grades (Tahara et al., 1995).

3.2. Influence of diluents on drug release

3.2.1. Effect of water soluble and insoluble fillers

Increasing the amount of lactose from 25% to 75% in the HPMC matrix resulted in an enhancement for the release rate of PPH (Fig. 2). The increased amount of dibasic calcium phosphate in the HPMC matrices led to the increasing of drug release rate (Fig. 3). By comparison, the matrix containing 100% dibasic calcium phosphate showed a greater drug release

Table 3 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution in pH 1.2 buffer solution to different release models.

Capsule	Power law		First order		Higuchi's		Zero order	
	cd	msc	cd	msc	cd	msc	cd	msc
HPMC K4M	0.9997	7.59	0.9962	5.20	0.9480	2.59	0.9851	3.85
HPMC K15M	0.9983	5.84	0.9947	4.89	0.9664	3.03	0.9734	3.26
HPMC K100M	0.9992	6.60	0.9955	5.04	0.9894	4.18	0.9805	3.58
HPMC E15LV	0.9989	6.28	0.9845	3.81	0.9610	2.88	0.9858	3.89
Lactose 25%	0.9880	3.82	0.9489	2.57	0.9641	2.93	0.9844	3.76
Lactose 50%	0.9990	6.33	0.9676	3.03	0.9710	3.14	0.9885	3.38
Lactose 75%	0.9979	5.39	0.9306	2.17	0.9810	3.47	0.9785	3.34
DCP 25%	0.9939	4.55	0.9381	2.42	0.9307	2.31	0.9904	4.29
DCP 50%	0.9972	5.27	0.9726	3.20	0.9751	3.30	0.9761	3.33
DCP 75%	0.9999	9.11	0.9187	2.01	0.9573	2.65	0.9916	4.28
Xanthan 25%	0.9992	6.53	0.9884	4.06	0.9916	4.38	0.9799	3.51
Xanthan 50%	0.9998	8.01	0.9906	4.27	0.9814	3.59	0.9899	4.20
Xanthan 75%	0.9995	7.05	0.9972	5.50	0.9827	3.69	0.9737	3.27
Chitosan 25%	0.9998	8.19	0.9816	3.66	0.9782	3.49	0.9816	3.66
Chitosan 50%	0.9989	6.25	0.9132	2.08	0.9013	1.95	0.9968	5.39
Chitosan 75%	0.9990	6.26	0.9257	2.15	0.9596	2.01	0.9990	6.46
$NaHCO_3$ 20%	0.9995	7.24	0.9871	3.98	0.9773	3.42	0.9847	3.81
$NaHCO_3$ 40%	0.9982	5.70	0.8680	1.58	0.9365	2.31	0.9966	5.26
$NaHCO_3$ 60%	0.9979	5.18	0.6876	0.49	0.8061	0.97	0.9831	3.41

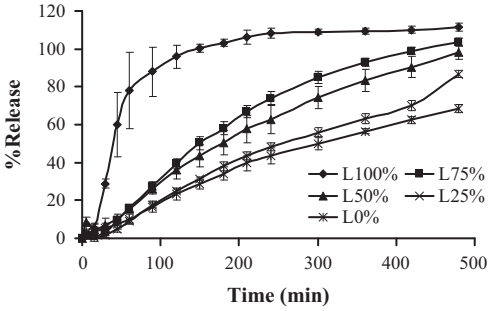

Figure 2 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing different amounts of lactose (L) in pH 1.2 buffer solution (mean ± SD, $n = 3$).

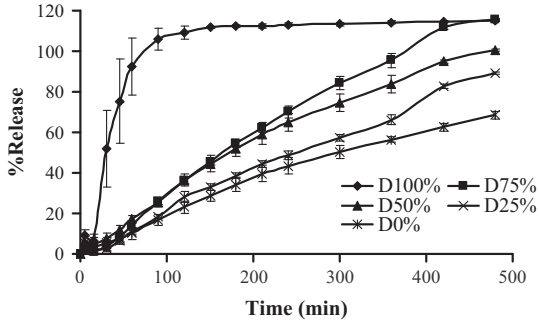

Figure 3 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing different amounts of dibasic calcium phosphate (D) in pH 1.2 buffer solution (mean ± SD, $n = 3$).

than the matrix containing only lactose as a diluent. The dissolution data from matrices containing only lactose and dibasic calcium phosphate were not used for the curve fitting because of the apparent fast release of the drug from the capsule. However, the incorporation of lactose or dibasic calcium phosphate in the HPMC matrix contributed to a drug release rate close to zero-order as presented in Table 3. The magnitude of the exponent n from the curve fitting to a power law equation could indicate a release mechanism such as Fickian diffusion, case II transport, or anomalous transport. In the present study (cylindrical shape) the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of n between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation), commonly called anomalous non-Fickian transport (Lotfipour et al., 2004). The k value can be regarded as a power law release constant with bigger values leading to faster drug release. Mathematically, an increasing n values bigger than 1.0 allows for a more desirable incremental release. To achieve a delayed release pattern that was therapeutically useful, n values were expected to be bigger and k values to be smaller with a prerequisite of acceptable lag time (Walker and Wells, 1982). From the release exponent (n), the release mechanism of formulations containing 25%, 50% and 75% lactose or dibasic calcium phosphate indicated non-Fickian transport (Table 3). The incorporation of lactose or dibasic calcium phosphate in the HPMC matrix system decreased the concentration of polymer in gel layers. Therefore, the diffusion of a medium into the capsule was facilitated and then the diffusion of the drug from the matrix was enhanced. As a result, the release rate of the drug from the matrices was increased. Increasing the polymer/filler ratio increased the release rate since the diffusivity of the drug in the gel layer was enhanced (Takka, 2003; Takka et al., 2001). Lactose or dibasic calcium phosphate exhibited the similar impact on the release of PPH from HPMC matrices because both of them could dissolve in this buffer.

3.2.2. Effect of polymer

The dissolution profiles of the drug from capsules filled with HPMC K15M, xanthan gum and chitosan, are shown in Fig. 4. All polymers sustained the drug release in pH 1.2 buffer solution for longer than 8 h, whereas the capsule filled with only chitosan prolonged the drug release for 4 h following the immediate drug release. The amino groups onto chitosan structure could be protonated in acidic media and then dissolved however this alteration gradually occurred (Tungtong et al., 2012). Thus the burst release at 4 h was owing to the complete protonation and the solubilized chitosan could not retard the drug release anymore. The drug release from HPMC K15M matrix was slower than those containing other polymers however it was slightly different from that containing xanthan.

The release profile of the formulation containing 50% xanthan gum in the HPMC matrix displayed slightly slower release than that containing only HPMC. However the release profile of the formulation containing 25% xanthan gum in the HPMC matrix showed a similar drug release profile to the system containing only HPMC (Fig. 5). The PPH released from HPMC–xanthan gum matrices was rather complex, because both HPMC and xanthan gum are hydrophilic polymers which, upon contact with aqueous fluid, are able to form quite a viscous gel. Xanthan gum could increase the viscous gel layer around the matrix core. Furthermore, synergism attributed to the intermolecular hydrogen-bonding between them could occur. The addition of sodium carboxymethylcellulose (NaCMC) to HPMC matrix increased the viscosity of the system since there was a strong hydrogen bonding between the carboxyl groups on Na CMC and the hydroxyl groups on

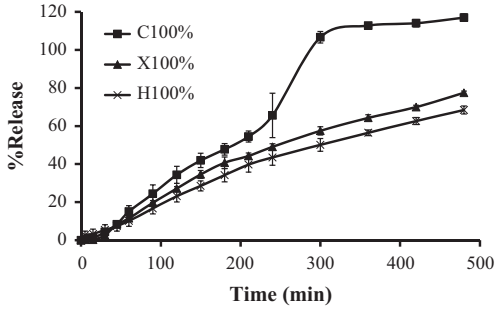

Figure 4 Dissolution profiles of PPH released from capsules filled with various polymers matrix (HPMC K15M (H), xanthan gum (X) and chitosan (C)) in pH 1.2 buffer solution (mean ± SD, $n = 3$).

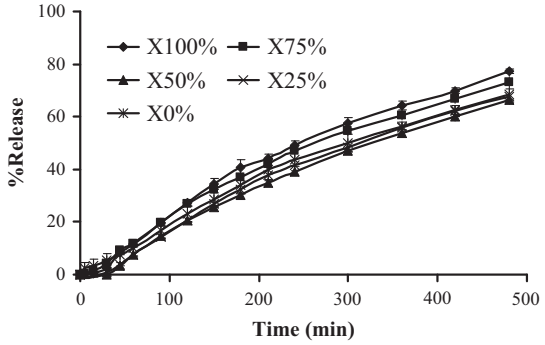

Figure 5 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing different amounts of xanthan gum (X) in pH 1.2 buffer solution (mean ± SD, n = 3).

HPMC, leading to strong cross-linking between the two polymers (Takka et al., 2001). Thus there was a possibility of interaction between xanthan gum and HPMC based on hydrogen bonding similar to the interaction between HPMC and Na CMC (Takka et al., 2001) or collagen (Ding et al., 2015) as previously reported.

Hence, the formulation containing 50% xanthan gum and 50% HPMC increased the viscosity of the gel layer and subsequently retarded the drug diffusion from the capsule. The other reason for the retardation of drug release with xanthan gum could be the ionic interactions between the drug and this anionic polymer. There was a considerable interaction between PPH and anionic polymers depending on the carboxyl functional groups of the anionic polymers (Varma et al., 2005; de la Torre et al., 2003).

In pH 1.2 buffer solution, the drug release from the matrix system containing chitosan was faster, as shown in Fig. 6. The formulation containing only chitosan exhibited immediate release after 4 h. The use of pure chitosan formulation in oral administration was limited owing to its fast dissolution in the acidic environment of the stomach. Some researchers noted that at least chitosan of 80% was needed to achieve the proper sustained release tablets (Sawayanagi et al., 1982). Capsules containing 75% chitosan in HPMC matrices also exhibited fast release after 4 h. This formulation released PPH nearly to 100% at 6 h. All formula comprising chitosan in HPMC matrices exhibited faster drug release compared to the matrix containing only HPMC in pH 1.2 buffer solution.

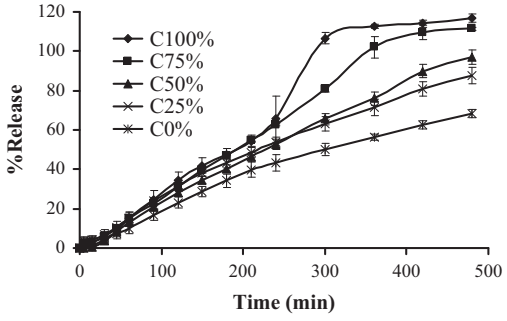

Figure 6 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing different amounts of chitosan (C) in pH 1.2 buffer solution (mean ± SD, n = 3).

The dissolution data of capsule containing HPMC–xanthan gum matrices were best fitted with the first order model (Table 3). Their release mechanism was non-Fickian transport with n values ranging from 0.57 to 0.65 (Table 4). The dissolution data of the formulation containing HPMC-chitosan matrices fitted well with the zero order as presented in Table 3. The release mechanism of the formulation containing 50% and 75% chitosan in HPMC matrices was non-Fickian transport (Table 4). The hydrophilicity of chitosan, due to the presence of amine and hydroxy functional groups in its repeat unit, makes the polymer soluble in diluted acidic solutions. It is insoluble in water but soluble at pH values under 6.5 in most acidic media (Oungbho and Müller, 1997). Therefore, the dissolution profile of PPH released from the chitosan matrix exhibited fast release after 4 h in pH 1.2 buffer solution. The incorporation of chitosan in HPMC matrices decreased the amount of drug released. Because of the gel forming ability of chitosan, synergism attributed to the intermolecular hydrogen-bonding between hydroxyl functional groups on chitosan, and hydroxyl groups on HPMC. However the release of PPH was increased as the chitosan content was increased owing to its solubility in an acidic environment.

3.2.3. Effect of sodium bicarbonate

The incorporation of 40% sodium bicarbonate (S) into the HPMC matrix prolonged drug release in pH 1.2 buffer solution (Fig. 7). Increasing proportion of sodium bicarbonate up to 60% in HPMC-bicarbonate matrices provided the slow drug release during the first 2 h and thereafter faster release. The capsule containing 20% sodium bicarbonate in the HPMC matrix showed similar drug release to the formulation containing only HPMC during the first 4 h. Subsequently, this formulation exhibited faster drug release than that containing only HPMC. The dissolution data of the formulations containing 40% and 60% sodium bicarbonate were fitted well with the zero order, while the formulation containing 20% sodium

Table 4 Estimate parameters from curve fitting of drug dissolution in pH 1.2 buffer solution to power law expression.

Capsule	k ± sd^10^{-1}	$t1$ ± sd (hr)	n ± sd
HPMC K4M	0.1835 ± 0.0039	0.59 ± 0.04	0.66 ± 0.01
HPMC K15M	0.2081 ± 0.0081	0.73 ± 0.06	0.60 ± 0.02
HPMC K100M	0.1855 ± 0.0062	0.51 ± 0.06	0.60 ± 0.02
HPMC E15LV	0.2179 ± 0.0095	0.53 ± 0.07	0.66 ± 0.02
Lactose 25%	1.8687 ± 0.0493	0.49 ± 0.49	0.73 ± 0.11
Lactose 50%	2.8426 ± 0.0081	0.57 ± 0.03	0.64 ± 0.02
Lactose 75%	3.4537 ± 0.0178	0.72 ± 0.06	0.62 ± 0.03
DCP 25%	1.7769 ± 0.0267	0.40 ± 0.23	0.79 ± 0.07
DCP 50%	2.8539 ± 0.0151	0.52 ± 0.06	0.64 ± 0.03
DCP 75%	2.9159 ± 0.0032	0.64 ± 0.01	0.72 ± 0.01
Xanthan 25%	2.3112 ± 0.0048	0.69 ± 0.03	0.57 ± 0.11
Xanthan 50%	1.8118 ± 0.0042	0.78 ± 0.04	0.65 ± 0.11
Xanthan 75%	2.1705 ± 0.0074	1.03 ± 0.06	0.58 ± 0.02
Chitosan 25%	1.5776 ± 0.0152	0.07 ± 0.10	1.01 ± 0.05
Chitosan 50%	1.7580 ± 0.0132	0.28 ± 0.11	0.84 ± 0.03
Chitosan 75%	2.3897 ± 0.0031	0.48 ± 0.01	0.64 ± 0.01
$NaHCO_3$ 20%	2.0049 ± 0.0049	0.63 ± 0.03	0.66 ± 0.01
$NaHCO_3$ 40%	1.3499 ± 0.0149	1.34 ± 0.15	0.86 ± 0.05
$NaHCO_3$ 60%	3.7267 ± 0.0219	1.78 ± 0.06	0.68 ± 0.05

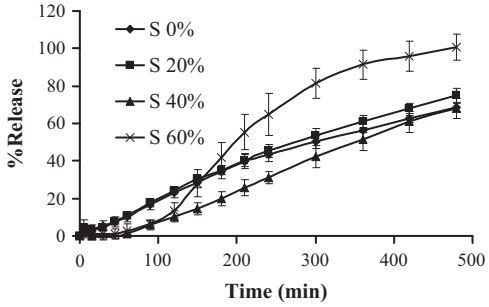

Figure 7 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing different amounts of sodium bicarbonate (S) in pH 1.2 buffer solution (mean ± SD, $n = 3$).

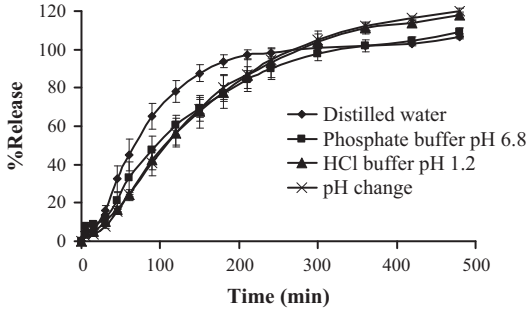

Figure 8 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing 75% lactose in different pH of dissolution medium (mean ± SD, $n = 3$).

bicarbonate in the HPMC matrix was close to the first order model, as presented in Table 3. The release mechanism of all formula containing sodium bicarbonate in HPMC matrices was non-Fickian transport (Table 4). Since sodium bicarbonate posed as the effervescence in high concentration acid conditions, it promoted a sustained drug release when a suitable concentration was employed. Sodium bicarbonate provided gas generation in pH 1.2 buffer solution. Therefore, the air bubbles which appeared in the swollen matrix posed as a transport barrier as previously reported (Ching et al., 2008). It has been reported that the incorporation of sodium bicarbonate into HPMC K4M matrix tablets reduced the release rate of diltiazem hydrochloride, since the *in situ* chemical interaction within the gelled structure might induce the alteration of matrix-swelling dynamics and the inhibition of drug dissolution (Pillay and Fassihi, 1999). In addition, the modification in micro environmental pH by adding sodium bicarbonate into this matrix leading to partly neutralization of PPH to free base, leading to greater drug release retardation in acidic media. The pH enhancement for micro-environment of sodium alginate matrix minimized the crack formation and prolonged the drug release by retarding the conversion of this polymer to alginic acid (Ching et al., 2008). Therefore the neutralization action of pH-modifier such as sodium bicarbonate was synergistically enhanced in the presence of carbon dioxide barrier formed by effervescing sodium bicarbonate, reducing drug release in the acid medium. However the high loading amount of sodium bicarbonate generated enough carbon dioxide after exposure to the acidic medium to expel and promote the gel erosion thereafter the fast drug release was evident for the 60% sodium bicarbonate incorporated in this matrix because the neutralization effect on drug release might have been countered by strong gel erosion. The matrix could form the mild gelation and mild gel erosion for the addition of 20% sodium bicarbonate thus the drug release was unaffected.

3.3. Influence of pH of dissolution medium and hydrodynamic force on drug release

To simulate the environment of the gastrointestinal tract, the effect of pH of the dissolution medium on the release of PPH from capsules was investigated A system containing 75% lactose and 25% HPMC was chosen for further investigation of the influence of the pH of the dissolution medium on the PPH release (Fig. 8). The drug release was faster in distilled water than that in pH 1.2 buffer solution, phosphate buffer pH 6.8 and pH change, while the release in the three latter dissolution fluids was similar. HPMC is non-ionic therefore acidic condition slightly affected the solubility and swelling (de la Torre et al., 2003). The hydrogel based on high-viscosity HPMC was known to deliver the drug at a constant rate, which was independent of the hydration, gel viscosity and relative permeability of the dosage form, because the drug release rate was related directly to the drug solubility (Varma et al., 2005). PPH is a weakly basic drug, therefore, it should exhibit pH-dependent release from the matrix due to its pH-dependent solubility. Its 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 PPH was faster in water and 0.1 N HCl compared to that in a phosphate buffer (de la Torre et al., 2003). However, the study indicated that PPH did not demonstrate the pH-dependent solubility from the HPMC matrix granule filled into the capsule.

The enhanced rotational speed or hydrodynamic force increased the drug release (Fig. 9). There was a more rapid erosion of the matrix at higher stirring rates because of the increased rate of detachment of polymer chains away from the matrix surface. This led to a thinner layer of gel forming at the surface of the dosage form at higher agitation rate (Goole et al., 2007) therefore the drug release from this matrix capsule changed easily due to physical agitation and probably peristaltic movement in the gastrointestinal tract.

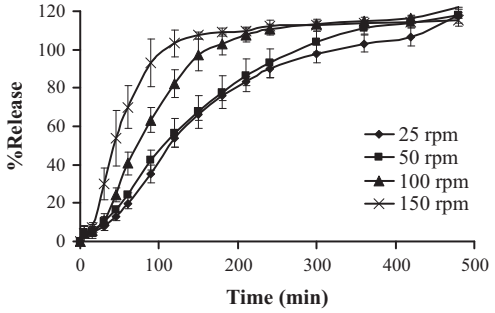

Figure 9 Dissolution profiles of PPH released from capsules filled with HPMC matrices containing 75% lactose by varying rotation speed of the paddle in pH 1.2 buffer solution (mean ± SD, $n = 3$).

4. Conclusion

The utilization of HPMC as a matrix former extended the release time of PPH from capsules. The viscosity grade of HPMC affected the drug release. The increased amount of fillers (lactose and dibasic calcium phosphate) increased the release rate of PPH from the HPMC matrices. Types and amounts of polymer apparently affected the PPH release from HPMC matrices. The physiochemical properties of polymers and the interaction between HPMC and polymers were the important factors for the prolongation of the drug release. The release mechanism from the HPMC-based matrices in capsules was non-Fickian transport.

Acknowledgements

This research work was kindly supported by Research and Development Institute, Silpakorn University and Faculty of Pharmacy, Silpakorn University, Thailand.

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