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Research paper

Biphasic release of indomethacin from HPMC/pectin/calcium matrix tablet: I. Characterization and mechanistic study

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Abstract

Calcium-induced crosslinking of pectin acts as the dominating factor controlling drug release from pectin-based matrices. The same interaction was employed to modify indomethacin release from HPMC/pectin/calcium matrix in this study. The aim was to characterize the release profiles, and to study the formulation variables and the underlying mechanisms. The matrix tablet was made up of pectin HM 70, calcium chloride and HPMC K4M, and prepared by the wet granulation method. In vitro release was performed in water and characterized by the power law. Matrix erosion was evaluated by studying the weight loss and pectin release. Biphasic release of indomethacin from the HPMC/pectin/calcium matrix tablet was observed, and extraordinary power law exponent n values of over 1.0 were observed. Increase in calcium amount led to more significant retardation on drug release. The two power law parameters, n and K, correlated to the amount of calcium in the matrix. A lag time of over 4 h can be achieved at HPMC/pectin/calcium chloride amount of 100 mg/100 mg/100 mg. Both matrix weight loss and pectin release were linearly correlated to indomethacin release, indicating erosion-controlled drug release mechanisms. The hybrid matrix showed retarded erosion and hydration rate, which served as the basis for retarded indomethacin release. It is concluded that the pectin/calcium interaction can be employed to modify drug release from HPMC/pectin/calcium matrix tablet with biphasic release patterns for potential timed or site-specific drug delivery.

Keywords: Pectin; HPMC; Calcium ions; Matrix; In situ crosslinking; Biphasic release

1. Introduction

Biphasic release is characterized by two distinct release periods. Efforts have been made to achieve biphasic release, also recognized as bimodal or sigmoidal release, with delayed release at initial stage and rapid release at later stages for timed and colon-specific delivery [1–3], or just for post-gastric delivery to avoid possible gastric degradation or stimulation to gastric tissues [4].

Biphasic release is common for coated drug delivery systems, but rare for matrix systems. In the previous study [3], we investigated the release behavior of a water-insoluble model drug, indomethacin, from a pectin matrix tablet containing a large amount of calcium chloride. Pectin is a natural polyanionic hydrocolloid that can be crosslinked by divalent calcium cations through an ''egg-box'' mode [5,6]. In that study, this interaction was employed to strengthen the pectin gel and retard drug release from the pectin/calcium matrix tablet, resulting in biphasic release patterns. When the power law was attempted to describe the release patterns, exponent n values as high as 1.20 were observed. Preliminary study on the relationship between matrix erosion and drug release suggested an erosion-controlled release mechanism [3]. However, pectin is a biopolymer of high hydrophilicity [7,8], and the gels formed after hydration lack robustness to withstand the tearing force generated by the gastric and intestinal movement although calcium salts may be added as crosslinker to strengthen the gels. Therefore, there is doubt whether the pectin/calcium

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matrix functions in vivo. For similar reason, evaluation of the matrix erosion was only conducted for a limited 4 h in the previous study, which compromised our conclusion on the erosion-controlled mechanism of drug release. It is mandatory to reinforce the pectin/calcium matrix with much stronger materials.

Hydroxypropyl methylcellulose (HPMC), a semisynthetic ether derivative of cellulose, has been used widely since the 1960's as matrices for oral controlled-release drug delivery systems [9,10]. It is non-toxic, readily compressible, and able to accommodate high levels of drug loading. Upon hydration, HPMC matrices rapidly form a gel layer of sufficient strength to achieve controlled drug release.

In the present study, HPMC was incorporated to strengthen the hybrid HPMC/pectin/calcium matrix. As the presence of HPMC may interfere with the interaction of pectin and calcium, the release behavior may differ from that of the previously studied pectin/calcium matrix [3]. It is necessary to understand the release characteristics of the new hybrid polymer. Here, we employed a semi-empirical equation, known as the power law [11–13], to characterize the release profiles. Special attention was paid to the effect of formulation variables. Furthermore, the matrix erosion was investigated for prolonged times encompassing almost the whole release process to find solid evidence on the drug release mechanisms.

2. Materials and methods

2.1. Materials

Micronized indomethacin (<5 μm in diameter) was purchased from Sine Pharmceuticals (Shanghai, China). Pectin HM (high methoxylated) 70 and PVP K30 were kindly gifted from Shanghai Representative Office, ISP (Hong Kong) Ltd. Calcium chloride ($CaCl_2$) was of analytical purity and purchased from Shanghai Chemical Regent Corp. (Shanghai, China). Hydroxypropyl methylcellulose (Methocel K4M) was a Dow Chemicals product and kindly gifted by Shanghai Colorcon Corp., Ltd. All other chemicals were of analytical grade.

2.2. Preparation of HPMC/pectin hybrid matrix tablet

Matrix tablets containing 25 mg of indomethacin were prepared using wet granulation following procedures similar to the previous study [3]. First, ingredients including indomethacin, HPMC, pectin and calcium chloride were mixed homogeneously in a laboratory shaker-mixer. Ten percent of (w/v) PVP K30 ethanol solution was added gradually and milled continuously to make paste. The wet mass was forced through a 20-mesh sieve and dried at 50 °C for 3 h. The dried granules were lubricated with magnesium stearate in 1% (w/w) and compressed into flat 10 mm tablets using a ZDY-8 model single punch compressor (Yuandong Pharmaceutical Machinery Co., Shanghai, China). The tablet formulations are given in Table 1. Each

Table 1
Composition, properties, power law correlation and release parameters of indomethacin (IMC) from HPMC/pectin/calcium matrix tablets

Formulation		Ingredient (mg)					Crushing strength (N, $n = 10$)	Thickness (mm, $n = 10$)	Weight (mg, $n = 20$)	Power law correlation			$T_{0.1}$ (h)	$T_{0.5}$ (h)	$T_{0.8}$ (h)
No.	Code	IMC	HPMC	Pectin	$Cacl_2$	Lactose				Time span	K	n	r		
1	P100C100	25	100	**100**	**100**	–	85 ± 5.3	4.40 ± 0.02	329.4 ± 0.3	0.5–26 h	0.01535	1.2539	0.9971	4.5	16.1	>26
2	P0C100	25	100	–	**100**	–	81 ± 5.0	3.46 ± 0.02	230 ± 1.2	2–26 h	0.03732	1.0563	0.9955	2.5	11.7	18.2
3	P100C0	25	100	**100**	–	–	83 ± 4.1	3.68 ± 0.02	227.7 ± 0.6	1–17 h	0.07789	0.9439	0.9977	1.3	7.2	11.8
4	P0L100	25	100	–	–	**100**	80 ± 2.8	3.80 ± 0.01	229.5 ± 0.4	0.5–26 h	0.03655	1.0740	0.9959	2.6	11.4	17.7
5	P100C15	25	100	100	**15**	–	86 ± 3.4	3.94 ± 0.01	242.2 ± 0.8	0.5–17 h	0.02681	1.3905	0.9918	2.6	8.2	11.5
6	P100C25	25	100	100	**25**	–	85 ± 6.0	4.10 ± 0.03	253.4 ± 1.3	0.5–17 h	0.01699	1.5204	0.9923	3.2	9.2	12.6
7	P100C50	25	100	100	**50**	–	87 ± 2.7	4.28 ± 0.01	276.8 ± 0.7	0.5–17 h	0.01334	1.5555	0.9944	3.7	10.3	13.9
8	P100C75	25	100	100	**75**	–	82 ± 5.5	4.32 ± 0.03	304.1 ± 1.0	0.5–26 h	0.01591	1.2806	0.9930	4.2	14.8	>26
(1)	P100C100	25	100	100	**100**	–	85 ± 5.3	4.40 ± 0.02	329.4 ± 0.3	0.5–26 h	0.01535	1.2539	0.9971	4.5	16.1	>26
9	P100C125	25	100	100	**125**	–	83 ± 3.6	4.58 ± 0.02	353.7 ± 2.7	1–26 h	0.01739	1.1873	0.9948	5.7	16.9	>26
10	P100C150	25	100	100	**150**	–	85 ± 4.8	4.88 ± 0.01	380.2 ± 1.5	0.5–26 h	0.01974	1.1105	0.9960	4.3	18.4	>26
11	P25C25	25	100	**25**	**25**	–	84 ± 3.5	3.16 ± 0.02	179.3 ± 0.9	0.5–26 h	0.02918	1.1380	0.9954	3.0	12.1	18.4
12	P50C50	25	100	**50**	**50**	–	88 ± 5.6	3.56 ± 0.03	228.6 ± 1.1	0.5–26 h	0.02419	1.2460	0.9913	3.1	11.4	16.6
(1)	P100C100	25	100	**100**	**100**	–	85 ± 5.3	4.40 ± 0.02	329.4 ± 0.3	0.5–26 h	0.01535	1.2539	0.9971	4.5	16.1	>26
13	P150C150	25	100	**150**	**150**	–	87 ± 4.3	5.34 ± 0.02	427.4 ± 1.6	0.5–26 h	0.02219	1.1850	0.9897	3.6	13.9	>26

tablet batch was monitored for weight, thickness, crushing strength, and friability (Table 1). Crushing strength was controlled to a narrow range to minimize possible effect of hardness on drug release. The tablets were sealed in glass bottles before tests.

2.3. Determination of indomethacin

Indomethacin amount in tablets and release medium was determined by an HPLC method [3]. The Agilent 1100 series HPLC system was composed of a quaternary pump, a degasser, an autosampler, a column heater, and a tunable wavelength UV detector. The separation was performed at 40 °C using a C18 column (Diamonsil®, 5 μm, 4.6 × 150 mm, Dikma, China) guarded with a refillable precolumn (C18, 1.0 × 20 mm, Alltech, USA). The mobile phase was a mixture of acetonitrile and 0.3% (v/v) acetic acid in the ratio of 58/42 pumped at a flow rate of 1.0 ml/min. Detection wavelength was set to 320 nm.

2.4. Indomethacin release study

Release tests were performed in 900 ml of distilled water (pH 6.5) thermostatically maintained at 37 ± 0.5 °C based on Chinese Pharmacopoeia (2005 Ed.) Method I. Basket rotational speed was set to 100 rpm. At specific time intervals, 5 ml of samples was withdrawn and filtered (Millex® AP, Millipore, 0.4 μm). The filtrate was analyzed by HPLC for indomethacin as described above. In the meantime, an equal volume of blank medium was added to keep constant volume. Tween 80 in a concentration of 0.2% (w/v) was added to the release medium to keep sink conditions. The power law (Eq. (1)) [11–13] was employed to describe the release kinetics, and the time of 10% ($T_{0.1}$), 50% ($T_{0.5}$) and 80% ($T_{0.8}$) drug release was also calculated from the power law equations.

$$\frac{M_t}{M_\infty} = Kt^n \tag{1}$$

where M_t is the amount released at time t, M_∞ is the total amount released, K is a constant incorporating the properties of the macromolecular polymeric system and the drug, and n is the diffusion exponent that depends on the transport mechanism and the shape of the matrix tested. For cylindrical matrix studied in the present study, the n values, 0.45, 0.45–0.89, 0.89 and >0.89, indicate Fickian, non-Fickian (anomalous), Case II and Super Case II transport [13,14]. When $n = 0.45$, the equation is similar to the Higuchi equation [15,16], indicating pure diffusion-controlled release mechanisms. As n value increased from 0.45 to 0.89, contribution of erosion overweighs diffusion gradually, and a constant release rate is achieved when $n = 1.0$.

2.5. Tablet erosion and water uptake study

Tablet erosion was evaluated in a release test assembly following similar procedures in the previous study [3]. Tablets were placed in the basket and subjected to erosion in 900 ml of distilled water at 37 ± 0.5 °C and a rotation speed of 100 rpm. At appropriate time points, the tablets were recovered and dried to constant weight in a vacuum dryer at 60 ± 2 °C. The amount of indomethacin released was also monitored simultaneously by HPLC, as described above, to calculate the amount of drug remaining in the tablet. The percent matrix weight loss at each time point was calculated from the equation:

$$\text{Percent weight loss}(\%) = \left[\frac{W_0 - (W_t - (X_0 - X_t))}{W_0}\right] \times 100 \tag{2}$$

where W_0 and X_0 are the initial weights of the matrix and the drug load, respectively, W_t is the dried weight of the tablet, and X_t is the amount of indomethacin released at time t.

Relative water uptake was also measured and calculated using the following equation:

$$\text{Relative water uptake}(\%) = \left[\frac{W_{\text{wet}} - W_t}{W_t}\right] \times 100 \tag{3}$$

where W_{wet} and W_t are the wet and dried weight of the matrix tablet at time t.

2.6. Calcium release study

Calcium release was monitored using the same apparatus under similar conditions to the release study. At time intervals after immersion into the release medium, 10 ml of release sample was collected and filtered (Millex® AP, Millipore, 0.4 μm). The filtrate was analyzed by atomic absorption spectrometry for calcium. Meanwhile, an equal volume of distilled water was added to keep constant volume.

Calcium in release media was assayed directly or after appropriate dilution using an atomic absorption spectrometer (Varian spectr AA 240, VARIAN) equipped with a 10 cm single element hollow cathode lamp [17,18]. The determination of calcium was carried out at a wavelength of 422.7 nm in a rich air–acetylene flame. Instrumental parameters for the determination of calcium were as follows: lamp current 10 mA; slit width 0.7 nm; air flow 13.5 l/min; acetylene flow 2.21 l/min. Within the concentration range of 0.25–5.0 μg/ml, absorbance was linearly correlated to calcium concentration in release media: $A = 0.05803C + 0.01044$ ($n = 5$, $r = 0.9968$). Accuracies at all concentration levels were within 100 ± 5%. Intra-day/inter-day precisions at concentration levels of 0.25, 1.0 and 5.0 μg/ml were 4.26%/6.59%, 3.31%/4.97% and 4.50%/5.22%, respectively. The limit of quantification was 0.25 μg/ml. To determine calcium in pectin matrix tablet, similar procedures were employed after extracting from the tablet with distilled water. The recoveries of calcium from pectin matrix tablet formulation were 98.36%,

99.05% and 98.17% at concentration levels of 0.25, 1.0 and 5.0 μg/ml, respectively.

2.7. Pectin release study

To understand the kinetics of pectin release, pectin was monitored simultaneously during the drug release test. At time intervals, 1 ml samples were withdrawn and the amount of pectin or its degradation product released was determined by a reported method employing a modified Dische's carbazole reaction for uronic acids [19–21]. First, the release sample (1 ml) containing galacturonic acid, the primary pectin degradation product, was treated with 5 ml of 0.025 M sodium tetraborate prepared in concentrated sulphuric acid. After galacturonic acid has been converted to furfural-type chromogene by heating for 10 min in a boiling water bath, 0.2 ml of 0.125% carbazole (in ethanol) was added and the solution was heated for a further 15 min at 100 °C to form a colored product upon cooling. The absorbance of the colored product was then measured at 530 nm [21].

Calibration graphs were constructed with D-galacturonic acid as a standard in distilled water. Within the concentration range of 4–40 μg/ml, D-galacturonic acid concentration (X) was linearly correlated to absorbance (Y): $Y = 0.0068X - 0.0217$, $r = 0.9999$. Accuracies at all concentration levels were within $100 \pm 1\%$. Intra-day/inter-day precisions at concentration levels of 4, 20 and 40 μg/ml were all below 2%.

3. Results and discussion

In order to evaluate the effect of pectin/calcium interaction, indomethacin release from HPMC/pectin (P100C0), HPMC/calcium chloride (P0C100), HPMC/lactose (P0L100) and HPMC/pectin/calcium chloride (P100C100) matrix tablet was studied and compared. Release profiles are given in Fig. 1. Power law correlation results and parameters for description of the release pattern ($T_{0.1}$, $T_{0.5}$ and $T_{0.8}$) are shown in Table 1.

As indomethacin was a water-insoluble drug, its release from the HPMC-based matrix tablet followed near zero-order kinetics primarily controlled by mechanisms of erosion [22], which was verified in this study for HPMC/lactose (P0L100) matrix with an n value of 1.07. HPMC matrix tablet containing the same amount of calcium chloride (P0C100) instead of lactose showed exactly identical release pattern with an n value of 1.05 and similar $T_{0.1}$, $T_{0.5}$ and $T_{0.8}$. This result indicated that there was no specific interaction between HPMC chains and calcium ions. As pectin was an anionic biopolymer of high hydrophilicity, it readily hydrated upon contact with water [8,23]. When it was incorporated into HPMC/pectin (P100C0) matrix, significant enhancement on indomethacin release with a near zero-order release kinetics ($n = 0.9439$) was confirmed. However, when pectin and calcium chloride were incorporated into HPMC matrix in pairs

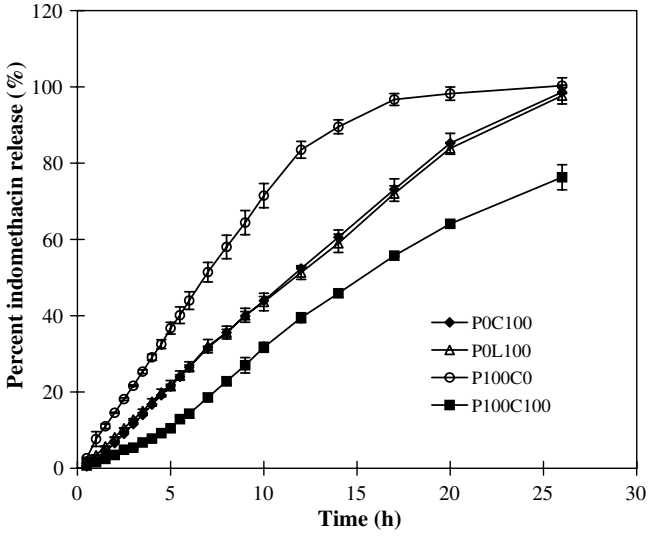

Fig. 1. Release profiles of indomethacin from HPMC/pectin (P100C0), HPMC/calcium chloride (P0C100), HPMC/lactose (P0L100) or HPMC/pectin/calcium chloride (P100C100) matrix tablets (mean ± SD, $n = 3$).

(P100C100), release was significantly retarded. A biphasic release pattern with characteristic initial slow release and incremental release at later stages was observed as a result of in situ crosslinking of anionic pectin chain and cationic calcium ions. Similar to previous findings with pectin/calcium matrix [3], exponent n values bigger than 1.0 (1.25 here) were achieved. Although several researchers have reported Super case II transport of hydrocolloid-based matrices with the power law n values slightly bigger than 1.0 [24–27], the release profiles cannot be termed "biphasic" at all. $T_{0.1}$, defined as lag time [28], was about 4.5 h. This time delay would be potentially beneficial for colonic drug delivery.

In the previous study [3], it was confirmed that the pectin matrix containing a large amount of calcium chloride could achieve biphasic release of indomethacin with a lag time. In this study, the retarding effect must also be attributed to the in situ crosslinking effect of pectin and calcium chloride, because there was no interaction between calcium ions and HPMC and pectin alone in HPMC matrix only accelerated drug release.

What was different from the case of pectin/calcium matrix was that HPMC, in 1/1 (w/w) ratio to pectin, might interfere with the crosslinking interaction of pectin with calcium ions. There was no doubt that the HPMC chains might present as spatial hindrance to the association of pectin and calcium ions. The pectin/calcium interaction exerted sufficient stress on the hybrid hydrogel, thereby led to retarded indomethacin release, even though its function was discounted.

Biphasic release was frequently observed in coated systems and rare for matrix systems. The focus of preference of a matrix-based delayed release system was its simplicity in production. From a practical point of view, it was imperative to learn more about the factors that influenced the

biphasic release characteristics. The objective of formulation development of this system would be to achieve adjustable and long enough time delay without sacrificing release speed at later stages to meet the demand of timed or colon-specific drug delivery. In our previous experience with pectin/calcium chloride matrix, longer lag time was always associated with reduced release rate at later stages. Changes in power law parameters (n and K) led to changes in the biphasic release pattern. K can be regarded as power law release constant with bigger values leading to faster drug release. Mathematically, increases in n values bigger than 1.0 would allow for a more desirable incremental release. To achieve 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.

Through tuning the amount of calcium chloride in HPMC/pectin hybrid matrix, a series of biphasic release profiles with different n and K values was obtained. Release profiles are shown in Fig. 2, and power law correlation results are presented in Table 1. There seemed to be a calcium dose-dependent release with more calcium in the matrix resulting in stronger retarding effect on indomethacin release. $T_{0.5}$ and $T_{0.8}$ values increased continuously as total calcium in the matrix increased. Lag time ($T_{0.1}$) also increased as a function of calcium in the pectin/calcium chloride ratio range of 100/0–100/125. When calcium chloride was added in extreme amount (100/150), $T_{0.1}$ began to decrease slightly due to the possible tunneling effect of the highly water soluble calcium salt. The power law correlation results did not show dose-dependent relationship between the parameters (n and K) and calcium amount. The exponent n increased to a peak value of 1.55 at pectin/calcium chloride ratio of 100/50, after which the n values started to decrease. The K values decreased to a valley at the same pectin/calcium ratio and increased after that as calcium amount increased. It was interesting that the peak n value happened with the lowest K value. Unfortunately, this situation was not accompanied by acceptable lag time. Favorable time delay was only achieved at higher calcium levels. The parameter K at lower values was not as a matter of course associated with longer lag time. In fact, if n values were very big, it is difficult to limit the initial drug release below a relatively lower level, even though K values may be much lower. Only when both n and K values were at relatively lower level was it possible to achieve much longer lag time. If long enough lag time was achieved through formulation development, it was nevertheless accompanied by a reduced release rate at later-stages. This was not a problem for colonic drug delivery purposes, because matrices containing pectin were readily degraded by colonic enzymes to accelerated drug release. For timed delivery purposes, it was ideal to optimize the formulation to obtain acceptable lag time without sacrificing later-stage release rate.

The role of pectin in the HPMC matrix was quite complicated. On one hand, pectin, as a hydrophilic polymer, weakened the hybrid hydrogel resulting in faster matrix erosion and drug release; on the other hand, together with calcium, strengthened the hydrogel as a result of in situ crosslinking interaction, leading to retarded matrix erosion and drug release. In order to perform significant retardation on indomethacin release, the total amount of pectin/calcium should not be too much or too little. Release profiles of the matrices containing different total amount of pectin/calcium chloride in ratio of 1/1 and power law correlation results are provided in Fig. 3 and Table 1, respectively. Even at much lower level, the effect of pectin/calcium on modified release of indomethacin could be seen. This crosslinking stress was strengthened with increase in total amount of the modifier pectin/calcium, and reached a peak at a pectin/calcium chloride level of 100/100 (mg/mg) per tablet. When the modifier was incorporated in extreme quantity, the hydrophilicity of pectin compromised its retarding effect on drug release that began to increase at pectin/calcium chloride ratio of 150/150.

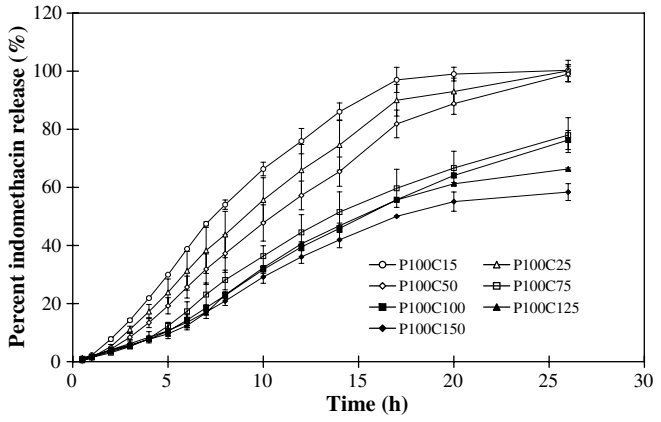

Fig. 2. Release profiles of indomethacin from matrix tablets prepared at various pectin/calcium chloride ratios (mean ± SD, $n = 3$).

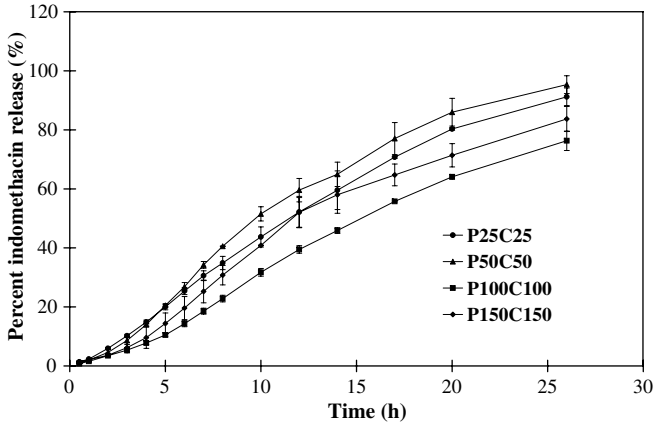

Fig. 3. Release profiles of indomethacin from matrix tablets prepared at various levels of calcium chloride and pectin as a total (mean ± SD, $n = 3$).

In the case with pectin/calcium chloride matrix [3], the matrix erosion correlated well with indomethacin release, based on which conclusion of erosion-controlled release mechanism for the biphasic release pattern was assumed. However, due to the fast erosion rate of pectin matrix, the erosion study was only conducted for a limited 4 h, beyond which correct measurement of the matrix weight loss was impossible. As HPMC was combined with pectin to form hydrogels, the swelled matrix tablets keep a cylindrical geometry for a prolonged time and correct measurement of matrix erosion can be performed for over ten hours. Erosion was evaluated for HPMC/pectin/calcium chloride (P100C100), HPMC/pectin (P100C0) and HPMC/calcium chloride (P0C100) matrix tablet, and profiles are shown in Fig. 4. The HPMC/pectin (P100C0) matrix showed the least initial weight loss, but the overall erosion rate was much faster than the other two matrices. The erosion (E) followed exponential kinetics ($E = 18.73t^{0.6097}$, $r = 0.9963$) and the bulk weight loss was as high as 95% at 14 h. The HPMC/calcium chloride (P0C100) matrix showed initial burst weight loss of about 50% at 1 h, followed by steady near zero-order erosion ($E = 2.5498t + 50.178$, $r = 0.9916$) for about 16 h with a total weight loss of about 90%. The modified release HPMC/pectin/calcium chloride (P100C100) matrix also showed initial burst weight loss of about 30% at 0.5 h, but in the following 4–5 h, only limited weight loss was observed, and erosion was about 76% at 16 h. It was obvious that the lagged matrix erosion rate was a result of the interaction of pectin and calcium ions. Linear correlation was performed for the erosion and indomethacin release data, and the result (Table 2) indicated that there was good linearity between them, which may suggest an erosion-controlled release mechanism.

As discussed in the previous study, the initial weight loss cannot be regarded as actual matrix erosion, because calcium chloride may release rapidly from the matrix resulting in the burst erosion pattern. In the present study, initial burst release of calcium from HPMC/pectin/calcium chloride (P100C100) and HPMC/calcium chloride (P0C100) matrix tablet was measured and results are given in Fig. 5. Both matrix systems followed first-order calcium kinetics releasing 40–50% at 0.5 h and over 80% at 2 h. It was evident that the majority of calcium had been released after 2 h.

To estimate the erosion of HPMC/pectin hybrid hydrogel, matrix erosion profiles were calibrated and redrawn deducing those parts ascribing to calcium release, assuming that calcium was released in chloride (Fig. 4 dashed line). It must be noted that actual weight loss associated with calcium may be more, because more chloride ions than calcium may be released due to the Donnan effect [29,30]. Good linearity existed between calibrated matrix erosion and indomethacin release data (Table 2). This result rein-

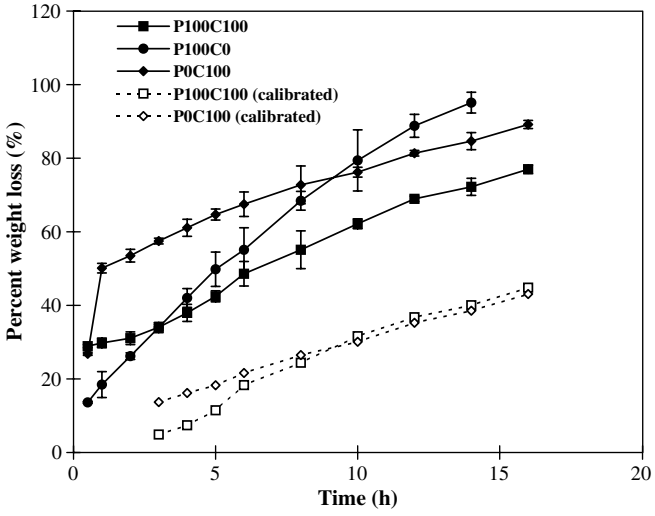

Fig. 4. Erosion profiles of HPMC/pectin/calcium chloride (P100C100), HPMC/pectin (P100C0) and HPMC/calcium chloride (P0C100) matrix tablets (mean ± SD, $n = 3$). The dashed lines represent calibrated erosion profiles deducing those parts belonging to calcium release.

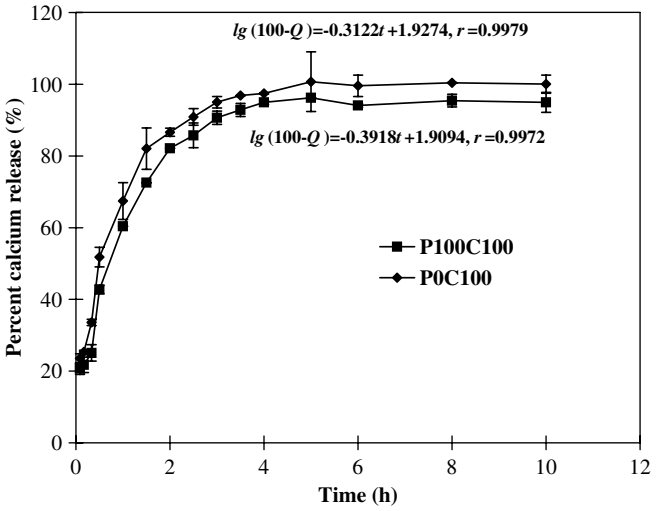

Fig. 5. Release profiles of calcium from HPMC/pectin/calcium chloride (P100C100) and HPMC/calcium chloride (P0C100) matrix tablet with first-order fitting results (mean ± SD, $n = 3$).

Table 2
Correlation results of indomethacin release data as a function of matrix erosion data

Formulation erosion data (X)	Formulation release data (Y)	Linear correlation equation	Correlation coefficient (r)	Correlation time range (h)
P100C100	P100C100	$Y = 0.9857X - 29.115$	0.9891	0.5–14
P100C0	P100C0	$Y = 1.0751X - 14.088$	0.9983	0.5–14
P0C100	P0C100	$Y = 1.6865X - 85.147$	0.9950	0.5–14
P100C100 (calibrated)	P100C100	$Y = 1.1213X - 2.2853$	0.9872	5–14
P0C100 (calibrated)	P0C100	$Y = 1.9287X - 14.665$	0.9990	5–14

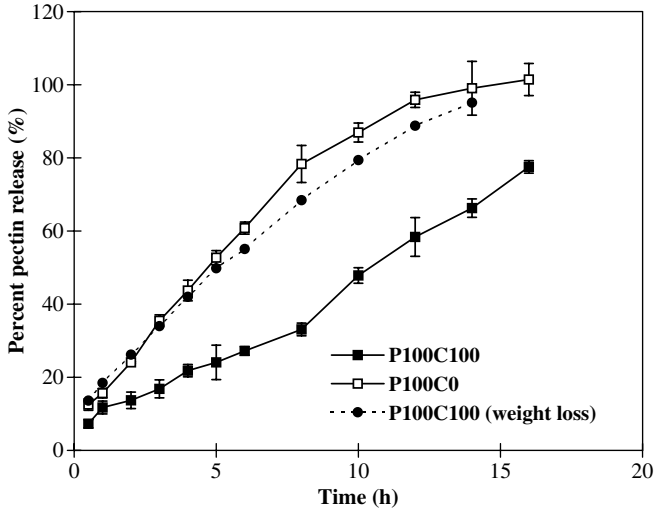

Fig. 6. Pectin release profiles from HPMC/pectin/calcium chloride (P100C100), HPMD/pectin (P100C0) matrix tablets (mean ± SD, $n = 3$). The dashed line represents erosion profile measured by weight loss.

forced the conclusion of erosion-controlled mechanism for biphasic release.

Upon hydration, the HPMC and pectin chains penetrate into each other to form inter-connected network with a definite degree of homogeneity. There was synchrony in the dissolution rate of the two polymers. The matrix erosion rate may also be characterized by measuring the remnants of degradation in the erosion medium. In the present study, leaching of pectin from the hybrid matrices was quantified. Pectin release profiles are shown in Fig. 6. The HPMC/pectin (P100C0) matrix eroded more quickly because of the hydrophilic nature of pectin. Within a time span of 0.5–8 h, linear release of pectin was obtained ($E = 8.9145t + 7.536$, $r = 0.9993$). At a time of 8 h, pectin release approached 80% and was completed at about 16 h. The fact that pectin release profile was similar to the weight loss profile (Fig. 6 dashed line) indicated that determination of pectin release could be applied as a useful method to quantify erosion of matrix containing pectin. The modified HPMC/pectin/calcium chloride (P100C100) matrix dissolved at much slower rate. The pectin release percentage at 8 h and 16 h was approximately 33% and 77%, respectively. Interestingly, pectin release pattern was biphasic too, indicating the effect of the interaction of pectin/calcium. Good linearity (Fig. 7) between pectin and indomethacin release for both HPMC/pectin and HPMC/pectin/calcium chloride matrix tablet added more evidence on erosion-controlled drug release mechanisms.

Hydration of the HPMC matrix tablet was also studied by measuring percent water uptake as a function of time (Fig. 8). At the beginning, matrix composed of only HPMC and pectin (P100C0) showed the least water uptake percentage, while the HPMC/calcium (P0C100) and HPMC/pectin/calcium (P100C100) matrix showed much higher water uptake of about 150% due to the presence of calcium chloride salt in the matrix. Gradually, the HPMC/pectin (P100C0) matrix took in more water in faster rate than

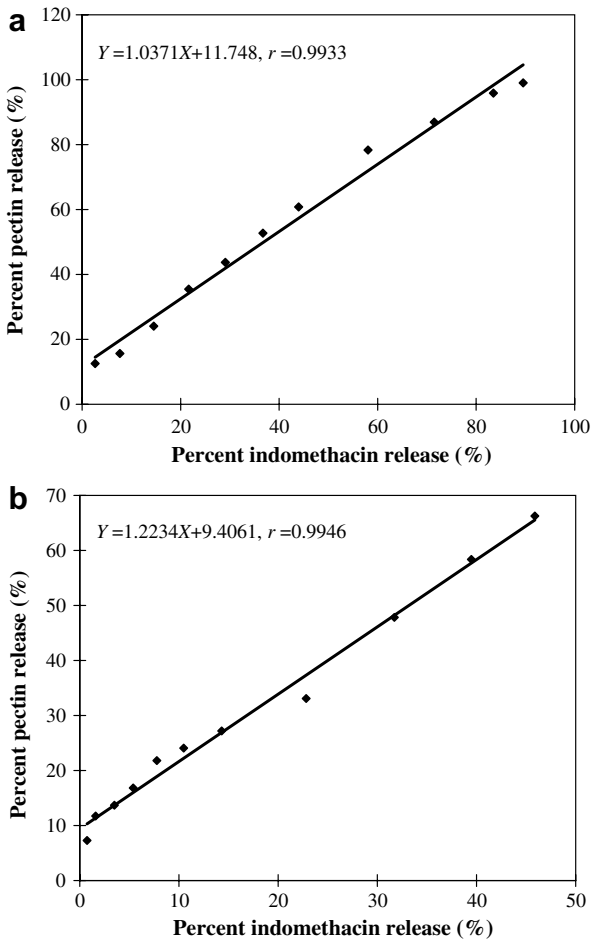

Fig. 7. Linearity between pectin and indomethacin release for HPMC/pectin (P100C0) (a) and HPMC/pectin/calcium chloride (P100C100) (b) matrix tablet.

the other two matrices. After 2 h, the HPMC matrix modified with pectin/calcium (P100C100) showed the least water uptake until a time of at least 8 h. The results indicated that the in situ crosslinking interaction has an effect of slowing matrix hydration, which may have resulted in further delayed erosion and thereby delayed drug release.

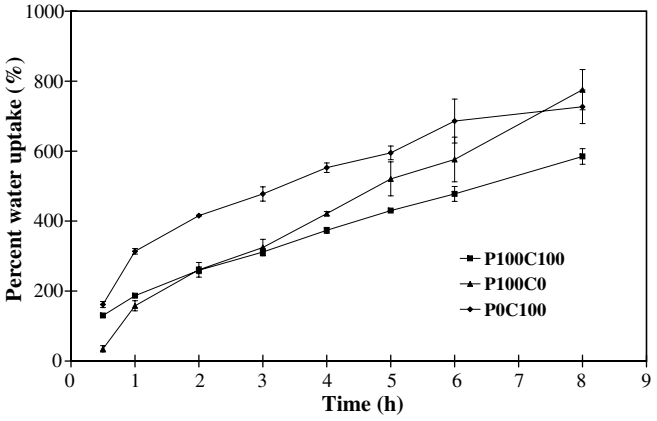

Fig. 8. Water uptake profiles of matrix tablets prepared with pectin/calcium chloride (P100C100), pure pectin (P100C0), pure calcium chloride (P0C100) and HPMC (mean ± SD, $n = 3$).

4. Conclusion

Indomethacin release from HPMC/pectin/calcium chloride hybrid matrix was retarded significantly as a result of in situ crosslinking of anionic pectin chain and calcium cations. When the power law was employed to characterize the biphasic release pattern, unusual exponent n value of 1.25 was observed at HPMC/pectin/calcium chloride amount of 100 mg/100 mg/100 mg. The 10% release time (lag time) was about 4.5 h, showing potential application in colonic drug delivery. Tuning the ratio and total amount of pectin/calcium chloride in HPMC matrix, biphasic release profiles with different n and K values were obtained. n values as high as 1.55 can be observed, but they were not accompanied by sufficient lag time to accommodate potential timed or colon-specific drug delivery.

Calcium release was extraordinarily quick, which contributed to the initial burst erosion of the modified matrix. The overall erosion rate was retarded largely as a result of in situ crosslinking of pectin and calcium ions. Erosion determined by both weight loss measurement and pectin release study was in good correlation with indomethacin release, which indicated erosion-controlled drug release mechanisms. There was also a retarding effect on matrix hydration as a result of in situ crosslinking of pectin and calcium ions.

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