European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 796–803

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Modeling of drug release from biodegradable polymer blends

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ARTICLE INFO

Article history:
Received 17 March 2008
Accepted in revised form 16 May 2008
Available online 6 June 2008

Keywords:
Drug release
Biodegradable polymers
Poly (ε-caprolactone)
Poly (DL-lactide-co-glycolide)
Blends
Paclitaxel
Release model
Partition coefficient

ABSTRACT

Numerous mathematical models that predict drug release from degradable systems have been reported. Most of these models cater only to single step, diffusion-controlled release while a few attempt to describe bi-phasic release. All these models, however, are only applicable to drug release from single (unblended) degradable polymer systems.

In this paper, we propose and test novel models for drug (notably paclitaxel) release from films made of neat poly (ε-caprolactone) PCL, neat poly (DL-lactide-co-glycolide) PLGA and their blends. The model developed for neat PCL consists of two terms: initial burst and diffusional release. On the other hand, a more complex model proposed for tri-phasic release from neat PLGA consists of burst release, degradative (relaxation-induced) drug dissolution release and diffusional release.

Finally, this very first model to predict release from blend of PLGA and PCL was developed based on a heuristic approach. Drug distribution between PCL-rich and PLGA-rich phases is dictated by partition coefficient, and the overall fraction of drug release is a summation of drug released from the two phases. The proposed models exhibited good prediction of the experimental data.

1. Introduction

Biodegradable polymers have received significant interest in the past few decades especially for applications in drug delivery [1,2]. Polyesters such as polylactide, polyglycolide, poly (ε-caprolactone) and their copolymers are a popular choice as carriers as they have good historical evidence as being approved for clinical use. These polyesters degrade by random chain scissions of ester bonds, which result in steady molecular weight reduction but delayed weight loss, usually termed bulk hydrolysis [3–5]. Mechanistic understanding, modeling and drug release studies from homopolymers, copolymers and blends of this family of polyesters are the focus of this paper.

Blends of biodegradable polyesters are gaining importance in biomedical implants, primarily due to the relatively small range of available polymers and copolymers for in vivo use. Such blends may be of two biodegradable polyesters, or of a polyester with a different type of polymer, such as poly (ethylene glycol) or PEG. In most cases, the motivations for blending come from the need to manipulate drug release rates and biodegradation rates. Very often, one makes use of the vastly different drug release rates from individual polymers in order to achieve an intermediate rate.

Numerous models that predict drug release from erodible systems have been reported in the literature. Basically they can be classified into models that predict release from *surface-eroding* and *bulk-eroding* degradable systems [6]. In general, it is easier to model drug release from surface-eroding systems because the drug is released concurrently with the layer-by-layer erosion from the outermost surface of the matrix.

Mathematical models for bulk-eroding systems (such as polyesters) include those based on the widely-accepted Higuchi model [7] for diffusion controlled non-degrading systems. Charlier et al. [8] replaced the constant diffusion coefficient, D_0, with a time-dependent diffusion coefficient, D_t, inversely dependent on polymer molecular weight, M_w. As molecular weight follows a first-order exponential decay, D_t increases exponentially with time and is expressed as $D_t = D_0 \exp(kt)$ where k is the degradation constant and t is time. Finally, the release model at pseudo-steady state was generated using the time-dependent diffusion coefficient, resembling the Higuchi model. A similar approach was taken by Faisant et al. [9,10], but with a different expression for time-dependent diffusion coefficient, i.e. $D_t = D_0 + (c/M_w)$ where c is a constant. These models are dominated by time-dependent diffusion and are applicable only for single-step *monophasic* drug release patterns.

A bi-phasic release model was proposed by Batycky et al. for macromolecular (glycoprotein) release from polylactide-co-glycolide 50/50 microspheres [11]. The model took into account the presence of initial burst followed by diffusion via interconnected pores. The onset of diffusion was delayed by the time taken for

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doi:10.1016/j.ejpb.2008.05.024

pore formation and coalescence and this so-called "induction period" was estimated by visual observation. Other researchers have adopted different modeling/simulation approaches. Cellular automata and/or Monte Carlo-based models divide polymer matrices into various domains/pixels. To simulate polymer erosion and drug dissolution, a "life expectancy" was defined for each pixel. This method has been successfully applied to surface-eroding as well as bulk-degrading polymers [12–15].

All these models demonstrated good agreement with experimental data. However, they are unable to predict a tri-phasic release pattern [16,17], usually observed from bulk-degrading systems. Therefore, in our previous work, a three-step release model was developed to describe a tri-phasic release pattern [18]. This three-step model is one of the important building blocks for the development of the model for blend systems in this paper.

Although degradation rate can be tailored to adjust drug release rate, it is often necessary to resort to porous degradable matrices and/or blend of two or more polymers to achieve desirable release kinetics and/or for other purposes. Lemaire and co-workers have critically analyzed and proposed a model for degradation and drug release from porous degradable matrices [19]. However, none of the models mentioned above are applicable to drug release from blended polymer systems. Thus, our aim was to develop a new model that can predict drug release from a blend of degradable polymers, and compare its predictions to experimentally measured release data.

2. Materials and methods

2.1. Materials

Poly (DL-lactide-co-glycolide) 53/47, PLGA, with intrinsic viscosity of 0.88 was purchased from Purac Far East, Singapore; poly (ε-caprolactone), PCL, with molecular weight (Mn) of 80,000 was purchased from Aldrich, Singapore; and paclitaxel was purchased from Hande, China. Phosphate buffer saline (PBS, pH 7.4) was purchased from Ohme-Scientific, Singapore while other organic solvents were purchased from Sigma–Aldrich, Singapore. All materials were used as received.

2.2. Experimental methods

Basically three groups of paclitaxel-loaded films were prepared through solution casting: (1) neat PCL, (2) neat PLGA and (3) blend of $PLGA_x/PCL_y$ films (x and y are the weight percentages of PLGA and PCL, respectively, $x + y = 100\%$). Depending on the film formulation, the appropriate polymer pellets were dissolved in dichloromethane and stirred continuously until homogenous polymer solutions were obtained. Paclitaxel with predetermined weight percentage (1% of total polymer weight) was added to the solution and stirred to ensure that all drug particles were completely dissolved. The polymer solution was then cast on a glass panel using an automatic film applicator at 25 °C in a fume cupboard. Subsequently the films were dried in a vacuum oven at 50 °C for 1 week to evaporate the residual dichloromethane. The thickness of each film was controlled to be in the range of 75–80 μm.

For in vitro release study, triplicate samples of each configuration were immersed in PBS, pH 7.4, supplemented with 10% (v/v) solubility enhancer (dimethyl sulfoxide). All samples were kept in incubator at 37 °C; the release medium was completely drawn and refreshed at every predetermined time point. Quantification of paclitaxel release was done using high performance liquid chromatography (HPLC, Agilent series 1100, Santa Clara, CA, USA). A ZORBAX Eclipse XDB-C18 column of pore size 5 μm was used with acetonitrile/water 50/50 (v/v) mobile phase. The flow rate was 1 ml/min and the detector's wavelength was set at 227 nm.

Molecular weight of PLGA and PCL films was determined as a function of degradation time using Size Exclusion Chromatography (Agilent series 1100, Santa Clara, CA, USA). A Scanning Electron Microscope, SEM (JEOL 5410), was utilized to observe changes in surface topography of films as a result of degradation.

3. Results and discussion

In our mechanistic and modeling analysis, drug release from biodegradable polymers follows a three-step sequence:

(1) solvent (water) penetration into the matrix;
(2) a degradation-dependent "relaxation of the network" that creates more free volume for drug dissolution; and
(3) drug removal to the surrounding medium usually by diffusion process.

The exact release profile varies and depends on factors such as the nature of drugs (hydrophilic/hydrophobic), polymer degradation rate, water permeability and drug–polymer matrix interaction.

At any time, the slowest step becomes the rate limiting step and ultimately controls the release rate. Sometimes one or more steps may proceed extremely fast and hence have no chance to control release rate and overall profile. In such cases, these steps will be omitted from release models as only the rate limiting steps determine the release rates and are reflected in the models.

3.1. Modeling of drug release from neat PCL film

PCL belongs to the class of slowly degrading polymers; it takes more than 2 years to be completely degraded under physiological conditions [20]. Our own degradation study also noted very mild molecular weight decay (see Fig. 1). In addition, PCL film surfaces observed under SEM did not show any notable sign of degradation after 28 days of immersion in release medium (Fig. 2). As such, degradation does not influence the drug release process for PCL in the time frame studied.

However, PCL has very low glass transition temperature ($T_g \cong -60$ °C). Hence, at test condition of 37 °C and surrounded by saline, PCL chains were in a highly flexible rubbery state. At the temperature of testing ($T_{test} \gg T_g$), there is sufficient free volume in the PCL matrix. This fact implies that step 2 (relaxation to create more free volume) was not a rate limiting step. Instead, after initial burst and sufficient water penetration to the matrix

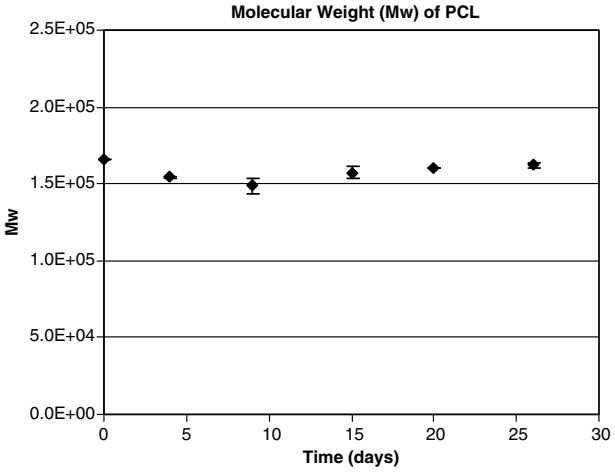

Fig. 1. Molecular weight of PCL as a function of degradation time.

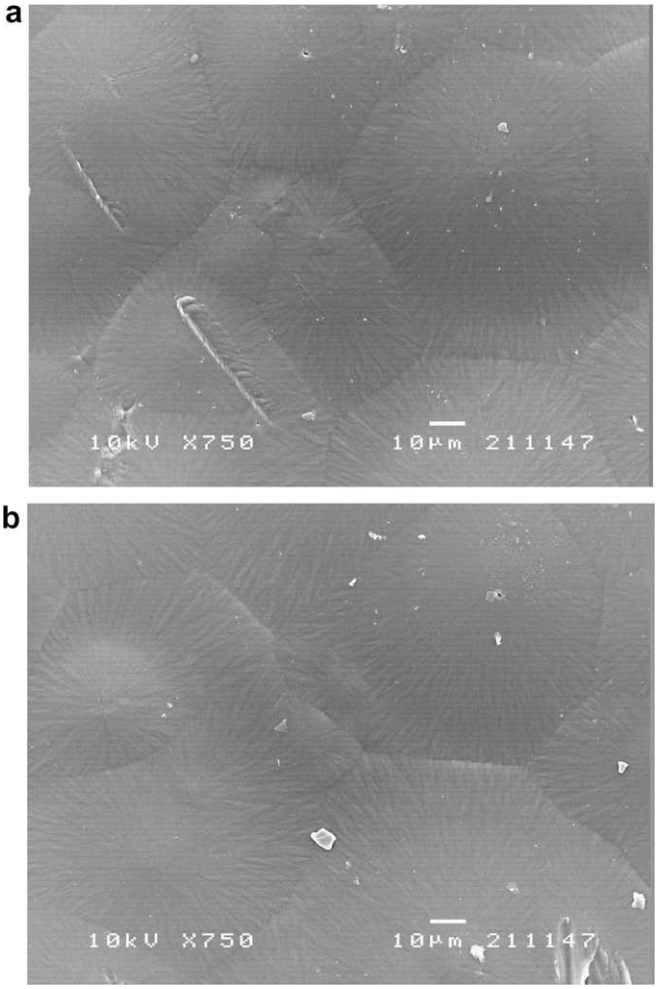

Fig. 2. SEM pictures of PCL films prior to immersion (a) and after 28 days of immersion in release medium (b).

(step 1), drug release proceeded to diffusion (step 3). Diffusion of paclitaxel through PCL matrix became the main mechanism that governed the release profile.

Therefore, the Fick's second law of diffusion under non-steady state condition for film/planar geometry was utilized.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

C is time and position-dependent drug concentration in the matrix (μg/ml), D is the drug diffusion coefficient (cm^2/s), t is time (s) and x is the position normal to the central plane of the film (cm). The following initial and boundary conditions were applied to solve Eq. (1):

$$C = C_0 \quad -l < x < l, t = 0 \tag{2}$$

$$C = 0 \quad \text{at } x = -l \tag{3}$$

$$C = 0 \quad \text{at } x = l \tag{4}$$

C_0 is the initial drug concentration in the matrix (μg/ml) while l is the half-thickness of the film (mm). Eq. (2) indicates uniform drug distribution in the film prior to diffusion. Eqs. (3) and (4) indicate that the surface concentration is equal to zero at any time. The solution to this diffusion problem is as follows [21]:

$$\left\{\frac{M_t}{M_\infty}\right\}_{\text{diff}} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\{-D(2n+1)^2\pi^2 t/4l^2\} \tag{5}$$

M_t is the amount of drug release at time t, M_∞ is the amount of drug release at infinity and (M_t/M_∞) is the fraction of drug release.Therefore, as shown later, Eq. (5) was used in our model to determine the fraction of drug release from PCL film through diffusion, $\phi_{d,PCL}$. The remaining fraction of drug was released through initial burst within the first few days of release study, denoted as $\phi_{b,PCL}$ ($\phi_{b,PCL}+\phi_{d,PCL}=1$). Burst occurs due to immediate desorption of drug particles located at or near the surface of a film following immersion in the release medium. The kinetics of initial burst follows an exponential relationship, as pointed out by Batycky et al. [11], and is dictated by the rate of drug desorption, termed burst constant, k_b

$$\left\{\frac{M_t}{M_\infty}\right\}_{\text{burst}} = 1 - \exp(-k_b t) \tag{6}$$

Based on the analysis above, we combined both modes of drug release in our proposed model. The total fraction of drug release from PCL, $(M_t/M_\infty)_{PCL}$, was described as the sum of drug release due to an initial burst (first term on the right-hand side) plus the diffusion-controlled release portion (second term on the right-hand side).

$$\left\{\frac{M_t}{M_\infty}\right\}_{PCL} = \phi_{b,PCL}\{1 - \exp(-k_{b,PCL}t)\} + \phi_{d,PCL}\left\{1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left(\frac{-D_{PCL}(2n+1)^2\pi^2(t - t_{b,PCL})}{4l^2}\right)\right\} \tag{7}$$

In Eq. (7), the second term on the right-hand side was slightly modified from Eq. (5) by the introduction of a new parameter, i.e. $t_{b,PCL}$. This parameter represents the end of burst release and at the same time, the commencement of diffusion-controlled release. All other parameters had been discussed earlier and are tabulated in Table 1 for a quick reference.

MATLAB, a programming software, was used to fit our proposed model, Eq. (7), to the experimental data and returned good agreement (R^2 = 0.994). Table 1 lists the values of all parameters determined by the model while Fig. 3 shows the plots of the model and experimental release profile. From Fig. 3, it is obvious that PCL suffered an extremely fast initial burst, up to 24%, in the first 2 days. This observation tallies with the model parameters which yielded, in Table 1, the fraction of drug release by burst, $\phi_{b,PCL}$, of 0.22, the burst constant, $k_{b,PCL}$, of 25 day^{-1} and the end of burst release, $t_{b,PCL}$, at day 2.48.

Following the initial burst, paclitaxel release was controlled solely by diffusion. The model was used to determine paclitaxel diffusion coefficient through PCL matrix, reported for the first time in literature, and was found to be 1.04×10^{-11} cm^2/s. Paclitaxel diffusional release from PCL proceeded relatively fast until release reached completion at around day 40. This somewhat easy diffusion agrees well with literature finding which indicates that PCL is permeable to lipophilic drugs such as steroids [22]. As such, paclitaxel, being lipophilic too, did not face much difficulty to diffuse through PCL.

3.2. Modeling of drug release from neat PLGA film

As highlighted in the beginning of Section 3, drug release from biodegradable polymers follows a three-step sequence. In the model for PCL, the relaxation-dependent release (step 2) was omitted due to PCL's low T_g and rubbery state. A completely different scenario, however, was presented by the PLGA film. In the early days, PLGA is a hydrophobic and glassy polymer with T_g of about 40–45 °C. As such, very limited free volume was available for paclitaxel transport pathway. It has to rely on degradation to break long chains and poly-

Table 1
Models parameters of paclitaxel release from neat PCL, neat PLGA and PLGA/PCL blend films

Parameters	Description	Unit	Pure PCL	Pure PLGA	PLGA/PCL 50/50	PLGA/PCL 55/45
Known parameters						
l	Half-thickness of film	mm	0.04	0.04	0.04	0.04
$k_{r,PLGA}$	Degradative relaxation constant of PLGA	day^{-1}	NA	0.093	0.093	0.093
$\phi_{b,PLGA}$	Fraction of burst release from PLGA phase	–	NA	0.023	0.023	0.023
Parameters determined by the model						
f_{PCL}	Fraction of drug released from PCL phase	–	1	0	0.831	0.801
f_{PLGA}	Fraction of drug released from PLGA phase	–	0	1	0.169	0.199
$\phi_{b,PCL}$	Fraction of burst release from PCL phase	–	0.22	–	0.45	0.33
D_{PCL}	Drug diffusion coefficient in PCL phase	cm^2/s	1.04×10^{-11}	–	1.99×10^{-11}	1.21×10^{-11}
$k_{b,PCL}$	Burst constant of PCL phase	day^{-1}	25.00	–	27.8	24.40
$t_{b,PCL}$	End of burst release from PCL phase	days	2.48	–	1.08	1.38
D_{PLGA}	Drug diffusion coefficient in PLGA phase	cm^2/s	–	6.29×10^{-12}	8.03×10^{-12}	8.10×10^{-12}
$k_{b,PLGA}$	Burst constant of PLGA phase	day^{-1}	–	0.10	0.26	0.32
$t_{b,PLGA}$	End of burst release from PLGA phase	days	–	20.16	19.43	18.77
$t_{r,PLGA}$	End of relaxation rel from PLGA phase	days	–	46.66	46.02	46.00
$\phi_{r,PLGA}$	Relaxation release coeff of PLGA phase	–	–	0.04	0.058	0.046
Goodness of fit						
R^2	Correlation factor	–	0.994	0.995	0.998	0.999
Calculation of partition coefficient						
K	Partition coefficient of drug, [PCL]/[PLGA]	–	–	–	4.917	4.889

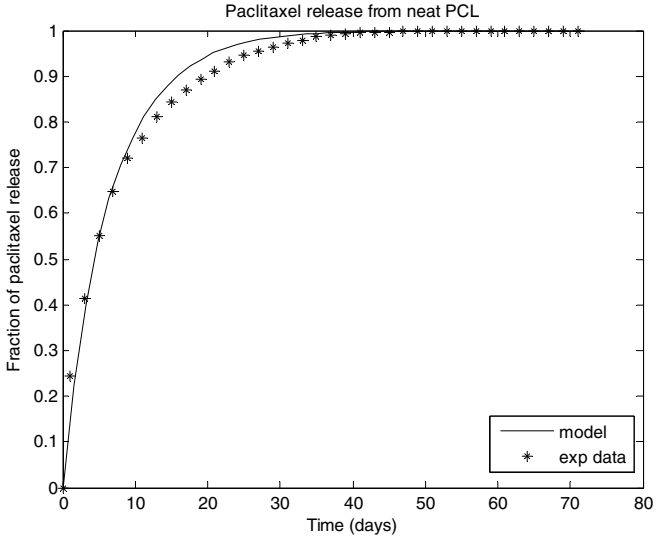

Fig. 3. Model and experimental data matching of paclitaxel release from neat PCL film.

mer relaxation to create a more "open" network. Therefore, during certain periods, degradation-dependent relaxation of the polymer chains (step 2) plays a critical role to create more free volume for drug dissolution and to promote further release.

The model developed for PLGA thus took into consideration all three steps as they became the rate limiting steps at different times throughout the period of release. The total fraction of drug release from PLGA film, $(M_t/M_\infty)_{PLGA}$, was a summation of burst release (first term on the right-hand side), relaxation-induced drug dissolution release (second term on the right-hand side) and diffusion-controlled release (third term on the right-hand side).

$$\left\{\frac{M_t}{M_\infty}\right\}_{PLGA} = \phi_{b,PLGA}\{1-\exp(-k_{b,PLGA}t)\} + \phi_{r,PLGA}\{\exp[k_{r,PLGA}(t-t_{b,PLGA})]-1\} + \phi_{d,PLGA}\left\{1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left(\frac{-D_{PLGA}(2n+1)^2\pi^2(t-t_{r,PLGA})}{4l^2}\right)\right\} \quad (8)$$

Eq. (8) was derived by expanding Eq. (7) and adding a term which represents relaxation-induced drug dissolution release, i.e. the second term on the right-hand side. $\phi_{r,PLGA}$ is the coefficient of relaxational release, $t_{r,PLGA}$ is the end of relaxation-induced release and $k_{r,PLGA}$ is PLGA degradative relaxation constant. More detailed explanation on this additional mechanism of release is discussed next. Meanwhile, all parameters in the first and third terms on the right-hand side bear equivalent meanings as described earlier for Eq. (7).

In the initial stage, after a very little burst, step 1 became the limiting factor as PLGA film started as a glassy polymer and water absorption was restricted (data not shown). Since paclitaxel is hydrophobic and has extremely low aqueous solubility, i.e. 0.25–0.70 μg/ml [23,24], limited water penetration hindered additional release. This period of negligible release activity is termed "latent period" and is given the symbol $t_{b,PLGA}$.

The second term on the right-hand side of Eq. (8) represents drug release induced by polymer relaxation that creates more free volume to aid (hydrophobic) drug dissolution and release (step 2). In the beginning, polymer chains were very long and there were large numbers of entanglement points. Due to the hydrolysis of ester bonds, chains became shorter and the degree of entanglement decreased. Some short chains (oligomers) "leached out" of the matrix and as a result, the remaining chains had to rearrange (also called relaxation motion) and in the process, created a more "open" network. In short, relaxation of the polymer matrix took place continuously in response to swelling (water penetration) and the dynamically changing chain length, M_w, due to degradation.

Other researchers have shown that the transport phenomena during relaxation can be described with an exponential expression, as in the second term on the right-hand side of Eq. (8), with relaxation constant k_r being the reciprocal of the average relaxation time, λ, which is usually dependent on the polymer chain length [25,26]. Clearly the relaxation constant, k_r, is dictated by how fast molecular chains relax as the polymer degrades and depends heavily on the rate of production of shorter polymer chains. Thus, as a first approximation, the value of k_r was taken to be of the order of the polymer's degradation constant. It was calculated from the first-order exponential decay: $M_{w,t} = M_{w,0}\exp(-kt)$ where $M_{w,0}$ and $M_{w,t}$ are the molecular weights at time zero and t, respectively. Fig. 4 shows PLGA molecular weight decay fitted with the first-order exponential equation to determine k_r value, 0.093 day^{-1}.

As degradation continued, water became easily available in the more open network; dissolution occurred fast enough and no long-

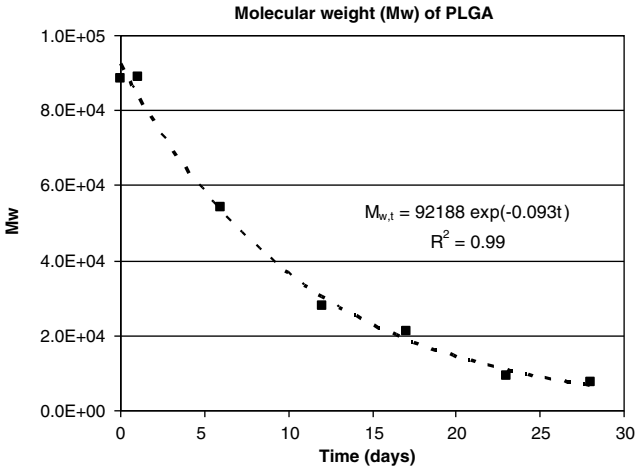

Fig. 4. Molecular weight of PLGA as a function of degradation time.

er controlled the release rate. At this point, lots of interconnected pores were formed and were accessible (water-filled). Thus, drug diffusion through water-filled pores (step 3) became the rate limiting step and controlled the release rate until saturation.

Again, MATLAB was used to fit Eq. (8) to our experimental data, and the values of all parameters are listed in Table 1. As shown in Fig. 5, good agreement between model and experimental data was obtained (R^2 = 0.995).

Only very little initial burst was observed, followed by a long induction-burst period. According to the model, this latent period ended at $t_{b,PLGA}$ = 20.16 and was verified by a separate water absorption measurement which recorded a near zero water absorption until about day 23 (data not shown). Despite the negligible burst, the model, Eq. (8), still takes into account the possibility of burst phenomenon as this might happen if the initial drug loading is increased significantly (beyond 1%). Once water absorption became significant, the second stage of drug release started. The degradation-dependent relaxation release was marked by the creation and growth of micropores as a result of dissolution of short oligomers and rearrangement of remaining polymer chains. Fig. 6 shows the SEM pictures of PLGA films prior to immersion and the presence of micropores after degradation. Afterwards, diffusion took control and became the main mechanism of release until completion.

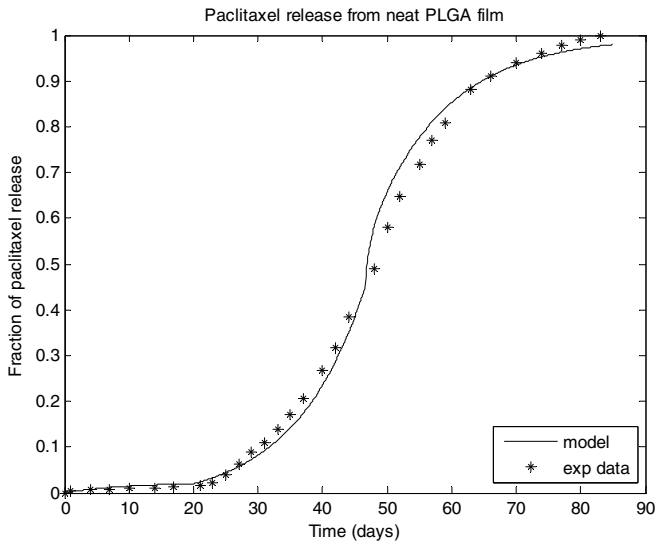

Fig. 5. Model and experimental data matching of paclitaxel release from neat PLGA film.

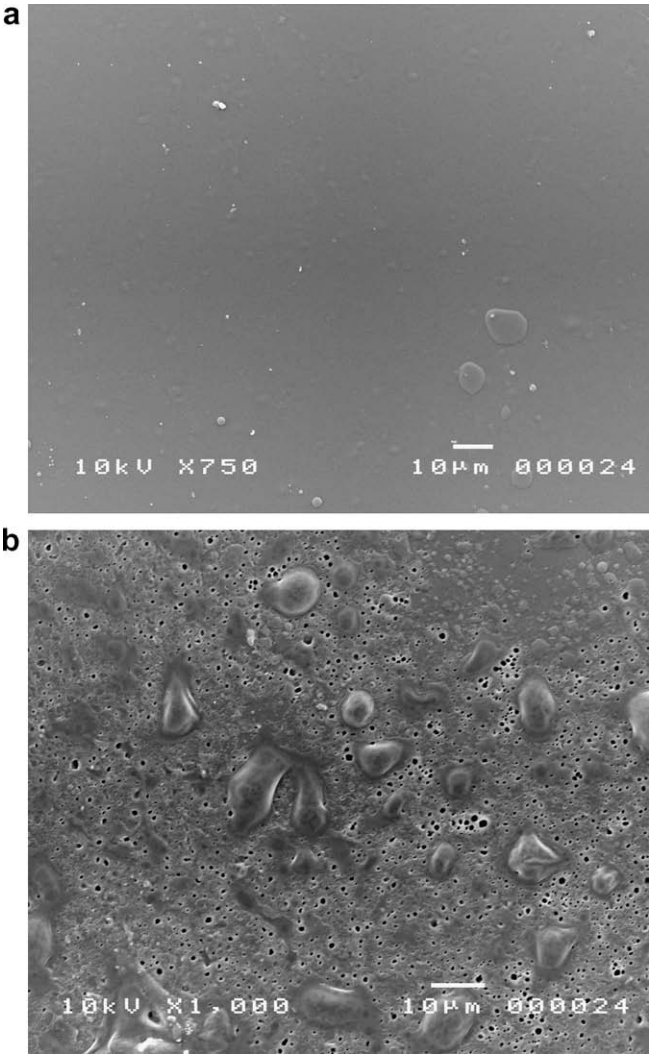

Fig. 6. SEM pictures of PLGA films prior to immersion (a) and after 28 days of immersion in release medium (b).

3.3. Modeling of drug release from blends of $PLGA_x/PCL_y$ film

For applications involving drug-eluting stents, controlled paclitaxel release of up to 3 months is desirable to combat restenosis (renarrowing of arteries) which is usually most active during this period. However, as seen from the release data for the neat polymers, release from neat PCL has an unacceptably short duration of release with high burst, whereas release of paclitaxel from neat PLGA has an unacceptably long induction period of zero to little release. Therefore, a blend of PCL and PLGA would give an intermediate (and acceptable) release profile that reflects the complementary effect of the two components. PCL contributes to paclitaxel release in the first half (up to 30 days) while PLGA contributes in the latter half (up to 85 days) of the release.

Given the low (or non-) miscibility of PCL and PLGA, it is reasonable to consider the blend system as consisting PCL-rich and PLGA-rich phases. In fact, Fig. 7 shows the SEM pictures of PLGA/PCL blend films at the start of release study and 4 weeks later. It is obvious that two separate phases were formed and as expected, the PLGA-rich phase degraded much faster than PCL-rich phase after immersion in release medium. Therefore, a "heuristic" approach

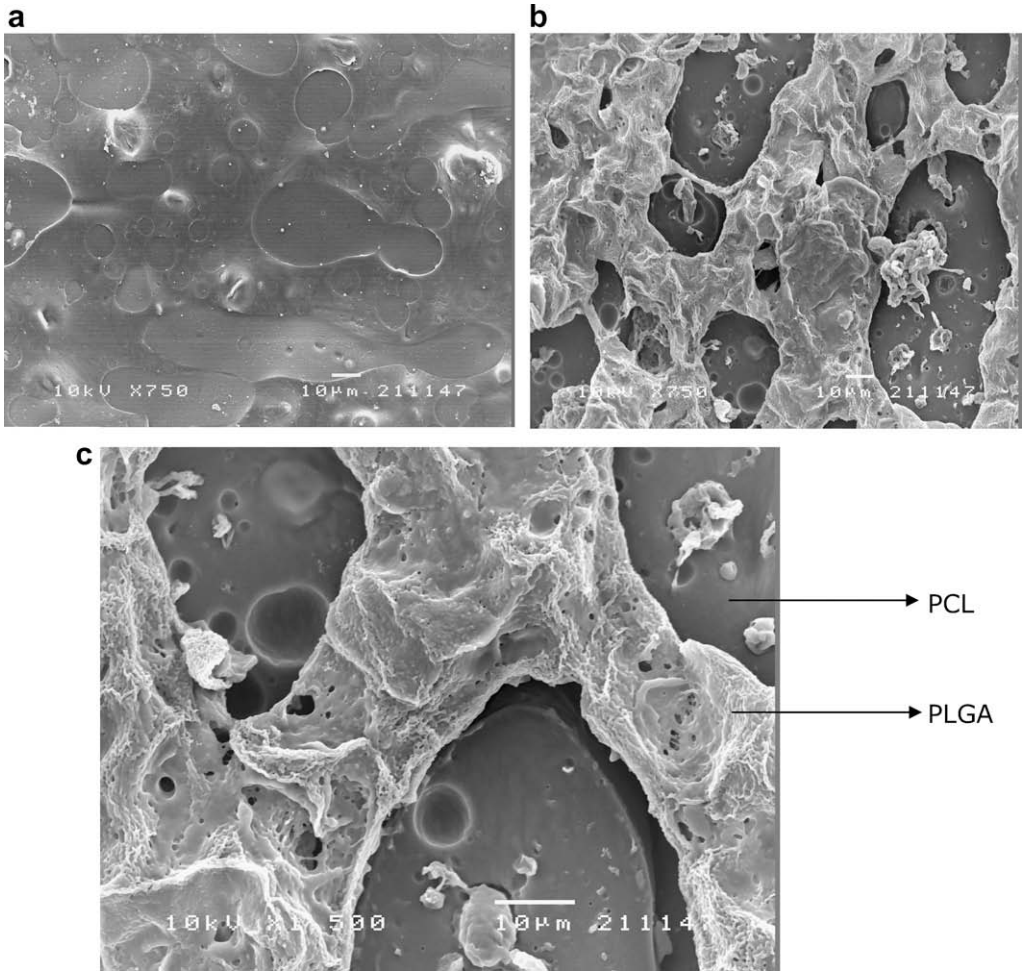

Fig. 7. SEM pictures of PLGA/PCL blend films prior to immersion (a) and after 28 days of immersion in release medium (b and c).

has been considered whereby it is postulated that drug partitions into either phase and remains in that particular phase until it is released. Further, the release from each phase follows the same mechanism of its respective unblended state. The overall fraction of drug release is a summation of drug released from PCL phase and PLGA phase.

Based on the assumptions above, the following model was developed for paclitaxel release from blend of PLGA/PCL films:

$$\left\{\frac{M_t}{M_\infty}\right\}_{blend} = f_{PCL}\left\{\frac{M_t}{M_\infty}\right\}_{PCL} + f_{PLGA}\left\{\frac{M_t}{M_\infty}\right\}_{PLGA} \quad (9)$$

Here, f_{PCL} and f_{PLGA} are the fractions of drug that partition into and are released from PCL and PLGA phases, respectively. The sum of the two fractions is equal to 1 ($f_{PLGA} + f_{PCL} = 1$). Substituting Eqs. (7) and (8) into Eq. (9) gave us the following extended equation for paclitaxel release from blend of PLGA and PCL:

Again, MATLAB was used to match the proposed model with in vitro release profiles obtained from two blend systems: PLGA/PCL 50/50 and PLGA/PCL 55/45. Excellent correlation factors were obtained for both compositions (R^2 values >0.99). Fig. 8 shows the agreement of model and experimental data while Table 1 lists all the parameters used and determined by the model in Eq. (10). Fig. 8 clearly shows a combined/additive effect of release mechanisms from both PCL and PLGA. PCL helped to contribute to drug release in the early days and hence eliminated the long induction period, characteristic of PLGA alone. On the other hand, PLGA helped to sustain drug release to longer time, up to 70 days, as opposed to only 40 days in PCL alone.

Further, Table 1 shows that the values of model parameters that control drug release from PCL phase of the blend are very similar to those given by the unblended PCL film. Burst constant $k_{b,PCL}$, end of burst release $t_{b,PCL}$, and diffusion coefficient D_{PCL} of blends were

$$\begin{aligned}\left\{\frac{M_t}{M_\infty}\right\}_{blend} = {} & f_{PCL}\left(\phi_{b,PCL}\{1-\exp(-k_{b,PCL}t)\} + \phi_{d,PCL}\left\{1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left(\frac{-D_{PCL}(2n+1)^2\pi^2(t-t_{b,PCL})}{4l^2}\right)\right\}\right) \\ & + f_{PLGA}\left(\phi_{b,PLGA}\{1-\exp(-k_{b,PLGA}t)\} + \phi_{r,PLGA}\{\exp[k_{r,PLGA}(t-t_{b,PLGA})]-1\}\right. \\ & \left. + \phi_{d,PLGA}\left\{1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left(\frac{-D_{PLGA}(2n+1)^2\pi^2(t-t_{r,PLGA})}{4l^2}\right)\right\}\right) \end{aligned} \quad (10)$$

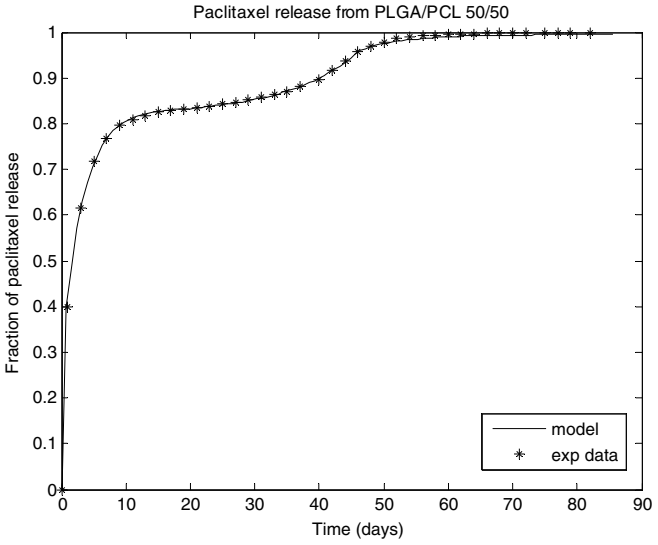

Fig. 8. Model and experimental data matching of paclitaxel release from PLGA/PCL 50/50 blend film.

consistent with those of PCL alone. Similarly, the values of model parameters that control drug release from PLGA phase of the blends did not change much from the values of the unblended PLGA film. These include all parameters (see Table 1) that dictate three release steps from PLGA: burst, relaxation-induced drug dissolution and diffusion. This consistency shows that there is no major shift/change in the release mechanism from each polymer phase before and after blending – as postulated prior to model development.

The only notable difference is a little increase in the fraction of burst of the unblended PCL from $\phi_{b,PCL} = 0.22$ to $\phi_{b,PCL} \approx 0.39$ for fraction of burst of PCL phase in the blends. It was caused by unequal drug partition in PLGA and PCL phases of blend which led to higher effective drug loading (>1%) in PCL phase of blend than drug loading in the unblended PCL (1%). Drug partition also holds a very crucial role in determining the fractions of drug release from each phase, f_{PLGA} and f_{PCL}.

Partition coefficient is an important parameter that specifically affects drug release profile from a blend system. It is the ratio of concentrations of the drug in the two phases of a mixture of immiscible matrices. Partition coefficient shows the drug distribution and its preference for either of the two phases in the blend system.Partition coefficient can be derived from f_{PCL} as follows:

$$f_{PCL} = \frac{\text{amount of drug in PCL}}{\text{amount of drug in PCL} + \text{amount of drug in PLGA}} \quad (11)$$

Given that the specific gravities of PCL and PLGA are quite similar ($\rho_{PCL} = 1.15$ g/ml, and $\rho_{PLGA} = 1.25$ g/ml),

$$f_{PCL} = \frac{W_{PCL}[PCL]}{W_{PCL}[PCL] + W_{PLGA}[PLGA]} \quad (12)$$

W_{PCL} and W_{PLGA} are the weight fractions of PCL and PLGA phases, respectively, whereas [PCL] and [PLGA] are the concentrations of drug in PCL and PLGA phases, respectively.By definition, partition coefficient $K = [PCL]/[PLGA]$, thus

$$f_{PCL} = \frac{W_{PCL}K}{W_{PCL}K + W_{PLGA}K} \quad (13)$$

From Table 1, the blend model in Eq. (10) gives f_{PCL} (PLGA/PCL 50/50) of 0.831. Using Eq. (13), the partition coefficient K was calculated to be 4.92. When the same modeling and calculation was done for another blend composition (PLGA/PCL 55/45), the partition coefficient K obtained was 4.89, very close to the first one. This finding was expected as partition coefficient is an intrinsic parameter of a constant value regardless of the ratio of the blend components. As such, this constant K value and excellent correlation coefficients confirm that our "heuristic-based" model is suitable for this blend system.

To further investigate the applicability of this blend model, the same partition coefficient K value was plugged back to Eq. (10) and used to predict the release profiles of other blend ratios. At the same time, several other blend films were prepared and their in vitro release profiles were recorded. Comparisons between the model and actual experimental data returned good matches for PLGA/PCL 60/40 and PLGA/PCL 65/35 blend films ($R^2 > 0.99$), as demonstrated in Fig. 9.

However, the experimental data deviated from the model for PLGA/PCL 75/25 blend film as seen in Fig. 10. The blend model works by the assumption that the total release is a sum of drug release contributions from two phases. The drug from each phase is released through interconnected paths of its own phase across the film. When the weight fraction of one component is reduced considerably, it is expected that the minor component will assume the forms of isolated islets within the major phase. The interconnectivity of the minor phase is thus lost. Therefore, drug release from the minor phase, in this case PCL phase, would be disrupted.

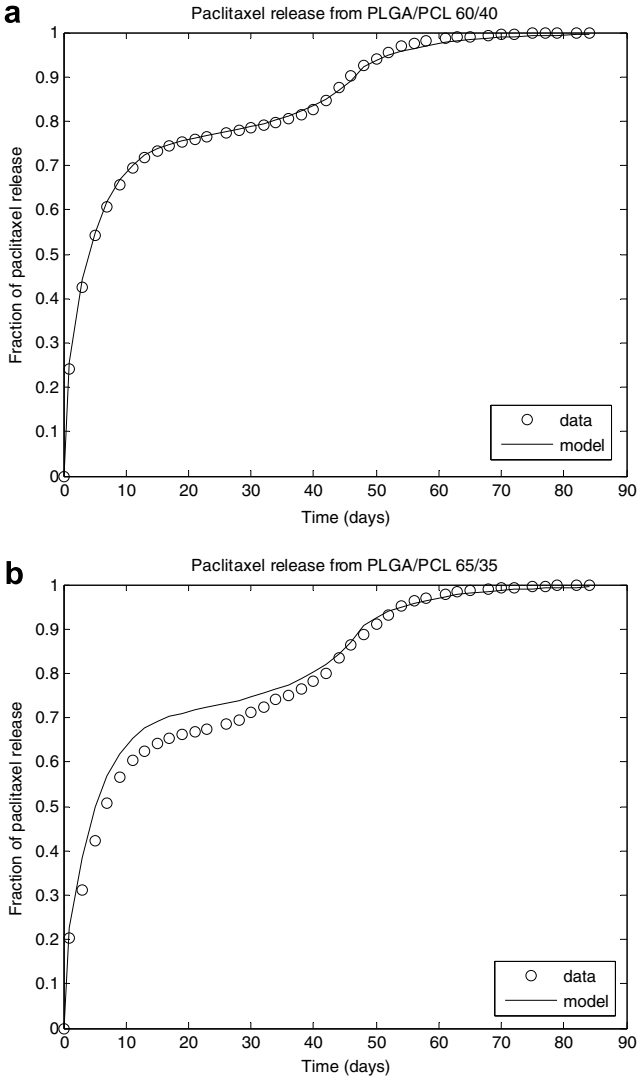

Fig. 9. Model predictions and experimental data of paclitaxel release from (a) PLGA/PCL 60/40 and (b) PLGA/PCL 65/35 blend films.

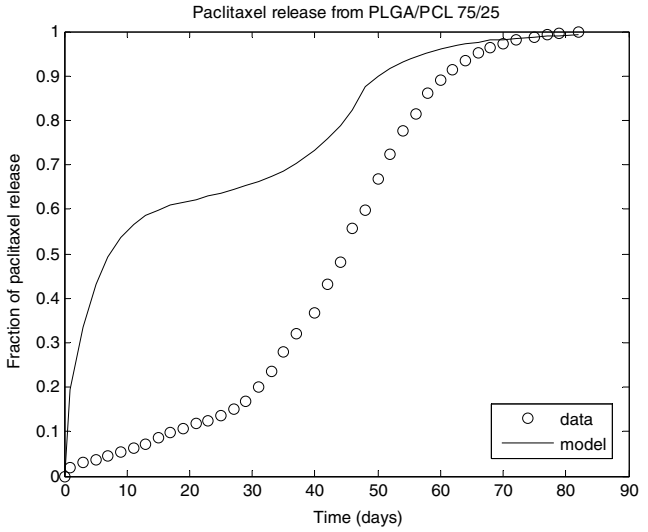

Fig. 10. Model prediction and experimental data of paclitaxel release from PLGA/PCL 75/25 blend film.

Thus in Fig. 10, it can be seen that the actual drug release was substantially less than that predicted by our model. A similar theory, called percolation theory [27], agrees with our finding and has reported that the critical fraction to obtain undisrupted continuous path in any blend systems is approximately 20–25%. Therefore, it can be concluded that the model deviation from actual data is caused mainly by the inability of the minor component (PCL) to form established interconnected paths.

4. Conclusions

This paper has assessed the drug/paclitaxel release mechanisms from various degradable polymers, including neat PCL, neat PLGA and blend of PLGA/PCL films. Appropriate release models for all three scenarios have been proposed and demonstrated good representations of actual experimental data.

The neat PCL film released its drug through initial burst and then followed by a relatively smooth diffusion until completion. The proposed model thus consists of two terms: initial burst release and diffusional release. On the other hand, the neat PLGA film displayed a more complex tri-phasic release pattern. Three different mechanisms governing the three phases of release were considered. Hence, the model consists of burst release, degradative relaxation-induced drug dissolution release and finally diffusional release. Here, degradative relaxation plays an important role to create free volume lacked in the initially glassy PLGA matrix and promotes additional release.

A heuristic model was proposed for drug release from a blend of low (or non-) miscible PLGA and PCL. The overall fraction of drug release is a summation of drug released from PCL-rich phase and PLGA-rich phase. The crucial parameter (partition coefficient K) that specifically controls drug distribution and release from such blend system was also determined. The applicability of this blend model has been tested and proven effective on a range of PLGA/PCL ratios. However, a deviation was observed when the minor component's fraction became so low that its interconnected phase, acting as drug release avenue, was disrupted.

Acknowledgements

The authors are very thankful to Mr. Terry Farmer for his assistance with the MATLAB programming software and Mr. Fok Shing Wai for his help in verifying some experimental results. Finally the authors would like to gratefully acknowledge financial support by Singapore Millennium Foundation (SMF), Singapore in this project.

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