

Modeling of drug release from biodegradable triple-layered microparticles

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Abstract: Numerous models that predict drug release from nonerodible reservoir-membrane sphere systems have been presented. Most of these models cater only to a phase of drug release from a constant reservoir. All these models, however, are not applicable to drug release from biodegradable triple-layered microparticle system, in which the drug-loaded core (reservoir) is surrounded by nondrug holding outer layers (membrane). In this article, a mathematical model was developed for ibuprofen release from degradable triple-layered microparticles made of poly(D,L-lactide-co-glycolide, 50:50) (PLGA), poly(L-lactide) (PLLA), and poly(ethylene-co-vinyl acetate, 40 wt % vinyl acetate) (EVA), where ibuprofen was localized within the nonconstant reservoir (EVA core). The model postulated that the drug release through the bulk-degrading PLLA and PLGA layers consisted

of two mechanisms: simple diffusional release followed by a degradation-controlled release through a rate-limiting membrane. The proposed model showed very good match with the experimental data of release from microparticles of various layer thicknesses and particle sizes. The underlying drug release mechanisms are dictated by three parameters determined by the model, including constant characteristic of diffusion, end time point of simple diffusion-controlled release and partition coefficient of drug. The presented model is effective for understanding the drug release mechanisms and for the design of this type of dosage form. © 2012 Wiley Periodicals, Inc. *J Biomed Mater Res Part A*: 100A: 3353–3362, 2012.

Key Words: biodegradable polymers, drug delivery, poly(lactic acid), poly(lactide-co-glycolide), release model

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INTRODUCTION

Biodegradable polymeric microparticles have received significant interest for applications in drug delivery over the past decade.^{1,2} However, single-layered polymeric microparticles have several inherent problems, including burst release of drugs and the inability to achieve constant drug release. Subsequently, this led to the development of double-layered and triple-layered microparticles, whereby the outer layers function as rate-limiting membranes to better control drug release.^{3–9}

Our group previously reported on the fabrication of biodegradable triple-layered microparticles composed of poly(D,L-lactide-co-glycolide, 50:50) (PLGA), poly(L-lactide) (PLLA), and poly(ethylene-co-vinyl acetate, 40 wt % vinyl acetate) (EVA) (shell to core).¹⁰ This triple-layered microparticle system can be envisioned as a membrane-based reservoir system with drug localized in the core. Ibuprofen (a model hydrophobic drug) was preferentially localized in the EVA core due to the hydrophobic interaction between hydrophobic ethylene chains in EVA and drug molecules.

Rubbery EVA is permeable to ibuprofen, which would not face much difficulty to dissolve in and diffuse through EVA, thus forming a dissolved drug reservoir system. The nondrug holding outer layers of PLGA and PLLA can serve as the rate-controlling layers for the release of ibuprofen. It has been shown that by changing particle parameters, including layer thickness and particle size the drug release kinetics and profiles can be altered,^{6,7} thus allowing for particles to be designed to suit a certain drug delivery application. For instance, multilayered microparticles could be envisioned to provide pulsatile drug release kinetics for vaccination. It would also appear that the sustained delivery of radiosensitizers and/or anticancer drugs by multilayered microparticles could be appropriate for cancer therapy. Furthermore, multilayered particulate system could function as a tissue scaffold and deliver bioactive molecules to cells.

Mathematical models have garnered much interest in the development of controlled release systems in the past few decades.^{11,12} Several physicochemical factors controlling drug release from polymeric dosage forms include water

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and drug diffusion, polymer swelling, drug and polymer dissolution, polymer degradation/erosion and osmotic effects.^{13,14} More notably, a review of the mathematical models for surface-eroding and bulk-eroding degradable systems has been conducted by Siepmann et al.¹⁵ As the polymers used in this work, polyesters, undergo bulk erosion, the majority of these drug release models are based on the Higuchi model with the implementation of time-dependent diffusion coefficient.^{16,17} However, these models are obtained only for monophasic drug release patterns when diffusion becomes the rate-limiting step throughout the release period. These models will not be applicable for biphasic drug release profiles. Apart from matrix systems, numerous models that predict the drug release pattern of a nonerodible reservoir-membrane system with varying coating thickness and device dimensions (e.g. slab, cylinder, and sphere) have been reported in the literature.^{18–20} Nevertheless, none of these models are applicable to bulk-eroding membrane-based reservoir systems. It is known that polymer chains mobility increases with decreasing molecular weight as a result of degradation, thus allowing drug molecules to diffuse more quickly from one cavity to another.^{17,21} In view of this, a more accurate predictive scenario would be to replace the constant diffusion coefficient (D_0) with a time-dependent diffusion coefficient (D_t).^{16,22} At the same time, because the drug content in the delivery system is finite, one must consider that the reservoir drug concentration becomes nonconstant as drugs are released. However, a mathematical model to illustrate the entire course of drug release from a non-constant reservoir with a degrading membrane has yet to be established.

In view of these, the aim of this study was to model and quantitatively describe the biphasic drug release profiles of biodegradable triple-layered microparticles of different layer thicknesses and particle sizes. This model would provide important insights concerning the identification of the dominant mass transport phenomena and the underlying drug release mechanisms from such multilayered particulate system. It can also be applied to quantitatively describe the effects of the structural composition and device geometry on the resulting drug release kinetics. Based on the dependency, this model would be applicable to describe a biphasic release pattern, usually observed from other multilayered particulate systems with the drug encapsulated within the core.^{3,4,7,23} This knowledge would thus facilitate the device design with desirable drug release profiles.

MATERIALS AND METHODS

Materials

PLLA (intrinsic viscosity/IV: 2.38, Bio Invigor), poly(D,L-lactic-co-glycolic acid, 50:50) (PLGA, IV: 1.18, Bio Invigor), EVA (molecular weight/MW: 42 kDa, Aldrich), and poly(vinyl alcohol) (PVA, MW: 30–70 kDa, Sigma–Aldrich) were used without further purification. The model drug, ibuprofen, was purchased from Sigma–Aldrich and used as received. Dichloromethane (DCM), tetrahydrofuran (THF), and chloro-

form from Tedia Company Inc. were of High-Performance Liquid Chromatography grade. Phosphate buffered saline (PBS) solution at pH 7.4 was purchased from OHME, Singapore.

Fabrication of microparticles

The (oil-in-water) emulsion solvent evaporation method was used to prepare the triple-layered PLGA/PLLA/EVA microparticles.^{10,24} Polymer solution at 7.5% (w/v) was prepared with a mixture of PLGA (0.2 g), PLLA (0.1 g), EVA (0.05 g), and ibuprofen (5%, w/w) dissolved in DCM. Subsequently, the resultant polymer solution was initially ultrasonicated for 1 min before adding to an aqueous solution containing PVA (0.5%, w/v), with an oil-to-water ratio of 0.013. After which, the emulsification was conducted at 400 rpm using an overhead stirrer (Calframo BDC1850-220) at room temperature (25°C). The evaporation of volatile DCM resulted in the formation of triple-layered PLGA/PLLA/EVA 4:2:1 microparticles. To retrieve these microparticles, the sample was centrifuged, rinsed with deionized water, lyophilized, and subsequently stored in desiccators for further characterization.

The same method was employed to produce triple-layered microparticles of different layer thicknesses (PLGA/PLLA/EVA 10:2:1 and 10:5:1).¹⁰ Ibuprofen-loaded triple-layered PLGA/PLLA/EVA 8:2:1 microparticles of various sizes were prepared in the similar manner as mentioned above. To obtain triple-layered microparticles of various size ranges, the poly-dispersed microparticles were sieved with various test sieves with pore size of 150 μm , 106 μm , 75 μm , 53 μm , and 38 μm (Cole-Parmer® U.S.A. Standard Test Sieve) for 30 min.¹⁷

Characterization

Morphological study. The surface and internal morphologies of microparticles were analyzed using a JEOL JSM-6360A scanning electron microscope (SEM) at an operating voltage of 5 kV. The samples were initially mounted onto metal stubs and cross-sectioned with a razor blade. After which, samples were coated with gold using a sputter coater model SPI-Module. For every batch of samples, 10 microparticles were randomly chosen to be viewed under the SEM. Only one representative SEM image is shown as a consistent morphology was observed for all 10 particles within each batch. Particle size (in diameter) and layer dimension were measured using the ImageJ software.

Determination of actual drug loading. The amount of ibuprofen loaded was determined using Thermal Gravimetric Analysis (TGA Q500 V6.5 Build 196). Approximately 10 mg of the ibuprofen-loaded microparticles was placed on a platinum pan. Ibuprofen is known to decompose at 160°C, which is lower than for the polymers (~300°C).⁷ Hence, the measurements (in triplicate) were performed at rate of 10°C min⁻¹ from initial room temperature to 160°C under nitrogen flow of 60 mL min⁻¹,

followed by isothermal heating at 160°C for 60 min, and finally ramping to 500°C.

In vitro hydrolytic degradation study

Forty milligrams of microparticles were placed in vials containing 30 mL of PBS solution (pH 7.4) in triplicate, and maintained at 37°C in a shaking incubator. The pH of the solution was monitored over time to ensure a stable pH of 7.4. Subsequently, at predetermined time intervals, the microparticles were removed from vials.

Mass loss. The samples were vacuum-dried and the dry mass (m_d) was recorded. Mass loss was calculated according to the difference between the initial mass (m_o) of the sample and m_d , and divided by the initial mass.

Molecular weight analysis. Agilent 1100 Series LC System was used to determine the molecular weight of each of the samples. The size-exclusion chromatography (SEC) experiments were performed at 30°C with chloroform as solvent, using a reflective index detector, and the flow rate used was 1 mL min⁻¹. Eight milligrams of triple-layered microparticles were initially immersed in 1 mL of THF to dissolve the PLGA and EVA constituent. PLLA remnants were separated from the polymer solution thorough centrifugation. The volatile solvent in the polymer solution containing PLGA and EVA was allowed for evaporation in air at room temperature for 48 h. After which, PLGA, EVA, and PLLA remnants were dried in an oven at 40°C for a week. Finally, PLGA/EVA mixture and PLLA dissolved separately in 1 mL chloroform were tested with SEC.

Drug release study

Ibuprofen-loaded microparticles (5 mg) were accurately weighed in triplicate and placed in vials containing 5 mL of PBS (pH 7.4), followed by incubation at 37°C. At predetermined time intervals, 1 mL of PBS medium from each sample was extracted and the concentration of ibuprofen released in PBS medium was determined using UV-Vis spectrometer (UV-2501, Shimadzu) at 220 nm. The removed PBS was replaced with fresh PBS solution. Drug release data from different sets of particles were evaluated by unpaired Student's *t*-test and the one-way analysis of variance analysis coupled with Tukey's multiple comparison tests. Differences were considered statistically significant when $p \leq 0.05$.

THEORETICAL METHODS

In the modeling analysis, drug release from the triple-layered PLGA/PLLA/EVA (shell to core) microparticles with ibuprofen localized in the EVA core follows a three-step sequential process:

- (1) water penetration into the microparticles;
- (2) drug release to the surrounding release medium by simple diffusion process;
- (3) a membrane-reservoir system: drug release is controlled by degradation where drug is diffusing out through a rate-limiting membrane that is undergoing degradation.

Several assumptions were considered in the modeling analysis of drug release:

- (1) The surrounding water bath is perfectly stirred.
- (2) Sink conditions. At the particle surface, drug concentration is zero when mass transfer limitation does not exist and the volume of surrounding medium is large.²⁵
- (3) Water penetration and drug dissolution in the core are much more rapid than the drug diffusion through the outer layers. The presence of relatively more hydrophilic PLGA shell arising from its fully amorphous structure results in appreciable water uptake. The EVA core has a very low glass transition temperature (−40°C). A highly flexible rubbery state of EVA chains at 37°C (test condition for drug release) creates sufficient free volume for drug dissolution.
- (4) No initial burst (i.e. no substantial amount of drug in the coating layer).
- (5) The diffusion of drug molecules is Fickian.
- (6) Diffusion coefficient and partition coefficient of drug are independent of its concentration.
- (7) Polymers are completely immiscible and phase separated.

As reported previously in the literature, before drug is released through a rate-limiting membrane in the membrane-reservoir system, a slow initial drug release is often observed when little or no drug is in the coating layer.¹⁹ Lag time is a finite time interval required to establish a steady state of drug concentration gradient across the membrane with easy drug partitioning, during which the drug diffuses through the membrane and is released towards the steady state value. As such, a temporal idiosyncrasy of initial slow release phase from a membrane-reservoir dosage form was included in the model. This suggests that, in the investigated system, the drug was first released by simple diffusion (stage 1).^{3,26} Drug release was subsequently controlled by polymer degradation (stage 2) where the formation of pores and significant decrease in molecular weight influence drug release more substantially than diffusion. During this stage, drug was released through a rate-limiting outer layer (membrane) where a concentration gradient profile of the drug in the membrane had been established (stage 2).

Herein, the Fick's second law of diffusion under non-steady state condition for drug release from microsphere is utilized for stage 2, as shown in Eq. (1).

$$\partial C/\partial t = (1/r^2)\{\partial/\partial r[Dr^2(\partial C/\partial r)]\} \quad (1)$$

D is the diffusion coefficient of drug, C is the drug concentration in the polymer matrix, t is time, and r is the position in the radial direction. In a membrane-reservoir system, drug located in the reservoir (core) has to diffuse through a membrane layer with thickness of $R - R_i$, where R and R_i are the outer and inner radii, respectively.¹⁸ Next, the boundary conditions were employed. The drug distribution within the shell ($R_i \leq r \leq R$) is obtained by solving Fick's second law of diffusion, where the reservoir concentration

($C_r = C_i/K$) is kept at the surface $r = R_i$, K is the drug partition coefficient at the interface between the reservoir and shell matrix. The concentration of drug at $r = R$ is zero. By considering a sufficient long time period, a steady state of drug concentration gradient across the membrane would be achieved, thus resulting in a constant diffusion rate of drug released from the reservoir. The solution to this diffusion problem is shown below [Eq. (2)]:

$$dM/dt = 4\pi[RR_i/(R - R_i)]DC_i \quad (2)$$

This mathematical model [Eq. (2)] was combined with an equation considering polymer membrane degradation. According to Charlier et al.,²² time-dependent diffusion coefficient, D_t is expressed as $D_t = D_o \exp(k_{deg}t)$ due to an exponential decay of the molecular weight (pseudo-first-order degradation kinetics), where k_{deg} is the degradation rate constant, D_o is the diffusion coefficient of drug in the nondegraded polymer ($t = 0$), and t is time. As such, Eq. (2) is modified to be as below [Eq. (3)]:

$$dM/dt = 4\pi[RR_i/(R - R_i)]D_o \exp(k_{deg}t)C_i \quad (3)$$

In contrast, because the dissolved drug content (below the drug solubility limit in the polymer matrix) in the system is finite, it is to be noted that the reservoir drug concentration becomes nonconstant upon drug release and is governed by the drug release rates. C_r has to be determined as a function of time according to mass balance using the following equation [Eq. (4)], where V is the volume of the core (i.e. reservoir):

$$-V(dC_r/dt) = dM/dt \quad (4)$$

$$-V(dC_r/dt) = 4\pi[RR_i/(R - R_i)]D_o \exp(k_{deg}t)C_rK \quad (5)$$

The left-hand side of Eq. (5) is the decreased amount of drug located in the core and the term on the right-hand side represents the amount of drug released into the surrounding medium. The variable concentration C_r can then be determined, as shown in Eq. (6):

$$C_r = C_o \exp\{(K/V)(4\pi)[RR_i/(R - R_i)]D_o(1/k_{deg}) \times [\exp(k_{deg}t) - \exp(k_{deg}t_a)]\} \quad (6)$$

t_a is the end of simple diffusion-controlled release (stage 1) and, at the same time, the commencement of degrading membrane-controlled release (stage 2), and C_o is the drug concentration in the core at time t_a .

The fraction of drug release from the triple-layered microparticles at the stage 2 only is

$$\begin{aligned} (M_t/M_\infty)_{\text{stage 2}} &= (V/M_\infty)(C_o - C_r) = [V/(C_oV)](C_o - C_r) \\ &= 1 - C_r/C_o \end{aligned}$$

and thus

$$\begin{aligned} (M_t/M_\infty)_{\text{stage 2}} &= 1 - \exp\{(K/V)(4\pi)[RR_i/(R - R_i)] \\ &\times D_o(1/k_{deg})[\exp(k_{deg}t) - \exp(k_{deg}t_a)]\} \quad (7) \end{aligned}$$

The complete analytical solution for the entire course of drug release is described below:

$$M_t/M_\infty = at^{0.43}, \text{ at } t \leq t_a \quad (8)$$

$$\begin{aligned} M_t/M_\infty &= at_a^{0.43} + (1 - at_a^{0.43})[1 - \exp\{-(K/V)(4\pi) \\ &\times [RR_i/(R - R_i)]D_o(1/k_{deg})[\exp(k_{deg}t) - \exp(k_{deg}t_a)]\}], \text{ at } t > t_a \end{aligned} \quad (9)$$

Eq. (8) is used for the period of $t \leq t_a$, which describes the simple diffusion-controlled release at stage 1,^{3,27,28} where a is the constant characteristic of diffusion. It is well known that a power law could approximate the Fickian diffusion from the sphere geometry, with an exponent of 0.43.¹² According to the analyses above, both modes of drug release are combined in the proposed model for the period of $t > t_a$. The cumulative fraction of drug release from triple-layered microparticles for the period of $t > t_a$ is described as the sum of drug release due to a simple diffusion-controlled release (first term on the right-hand side) plus the degrading membrane-controlled release (second term on the right-hand side), as described in Eq. (9).

MATLAB[®], a programming software (Mathwork, 2007a), was then used to fit the proposed model, Eqs. (8) and (9), to the experimental data of drug release from the triple-layered microparticles with different layer thicknesses and various sizes. The correlation coefficients (R^2) between the experimental and theoretical results were compared to obtain a precise theoretical description for the drug release model.

RESULTS

Particles of different layer thicknesses

The diffusion coefficients of drug, D_o , in the nondegraded PLLA and PLGA at time = 0 were determined by fitting $D = D_o \exp(k_{deg}t)$ and Eq. (10) to sets of experimentally measured ibuprofen release rates of PLGA- and PLLA-based neat microparticles.

$$M_t/M_\infty = 1 - 6/\pi^2 \sum_{n=1}^{\infty} (1/n^2) \exp[-n^2\pi^2Dt/R^2] \quad (10)$$

Eq. (10) describes the dissolved drug system where initial drug loading is below the drug saturation limit in the polymer matrix; therefore the drug is dissolved in the polymer matrix.²⁹ M_t/M_∞ is the cumulative fraction of drug release at time t , and R is the radius of the microparticles. The value of k_{deg} was obtained by fitting the pseudo first-order equation describing an exponential decrease in the molecular weights of polymers with degradation time ($MW = MW_o \exp(-k_{deg}t)$) into the experimental SEC results,^{22,30} where MW_o is the initial polymer molecular weight before immersion in the release medium. The apparent degradation rate constants, k_{deg} , of polymers with a good agreement ($R^2 > 0.9$ in all cases) were obtained. The k_{deg} value of PLLA and PLGA were 0.0566 day⁻¹ and 0.2655 day⁻¹, respectively. The diffusion coefficients of ibuprofen, D_o , in the

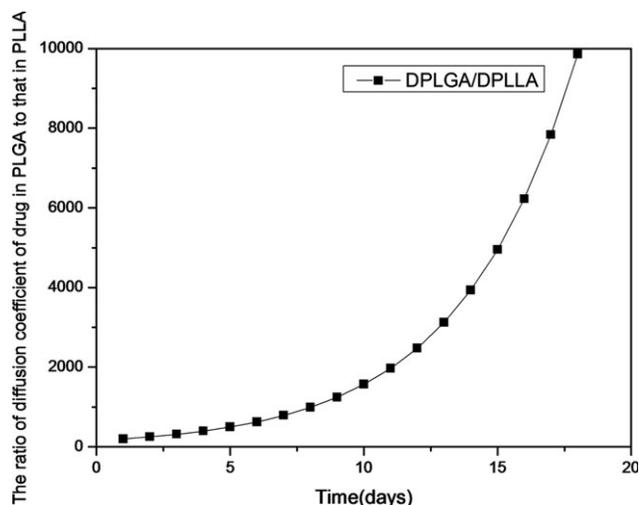


FIGURE 1. Plot of ratios of diffusion coefficient of ibuprofen in PLGA to that of PLLA over the degradation time.

nondegraded PLLA and PLGA were found to be $4.1829 \times 10^{-12} \text{ cm}^2/\text{s}$ and $6.59 \times 10^{-10} \text{ cm}^2/\text{s}$, respectively. The diffusion coefficient values obtained are in agreement with those measured by other groups for similar system.^{21,31}

Figure 1 plots the ratio of diffusion coefficient of drug in PLGA to that in PLLA over the degradation time for the tri-

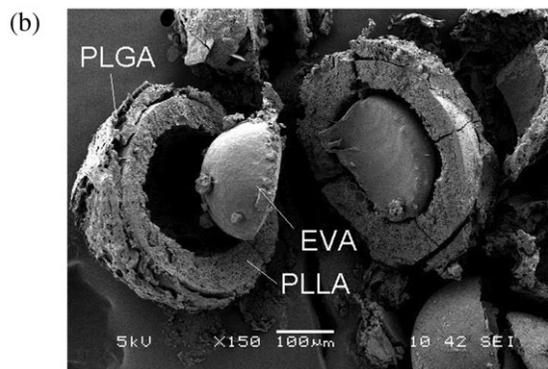
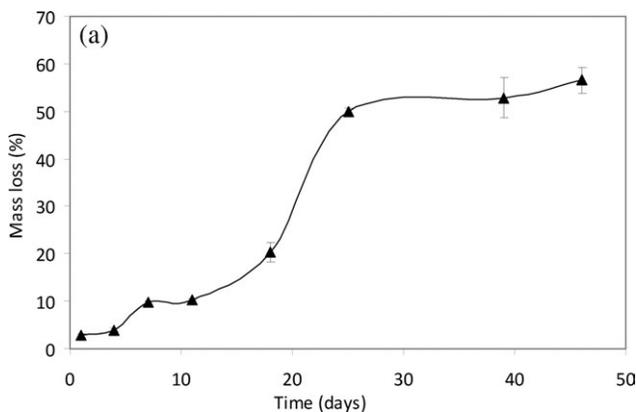


FIGURE 2. (a) Mass loss of the degrading triple-layered PLGA/PLLA/EVA 4:2:1 microparticles as a function of incubation time. (b) SEM image of the degrading ibuprofen-loaded triple-layered PLGA/PLLA/EVA 4:2:1 microparticles after 15 days *in vitro*.

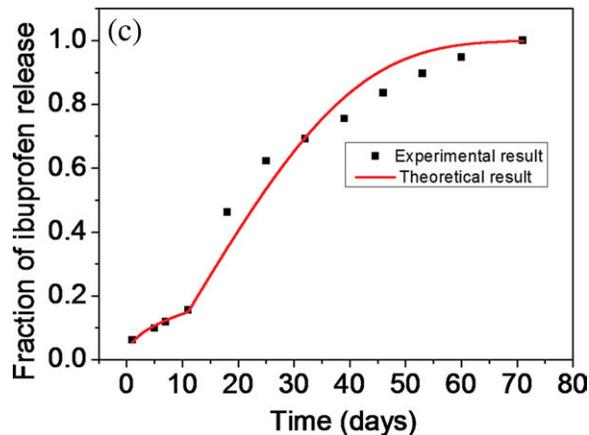
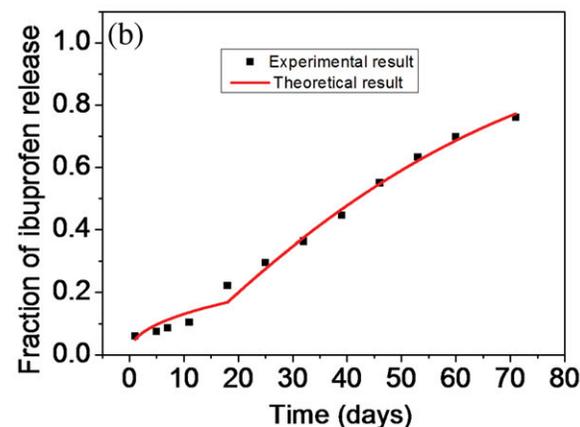
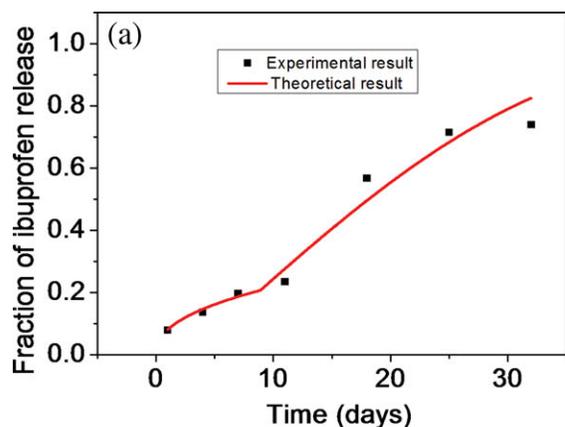


FIGURE 3. Model and experimental data matching of ibuprofen release from triple-layered microparticles. Polymer mass ratios PLGA/PLLA/EVA (a) 4:2:1, (b) 10:2:1, and (c) 10:5:1. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ply-layered PLGA/PLLA/EVA 4:2:1 microparticles. After 10 days *in vitro*, the diffusion coefficient of drug in PLGA is about 2000 times higher than that in PLLA. As can be seen in Figure 2, massive mass loss causing the formation of pores in PLGA shell was observed for the triple-layered PLGA/PLLA/EVA 4:2:1 microparticles after 10 days *in vitro*. The porosity of the PLGA shell would allow for the direct access to the release medium to the inner layers.³² As such,

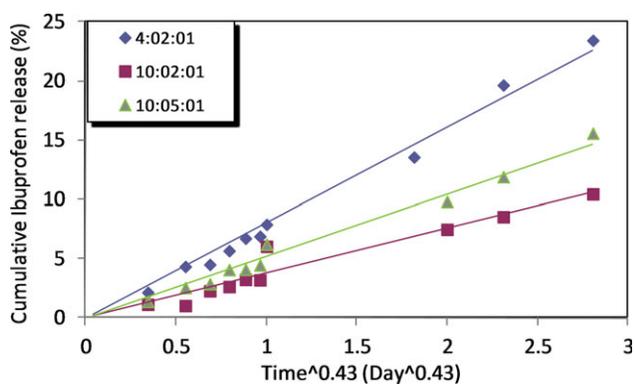


FIGURE 4. Plot of cumulative ibuprofen release from triple-layered microparticles with various polymer mass ratios (PLGA/PLLA/EVA) versus time^{0.43}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the partitioning of drug from PLLA middle layer into PLGA shell and the release through the PLGA shell would be rapid. These results imply that the rate-limiting step would predominantly occur in PLLA due to its high glass transition temperature, increased crystallinity and slow degradation rate.⁵ The effect of PLGA shell on the drug release rates during stage 2 is thus omitted from the release models because only the rate-limiting step of PLLA layer determines the release rate and is reflected in the models.

The actual drug loading of all samples were at $4 \pm 0.5\%$ (w/w). Figure 3 shows the plots of the model and experimental release profiles with good correlation coefficients ($R^2 \approx 0.99$). From Figure 3, biphasic drug release patterns were observed for all triple-layered microparticles with different thicknesses but with comparable particle sizes. As highlighted in the theoretical model, ibuprofen was first released through a simple diffusional process, and subsequently released through a rate-limiting outer layer of PLLA that was undergoing hydrolytic degradation. The plot of the initial drug release data for cumulative release percentage versus time^{0.43} shows a linear profile ($R^2 > 0.9$ at

all cases) (Fig. 4), suggesting the simple-diffusion controlled release of ibuprofen that had diffused into the outer layer upon water ingress during the early release period.^{3,12,26–28} According to Raghuvanshi et al.,³³ the initial stage of degradation involves random chain scission with no appreciable mass loss, as observed from Figure 2(a). Drug release was therefore controlled by simple diffusion during this initial stage of degradation.

Table I lists the values of all known parameters and parameters determined by the model for the triple-layered microparticles of different layer thicknesses but with comparable particle sizes and actual drug loadings of $4 \pm 0.5\%$ (w/w). The constant characteristic of diffusion of triple-layered PLGA/PLGA/EVA 4:2:1 microparticles was found to be the highest. In contrast, drug diffusion of the microparticles with the mass ratios of PLGA/PLLA/EVA 10:2:1 seems to be slower than 10:5:1 microparticles.

Partition coefficient is the ratio of concentrations of the drug in the two phases (i.e. PLLA and EVA). It was observed that the partition coefficient of drug increased with increasing PLLA degradation rates, as shown in Table I. In contrast, the longest end time of stage 1 (t_a), at day 18, was observed for the triple-layered PLGA/PLLA/EVA 10:2:1 microparticles, whereas relatively similar t_a (i.e. 8.9 and 11 days) were observed for 4:2:1 and 10:5:1 microparticles.

Particles of various sizes

Figure 5 shows the cumulative ibuprofen release versus time for five different particle size ranges. The actual drug loading of all samples were approximately 4% (w/w). Clearly, it was observed that each microparticle system of different sizes exhibited a different release pattern of ibuprofen in which a trend of an increasing drug release rate with decreasing particle size was shown.

The same approach was utilized to model the drug release profiles of triple-layered PLGA/PLLA/EVA 8:2:1 microparticles, and to determine the model parameters of ibuprofen release from triple-layered PLGA/PLLA/EVA 8:2:1 microparticles of various sizes, as listed in Table II. As

TABLE I. Model Parameters of Ibuprofen Release from Triple-Layered PLGA/PLLA/EVA Microparticles with Different Layer Thicknesses

Parameters	Description	Unit	4:2:1	10:2:1	10:5:1
<i>Known parameters</i>					
R_{particle}	Radius of particle (PLGA + PLLA + EVA)	μm	135.2	134.7	141.5
R	Second inner radius (PLLA + EVA)	μm	113.5	76.8	108.8
R_i	Innermost radius (EVA)	μm	77	51.1	57.6
$R_{\text{particle}} - R$	PLGA layer thickness	μm	21.7	57.9	32.7
$R - R_i$	PLLA layer thickness	μm	36.5	25.7	51.2
k_{deg}	Degradation rate constant of PLLA	day^{-1}	0.0357	0.0089	0.0330
D_o	Drug diffusion coefficient in PLLA phase	cm^2/s		4.1829×10^{-12}	
<i>Parameters determined by the model</i>					
a	Constant characteristic of diffusion	$\text{s}^{-0.43}$	0.08097	0.04211	0.04867
t_a	End of simple diffusion-controlled release (stage 1)	days	8.9	18	11
K	Partition coefficient of drug, [PLLA]/[EVA]	–	0.547	0.139	0.336
<i>Goodness of fit</i>					
R^2	Correlation factor	–	0.98440	0.99552	0.99006

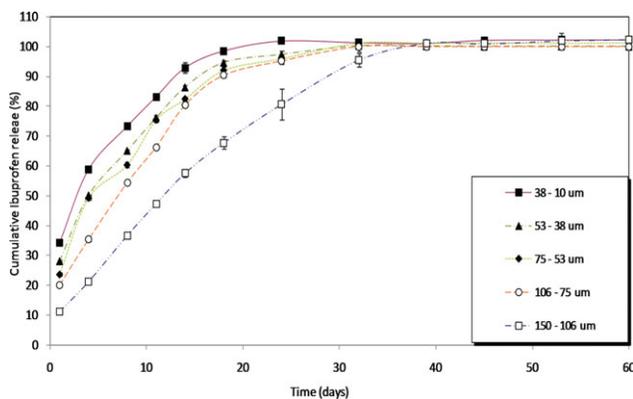


FIGURE 5. Release profiles of ibuprofen from triple-layered PLGA/PLLA/EVA microparticles of various sizes (in diameter). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

shown in Figure 6, good agreement between model and experimentally measured data for the microparticles of various size ranges was obtained ($R^2 > 0.99$). The constant characteristics of diffusion were observed to increase with decreasing particle size. Interestingly, it was found that the end of stage 1 for all the investigated size ranges was at around day 8. Similar to the modeling result of the particles of different layer thicknesses, the partition coefficient of drug increased with increasing degradation rate of the PLLA rate-limiting layer.

DISCUSSION

Particles of different layer thicknesses

Three parameters, including constant characteristic of diffusion, end time point of simple diffusion-controlled release and partition coefficient of drug, could be determined by the model. The highest constant characteristic of diffusion for the triple-layered PLGA/PLLA/EVA 4:2:1 microparticles indicates the fastest rate of diffusional release for the thinnest outer layers (the shortest diffusion length). In contrast, the drug diffusion rate of PLGA/PLLA/EVA 10:2:1 microparticles was slower than 10:5:1 microparticles, partly because of the slower degradation of PLLA layer in 10:2:1 microparticles, as shown by the degradation rate constants in Table

I. More open structure resulting from a higher content (77 wt %) of fully amorphous PLGA would allow more basic ions (from the phosphate buffer) to diffuse into the PLLA middle layer of triple-layered PLGA/PLLA/EVA 10:2:1 microparticles, neutralizing the generated acidic oligomers,²¹ when compared with lower PLGA content of 62.5 wt % for 10:5:1 microparticles. In addition, thinner PLLA layer would reduce the occurrence of autocatalytic effects, resulting in a slower degradation rate of PLLA in 10:2:1 microparticles.³⁴

The molecular weights of degraded PLLA in 4:2:1, 10:2:1, and 10:5:1 microparticles at day t_a were 98 kDa, 180 kDa, and 101 kDa, respectively. This implied that the extent of degradation at which the mass transport phenomena switching from simple diffusion to diffusion through the eroding rate-limiting layer was varied with particles of different layer thicknesses (polymer mass ratios). Therefore, this switch of mass transport phenomena is dependent on the extent of degradation and layer dimensions. When the polymer layer has undergone a certain extent of degradation, shorter t_a would be obtained for the thinner layer due to its decreased diffusion pathway length. For triple-layered PLGA/PLLA/EVA 10:2:1 microparticles (with the thinnest PLLA layer), the longer time (18 days) required to establish a drug concentration gradient across the membrane with easy drug partitioning could be attributed to its significantly slower degradation of PLLA layer ($k_{deg} = 0.0089 \text{ day}^{-1}$), when compared with 0.0357 day^{-1} and 0.0330 day^{-1} for 4:2:1 and 10:5:1 microparticles, respectively. This slow degradation rate resulted in a denser and less permeable layer structure, and prolonged the simple diffusional release.

In the early stage of degradation, PLLA is a relatively hydrophobic and highly glassy polymer. Therefore, very limited free volume was available for ibuprofen to partition into the PLLA layer. This drug partitioning is dependent on polymer degradation, causing chain scission and polymer relaxation to produce a more "open" network. The creation of more free volume as a result of the significantly decreased molecular weight (degradation) facilitates the drug partitioning and promotes further release. Therefore, the partition coefficient of drug was observed to increase with increasing PLLA degradation rates.

TABLE II. Parameters of Ibuprofen Release from Triple-Layered PLGA/PLLA/EVA 8:2:1 Microparticles of Various Sizes

Parameters	Description	Unit	38–10 μm	53–38 μm	75–53 μm	106–75 μm	150–106 μm	
<i>Known parameters</i>								
R_{particle}	Radius of particle (PLGA + PLLA + EVA)	μm	10	20.8	28.1	39.7	68.65	
R	Second inner radius (PLLA + EVA)	μm	7.4	15.5	20.9	29.5	51.0	
R_i	Innermost radius (EVA)	μm	5.1	10.7	14.4	20.3	35.2	
k_{deg}	Degradation rate constant of PLLA	day^{-1}	0.0237	0.0332	0.0352	0.0395	0.0418	
D_o	Drug diffusion coefficient in PLLA phase	cm^2/s	4.1829 $\times 10^{-12}$					
<i>Parameters determined by the model</i>								
a	Constant characteristic of diffusion	$\text{s}^{-0.43}$	0.30013	0.27062	0.25084	0.20906	0.14659	
t_a	End of simple diffusion-controlled release (stage 1)	days	8	8	8	8.1	7.6	
K	Partition coefficient of drug, [PLLA]/[EVA]	–	0.009	0.013	0.052	0.103	0.130	
<i>Goodness of fit</i>								
R^2	Correlation factor	–	0.9955	0.99693	0.99765	0.99791	0.99834	

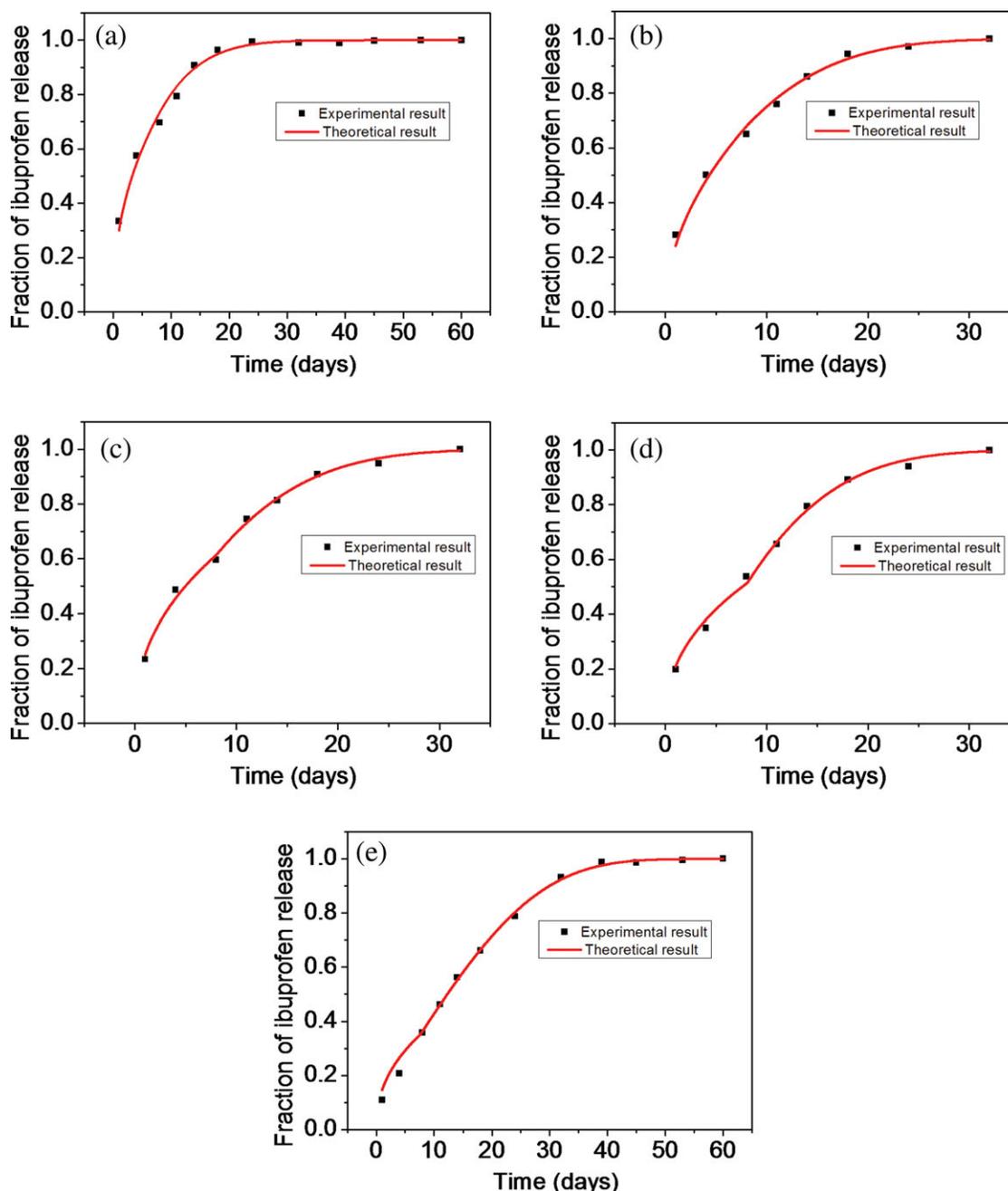


FIGURE 6. Model and experimental data matching of ibuprofen release from triple-layered PLGA/PLLA/EVA microparticles. Particle sizes (a) 38–10 μm , (b) 53–38 μm (c) 75–53 μm , (d) 106–75 μm , and (e) 150–106 μm . [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

As a result, the modeling demonstrate that the change in polymer mass ratio (thus the layer thickness) resulted in distinct physicochemical properties (i.e. constant characteristic of diffusion, drug partition coefficient, transition of the mass transport phenomena) of particles arising from their different degradation rates, thus altering the drug release kinetics and profiles.

Particles of various sizes

An increasing drug release rate with decreasing particle size was observed. Surprisingly, the phenomenon observed by

Klose et al.,²¹ who reported that autocatalytic effects compensated for the increased diffusion pathway lengths of drug, resulting in the similar release rates of particles with various sizes, was not seen in the present investigated system. To better understand the drug release mechanism, the degradation behavior of the polymer within the triple-layered microparticles and the theoretical model of drug release profile were investigated.

From Table II, the PLLA degradation rate increased with increasing microparticle size as a result of autocatalytic

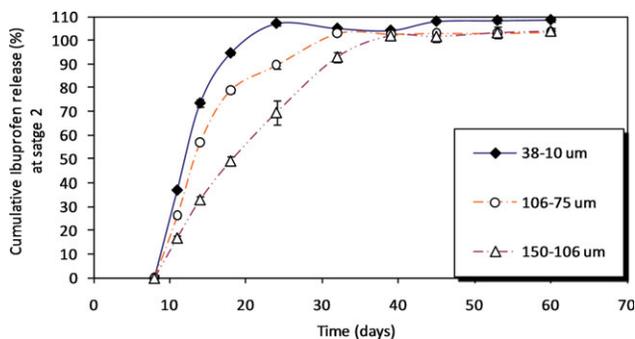


FIGURE 7. Cumulative ibuprofen release from triple-layered PLGA/PLLA/EVA microparticles of various sizes during stage 2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

effect. This result could be attributed to the rapid diffusion of acidic degradation products into the surrounding bulk fluid for the smaller microparticles. In addition, as a result of higher concentration gradients, basic ions from the phosphate buffer could diffuse into the microparticles more easily with decreasing particle dimension, thus neutralizing the generated acids.

As shown in the modeling results, a shorter diffusion pathway can be achieved with decreasing particle size, thus increasing the constant characteristic of diffusion. In contrast, the end of stage 1 (t_a) for each of the investigated size range was at around day 8. Although the decreased polymer degradation rate with decreasing device dimension would decrease the drug diffusion coefficient in the membrane, the decreased particle size (decreased diffusion pathway length) was shown to compensate for this effect, achieving similar diffusion rates. Time taken for drug molecules to diffuse and establish a concentration gradient across the membrane with easy drug partitioning (after certain extent of degradation) for various particle sizes would be the same (i.e. at around 8 days). As such, the interplay between the extent of degradation and layer dimensions was substantiated to determine t_a .

Denser structure of slowly degrading PLLA would hinder the partitioning of drug from the core into the PLLA layer. In spite of this, the drug release from the smaller-sized triple-layered microparticles still proceeded relatively faster at stage 2 due to a decreased diffusion pathway length, as shown in Figure 7. From the modeling results, it is suggested that the change in particle sizes greatly affected the diffusion pathway length, thus varying the drug release rates, rather than achieving partition- and degradation-controlled release in the investigated system (size range 10–150 μm in diameter).

CONCLUSIONS

Appropriate release model for the triple-layered microparticles of different layer thicknesses and particle sizes, where ibuprofen was localized in the core, has been proposed in this article. This theoretical model demonstrated good agreements with experimentally measured data. The triple-layered microparticles released its drug through initial sim-

ple diffusion followed by a release through a rate-limiting outer layer (membrane) that was undergoing hydrolytic degradation. Three parameters, including constant characteristic of diffusion, transition time point between two drug release mechanisms and partition coefficient of drug, were determined by the model. These parameters were shown to provide mechanistic insights into a range of drug release profiles of triple-layered microparticles with various device configurations and dimensions.

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