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RESEARCH ARTICLE

Mathematical modeling of drug release from biodegradable polymeric microneedles

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Abstract
Transdermal drug delivery systems have overcome many limitations of other drug administration routes, such as injection pain and first-pass metabolism following oral route, although transdermal drug delivery systems are limited to drugs with low molecular weight. Hence, new emerging technology allowing high molecular weight drug delivery across the skin—known as 'microneedles'—has been developed, which creates microchannels that facilitate drug delivery. In this report, drug-loaded degradable conic microneedles are modeled to characterize the degradation rate and drug release profile. Since a lot of data are available for polylactic acid-co-glycolic acid (PLGA) degradation in the literature, PLGA of various molecular weights—as a biodegradable polymer in the polyester family—is used for modeling and verification of the drug delivery in the microneedles. The main reaction occurring during polyester degradation is hydrolysis of steric bonds, leading to molecular weight reduction. The acid produced in the degradation has a catalytic effect on the reaction. Changes in water, acid and steric bond concentrations over time and for different radii of microneedles are investigated. To solve the partial and ordinary differential equations simultaneously, finite difference and Runge–Kutta methods are employed, respectively, with the aid of MATLAB. Correlation of the polymer degradation rate with its molecular weight and molecular weight changes versus time are illustrated. Also, drug diffusivity is related to matrix molecular weight. The molecular weight reduction and accumulative drug release within the system are predicted. In order to validate and assess the proposed model, data series of the hydrolytic degradation of aspirin (180.16 Da)- and albumin (66,000 Da)-loaded PLGA (1:1 molar ratio) are used for comparison. The proposed model is in good agreement with experimental data from the literature. Considering diffusion as the main phenomena and autocatalytic effects in the reaction, the drug release profile is predicted. Based on our results for a microneedle containing drug, we are able to estimate drug release rates before fabrication.

Keywords Mathematical modeling · Microneedle · Polymer degradation · Drug release · Poly(lactic-co-glycolic acid) · Autocatalytic effect

Introduction

Mathematical modeling of drug delivery and predictability of drug release is a subject of steadily increasing academic and industrial importance, with a broad future potential. Because of the significant advances in information technology (IT), the in silico optimization of novel drug delivery systems

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(DDS) can be assumed to significantly enhance accuracy [1–10].

Some drugs require parenteral delivery because of instability and enzymatic degradation in the gut in order to avoid first-pass metabolism and gastrointestinal side effects. The difficulty with injections is that they usually have to be administered by professionally trained staff and tend to cause pain [11]. Transdermal drug delivery (TDD) offers an alternative to oral and parenteral routes to avoid gastrointestinal drug degradation, first-pass metabolism and pain, and to prolong drug release and improve patient compliance. The first technology developed and licensed was the transdermal 'patch' in 1979. However, these traditional TDD systems are limited to drugs of low molecular weight (M_W) (< 500 Da), moderate lipophilicity (log p 1–3), aqueous solubility (> 100 μg/mL) and high potency (daily dose < 10 mg/day) [11]. This is because the stratum corneum (SC), which is the outermost layer of the skin, constitutes the major barrier.

In recent years, microneedle technology, as proposed by Henry et al. (1998), has been developed as an advanced technique for penetration of large M_W and hydrophilic compounds into the skin [12]. Microneedles are needle-like structures with diameter in the size order of microns and lengths up to 1 mm. These structures are used to pierce the upper layer of the skin to enable (trans)dermal drug delivery (microneedle technologies). In the research described here, the application of microneedles in drug delivery is focused on both 'solid' and 'hollow' microneedles as the common types of microneedles.

Solid microneedles are usually manufactured such that they pierce the upper layer of the skin and allow drug passage to the lower layers, where diffusion will be faster. A drug can be coated on the solid microneedle surface such that when they enter the skin, the drug dissolves and the microneedle exits. Also, the drug can be loaded in the microneedle matrix. In non-degradable ones, drugs with low M_Ws will diffuse to the outer medium, while in degradable matrices drugs with higher M_Ws can be released as the polymeric matrix degrades. In comparison with hollow microneedles, it is easier to fabricate solid microneedles, which have higher mechanical strength and sharper tips.

A process is defined as a series of operations done on materials. One of the goals of mathematical modeling of a process is to obtain a number of equations that explain the process behavior. Solving these equations illustrates the process response versus different input data. The process type determines whether the equations are algebraic, differential or a combination of both of them [13]. Mathematical modeling of drug delivery and drug release prediction has a profound importance nowadays. *In silico* optimization of novel drug release systems has a lot of advantages. It can be expected that mathematical modeling can be used for designing new dosage forms. Suitable approximations for geometry, dimensions and polymeric matrix molecular weight, etc., can be employed, so fewer experimental studies are required for developing a product, which leads to saving time and costs. Quantitative analysis of physical, chemical and biological phenomena involved in controlling drug release can explain drug release mechanisms [14].

Experimental procedure

Polymer degradation is a chain scission process in which polymer chains are broken into monomers and oligomers. Degradation of water-insoluble polymers in aqueous media is a part of their erosion process. Depending on relative water diffusion and polymer chain scission rates in such systems, two types of erosion can be defined: surface erosion and bulk erosion. In the first case, chain scission is much faster than water penetration into the system, so the main degradation process occurs in the outer layers. Polymers with less active groups, such as poly(lactic-co-glycolic acid), have more tendency to undergo bulk erosion [14]. Bulk biodegradable polymers are frequently used as drug delivery carriers. For example, one of the applications is microneedle fabrication based on degradable polymers for drug delivery purposes.

In this study, a conical microneedle loaded with drug is considered. Drug release rate and profile from the microneedle is modeled as a function of matrix degradation rate. Simplifying assumptions are required that will be discussed later. Also, model limitations will be described. It is expected that, with knowing a desired drug release rate, we will be able to design a suitable system. At first, matrix degradation and chain shortening is modeled, which is later related to drug diffusion rate changes. The proposed model is a theoretical model based on a mass conservation equation for each component with consideration of physically and chemically involved parameters in polymer degradation and drug release. All these parameters are independently estimated. After deriving the matrix degradation rate, the drug release profile can be predicted. The obtained model led to three simultaneous differential equation systems. The finite difference method for solving partial differential equations and the Runge–Kutta method for ordinary differential equations are employed. Programming code in MATLAB is developed, and experimental data from various articles are utilized for model validation assessment.

The proposed model for polymer degradation—and ultimately, drug release—is based on the involved phenomena and mechanisms. Governing equations for each component's diffusion and reaction are considered. Since the model is based on governing equations, it is applicable for a wider range of polymer types, provided that assumptions and conditions that are used in deriving the equations are met. In this article, the focus is on aliphatic polyesters, especially

Table 1 Abbreviated signs used in the literature

Abbreviated signs	Definition
t	Time
k	Reaction rate constant
M_n	Number average molecular weight
M_n^0	Initial number average molecular weight
v_{cone}	Cone volume
v_e	Cylinder volume
L	Height
L_e	Equivalent height
D	Diameter
D_e	Equivalent diameter
R	Radius
C_w	Water concentration
C_p	Polymer (ester bonds) concentration
C_p^0	Initial polymer (ester bonds) concentration
C_a	Acid concentration
C_d	Drug concentration
D_w	Water diffusion coefficient
D_a	Acid diffusion coefficient
D_d	Drug diffusion coefficient
D_d^0	Initial drug diffusion coefficient before degradation
ρ	Density

poly(lactic-co-glycolic acid) (50:50 molar ratio), due to the abundance of experimental data.

Various theories for the degradation of aliphatic polyesters are suggested. The assumptions and fundamentals of each one are summarized, and their advantages and disadvantages are discussed. In the end, an autocatalytic model is achieved with the ability to predict average molecular weight changes and accumulative drug release. The symbols and abbreviations used in this paper and literature are listed in Table 1.

Pseudo-first-order kinetics

When studying the rate of the chain scission reaction in poly(ε-caprolactone), Pitt et al. [15] suggested that the hydrolysis rate, in the absence of autocatalytic effects, has first-order kinetics, whereas autocatalytic hydrolysis has second-order kinetics. In deriving the model, it is assumed that the degradation has pseudo-first-order kinetics. Only the carboxylic acid concentration is considered; the ester concentration is ignored, although the hydrolysis rate depends on both concentrations. The model's advantage is that only simple calculations are needed to characterize molecular weight reduction [16].

Second-order kinetics

In the research done by Lyu et al. [17], it was assumed that the degradation rate depends on both water and esteric bond concentrations; hence, second-order kinetics would apply. However, autocatalytic effects of the degradation products are neglected, and it is assumed that the water concentration remains constant inside the polymer. The rate equation obtained is first order and is a basis for description of polymer bulk degradation, weight loss during surface erosion or degradation with a moving degradation front. The advantage of this model is that the mass loss is predicted for a polymer, which degrades according to a surface process or with a moving erosion front. The disadvantage of the model is that an autocatalytic behavior of degradation in the model derivation is ignored [16].

Here, we focus on modeling of systems with bulk degradation, which has complicated reaction behaviors. Previous studies of Lee et al. demonstrated that hydrolytic chain scission of poly(lactic-co-glycolic acid) and other similar polyesters are autocatalyzed by carboxylic acid end groups (COOH) [15]. The following equation is proposed to show this effect [15]:

$$\frac{d[\text{COOH}]}{\text{d}t} = k \times [\text{H}_2\text{O}] \times [\text{PLGA}] \times [\text{COOH}] \quad (1)$$

where $[H_2O]$, [PLGA] and [COOH] are the water, ester and carboxylic acid end group concentrations in the polymer bulk, respectively. In Lee's study, water and ester concentrations were assumed to be constant because in the first stages of degradation the number of chain scissions is low. With a simple calculation and relating the carboxylic acid end group concentration to the number average molecular weight, Eq. (1) is transformed into Eq. (2):

$$\frac{M_n}{M_n^0} = \exp(-k \times [\text{H}_2\text{O}] \times [\text{PLGA}] \times t) = \exp\left(-k' t\right) \quad (2)$$

It can be understood that the assumption of constant water and ester concentrations is only acceptable for the very early periods of degradation initiation. As the polymer chains are broken, it is expected that the water content, ester concentration and system porosity would increase.

Assumptions

- Microneedles are considered to be separate, and the overall drug release amount will be achieved by summation of individual microneedle releases.
- Usually, microneedles are conic in order to pierce the skin easily. For simplifying the model and avoiding two-dimensional equations, the conic needles are assumed to be cylinders with the same volume (see Fig. 1). Since degra-

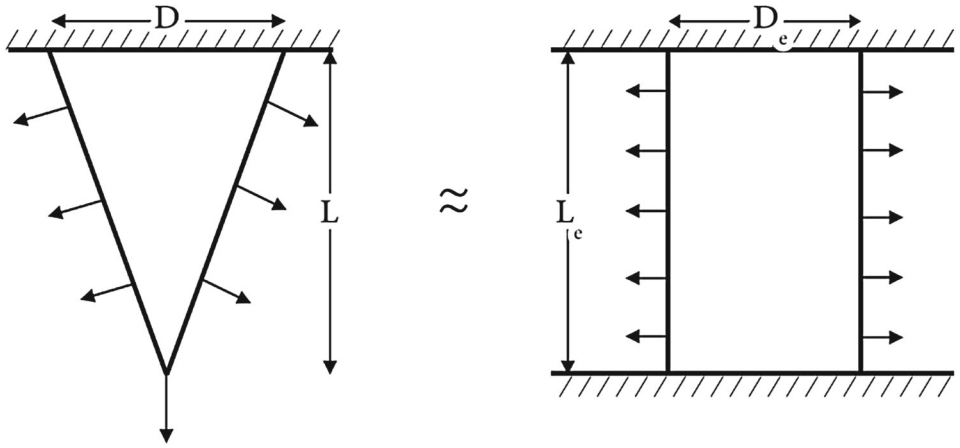

Fig. 1 Equivalent cylinder to conic microneedle: D, D_e, L, L_e denote diameter, equivalent diameter, height and equivalent height, respectively

dation in this case is a bulk degradation, this assumption can be acceptable; sharp tips of the needle are just designed to facilitate needle entrance into the skin.

Thus, the following equations apply:

$$v_{\text{cone}} = \frac{1}{3}\left(\frac{\pi D^2}{4}\right)L \tag{3}$$

$$v_e = \left(\frac{\pi D_e^2}{4}\right)L_e \tag{4}$$

$$v_{\text{cone}} = v_e \tag{5}$$

$$\text{if} \rightarrow L = L_e \Rightarrow D_e = \frac{\sqrt{3}}{3}D \tag{6}$$

- The constitutive monomers of PLGA are lactic acid (LA) and glycolic acid (GA). Thus, there are four different ester bonds: LA–LA, GA–GA, LA–GA and GA–LA. One of the hypotheses is that the ester bonds ratio remains constant during degradation.
- The drug is distributed uniformly in the polymeric cylinder matrix and not on its surface.
- The main degradation mechanism is hydrolysis. Water enters the bulk of the system in the cylinder and reacts with the ester bonds of the chains, leading to chain scission and conversion of chains into oligomers and monomers.
- Edge effects are neglected, and there is no mass transfer from the bottom cross section of the cylinder—so the mass transfer in the cylindrical coordinate will be one dimensional. The results will be more accurate when the $\frac{L}{D}$ ratio is higher.
- Degradation products have good water solubility and can exit the control volume easily.
- The reaction rate constant of hydrolysis of the ester bonds during the reaction is assumed to be the same for all of them.

Table 2 Required model parameters

	Unit	Siegel et al. [18]	Shah et al. [19]
Cylinder radius	cm	0.6	6.5
Cylinder height	cm	0.1	0.04
Polymer molecular weight	g/mol	63,000	18,000
Polymer density	g/cm^3	1	1
Water diffusivity	cm^2/s	3×10^{-6}	1.05×10^{-5}
Average acidic monomer diffusivity	cm^2/s	1×10^{-10}	3.5×10^{-10}
Degradation time	Day	38	35
Drug	–	Aspirin	Albumin
Drug diffusivity	cm^2/s	1×10^{-8}	5.92×10^{-10}
Drug molecular weight	g/mol	180.16	66,000
Drug weight percent	–	0.2	0.17

Estimation of model parameters

Besides the parameters related to the geometry and drug distribution in the matrix, model parameters related to the polymer rate degradation (such as rate constant of polymer degradation, diffusion coefficient of water, acidic monomers and drug in polymeric matrix) must be estimated. The parameters related to the degradation rate are matrix dependent. The assumed values, which were extracted from previous publications, are summarized in Table 2.

To calculate the reaction rate constant (k), data from published diagrams of molecular weight versus time were used.

$$k = 0.75 \times 10^{-15}\left(\frac{\text{mol}}{\text{m}^3}\right)^{-2}\left(\frac{1}{\text{s}}\right) \tag{7}$$

Governing equations

System governing equations based on the main phenomena, such as molecular diffusion and chemical reaction, for all components were written. To account for water concentration changes due to water diffusion into the control volume and water consumption in the hydrolysis reaction, the mass conservation equation is as follows:

$$\frac{\partial C_w}{\partial t} = \frac{D_w}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_w}{\partial r}\right) - kC_pC_aC_w \tag{8}$$

In the first moment, no water has entered the system; its concentration is zero in the whole cylinder. While the time passes, at the center line of the cylinder, there is no concentration change due to symmetry, so it remains zero. At the surface, the concentration will remain constant, the same as solution value.

The mass conservation equation for acid, which considers the acid concentration changes due to acid diffusion to the outer medium of the control volume and acid production in the hydrolysis reaction, is as follows:

$$\frac{\partial C_a}{\partial t} = \frac{D_a}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_a}{\partial r}\right) + kC_pC_wC_a \tag{9}$$

At first, the acid concentration is a determined value, since the polyester chains have acidic end groups. This concentration can be measured using the end group analysis method or by knowing the number average molecular weight and polymer mass. The mole number of acidic groups can be determined, and by dividing it by the volume, the initial molar concentration of acid can be calculated.

At the cylinder center line, due to symmetry, there are no concentration changes. At the cylinder surface, the acid concentration is equal to zero as the acidic monomers have good water solubility; as soon as exiting the control volume, they dissolve in the medium. This meets the perfect sink condition. Hence, this boundary condition was used.

The mass conservation equation for the polymer, which involves the ester concentration changes due to ester consumption in the hydrolysis reaction, is as follows:

$$\frac{\partial C_p}{\partial t} = -kC_wC_aC_p \tag{10}$$

The mass conservation for the drug, which accounts for the drug concentration changes due to diffusion to the outer parts of the control volume, is as follows:

$$\frac{\partial C_d}{\partial t} = \frac{D_d}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_d}{\partial r}\right) \tag{11}$$

At first, the drug—with a certain concentration—is distributed uniformly in the polymeric matrix. At the cylinder center line, it is theoretically presumed there are no concentration changes due to symmetry. At the cylinder surface, due to the sink condition, the drug concentration is equal to zero.

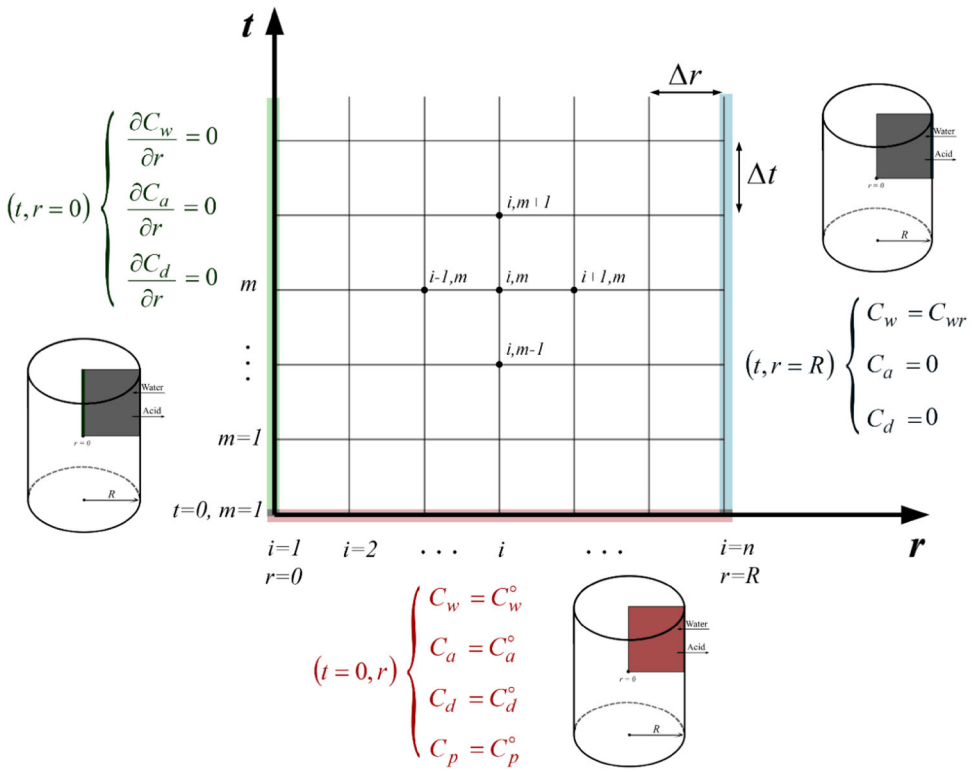

Fig. 2 Boundary conditions and meshing the space

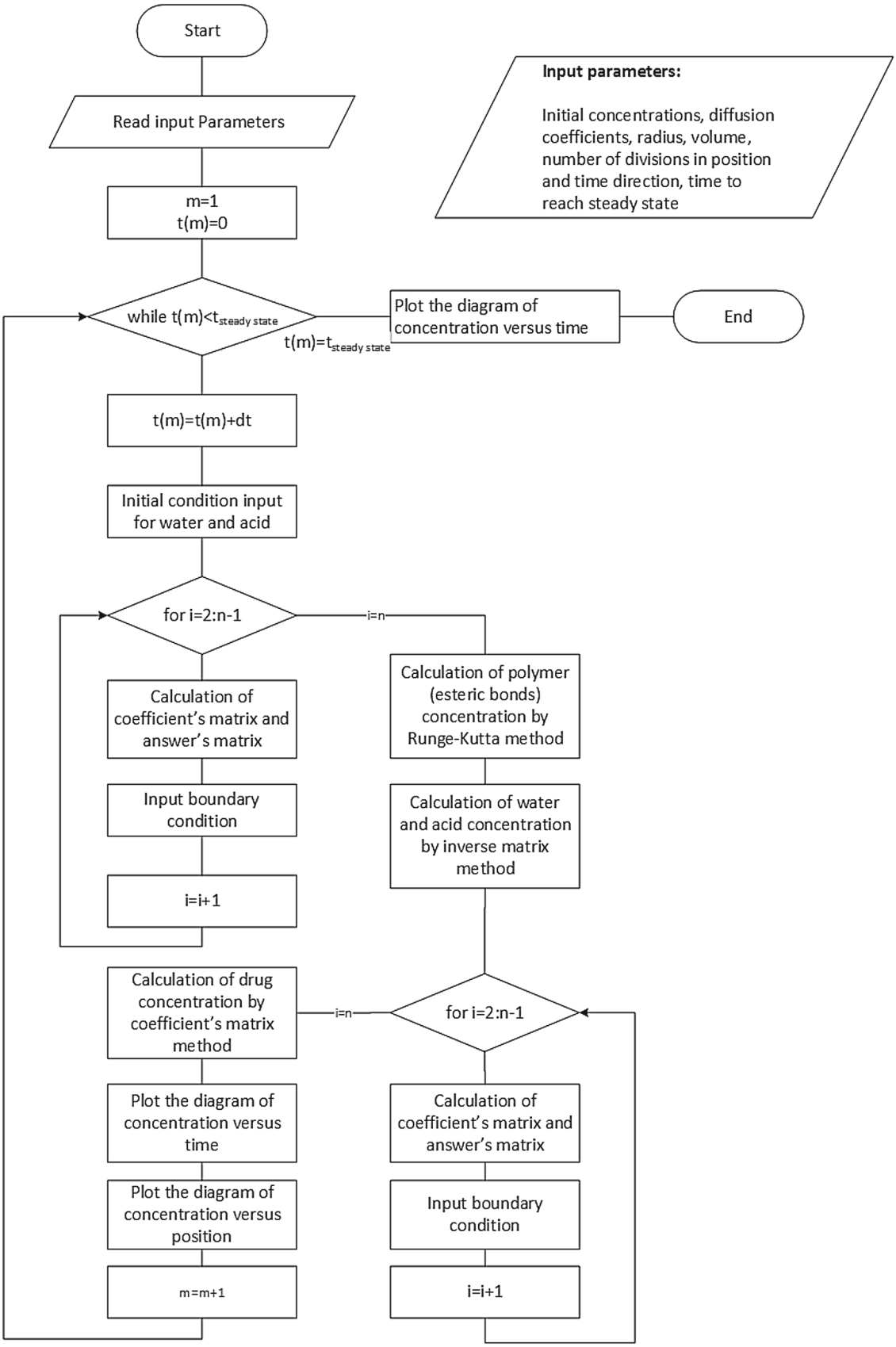

Fig. 3 The applied algorithm in MATLAB for solving the equation systems

The drug diffusion coefficient does not remain constant. As degradation occurs, the drug diffusion coefficient increases. With polymer degradation, the polymer molecular weight decreases, and the drug diffusion coefficient is proportional to the inverse of polymer molecular weight.

$$\frac{D_d(t)}{D_d^\circ} = \frac{M_n^\circ}{M_n(t)} \tag{12}$$

The boundary conditions and meshing of the space are shown in Fig. 2. Also, the applied algorithm in MATLAB for solving the equation systems is provided in Fig. 3.

Results and discussion

Dimensionless water concentration changes with time following immersion of the drug-loaded cylinder, which is demonstrated in Fig. 4. The water content of the system increases rapidly to a constant value. The extent of water content of the system depends on the polymer type, its hydrophobicity extent, matrix porosity, rate of polymer degradation, etc.

Figures 5 and 6 show changes in ester bond concentration with time and radius of cylinder, respectively. In Fig. 5, initially, the concentration of ester bonds susceptible to breakage is the maximum value, and as degradation time increased, it reached zero. It is expected that the rate of polymer chain breakage would be slow at the beginning unless acidic end groups are initially present and accelerate the reaction. Over time, the carboxylic acid formation reaction rate will be accelerated as they autocatalyze the degradation reaction. In the final stage, most of the steric bonds in the chains have reacted. As a result, the reduction in molecular weight occurs more slowly. A large number of acidic end groups in

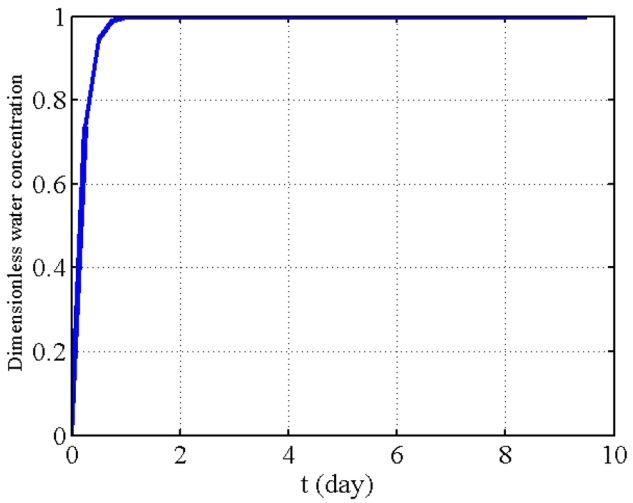

Fig. 4 Dimensionless water concentration versus time

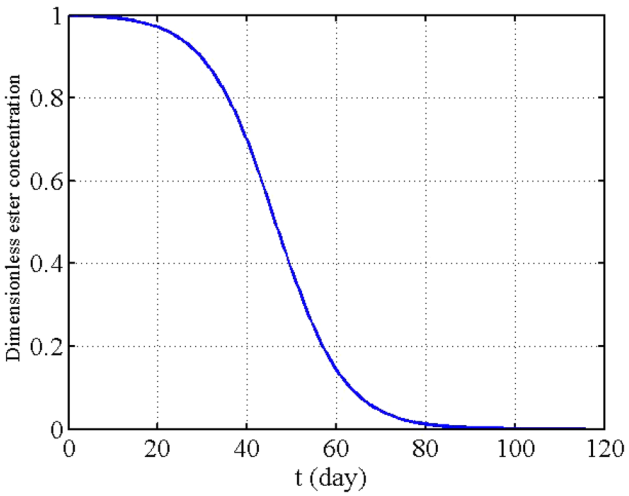

Fig. 5 Dimensionless ester concentration versus time

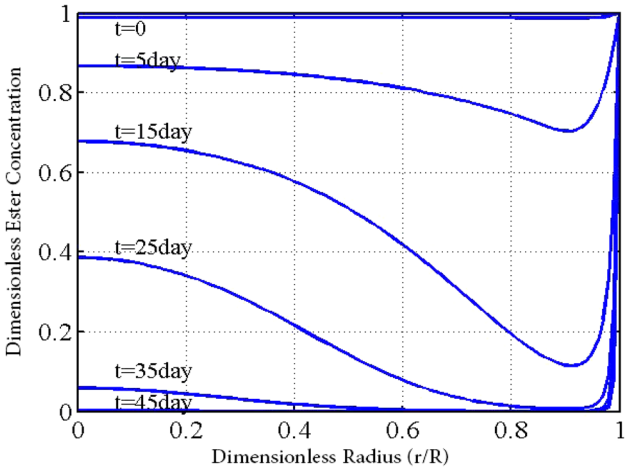

Fig. 6 Dimensionless concentration of esteric bonds versus dimensionless radius of cylinder. $\left(\frac{r}{R}\right) = 0$ is the center of the cylinder, and $\left(\frac{r}{R}\right) = 1$ is the cylinder surface

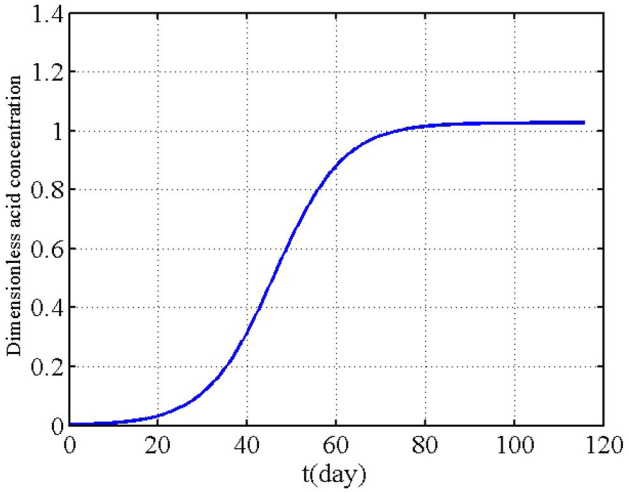

Fig. 7 Dimensionless carboxylic acid concentration versus time

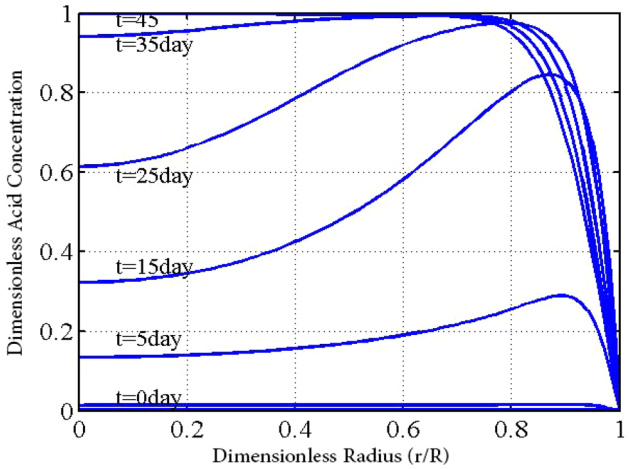

Fig. 8 Dimensionless concentration of esteric bonds versus dimensionless radius of cylinder. $\left(\frac{r}{R}\right) = 0$ is the center of the cylinder, and $\left(\frac{r}{R}\right) = 1$ is the cylinder surface

the initial polymer would lead to an autocatalytic effect and fast polymer breakage from the first stages of degradation. Indeed, reduction in polymer molecular weight would occur with a rapid speed from the first, and because there will be no initiation time for producing acidic products, the degradation profile is 'S' shape. In Fig. 6, at $t = 0$, the ester concentration is almost constant and decreases with time. The lowest concentration of ester is inside the cylinder, near the surface.

Figures 7 and 8 show changes in acidic bonds concentration over time and through the radius of cylinder, respectively. As is obvious in Fig. 7, because of the autocatalytic effect, the rate of the increase in acid concentration increases with time. In the end, because the total ester bond amount decrease, the acid concentration reaches a constant value. Figure 8 shows the decrease in ester bond concentration and the increase in the acid concentration.

Hydrolytic degradation of the polymeric matrix is assessed by changes in number average molecular weight $\left(\overline{M_n}\right)$. According to the predicted degradation rate, knowing the acid concentration profile and the relationship of number average molecular weight to acid concentration, the charts described below are obtained (Figs. 9 and 10). To validate this model, the density of the polymer, initial concentration of carboxylic acid end groups and the ratio of monomers in the copolymer are required. The initial number the carboxylic acid groups in the polymer is calculated as follows.

By knowing the initial value of average molecular weight in relation to the concentration of the polymer chains, calculation of the initial concentration of the carboxylic acid groups can occur. Each polymer chain contains one carboxylic acid end group, and thus, the concentration of carboxylic acid end groups (C_a) is equal to the polymer chain concentration.

$$C_a(t=0) = \frac{\rho}{M_n^0} \tag{13}$$

$$C_p^0 = \frac{m}{M_n^0 V} = \frac{\rho}{M_n^0} \tag{14}$$

As mentioned previously, data related to the drug and matrix are summarized in Table 2. Two independent series of data for model validation are used. The only way for testing and verifying the model and assumptions accuracy is to compare the results with different and various experimental data. In general, in the figures below, the plotted points represent experimental data and the lines represent the predictions of the model.

In Figs. 9 and 10, model predictions of number average molecular weight versus time, based on the data from the literature, are tested. The data of the systems that are used are as follows:

Aspirin releases from poly(lactic acid-co-glycolic acid) with a molar ratio of 1:1, with aspirin having molecular weight of 180.16 grams per mole and the polymer matrix

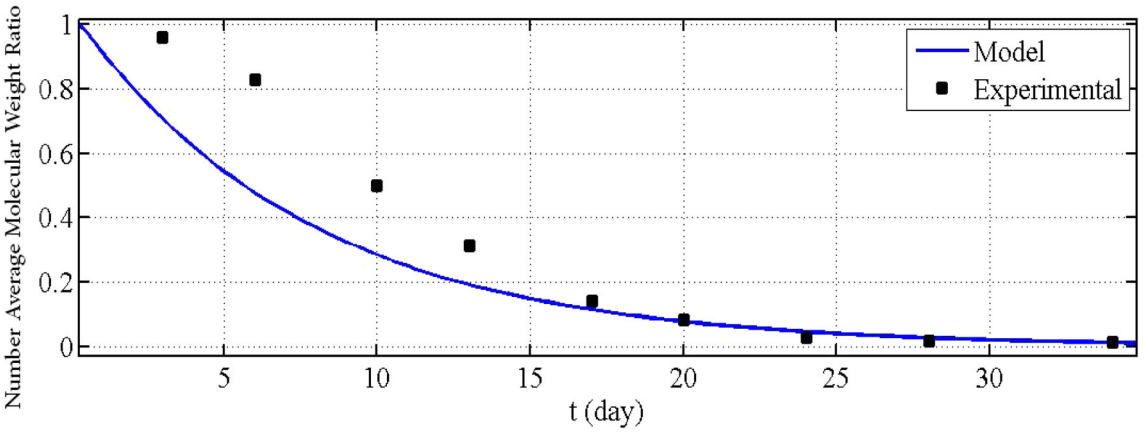

Fig. 9 Number average molecular weight versus time. Comparison of data from [16] with the model predictions. Solid line represents model predictions, and square signs represent experimental data

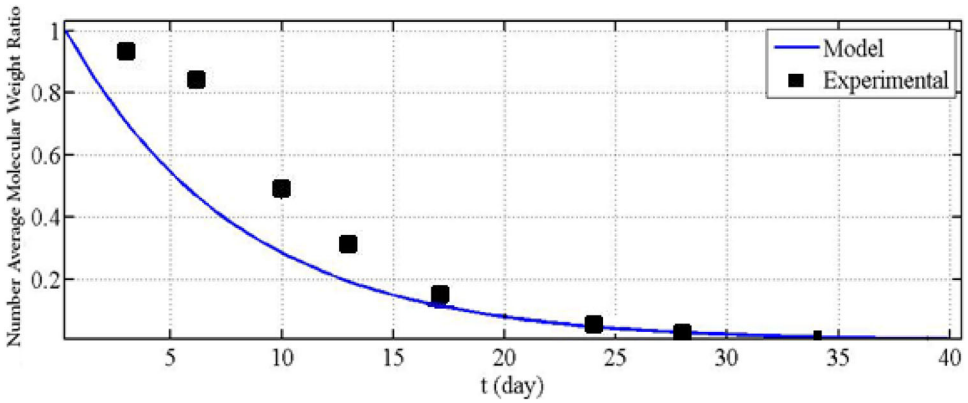

Fig. 10 Number average molecular weight versus time. Comparison of data from [20] with the model predictions. Solid line represents model predictions, and square signs represent experimental data

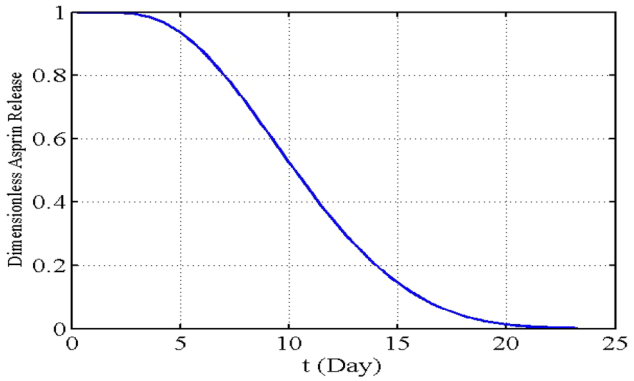

Fig. 11 The ratio of released aspirin to the initial amount in the PLGA 50:50 versus time

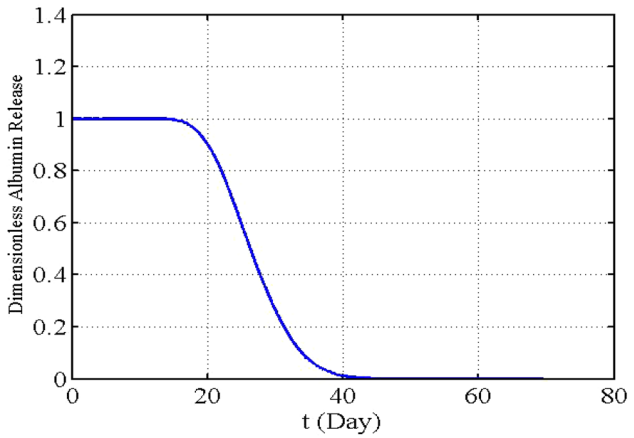

Fig. 12 The ratio of released albumin to the initial amount in the PLGA 50:50 versus time

having a molecular weight of 63,000 grams per mole. 100 mg aspirin and 400 mg of PLGA are mixed in solvent casti, ultimately leading to a matrix with 20% by weight Aspirin (data provided in Fig. 9) [16].

Bovine serum albumin (BSA) releases from PLGA polymer matrix with a mole ratio of 1:1. BSA has a molecular weight of 66,463 grams per mole, and polymer matrix had M_w of 18,000. 75 mg of PLGA polymer and 30% weight of the drug, which is equivalent to 22.5 mg albumin insolvent, are produced in the blend (data in Fig. 10) [20]. Also, the ratio of released aspirin and albumin to the initial amount in the PLGA 50:50 versus time is provided in Figs. 11 and 12, respectively.

Figure 13 corresponds to the accumulative release of aspirin from the PLGA. Qualitatively, the f model prediction shows good agreement with the experimental data. Figure 14 corresponds to the accumulative release of albumin from PLGA.

As seen, the predicted trend for dimensionless aspirin release (Fig. 11) and the experimental accumulative aspirin release (Fig. 13) is the same, except that the first one is decreasing and the other one is increasing. In other words, as the amount of aspirin in the PLGA is decreased, its total released amount in the medium increases with the same velocity. The same is true about BSA.

One of the parameters associated with the cylindrical geometry is the radius of the cylinder, which is important in microneedle design. In Fig. 15, the changes in drug release rate are investigated by varying the radius of the cylinder. As seen, increasing the radius of the cylinder leads to the decrease in drug release rate (which is the slope of the diagram). As a result, one of the parameters that can be used to control the release rate of the drug is the radius of the cylinder. For example, to achieve a dose of 3.5 mg of aspirin per day, a molecular weight of 63,000 g per mole for polymer and 43 microneedles with the radius and height of 500 and 1000 mm are required.

Another parameter that can control the polymer degradation rate—and finally, the drug release rate—is the molecular weight of the polymer matrix. It is expected that with increasing matrix molecular weight, degradation would occur more slowly. In Fig. 16, the dimensionless number average molecular weight (the ratio of molecular weight in each time to initial molecular weight) versus time is plotted. As seen in Fig. 16, with increasing molecular weight, the polymer degradation occurs more slowly.

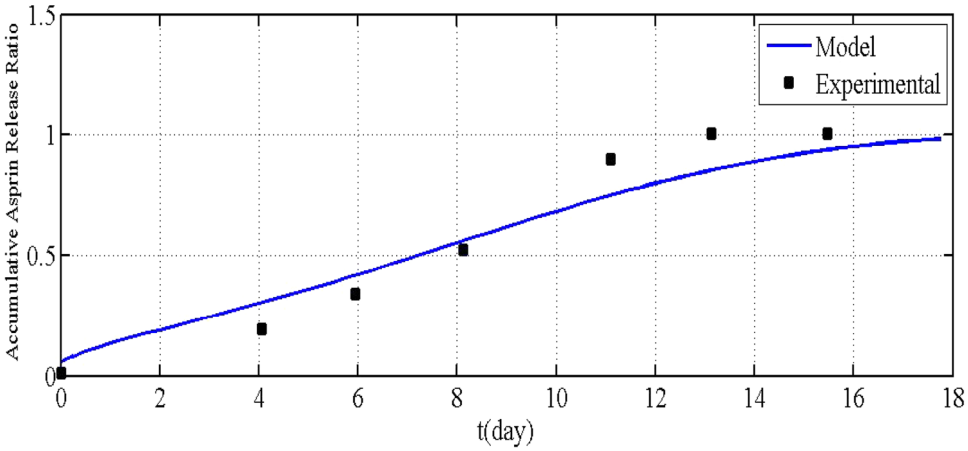

Fig. 13 Comparison of experimental data [18] and model for accumulative amount of aspirin released from PLGA 50:50

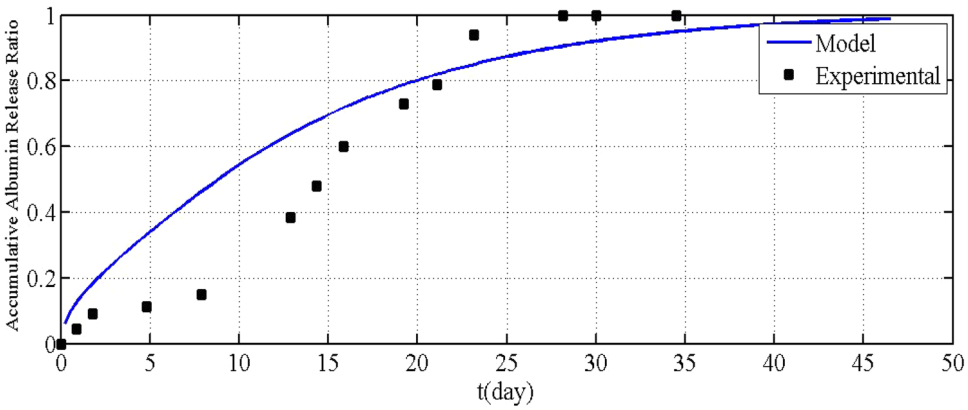

Fig. 14 Comparison of experimental data [19] and model for accumulative amount of albumin released from PLGA 50:50

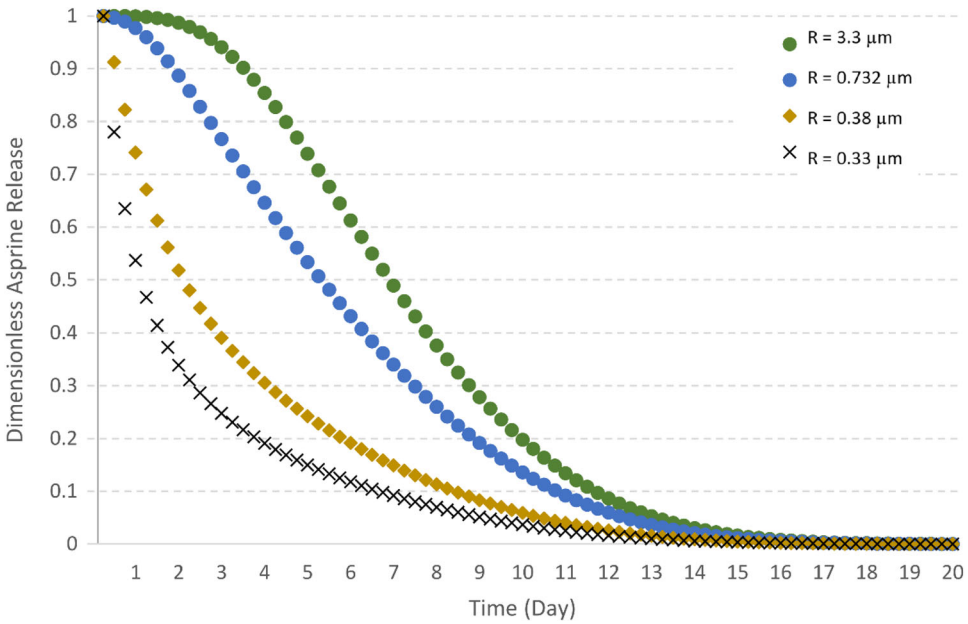

Fig. 15 The dimensionless drug release rate versus changing the radius of the cylinder

Conclusion

Based on several simplifying assumptions, the mass conservation equations for all system components were derived and solved, leading to a predicting model that can predict polymeric matrix degradation and drug release rate of the cylindrical needle. To calculate partial and ordinary differential equations simultaneously, the finite difference and Runge–Kutta methods were employed, respectively. By correlating the polymer degradation rate with the molecular

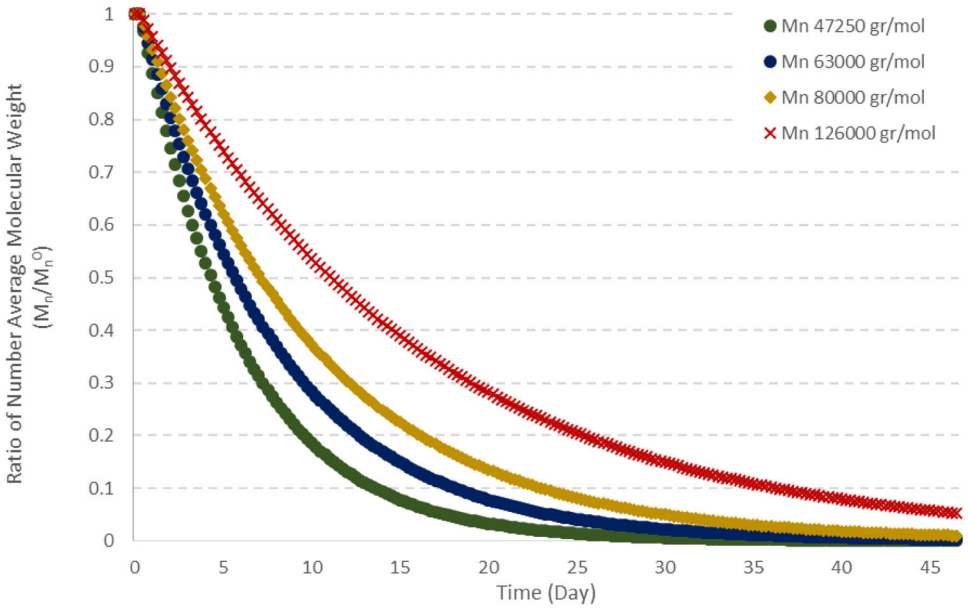

Fig. 16 Dimensionless number average molecular weight of matrix versus time for four different Mn

weight, molecular weight changes versus time were illustrated. Also, the drug diffusivity was related to the matrix molecular weight. Molecular weight reduction and accumulative drug release within the system were determined. In order to validate and assess the proposed model, a set of data of hydrolytic degradation of aspirin (180.16 Dalton)- and albumin (66,000 Dalton)-loaded PLGA (1:1 molar ratio) were used for comparison.

The proposed model is in good agreement with experimental data from the literature. Considering diffusion as the main phenomena and autocatalytic effects in the reaction, the drug release profile is predicted. As a result, for a microneedle containing drug, we will be able to estimate the drug release rate before fabrication. The prediction procedure of the proposed model shows a qualitatively suitable adjustment to experimental data. The main reason for the differences between model and experimental results can be referred to the estimation of some needed parameters of the model, because finding the parameters in exactly the same utilized condition is difficult. Under ideal conditions, it is better to measure the needed parameters for the exact same experiment conditions used in the theory. Also, the simplifying assumptions utilized (e.g., one-dimensional diffusion in the cylinder) can add to the error amount.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

Ethical approval This paper does not contain any studies with human or animal subjects.

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