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A comprehensive mathematical model describing drug release from collagen matrices

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Biodegradable collagen matrices have become a promising alternative to synthetic polymers as drug delivery systems for sustained release. For the accurate design and optimization of such collagen systems there is a strong need in mathematical models. Here, an overall mathematical model is presented that describes drug release from collagenous drug carrier systems. The relevant processes are penetration of water into the matrix, matrix swelling, matrix degradation by enzymatic cleavage and simultaneous drug release. Our mathematical model is based on experimental investigations and measurements; cf. [5, 6]. Thereby the relevant processes were identified and characterized. In former publications (cf. [8, 9]) the capability of the model components to describe reliably drug release by matrix swelling and enzymatic matrix degradation was demonstrated by a careful comparison of measurements and numerical simulations. Here, we focus on establishing an overall mathematical model by combining the components that were developed in [8] on the one hand and in [6, 9] on the other hand.

1. Introduction

Collagen is the major constituent of connective tissue; cf. [3]. Due to its wide distribution in the mammalian body, it has become a promising material for biodegradable drug delivery systems. Dense collagen matrices for sustained release of higher

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weight drugs such as proteins or polysaccharides offer an alternative to implants based on synthetic polymers; cf. [3]. Especially drug release from insoluble collagen devices is of interest since drug liberation can be controlled by swelling and enzymatic degradation. Initially the matrix swells and drug is released by diffusion. This phenomenon was described previously in a mathematical model; cf. [8]. Subsequently, degradation by collagenolytic enzymes occurs and the release rate becomes additionally dependent on the enzymatic binding and cleavage rate. This phenomenon was described in a mathematical model and investigated carefully recently; cf. [6, 9]. Moreover, in [8, 9] the model components were analyzed accurately from the mathematical point of view. In particular, the existence and uniqueness of solutions of the model equations could be ensured. Further, reliable and accurate numerical approximation schemes were suggested and studied in numereous experiments. For validation, the numerically calculated data were compared with experimental measurements and a good agreement between the either data was observed; cf. [8, 6, 9]. Eventhough the either mechanisms of drug release – release by matrix swelling and release by matrix degradation – occur simultaneously, we have separated them in their investigation, mathematical modelling and numerical simulation. This seems reasonable since the processes proceed on strongly different time scales, as our experimental studies have borne out; cf. [5]. Whereas drug release due to swelling is restricted to an initial period of some minutes (up to 30 minutes approximately), drug release by matrix degradation takes place over several days (up to 14 days possibly). The approach to separate the either mechanisms of drug delivery enables us to apply more adapted mathematical and numerical methods to the separated subprocesses.

However, a comprehensive mathematical model combining water penetration, matrix swelling and drug release by diffusion on the one hand and matrix degradation by enzymatic cleavage and simultaneous drug relase is still missing. Such a model will be proposed in the sequel and will allow the design and optimization of collagen drug carrier systems. Other models that were published in the literature (cf., e.g., [7, 11, 12] and the references therein) to describe drug release from biopolymers are less complete or consider only one of the either drug delivery mechanisms.

2. Mathematical Model

In the sequel we consider a cylindrical collagenous drug delivery system. The matrix is of thickness $2X_0$ and radius R and is placed in a well-stirred medium (cf. Figure 1) that contains an enzyme (collagenase), at a concentration which is supposed to be constant all over the process. In the ambient fluid, the polymer takes up large quantities of liquid and swells. The free active agent (i.e. drug) then diffuses out of the swollen matrix system. Concomitantly, the enzyme penetrates into the matrix and binds at the collagen fibers to form an enzyme-substrate complex. This complex then breaks down into hydrolized collagen (the product of the reaction) and enzyme. The part of the active agent which is initially immobilized due to physical entrapment by the collagen fibers, becomes more and more free and can diffuse out of the matrix. To summarize, the relevant processes to be described mathematicaly are

- the swelling of the collagen matrix,
- the diffusion and transport of the enzyme in the matrix,
- the adsorption of the enzyme from the fluid to the collagen fibers,
- the enzymatic degradation of the polymer,
- the release of the drug.

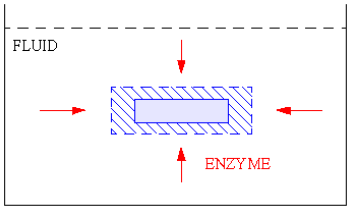

Fig. 1. Schematic of the model.

First, we shall describe the matrix swelling process; cf. [8]. Our mathematical model assumes a Fickian diffusion mechanism, i.e. the characteristic chain relaxation time is much smaller than the characteristic penetrant diffusion time. We further assume that the swelling and degradation of the polymeric substrate by the enzyme is independent of the active agent (drug). The governing equation for the transport of the penetrant solvent and of the drug in the polymer is

$$\begin{aligned} \partial_t C_L - \nabla \cdot (D_L(C_L)\nabla C_L) &= 0 \quad \text{in} \quad \Omega(t), \\ C_L(0,\mathbf{x}) &= C_L^0(\mathbf{x}) \quad \text{in} \quad \Omega(0), \quad \text{at} \quad t=0, \\ C_L(t,\mathbf{x}) &= C_L^{ext} \quad \text{on} \quad \partial\Omega(t), \end{aligned} \tag{1}$$

where C_L is the concentration of liquid in the polymer, C_L^0 the initial concentration of water in the matrix and $\Omega(t)$ is the domain at time $t \geq 0$. We note that throughout this paper the concentrations are expressed in mol per volume. We prescribe the concentration of water at the swelling front to be equal with C_L^{ext}, which is the concentration of the water in the fully swollen gel. According to the free-volume theory, a Fujita-type [4] exponential dependence of the diffusion coefficient for the penetrant solvent D_L on the solvent concentration has been assumed with $D_L = D_L^{eq}\exp(-\beta_L(1 - C_L/C_L^{ext}))$, where β_L is a dimensionless constant and D_L^{eq} are the diffusion coefficients of water in the fully swollen collagen matrix. A crucial point of the model is how to describe the moving of the free boundary. We assume that the total volume expanded due to swelling is given by the volume of the extra fluid in the matrix. Accordingly, the movement of the swelling front is given by the following volume balance

$$V(t) - V(0) = v_m \int_{\Omega(t)} C_L(t,\mathbf{x})\,\mathrm{d}x - v_m \int_{\Omega(0)} C_L(0,\mathbf{x})\,\mathrm{d}x, \tag{2}$$

where $V(t)$ is the volume of the matrix at time t and v_m is the molecular volume of water. To close our model describing the swelling process we also need an assumption on the shape of the matrix. In the one-dimensional case (see [8]) equation (2) has the form

$$X(t) - X_0 = v_m \int_0^{X(t)} C_c(t,x)\mathrm{d}x - v_m \int_0^{X_0} C_c(0,x)\mathrm{d}x, \tag{3}$$

which further implies the relation

$$\dot{X}(t) = \frac{v_m}{1 - v_m C_L^{ext}} D_c \partial_x C_L(t, X(t)). \tag{4}$$

The one dimensional case can be applied when the ratio between radius and hight of the cylinder is bigger than 12, as it was pointed out in [7]. Analogous relations can be derived in the two or three dimensional case.

Now we shall describe the enzymatic matrix cleavage process. The general behaviour of an enzymatically catalyzed degradation process can be described by (cf. [2])

$$\mathbf{E} + \mathbf{S} \xrightarrow{k_1} \mathbf{ES} \tag{5}$$

$$\mathbf{ES} \xrightarrow{k_2} \mathbf{E} + \mathbf{P} \tag{6}$$

In our case, collagen represents the substrate, collagenase is the enzyme whereas the hydrolized collagen is the product. Further, k_1 and k_2 denote rate parameters. The first of the either reactions represents the adsorption process and the second one describes the cleavage of the substrate complex into a product and enzyme. The adsorption may be considered either as an equilibrium process or a kinetic one, depending on its time scale compared to the diffusion process. Here, the adsorption process is described by a Freundlich type isotherm which is based on our experimental investigations; cf. [5, 6]. This is in agreement with [10], where different curves were investigated and the best results were obtained also with a Freundlich-type isotherm.

We further assume that the enzyme does not only diffuse in the matrix but in the first phase, i.e. swelling phase, is also transported by the penetrating fluid. Consequently, an advection-diffusion equation with a reactive term is used to describe the evolution of the enzyme. The enzyme-substrate complex (ES) is supposed to be immobile, whereas the product is free to diffuse out of the collagen matrix. By recalling the equations (5) and (6), the enzymatic degradation of polymer matrix is mathematically described by

$$\begin{aligned}
\partial_t C_E - \nabla \cdot (D_E(C_K)\nabla C_E - \boldsymbol{q} C_E) + k_{\mathrm{act}} C_E &= -k_1 (C_E)^\alpha C_K + k_2 C_{ES}^\gamma \,, && (7)\\
\partial_t C_{ES} &= k_1 (C_E)^\alpha C_K - k_2 C_{ES}^\gamma \,, && (8)\\
\partial_t C_K &= -k_1 (C_E)^\alpha C_K \,, && (9)\\
\partial_t C_P - \nabla \cdot (D_P(C_K)\nabla C_P) &= k_2 C_{ES}^\gamma \,. && (10)
\end{aligned}$$

We consider solving (7)–(10), equipped with the initial conditions

$$C_E(0,\mathbf{x}) = 0\,, \quad C_{ES}(0,\mathbf{x}) = 0\,, \quad C_K(0,\mathbf{x}) = C_K^0\,, \quad C_P(0,\mathbf{x}) = 0 \tag{11}$$

and the boundary conditions

$$C_E(t,\mathbf{x}) = C_E^{\text{ext}}\,, \quad C_P(t,\mathbf{x}) = 0 \quad \text{on } \partial\Omega(\mathrm{t})\,. \tag{12}$$

Here, C_E, C_{ES} and C_P denote the concentrations of the free enzyme, enzyme-collagen complex and product, respectively, and $\boldsymbol{q} = -D_L\nabla C_L$ stays for the fluid flux. The enzyme activity decays in time which is incorporated in (7) by means of the term $k_{\text{act}}C_E$, with k_{act} being a dimensionless constant that has to be determined experimentally. In (7)–(9), the quantity α denotes the parameter of the Freundlich isotherm and k_1, k_2 are the rate parameters of (5), (6). In particular, $\alpha \in (0,1]$ is satisfied. In [6, 9] it was shown that a nonlinear dependence of the right-hand side terms in (7)–(10) on C_{ES} is necessary to describe adequately the enzymatic matrix degradation by the set of equations (7)–(10). Thus, the parameter $\gamma > 0$ is of empirical origin. We remark here that the parameters α and γ are material dependent. They are mathematically fitted by using a set of data in a simplificated situation, i.e. by considering only fully swollen matrices (see [6, 9] for details).

We further mention that C_K^0 in (11) denotes the collagen concentration at the initial time and C_E^{ext} in (12) is the enzyme concentration in the ambient aqueous solution that has to be prescribed. Due to the degradation process occuring concurrently, the matrix phase through which the diffusion takes place changes continuously as a function of the extend of hydrolysis of the polymer. Therefore, the diffusion coefficient D_E of the enzyme can not be considered as a constant but rather as a function of the fluid or collagen concentration. Again we assume a Fujita-like dependence (cf. [4]) on the concentration of the collagen C_K, i.e. $D_E = D_E^0 \exp\left(-\frac{\beta_E C_K}{C_K^0}\right)$, with D_E^0 denoting the diffusion coefficient of the enzyme in water and β_E being a dimensionless constant. The same assumption is made for the diffusion coefficient D_P of the product in the ambient fluid. Accordingly, we have $D_P = D_P^0 \exp\left(-\frac{\beta_P C_K}{C_K^0}\right)$. The parameters D_E^0 and D_P^0 can be determined by measurements; cf. [5, 6].

We close the model by the equations for the drug release. It was experimentally observed that if degradation would not occur then a certain amount of drug would remain unrealesed in the matrix, and this because the drug molecules are physsicaly immobilized by the collagen fibers. It is then naturally to assume (as also done, for instance, in [11]) that the initial load of active agent is composed of two pools: a pool of mobile active agent which is free to diffuse upon hydration of the matrix by the ambient aqueous solution, and some part which is immobilized by the polymer. As the polymer degrades, the concentration of collagen becomes lower and more and more drug is free to diffuse.

In terms of equations we describe the release of the active agent by a diffusion equation with a source term that models the liberation of the immobilized active agent by matrix degradation together with initial and boundary conditions:

$$\begin{aligned}
\partial_t C_A - \nabla\cdot(D_A(C_K)\nabla C_A) &= -\partial_t C_{A_i} \quad \text{in} \quad \Omega(t), \\
C_A(0,\mathbf{x}) &= C_A^0(\mathbf{x}) \quad \text{in} \quad \Omega(0), \quad \text{at} \quad t=0, \\
C_A(t,\mathbf{x}) &= 0 \qquad \text{on} \quad \partial\Omega(t),
\end{aligned} \tag{13}$$

where C_A, C_{A_i} denote the concentrations of free and immobilized drug, respectively. The initial concentration C_A^0 of the active agent that is free to diffuse can be determined experimentally by measuring the quantity of drug which would remain in the matrix if no degradation occurs, i.e. if no enzyme is available.

As mentioned previously, the diffusion is entangled because of the physical entrapment. In the equations above this effect is described by the source term $\partial_t C_{A_i}$ and we still have to establish a relation connecting the concentrations of the immobilized active agent and of the collagen. Following [6, 9], we consider

$$C_{A_i} = \sigma C_K^{\eta} \,. \tag{14}$$

This is based on experimental studies, which did not confirmed the assumption of a linear dependence as used in [11]. The parameters σ and η are constants. The first one, σ, denotes the immobilizing capacity of the polymer, equal to the number of hindering crosslinks or entanglements per mole of (fully swollen) substrate and its value can be easily determinated experimentally. The second parameter, i.e. η, it is also material dependend and has to be mathematically fitted. Like in the case of the parameters α and γ, this is done by considering fully swollen matrices (see [6, 9] for details). Similarly to the enzyme, for the diffusion coefficient of the active agent in the matrix a functional form $D_A = D_A^0 \exp\left(-\frac{\beta_A C_K}{C_K^0}\right)$ is used, where D_A^0 denotes the diffusion coefficient of the drug in the undegraded matrix and β_A is a dimensionless constant; cf. [4].

3. Conclusions

A new mathematical model for describing drug release from insolluble collagen matrices undergoing swelling and enzymatic degradation was established. The model consists on four partial differential equations and two ordinary differential equations in a variable domain. A very challenging multi-dimensional free boundary problem arises. Simplification of the model were previuos considered, implemented and tested (see [8, 6, 9]). This was done in order to identify and correctly mathematicaly describe the different process occuring simultaneously. The very good corellation between the experiments and numerical simulations motivated us to consider this general model. The implementation of the equations in a finite element code is our next step.

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