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On a dissolution–diffusion model. Existence, uniqueness, regularity and simulations

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ABSTRACT

We perform a mathematical analysis of a model for drug dissolution–diffusion in non erodible nor swellable devices. We deduce a model and obtain a coupled nonlinear system which contains a parabolic equation for the dissolved drug and an ordinary differential equation for the solid drug, which is assumed to be distributed in the whole domain into microspheres which can differ in size. We analyze existence, uniqueness, and regularity properties of the system. Existence is proved using Schauder fixed point theorem. Lack of uniqueness is shown when the initial concentration of dissolved drug is higher than the saturation density in a region, and uniqueness is obtained in the non-saturated case. A square root function appears in the equation for the solid drug, and is responsible for the lack of uniqueness in the oversaturated case. The regularity results are sufficient for the optimal a priori error estimates of a finite element discretization of the system, which is presented and analyzed here. Simulations illustrating some features of the solutions and a good agreement with laboratory experiments are presented. Finally, we obtain error estimates for the finite element method used to compute the simulations.

1. Introduction

Numerous mathematical approaches have been proposed to give an adequate theoretical background to the modeling of drug release from polymeric devices [1,2]. The interest in this kind of systems has increased in the medical and pharmaceutical industry, because controlled drug-release systems allow for predictable release kinetics, small fluctuations of plasma drug level, diminishing the amount of toxic secondary effects, among other advantages [3,4]. A precise application is a progesterone-releasing intravaginal device called CIDR (Controlled Internal Drug Release, InterAg Manufacturing, New Zealand) depicted in Fig. 1. This is an intravaginal progesterone insert used in the beef cattle, dairy cattle, goat and sheep industries, to release the progesterone at a controlled rate into the bloodstream. In all species, CIDRs are used for the synchronization of estrus, which can be highly beneficial in large herds because groups of cows and heifers can be bred at the same time in a narrow window, achieving a higher pregnancy rate and precise calving dates [5,6].

We focus here on a model based on a diffusion equation including a continuous dissolution source described by the Noyes–Whitney equation; other models are based on a moving dissolution front separating a region of coexisting solid and dissolved drug from a region of completely dissolved drug; see [7,8] for a detailed description of other models.

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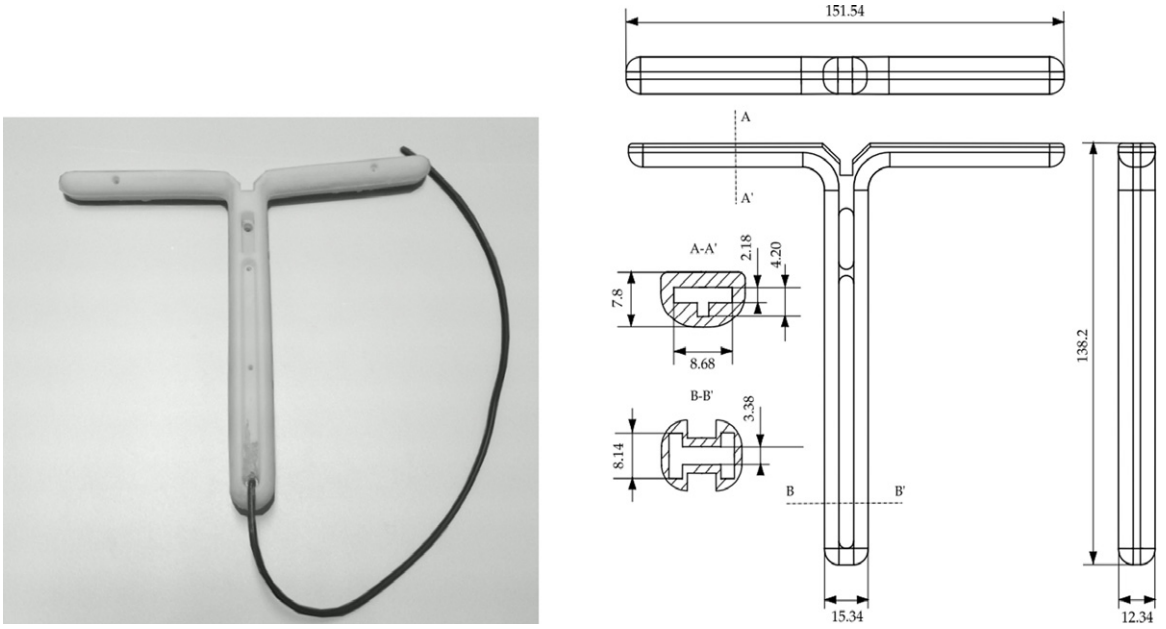

Fig. 1. CIDR device (InterAg Manufacturing, New Zealand). Photograph (left) and scheme (right). The inner structure can be observed through transversal cuts denoted by A–A′ and B–B′. Lengths are measured in millimeters.

Up to now, all mathematical studies have consisted in finding exact solutions for simple geometries using Fourier analysis, or simplified quasi-stationary assumptions, such as fast or slow dissolution rates relative to the diffusion of the already dissolved drug; which are not realistic in many situations (see [9] and references therein). The goal of this article is to study qualitative as well as quantitative properties of a dissolution–diffusion problem modeling the kinetics of a drug inside a polymeric device, avoiding the assumption of fast or slow dissolution rate relative to the diffusion. We want to avoid this kind of assumption to have a model with a wider range of applicability, since there is a large variety of polymers and drugs, which are combined to design drug-releasing devices [4].

We first prove existence of solutions, and study uniqueness and regularity properties. Secondly, we propose and analyze an algorithm for the numerical approximation of the solutions, where the regularity estimates are instrumental for obtaining optimal a priori error estimates. The numerical approximations allow us to visualize the behavior of the solutions and compute some measurable quantities with a striking agreement to laboratory experiments performed on CIDR devices.

The rest of the article is organized as follows. In Section 2 we deduce the mathematical model and prove existence of solutions in Section 3. Uniqueness of solutions is discussed in Section 4 where uniqueness is proved under the assumption that the initial concentration of dissolved drug is less than or equal to the maximum solubility, and the existence of multiple solutions is proved in a situation where the initial concentration of dissolved drug is above saturation. In Section 5 regularity estimates are obtained for both state variables, concentration of dissolved drug C and area of solid particles per unit volume a. In Section 6 we propose a finite element discretization and show some numerical results, which illustrate on the regularity of the solutions and the good agreement with laboratory experiments. Finally, in Section 7 we prove optimal a priori estimates for the proposed time–space discretization. We end this article with a concluding section summarizing our contributions and discussing potential future work.

2. Mathematical model and weak formulation

We start this section by briefly deducing a model for drug dissolution–diffusion in a non-erodible polymeric device. We consider a model for one drug, which can be either in a solid or in a dissolved state. We assume that the solid drug is distributed in particles of equal density, dispersed throughout the whole device, which can differ in mass and volume, but keep a spherical shape when dissolved [7]. We also assume that these non-dissolved particles are so small that they do not affect the diffusion of the dissolved drug, which thus evolves by diffusion with constant coefficient.

Under these assumptions we can state the mathematical model on a domain $\Omega \subset \mathbb{R}^3$, occupied by the polymeric device. If C denotes the concentration of dissolved drug, following the same steps used to obtain the diffusion equation with Fick's law we arrive at the following equation:

$$\frac{\partial C}{\partial t} - D\Delta C = -\frac{\partial m}{\partial t}, \quad x \in \Omega,\ t > 0, \tag{2.1}$$

where D is the drug diffusion coefficient and m is the mass of solid drug per unit volume, so that $-\frac{\partial m}{\partial t}$ is the mass of solid drug being dissolved per unit volume per unit time.