MODELS OF RELEASE OF ACTIVE COMPOUNDS FROM NANOSTRUCTURED MULTI-LAYERED MATERIALS

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Abstract

Controlled drug release is the transport of an active compound of biologically active agents with a defined time-concentration function. The release of these active compounds from materials is currently achieved by numerical models, based on simple kinetics of the first order, that are used to analyze experimental processes.

In this contribution, we propose a model that enables us to design complex, multi-layered material and define the desired time-concentration function for the release. This approach enables us to tailor the material in such a way that each layer has an individual concentration of the active compound. The result of programming work in models provides instructions for the design of the materials, which are specifically suited to certain situations. The model corresponds to real material structures from nanostructured electrospun material, in which the layers are pasted together with continuous hydrogel layers (for example, collagen).

The final version of the model will enable us to design the patches in the medicine where the release of antibiotics, healing or nutritional compounds will be programmed according to a certain time-release protocol. It is assumed that it will be possible to synchronize the controlled release of two or more compounds, each with different time protocols.

Keywords: Release, layered material, model, medical, electrospun

1. INTRODUCTION

A means of achieving the controlled release of active compounds from polymers and gels has been presented in the literature in recent years and is a widely discussed topic in the field of medicine. The controlled release from various materials is also a suitable method of achieving the fine dosage of compounds to the reaction system, permitting the slow addition of small doses of the compounds to the system. The main strategy in the literature is to find the composition with the optimal physical and chemical structure; this is then optimized to achieve the desired release. The results involve relatively complex physico-chemical systems that control the released amount. The release by such systems is usually described by relatively simple computer models [1].

This article presents the opposite approach; that is, we describe a relatively simple physical and chemical system that is a combination of the diffusion sorption and desorption. We believe that the release behavior of such a system can be designed and controlled with the aid of specific software.

The main aim of this study is to propose a computer program through which a user will define the time profile of the release (that is, how the compound should be released within a certain time-limited interval). The result of the model will be the appropriate design of a substrate with a certain gradient of composition and with the desired release function. A substrate will therefore be proposed that contains a certain gradient of concentration in some compounds (or some other function of concentration). A user will produce a substrate with an initial surface composition, following which a model will be produced for the material, including a programmable release.

Various up-to-date mechanisms of controlled release appear in the literature. The most frequent mechanism is controlled diffusion [2,3]. The next-most frequent mechanism is a release accompanied by the degradation of the substrate material, mostly biodegradable and bioresorbable materials [1,4]. The third mechanism is the release from hydrogel networks, which process involves two steps. The first step is the release of the compound from the network, followed by the desorption of a low molecular compound that is adsorbed on the macromolecules. The second step is slower than the first [5]; it is a gradual release that is intended to be stable for a certain period of time.

There is a special aspect to the release from electrospun material [6,7]: the material is porous and the release from it is relatively slower and more gradual than from solid material.

Our model combines the diffusion, sorption–desorption, and capillary forces. The diffusion is described by Fick's laws: the first law relates to the flux through two arbitrary points in the material, while the second law states that it is possible to derive a relationship between the concentration gradient and changes to the concentration over time. The sorption and desorption were performed by the first law of kinetics, and the capillarity serves to control the flux in one direction. A similar technique is thin-layer chromatography, which has both a mobile and stationary phase.

2. MODELS AND METHODS

The model is connected to a specific type of layered material. The basic patches are geometrically very simple, forming a layer with a uniform concentration of a low molecular compound. The patch can be produced as a single homogenous block of material (**Figure 1.I**). Our new design has a vertical concentration gradient (**Figure 1.II**). The material can be modified by adding thin layers of varying concentrations. The final result will be a patch with a custom concentration profile and a greater amount of released compound (**Figure 1.III**).

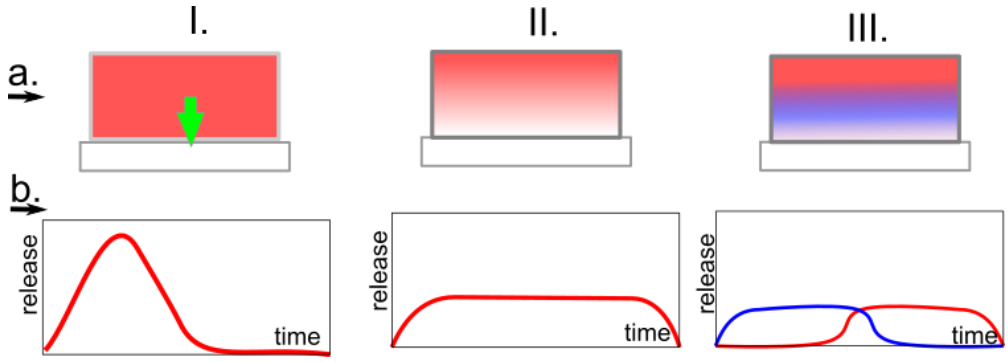

Figure 1 Design of layered materials with I. a homogenous concentration in the substrate; II. a gradient of concentration (single compound); III. a gradient of concentration (more compounds). III.a. design of material; III.b. presumed release curve. Arrow =direction of release.

This article presents the first phase of the model. In the final version of the model, the input is a user-defined time-concentration profile (**Figure 1: II.b.–III.b.**). The output of the model is the concentration function in the substrate (**Figure 1b**), which will be designed in such a way that it can achieve the desired release function.

The input parameter of the model described in this paper is the concentration of layers, and the result is the cumulative time-release function.

The model's mathematical background is analogous to the description of the thin-layer chromatography. The model defines the low molecular compound in both the stationary and mobile phases. Each phase has its own concentration profile. The stationary phase represents the active compound adsorbed on the surface of the substrate. The mobile phase is where the compound is actually desorbed from the substrate and can be transferred by diffusion or capillarity.

2.1. General model

Let us consider a small segment of the volume in the substrate.

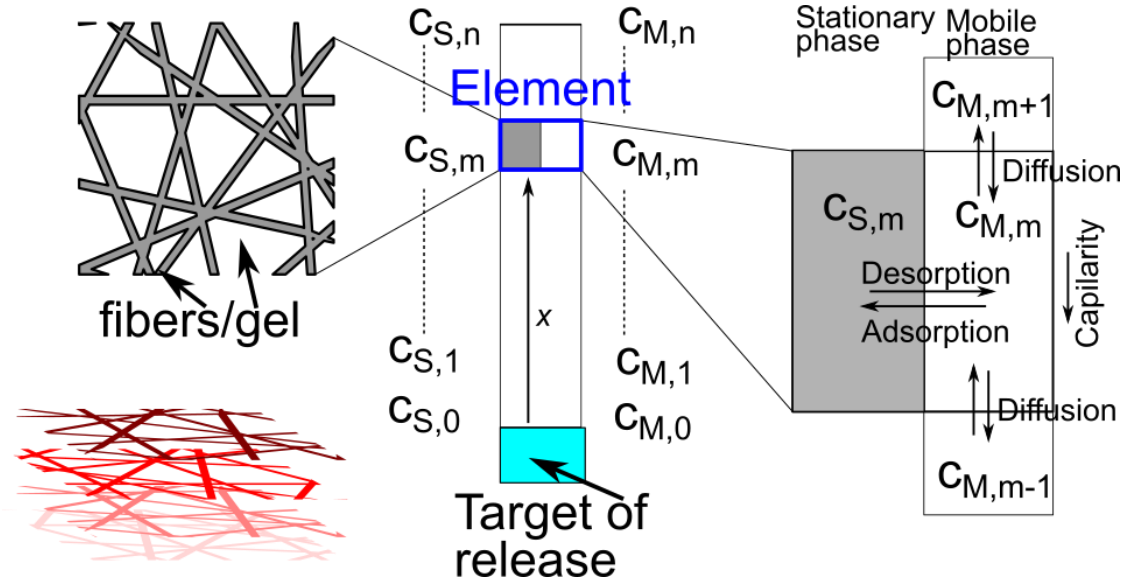

Figure 2 Model of the layered materials: left picture—hydrogel structure; middle picture—model schema of entire multilayer material; right picture—transfer of concentration between volume elements. C_S = stationary phase (concentration of compound adsorbed on surface); C_M = mobile phase (concentration of compound in liquid); x = distance from the release target.

The segment of volume is a certain distance x from the release surface. The concentration is added by desorption from the stationary phase or by transport from neighboring regions (i.e., diffusion vs. capillarity).

1) The desorption and adsorption are solved as kinetics of the first order:

$$-\frac{dC_S}{dt} = \frac{dC_M}{dt} = kC_S. \quad (1)$$

These first-order kinetics mean that the rate of desorption is directly proportional to the concentration of adsorbed compound in the solid material.

2) The capillarity is introduced using the simplest approximation. The front of the solvent during the capillary elevation moves according to the square root of time:

$$x_{fr} = AS\sqrt{t}, \quad (2)$$

where S is the sorptivity coefficient, which depends on the porous structure.

2.2. Model of diffusion

We propose the first simplified version of the complex model shown in **Figure 2**. This equation employs the diffusion equation according to Fick's second law. This equation describes the relationship between differential of the concentration in the time interval and the concentration gradient:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \tag{3}$$

where c = concentration, t = time and x = distance from the release target. The equation describes the flow of the compound between two neighboring segments. All concentrations in the profile are coded using an array of concentrations:

$$\mathrm{c} = \{c_1, c_2, \ldots c_n\} \tag{4}$$

The system of n differential equations describes the flow inside the sample.

Generally speaking, diffusion is a common computing task, and the solution has been described many times. Usually, the task is solved as a diffusion in an extremely thick layer. Mathematically, the boundary approaches ∞, and the concentration on the boundary is 0.

In the case of this material, however, we define specific boundary conditions. The released compound is usually consumed in the release target. For all time intervals, the compound must be removed from the boundary of the model and added to the release profile:

$$\forall t\colon c_n = actual; \rightarrow c_n = 0;\ c_r = c_r + actual, \tag{5}$$

where c_r is the cumulative released concentration. The actual removed amount is added to the time profile of the release. In this case, the actual amount of released substance must be subtracted from the substrate.

The consistency of the solution is verified by the condition of mass conservation. The mass of the low molecular weight compound in the substrate and the released fraction must be conserved as a constant during the simulation in each time interval:

$$c_r + \sum_{i=1}^{n} c_i = const. \tag{6}$$

The basic profile occurs when the compound is uniformly distributed in the sample.

The result of the simulation must be in accordance with Fick's first law:

$$J = -D\frac{\partial c}{\partial x}, \tag{7}$$

where $\frac{\partial c}{\partial x}$ is a gradient of concentration. The solution is based on the standard ordinary differential equation (ODE) solvers seen in the MATLAB environment.

3. RESULTS AND DISCUSSIONS

The first modification of the model serves to verify the standard release. The model describes the sample in which the concentration is equally distributed in the substrate, as it is the most frequently seen case in experiments. Here, the release function is an exponential growth function.

The 1D-diffusion problem was solved numerically. The adjustable parameters are the initial concentration of the active compound in the substrate, the diffusion coefficient, and the thickness of the layer. The function of release was modelled from 0.350 mm multi-layer material divided into 350 layers, each 1 μm. The time step was 0.001s, and the diffusion coefficient was 10^{-10} m^2s^{-1}.

The first standard concentration profile is presented in **Figure 3**. Here, the cumulative function of the release profile shows an exponential growth.

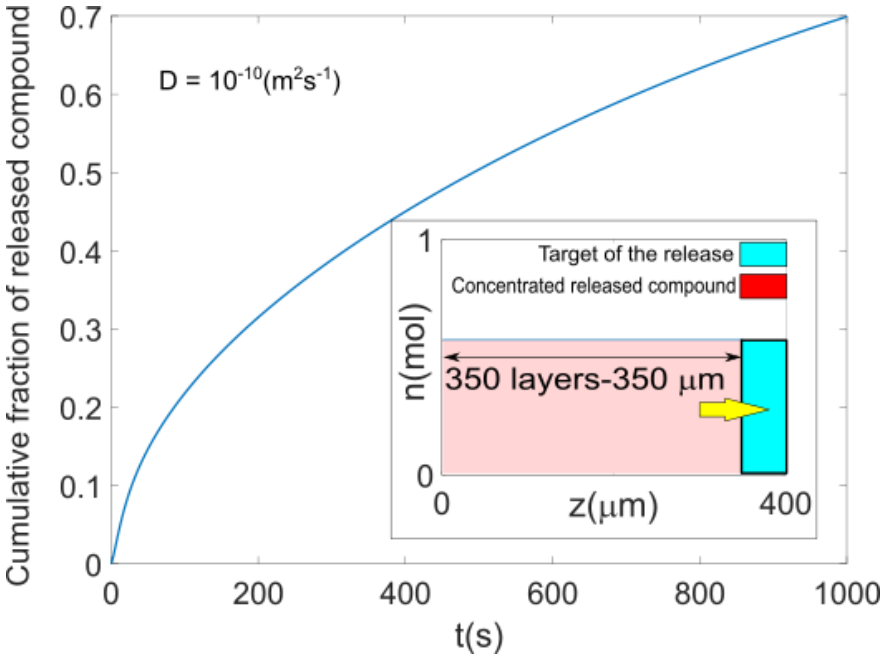

Figure 3 Model's control settings: thin-layer thickness 350 μm

The second version describes a situation in which a more complex release was expected. The total concentration of the compounds is equal to the sample in **Figure 3**. The active compounds are concentrated in two layers, and the concentration profile is defined in the z-direction. As in **Figure 3**, the diffusion coefficient, thickness of the layers, and number of layers are shown.

The results are presented in **Figure 4**. There is an observed bimodal distribution, in which the material runs in two waves. The first release is relatively quick, while the second is slow and gradual.

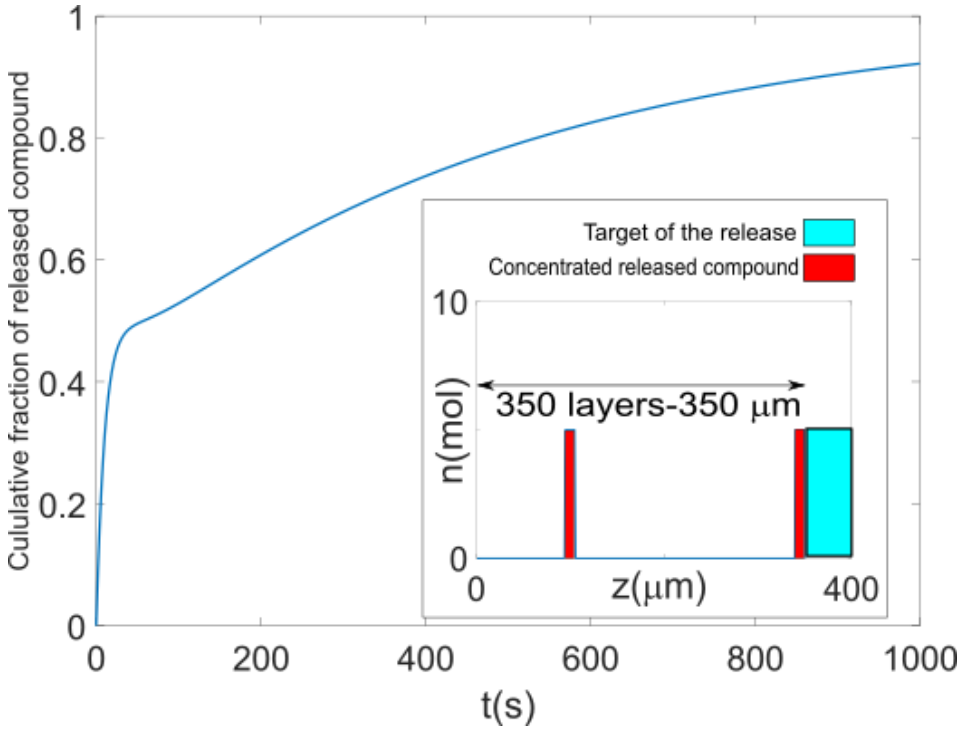

Figure 4 Release of the material's active compound, showing two concentrated layers.

The aim of this article has been to confirm the function of the model shown herein. It has been found that, when the model describes the standard release presented in the literature, it outputs the standard cumulative release function. Where a concentration profile is introduced, the more complex release function is observed. It seems that, when mathematical optimization is applied, it is possible to tailor a user-defined release function through the definition of layer concentrations. However, it seems that it is not possible to program any arbitrary release function, and the release function will be always limited by diffusion.

4. CONCLUSION

The paper examines the model-controlled release of active compounds from a complex material. The aim of the model is to effectively predict the release from layered materials, in which each layer can have a different concentration of compound. The model was tested using a standard, uniform sample concentration, which is the most often-used experimental configuration. The release function showed exponential growth, which is similar to the experiments. The second version of the model involved the definition of concentrated layers and the complex release. It was also verified that the model is able to produce both standard and complex release functions.

The next step for our model is to construct layered material from nanostructured layers, with a custom concentration profile for each layer. The custom concentration profile will produce programmable release functions with waves of release at desired times.

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