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Release of the Model Substance Through the Polymer Membrane into the Biological Environment

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Abstract

Modeling the transport or release of a substance from a gel system into a biological environment using COMSOL Multiphysics software plays an important role in understanding the processes required for proper design and optimization of an appropriate model. This model should accurately simulate transport and release of the substances from the gel three-dimensional structure in a certain biological environment (organism, soil). In this work, a two-dimensional axisymmetric model with defined materials is developed and evaluated, for which different values of porosity and diffusion coefficient are included. The diffusion coefficient is the most interesting variable in the field of transport properties, as it is influenced by the size of the molecules and the characteristics of the polymer network. By changing this variable, the course of release of the model substance can be influenced, which makes it possible to change the properties of the designed hydrogel systems according to the required applications. *Transport of Diluted Species* physics, in which the *Porous Medium* condition is included, and *Laminar Flow* physics are also present in the model, although the flow rate is zero, the gravity condition is introduced. The obtained graphs of the dependence of concentration on time and the model describe the course of transport and release of the substance through the polymer membrane into the biological environment. The designed model should correspond to a real sample of fertilizer or gel sphere containing a medicinal or bioactive substance (in this case filled with a model dye) to determine the release properties using appropriate experimental methods.

Keywords: Release, polymer membrane, transport phenomena, COMSOL Multiphysics.

1. Introduction

An important step in the development of new systems for the delivery of certain substances to the target site is such that the administered substance does not cause adverse effects. This method has several advantages compared to conventional drug administration, including reduced toxic side effects, reduced cost, reduced dose, and most importantly improved efficacy. Targeted delivery can be achieved through hydrogel systems, nanoparticles, carbon nanotubes, micelles, liposomes and microfluidics. Hydrogels are an attractive option as they enable controlled drug release. The response of hydrogels to stimuli such as pH, temperature, ultrasound, magnetic field and light can be used to control drug release [1], [2].

Currently, there is great interest in the study of gels, especially their transport and release properties. Hydrogels have numerous definitions, but generally speaking, they are hydrophilic systems with a three-dimensional structure that tend to swell and retain large amounts of water and physiological fluids within their structure, ultimately leading to increased biodegradability and biocompatibility. These properties give them diversity and versatility in various fields of human activity, making them ideal candidates for various applications such as targeted drug delivery, agriculture, etc.[3].

The choice of materials and the production of the mesh control the rate and manner of release of substances from the hydrogel matrices. The ideal material needs to be biocompatible, biodegradable and easy to apply, highly stable and in certain cases to have the ability to protect against infections. Such a role can be fulfilled by biopolymers, or synthetic polymers. Synthetic polymers are more chemically resistant than biopolymers because their mechanical strength results in a slow rate of degradation, thus providing durability. However, the disadvantage of synthetic polymers is their poor cellular interaction, which is why they are mostly surface-treated or combined with biopolymers. Biopolymers, or natural polymers, come from renewable sources widely distributed in nature, i.e. algae, plants, etc. In the field of transport properties, the most relevant variable is the diffusion coefficient, which is influenced by the size of the molecules and the characteristics of the polymer network. The crosslinking density of the hydrogel affects the diffusivity to a large extent. Understanding transport and physical properties are particularly important in modeling the release of molecules [4], [5], [6].

Understanding the basic parameters for controlling the release of substances through the polymer membrane is the first step to accurately simulate and predict the entire release profile. Controlled diffusion is the most common mechanism used, with Fick's law of diffusion with constant or variable diffusion coefficients also commonly used in modeling [7], [8].

This work is focused on the modeling of transport, or release of a model substance through a polymer membrane into the biological environment using the COMSOL Multiphysics 6.1 computing platform. An overview of the properties of the prepared two-dimensional axisymmetric model with specified material parameters is discussed here, including the influence of changes in the values of the diffusion coefficient and porosity of the membrane. The obtained graphs of the dependence of concentration on time serve as a supplement to the discussion.

2. Experimental

2.1 Model Formulation

Biological environment exist, into where we put a substance that immediately starts to release, or act. In certain cases, there could be a need for more frequent use of the substance, which would cause adverse effects in the environment. Therefore, there is a thin polymer membrane that achieves controlled release, which is the delivery of a substance to a certain place, which will act for a defined period of time [9].

Figure 1 shows the design of the model, representing a sphere containing a model substance with a concentration of 0.5 M and coated with a thin layer of polymer, enabling controlled release into the biological environment. The resulting ball model should correspond to a real sample of polymer-coated fertilizer, or a gel ball filled with medicine, or bioactive substance. This model could then be used for modeling in future studies or to verify the accuracy of experiments dealing with the determination of transport or release properties.

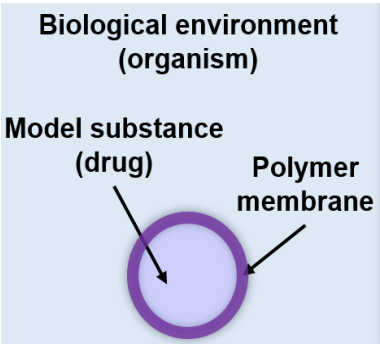

Figure 1. Model design

2.2 Use of software COMSOL Multiphysics 6.1

2.2.1 Geometry

In the COMSOL Multiphysics software, the geometry of the model (see Figure 2) with the unit cm was built according to the proposed image. The geometry includes 2 semicircles, representing the model substance (radius 1 cm) and the membrane (radius 1.1 cm). Base position of both semicircles is at the center. The biological environment is represented by 1 rectangle, the width of which is 5 cm, and the height is 6 cm. Base's position of rectangle at corner.

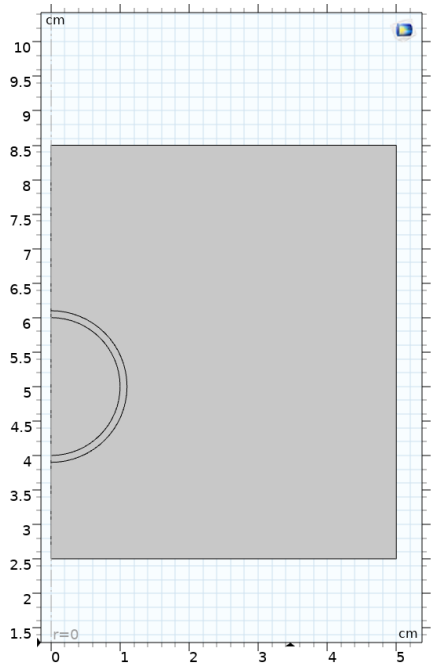

Figure 2. Model geometry

2.2.2 Materials

Materials are set in the model. Water, which is available by the material library, was chosen for the definition of the biological environment. Blank material was used to set the membrane. Materials parameters are listed in Table 1

Table 1. Parameters of the materials used in the model setting

Material 1 – H2O (water) [liquid]	
Diffusion coefficient [m^2/s]	$2.296 \cdot 10^{-9}$
Material 2 – Membrane	
Porosity [-]	0.15
	0.5
Diffusion coefficient [m^2/s]	$0.28 \cdot 10^{-9}$
	$0.28 \cdot 10^{-10}$
	$0.28 \cdot 10^{-11}$

2.2.3 Mesh

Figure 3 shows the mesh setup. Sequence type of mesh is physics-controlled with element size *Normal*.

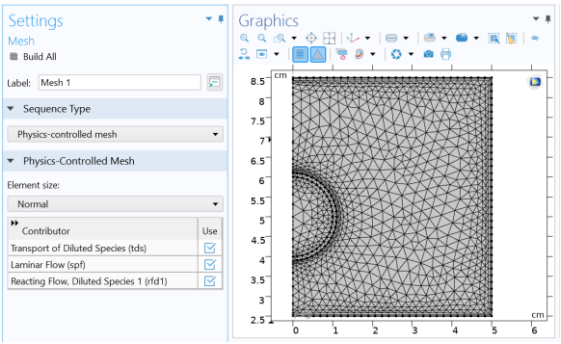

Figure 3. Mesh settings

2.2.4 Transport of Diluted Species in Porous Media

Governing Equations

The transport of diluted species in a porous medium is described by the diffusion equation, which represents the change in concentration within the closed system due to diffusion only:

$$\frac{\partial c}{\partial t} = \nabla \cdot \left(-D \nabla c\right) \qquad (1)$$

, where t is time, c is the concentration of the species, D is the diffusion coefficient, which represents how quickly the species diffuses through the porous medium.

Boundary Conditions

A *No Flux* boundary condition was used to properly set up the model for the simulations.

2.2.5 Laminar Flow

Governing Equations

In this physics, zero velocity and gravity are present, due to which the Navier-Stokes equations for fluid flow are not defined. Instead, a gravity term is considered, which affects the transport of substances through water. The resulting equation is as follows:

$$-\nabla \cdot \left(\rho g\right) = \nabla p \qquad (2)$$

, where $-\nabla \cdot (\rho g)$ represents the divergence of the gravitational force and corresponds to the pressure fluctuation in the fluid caused by the gravitational field, p is the pressure gradient and describes how the pressure changes in space. In our case, the pressure gradient is driven by the gravitational force.

Boundary Conditions

The boundary conditions that were used for the correct implementation of the simulation were as follows: *Wall*, *Pressure Point Constraint* and *Gravity*.

3. Results and Discussion

The polymer membrane-coated sphere model and concentration-time graphs, as obtained results, correspond to a temperature of 25 °C, which was set for all physics present in this study.

Figure 4 and Figure 5 shows the resulting model for time 0 and 144 hours. The model provides information about the concentration in a certain location of the investigated system. We can determine the approximate concentration of the released substance at a specific distance from the system interface. However, it is not possible to determine the total concentration of the released substance in aqueous or biological environment.

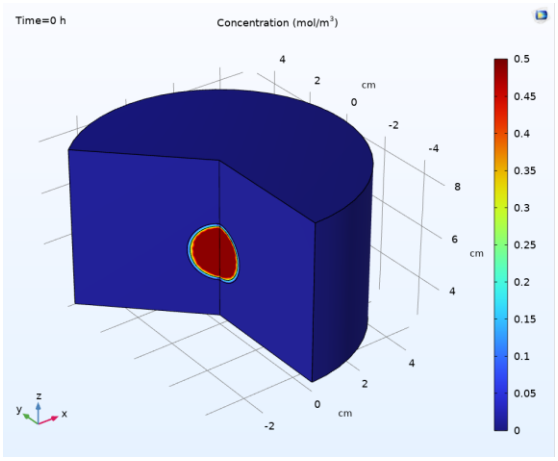

Figure 4. The resulting model for time 0 h

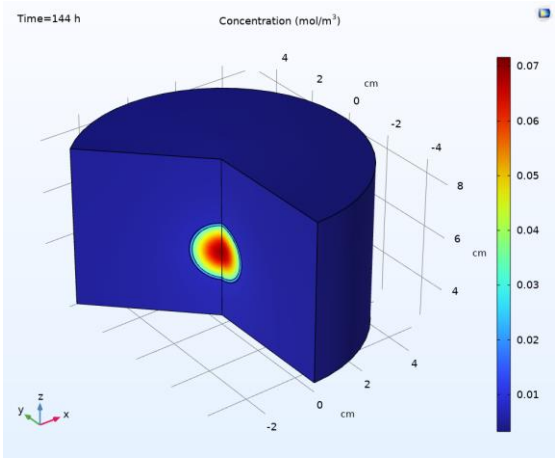

Figure 5. The resulting model for time 114 h

Surface Average (*Derived Values*) was used to evaluate the average concentration of the model substance released into the environment. The output are tables for individual "samples". These tables were used to create graphical representations of the change in concentration of the released model substance over time using *Line Graph* (*1D Plot Group*). Graphical representations of the simulation of dependence of concentration on time for samples with different values of porosity (0.15 and 0. 5) and diffusion coefficient ($0.28 \cdot 10^{-9}$ m^2/s (blue), $0.28 \cdot 10^{-10}$ m^2/s (green), $0.28 \cdot 10^{-11}$ m^2/s (red)), which show the course of the release of the model substance through the polymer membrane into the environment and are shown in Figure 6 and Figure 7. Comparing both graphs, the same course is evident, even though they differ in concentration values. Samples with a diffusion coefficient of

$0.28 \cdot 10^{-9}$ m^2/s have a faster course, than models with diffusion coefficients of $0.28 \cdot 10^{-10}$ m^2/s and $0.28 \cdot 10^{-11}$ m^2/s, where the release rate of the model substance through the polymer membrane is significantly reduced. However, in all cases, a decrease in the release rate is noticeable until it becomes almost constant. Considering that, by changing certain parameters of the polymer membrane, the properties of the systems can be adjusted according to the desired application.

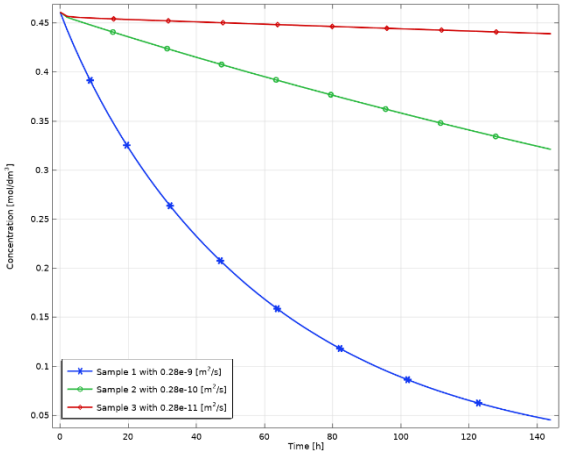

Figure 6. Simulation of dependence of concentration [M] on time for samples with the 0.15 porosity and different diffusion coefficients

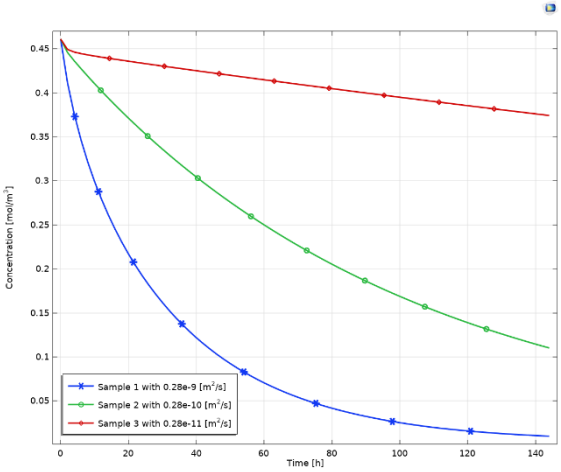

Figure 7. Simulation of dependence of concentration [M] on time for samples with the 0.5 porosity and different diffusion coefficients

3.1 Model Example

An example of such model can be a sodium alginate gel ball filled with methylene blue (MB) as a model dye. The gel system was prepared by dropping sodium alginate solution with MB into calcium chloride solution. By combining alginate with divalent cations (in this case Ca^{2+}), gel networks are formed [10]. The resulting gel beads had a smooth surface, while the sol solution is present inside. (see Figure 8).

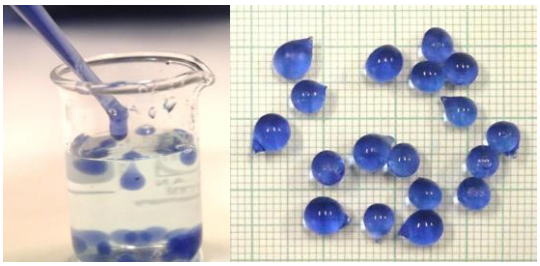

Figure 8. Gel beads based on sodium alginate filled with methylene blue

Figure 9 shows beads after 1 and 4 days in water. The passage of the dye through the polymer membrane from its structure to the surrounding is evident, which can be seen by the beads discoloration and subsequent disintegration.

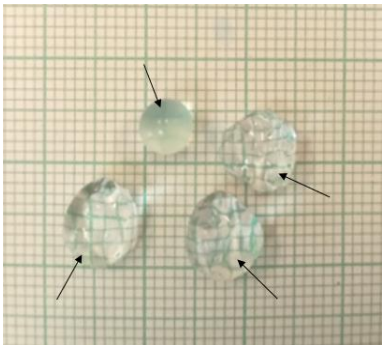

Figure 9. Gel beads *based on sodium alginate filled with methylene blue after 1 and 5 days in water*

However, care must be taken in the selection of materials to avoid electrostatic interaction between the structure of the polymer membrane and the substance. This leads to a slower release of the substance, as a certain part of the substance binds to the structure of the systems and is not released.

4. Conclusions

Using the COMSOL Multiphysics software, we were able to quantitatively evaluate the release process of the model substance through the polymer membrane into the biological environment and investigate the influence of various factors, including changes in the diffusion coefficient values and the porosity of the polymer membrane. In the study devoted to the time dependence, all the data obtained indicate that by changing the diffusion coefficient or the porosity of the membrane, the course of the release of the model substance can be influenced. This makes it possible to change the transport or release properties of the hydrogel systems according to the desired application.

Modeling of transport profiles, or the release of substances through the polymer membrane structure remains a challenge in research areas, although different mechanisms are being revealed. These advances lead to more efficient work in laboratories during the design and optimization of systems according to the required applications. Given the challenges mentioned, the next steps are

to develop the model with the help of other physics from the library of physics and test the preparation and optimization of the system in the laboratory, and last but not least, its verification by appropriate experimental methods.

5. References

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