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DEVELOPMENT AND VALIDATION OF A NUMERICAL MODEL FOR CONTROLLED INTRAVAGINAL DRUG RELEASING DEVICES

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Abstract. Controlled Intravaginal Drug Releasing (CIDR) devices are often used in veterinary science to synchronize cattle estrus. Design process of such devices is strongly based on laboratory and field experimentation. In this scenario, model development is an attractive work since it reduces experimental research time and allows discard preliminary designs and material properties in an easy way. In this line, device re-engineering is an active field of work, looking for lower residual loads, better drug releasing control and lower costs.

Based on a novel mathematical model early proposed, a numerical model is developed using a Finite Volume discretization in order to give an effective tool in CIDR re-engineering and design. The model requires coupling between Partial Differential Equations and Ordinary Differential Equations with non-linear sources which represents a big challenge. Moreover, proper discretization leads to highly refined unstructured meshes being necessary the use of parallel solvers. Taking into account this requirements, implementation via OpenFOAM® libraries is carried out and a parallel solver is obtained. Mathematical model is presented with its physical, mathematical and numerical assumptions. On the other hand software implementation details are also discussed. Finally, numerical and experimental results are compared showing good agreement.

1 INTRODUCTION

Drug intervention programs to estrous synchronization in cattle are widely adopted by cattle producers to procure economic benefits of artificial insemination. Among the arsenal of current drugs and therapeutic approaches available to estrous synchronization programs, progesterone-releasing intravaginal devices based on silicone have proved to be a useful tool (Rathbone et al., 1997, 1998, 2001, 2002). One challenge to successful performance of bovine intravaginal inserts is to achieve synchronism between the hormone release-rate from the polymeric insert and the excretion rate in order to obtain sustained patterns of circulating blood progesterone above supraluteal concentrations ($> 1\,\mathrm{ng\,mL^{-1}}$) during the treatment (typically 7 days) (Rathbone et al., 2002; Turino et al., 2010). In current art practice to address this concern, solution-oriented approaches based on trial and error have only been applied due to the absence of rigorous mathematical models that explain mechanisms involves in drug delivery from nondegradable matrixes.

In literature, different mechanistic models varying in complexity, details and solution methodology are examined to describe the progesterone release from the coating of silicone rubber covering the T-shaped nylon spine of CIDRs. The simplest model comes from Higuchi's square-root time law equation, which offers simplicity, friendly numerical manipulation, and good capability of describing the effects of the initial progesterone load and exposed area of progesterone-releasing silicone devices (Higuchi, 1961; Rathbone et al., 1998; Mariano et al., 2010). The most complex model, includes a very detailed 3D architectural description of CIDRs, allowing analyze effects of the shape, size of the device, spatially non-uniform drug loadings and/or non-uniform size distribution of drug particles (Cabrera et al., 2006). Nevertheless this kind of mathematical formulation generally requires of numerical solutions in order to manage industrial geometries.

In this context, the objective of this work is to present the development and validation of a successful numerical model for diffusion/dissolution in CIDR devices, based on the mathematical description given by Cabrera *et.al.* It is developed using a Finite Volume discretization which usually leads to highly refined unstructured meshes being necessary the use of parallel solvers. The main objetive of this tool is device design and re-engineering.

2 EXPERIMENTAL

2.1 Materials

Progesterone (P4) (99.2%, Sigma-Aldrich, Argentina) was US Pharmacopeia grade. Ethanol (99%, Cicarelli, Argentina) and distilled water were used throughout the experiments. CIDR inserts (InterAg Manufacturing, New Zealand) of 1.9 g of P4 were used for In vitro release assays.

2.2 Methods

2.2.1 In vitro release assays

The In vitro release assessment method was developed according to guidelines for drug dissolution and release found in the US Pharmacopoeia. A Hanson Dissolution Testing Station (Hanson SR8-plus Dissolution Test Station, Hanson Research Corp) was used in our studies. Flasks filled with 1100 mL of release media (it was the minimum volume that maintained com-

plete submersion of the veterinary product) were maintained at $37\pm0.5\,^{\circ}\mathrm{C}$ and stirring speed was 100 rpm. CIDR was submerged in the release media by means of the paddle holder. Samples of 4 mL were collected at selected time point. The P4 content was analyzed by UV at 244 nm.

Short times release assays To verify the correlation between apparent diffusion coefficient (D_{ap}) and percentage of ethanol in release medium assumed by the model (see below, point (vi)), assays were performed in three different compositions of ethanol 30, 40 and 60 v/v. Selected sample point were 5, 30, 60, 120, 180, 240, 300 and 360 min. D_{ap} was estimated by fitting the experimental data with Higuchi's equation.

7 days release assays The evaluation of the proposed model was carried out by comparing the theoretical results from numerical integration with experimental release data obtained at two levels of ethanol in the release medium (40 and 60 % v/v). Selected sample points were 0, 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, 96, 120, 144 and 168 hrs.

Scanning Electron Microscopy The morphological structure of intravaginal insert and drug diffusion/dissolution characteristics were examined using scanning electron microscopy (SEM). Devices were cut and analyzed when short and long time releasing tests were finished. Also untested CIDRs were photographed to analyze the initial drug distribution in the silicone matrix. All samples were bonded to a metal stub and sputter coated with gold under argon atmosphere (SPI SUPPLIES, 12157-AX) in two sections of 40 seg each one at 18 mA. SEM micrographs were then obtained using a JEOL JSM-35C with an acceleration voltage of 20 kV.

2.2.2 Mathematical Model describing progesterone release rate from CIDR

Mathematical model of simultaneous dissolution and diffusion controlled drug release from matrix systems was previously developed by our research group (Cabrera et al., 2006). It is assumed that the solid drug dissolves and diffuses out to the surrounding medium through the matrix. As the solid drug dissolves, the size of the particles associated to mass dissolution sources reduces with a position-dependent dissolution rate dynamics. After a certain time, the exhaustion of particles begins and progresses inward the matrix, source by source, until all the solid drug particles vanish. Thus, the diffusion/dissolution controlled system progressively advances to one governed by diffusion alone.

Model assumptions The underlying assumptions of the mathematical model are: (i) The drug diffusion process is described by the Fick's second law; (ii) The drug dissolution rate is described by the Noyes-Whitney equation; (iii) The solid drug is present as particle assembles on the cross-sectional area of the matrix; (iv) The solid drug particles of each assemble all have the same size, which reduces as the drug dissolution advances until complete exhaustion of the particles; (v) The solid particles are adopted to be spherical for simplicity, but any shape could be used; (vi) The apparent diffusivity coefficient of the drug in the matrix is assumed to be progesterone concentration independent but ethanol concentration dependent (Maitani et al., 1995); (vii) Equilibrium between the surface and the external medium is assumed at all times;

(viii) The mass transfer resistance in the external-side boundary layer is not negligible and the mass transfer coefficient is a constant; (ix) The matrix is non-swellable and non-erodible and (x) The system is isothermic.

Based on the above assumptions, the release process is mathematically described by a set of unsteady-state mass balance equations (Equations 1-2).

$$\frac{\partial C\left(x,y,z,t\right)}{\partial t} - D_{ap}\nabla^2 C\left(x,y,z,t\right) = \frac{N\,K_d\,a\left(x,y,z,t\right)}{V_{\text{tot}}}\left[C_s - C\left(x,y,z,t\right)\right] \tag{1}$$

$$\frac{\partial a\left(x,y,z,t\right)}{\partial t} = \frac{-2}{3\,m_0}\,K_d\,\sqrt{a_0^3}\,\sqrt{a\left(x,y,z,t\right)}\,\left[C_s - C\left(x,y,z,t\right)\right] \tag{2}$$

Boundary conditions were set such that concentration and area were zero at exterior walls. Device has an internal nylon spine; in such internal silicone walls zero flux boundary condition was set for both crystals area and concentration. Initial conditions and model constants were set as is indicated in Table 1.

Table 1: Initial conditions and model constants

$C\left(x,y,z,0\right)$	$0.513\,\frac{\text{kg}}{\text{m}^3}$
$a\left(x,y,z,0\right)$	$4.5239\times10^{-10}\text{m}^2.$
D_{ap-40}	$1.670\times10^{-10}\,\frac{\text{m}^2}{\text{sec}}$
D_{ap-60}	$2.701\times10^{-10}\,\frac{\text{m}^2}{\text{sec}}$
N	$4.4791813886256\times10^{8}$
K_d	$6.59\times10^{-6}\,\frac{\text{m}}{\text{sec}}$
C_s	$0.513\,\frac{\text{kg}}{\text{m}^3}$
a_0	$4.5239\times10^{-10}\,\text{m}^2$
m_0	$1.0550\times10^{-12}\,\text{kg}$
V_{tot}	$4.76875\times10^{-6}\,\text{m}^3$

3 RESULTS

3.1 D_{ap} determination

The assumption number vi) for model implementation was experimentally corroborated. The D_{ap} points were drawn versus the ethanol concentration and a linear regression was conducted. The correlation coefficient R^2 was 0.9997. This is in well agreement with Maitani *et. al.* (Maitani et al., 1995).

3.2 Implementation and numerical results

Implementation was carried out by means of an in-house code relying in the Finite Volume Method (FVM) using OpenFOAM® FVM libraries (Weller et al., 1998). Model non-linearities were circunvented by a segregated solver which integrates both equations in sequence.

Model was run from initial conditions to a final time of seven days, with a timestep of 30 sec using Backward Euler scheme. Systems were solved with PCG+DIC in case of C and with

a direct solver in case of a due it has a diagonal matrix system. Geometry was meshed with 3,816,762 tetrahedron (preliminar tests were carried out in a mesh of 1,031,995 elements) with refinement towards the exterior wall and taking into account the symmetry along two orthogonal planes (See Figures 1-2).

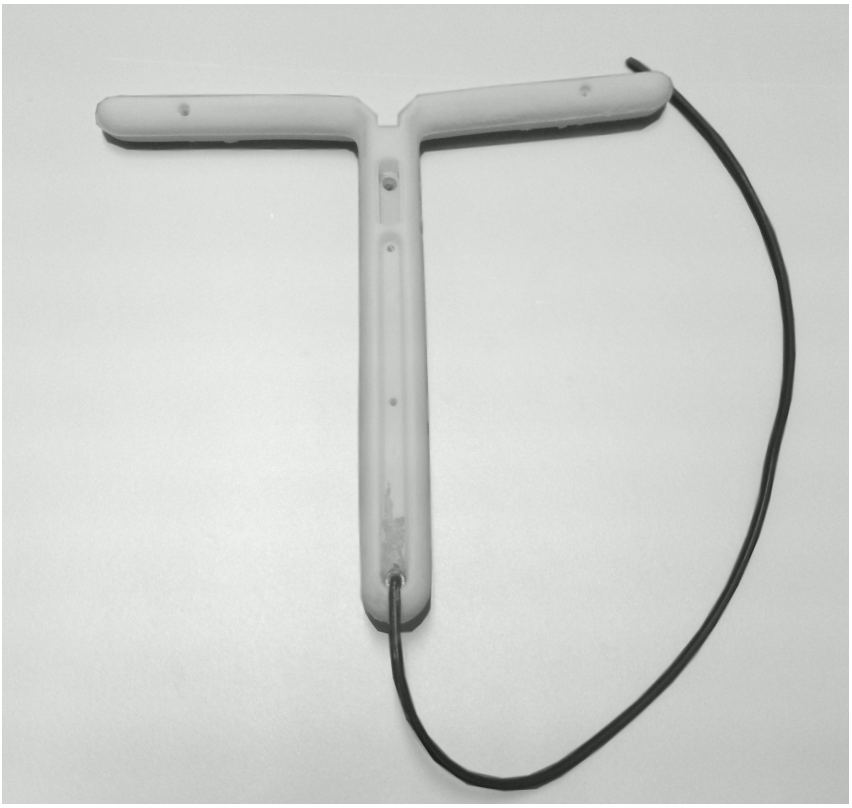


Figure 1: Photograph of a T-shaped CIDR

In order to analyze the evolution of drug releasing along time progesterone load, L, was calculated for each saved state. Drug is considered to be only in crystals without taking into account the load in the polymer. So that, summing in all mesh (See Equation 3)

$$L(t) = \sum_i \frac{\frac{4}{3}\pi \left(\sqrt{\frac{a(x,y,z,t)}{4}}\,\pi\right)^3 \cdot \rho_p \cdot V_i}{V_{\text{tot}}\, N} \tag{3}$$

where V_i is the volume of i-eth cell, V_{tot} is the total volume of CIDR and $\rho_p = 1166 \frac{\text{kg}}{\text{m}^3}$ the density of progesterone micro-spheres. Knowing the load for each time it is possible to obtain the values for drug releasing as $R(t) = L(0) - L(t)$. Curves for drug releasing in both analyzed ethanol concentrations are shown in Figures 3 and 4. Both figures show excellent agreement between experimental data and predicted results, so that numerical model is validated for such cases.

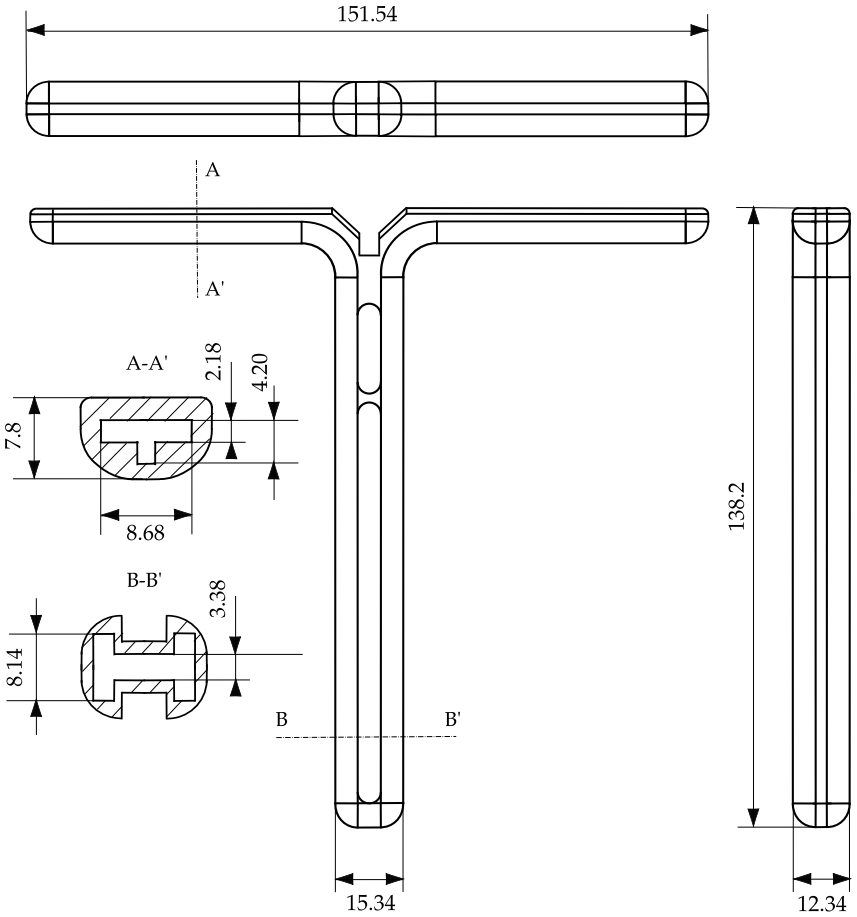


Figure 2: Geometry for CIDR device (dimensions in mm)

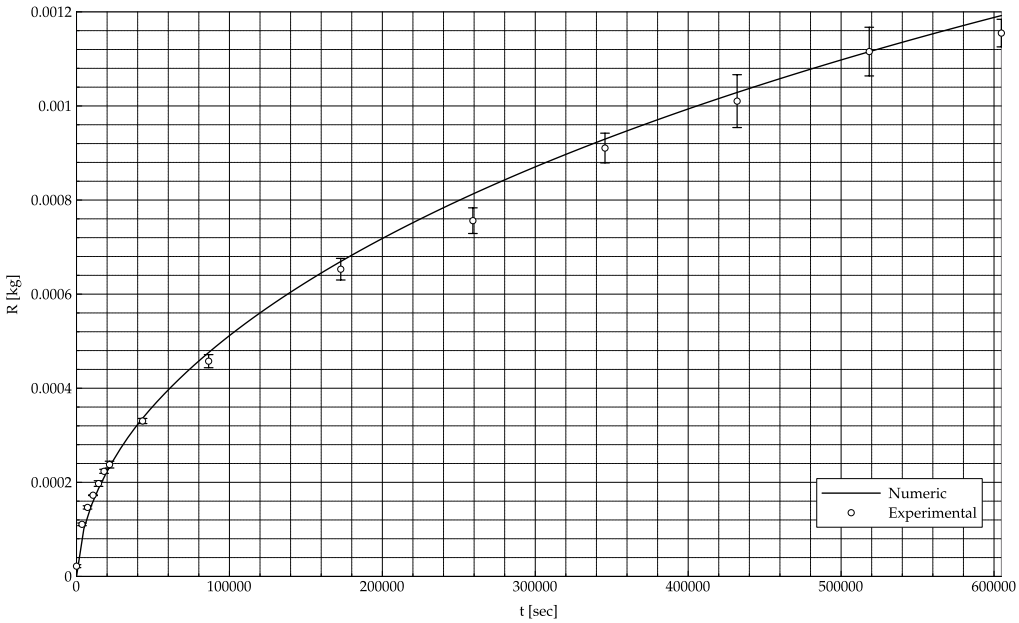


Figure 3: Drug releasing (R) along time for analyzed meshes (values accounts for the complete geometry, not a quarter) for 40% of ethanol in the release medium

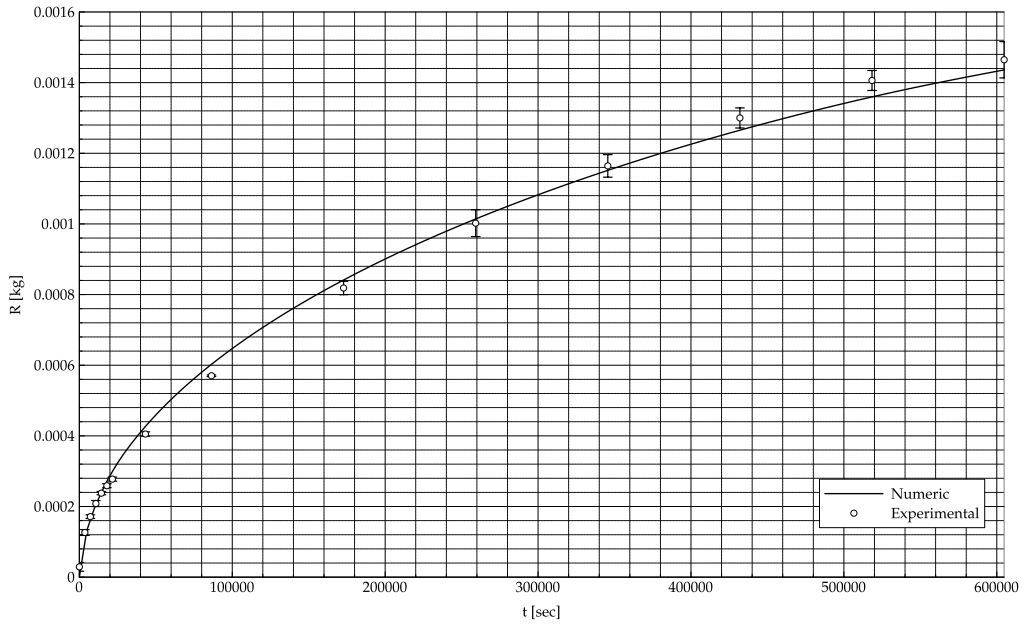


Figure 4: Drug releasing (R) along time for analyzed meshes (values accounts for the complete geometry, not a quarter) for 60% of ethanol in the release medium

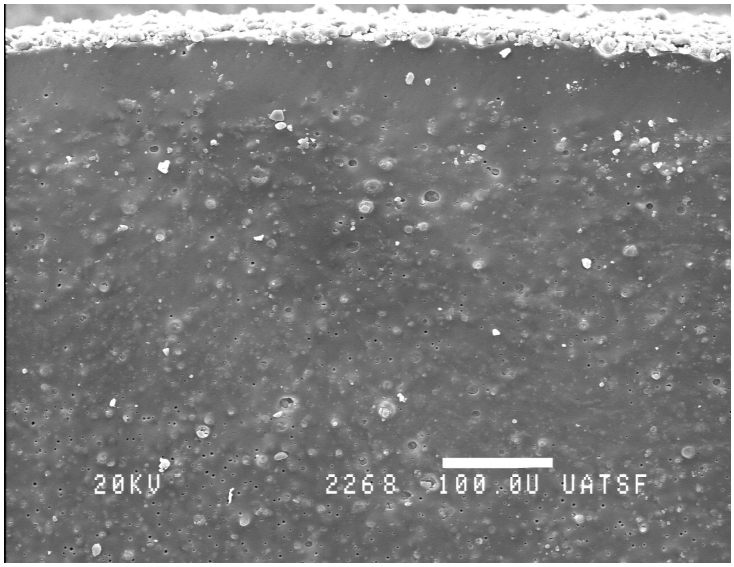
Another valuable comparison is given by results in prediction of drug dynamics within the device. As is presented in Figure 5, SEM photographs show a drug erasing front. This behaviour has been previously reported by Rathbone (Rathbone et al., 2002) and is taken into account in the present model (Cabrera et al., 2006). Figure 6 shows that drug erasing front is properly predicted by the numerical model.

4 CONCLUSIONS

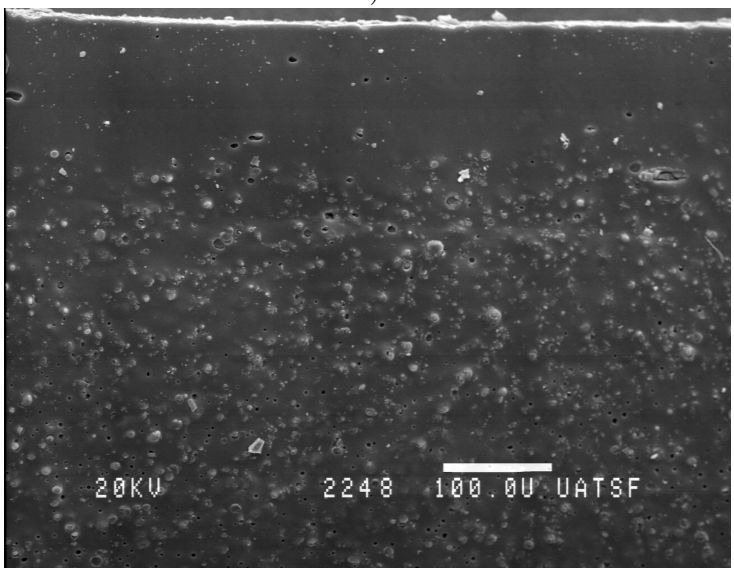
The showed correlation between experimental data and model fitting curve demonstrated that diffusion/dissolution equations and its numerical implementation are a well approach to calculate progesterone release behavior from silicone matrixes. Also the model predicts a releasing front corroborated by SEM and results presented in literature.

Changing structural and compositional parameters, the model can be applied in other intravaginal devices available in the market like PRID or DIB, among others, in attempt to a better understanding of drug release phenomenon and validation of model robustness. This powerful tool might replace solution-oriented approaches based on trial and error applied in practice due to the absence of mathematical models for making in vivo progesterone concentrations predictions.

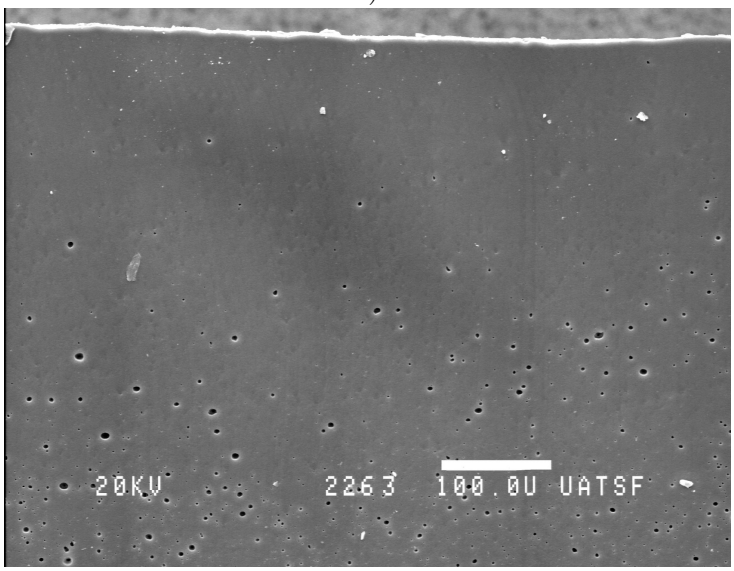
Finally, the presented model has a strong dependence between D_{ap} and ethanol concentration which could be solved by modifying the boundary conditions. This task is set as future work, where CIDR will be modeled with its intrinsic diffusivity and with Robin boundary conditions.



a)



b)



c)

Figure 5: Scan electron microscopy of PDMS silicone matrix after initial time, b) 2 h and c) 7 days of progesterone release. In these three cases, releasing wall is on the top of the pictures.

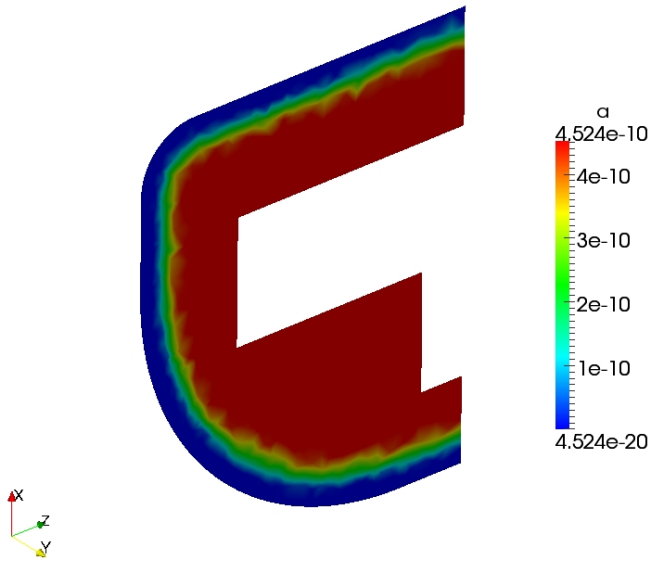


Figure 6: Isovalues of a for $t = 7$ days in a transversal cross section

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