Multiscale Experimental and Computational Modeling Approaches to Characterize Therapy Delivery to the Heart from an Implantable Epicardial Biomaterial Reservoir

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1. Introduction

Epicardial delivery of biological agents loaded onto biomaterials for treatment of a variety of cardiovascular diseases and pathologies is a promising area of research and development.[1,2] Standard methods of therapeutic delivery—intravenous, intracoronary, and oral—are often limited by tissue uptake and system recirculation.[1,3] Conversely, an epicardial strategy, where therapy is delivered directly to the outer surface of the heart, confers many advantages and can overcome these limitations. In one exemplary configuration of this strategy, a biomaterial loaded with therapeutic agents acts as a reservoir on the surface of the heart, providing sustained release to a localized region, thereby preventing adverse systemic effects and increasing myocardial uptake.[1] A wide variety of therapeutics ranging from small molecules such as amiodarone,[4] epinephrine,[5] dobutamine[6] to larger biomolecules such as peptides,[7] growth factors,[3] exosomes,[8] cells,[9–13] and gene therapies[14] preloaded onto biomaterials and implanted on the epicardial surface have been investigated in animal models of a range cardiovascular conditions. Enhanced therapeutic benefit relative to the more standard methods of delivery has been shown in these studies, demonstrating that the epicardial strategy may accelerate clinical translation of these strategies. Additional advantages of the epicardial strategy include the ability to simultaneously provide passive mechanical support to a weakened heart[15,16] and to guide and influence the remodeling process[17] by providing tunable mechanical restraint in certain conditions such as heart failure following a myocardial infarction. These mechanical aspects of biomaterials placed on the epicardial surface enhance cardiac function even without any biological agents loaded onto the biomaterials; in combination, they act as a polytherapeutic mechanobiological approach.[18,19]

While there is extensive literature characterizing the therapeutic benefits of a range of biomaterials loaded with many different biological agents for treatment of various cardiovascular pathologies, there is limited reported research on the factors...
that govern drug delivery from the biomaterial systems to the cardiac tissue and a scarcity of computational approaches to characterize transport from such systems. For other cardiovascular drug delivery vehicles, such as drug-eluting stents, there has been significant effort to guide design by experimentally characterizing material properties, device geometries, and tissue properties and coupling to computational investigations based on fundamental principles that govern transport of biological agents from the device to the target tissue to optimize therapeutic benefit.[20–23] Such investigations have guided device design iterations leading to enhanced implants. A similar effort in epicardial drug delivery systems could be potentially transformative in field of cardiovascular drug delivery research and could help researchers design smart systems based on tissue, material, and design parameters that are dominant in governing drug delivery. However, there are many challenges that currently discourage such studies. One major limitation is that the cardiac tissue is highly anisotropic and heterogeneous, which means that determining important parameters such as drug diffusivities through the tissue are complex to characterize through typical experimental set-ups such as Franz cell diffusion chambers. Furthermore, viability of cardiac ex vivo cardiac tissue limits the time scales on which transport of biologic agents through cardiac tissue can be studied. Additional challenges include the high degree of vascularity of the cardiac tissue which adds a convective element of transport and a paucity of literature characterizing reaction kinetics of biologic agents to their target receptors on cells in the epicardial layer.

Herein, we report a multiscale model to characterize the diffusive component of transport of a drug analog from an epicardial drug delivery system. We present a multiscale model characterizing drug delivery from a therapeutic-loaded biomaterial placed on the epicardial surface through the myocardial tissue. Our model is based on an implantable epicardial reservoir device recently described by our group called Therepi[24] that enables multiple noninvasive replenishments of localized cardiac therapy from a subcutaneous port (Figure 1A).

We previously showed that the device allows replenishment of therapy to a biomaterial-based reservoir contained in a capsule with a tunable porous interface to the heart in a preclinical rodent model.[24] Briefly, the reservoir was attached to the epicardial surface of an infarcted rat heart and an implantable catheter was used as a conduit between this reservoir and a subcutaneous port. The reservoir was refilled with therapy through the port at defined time points enabling multiple dosing. Our experimental observations on factors that influence delivery of biological agents from the Therepi device, and limited literature guiding design of pericardial and epicardial drug delivery systems based on computational simulations, we experimentally and computationally model the design and material parameters that could optimize the potential for drug transport from this device. This includes characterizing the microstructure of each of the device components and the tissue that will affect bioagent transport (Figure 1B). Indeed, the are multifactorial (Figure 1B,C), yet the scope of this work is to optimize the material and design parameters. In pursuit of a device design optimized for drug delivery...
penetration into the myocardium, we first employ experimental techniques and microscale computational modeling to characterize the diffusivity, porosity, and permeability of the device components. Next, we create a macroscale in silico simulation of the drug distribution and transport from the implantable reservoir into cardiac tissue employing these bulk material parameters (Figure 1C). With this macroscale model, we can easily modify component geometries and material properties with the goal of optimizing the delivery of therapeutic agents to the myocardial tissue. By this adjustment and tuning of device parameters to characterize their effect on transport through the device and into the epicardium and myocardium, we demonstrate utility of an in silico tool to guide future iterations of device design, dosing regimen, and placement strategies and to elucidate insights into epicardial drug delivery that had hitherto been underreported.

2. Results and Discussion

2.1. Computed Tomography Imaging of Tissue Penetration of Drug Analog

We implemented an experimental technique using micro-computed tomography (µCT) scanning to track penetration of a drug analog into tissue over time. We obtained explanted hearts from Wister rats (female, 200–250 g) directly postsacrifice and transported them immediately in ice-cooled saline to a µCT scanner (Scanco Medical µCT100). The Therepi device as described in our previous work was attached to the epicardial surface of the left ventricular wall of the ex vivo heart using sutures to ensure conformance. To allow imaging of diffusion from the device into heart tissue with the µCT, we chose the contrast agent phosphomolybdic acid (PMA, molecular weight 1825 g mol\(^{-1}\), Sigma Aldrich, Ireland) as a drug analog due to its ability to discriminate soft tissue microstructure. We injected 100 µL of PMA into the device through the subcutaneous port under three different loading conditions: 2.5% w/v, 12.5% w/v, and 20% w/v PMA.

Next, we scanned the whole, fresh ex vivo rat heart with the epicardially fixed device every hour for 24 h to visualize the penetration of the analog into cardiac tissue (Figure 2A).

We then calculated the diffusion length of PMA over time using a pixel intensity methodology to track PMA intensity over a
given line in given direction in ImageJ software (Figure 2B) and applying a 1D Fickian diffusion length equation, assuming a point source

\[ n(x, t) = n_0 \text{erfc} \left( \frac{x}{2\sqrt{Dt}} \right) \]  

(1)

where \( x \) is the diffusion length (distance from source), \( n \) is the drug concentration, \( n_0 \) is the initial drug concentration, \( t \) is the diffusion time, \( \text{erfc} \) is the error function, and \( D \) is the diffusion coefficient. We repeated this calculation for each hourly scan for each of the three scan views (Figure 2A) (lateral, caudal, and anterior) for each diffusion direction (24 scans \( \times \) 3 views \( \times \) 4 directions for each device) to calculate the anisotropic diffusion matrix. Next, we segmented and reconstructed the PMA volume using a mask thresholding methodology in Mimics Research v.18.0 (Materialise NV, Leuven, Belgium). Finally, the segmented mask was exported as an .stl file for visualization and measurement of 3D diffusion profile of the therapy analog in tissue. The measured values matched the theoretical values as calculated by 1D Fickian diffusion with a point source (Figure 2B,C) at representative time points of 8 and 11 h.

2.2. Experimental Measurement of Diffusivity of Drug Analog through Device Components

Next, we characterized relative diffusivity constants of the existing device components, and additional alternatives using a Franz diffusion cell (PermeGear, Hellertown, PA, USA) with a 7 mm diameter aperture and 8 mL volume. As shown in Figure 3A, the Franz cell consists of two chambers: an upper donor chamber and a lower receptor chamber separated by an

**Figure 3.** Experimental measurement of diffusivity of drug analog through device components. A) Franz cell set-up for quantifying diffusivity of device components. B) Example of measured data from diffusion tests. C) Scanning electron microscopy images of porous membranes with varying pore size. D) Test data for 0.45, 0.8, and 10 \( \mu \text{m} \) pore size membranes (PCM = polycarbonate membrane). E) Diffusion coefficients as they relate to pore size.
aperture. We placed the samples in the aperture and clamped them, and then filled the donor chamber with 4 kDa Fluorescein isothiocyanate (FITC)-dextran solution (Sigma Aldrich, USA) at a concentration of 2 mg mL⁻¹. We then monitored the concentration of solute in the receptor chamber over time by taking samples and measuring the absorbance of the solution at 565–650 nm wavelengths with a fluorometer (DeNovix, DS-11, Wilmington, DE, USA).

Next, we estimated the diffusion coefficient $D$ using a time-lag method assuming 1D Fickian diffusion as follows

$$V_{b0} C_{b0} = \frac{ADC_{b0}}{l} \left( 1 - \frac{l^2}{6D} \right)$$

where $V_{b0}$ is the initial volume of the receptor chamber (3000 µL), $C_{b0}$ is the concentration of solute in the receptor chamber measured over time $t$, $A$ is the surface area of the membrane (=38.5 mm²), $C_{b0}$ is the initial concentration of solute in the donor chamber, and $l$ is the thickness of the membrane. We plotted the left-hand side of the equation versus time as shown for an example porous membrane in Figure 3B. The diffusion coefficient was calculated from the slope of the plot using the known parameters for length, volume, and area (Table 1).

We repeated this process for a range of porous membranes, with scanning electron microscopy (SEM) images (Figure 3C). The data for each membrane is shown in Figure 3D, and the calculated diffusivity constants are shown in Table 1. The diffusion constants were found to correlate with pore size more strongly than with porosity, likely due to the inverse relationship between pore size and resistance to flow.

### 2.3. Component Permeability Calculation Using a Microscale Model and Experimental Methods

We calculated the permeability of the existing components of the Therapi device, which include a polycarbonate membrane and a Gelfoam, biomaterial reservoir. To calculate the permeability of Gelfoam, we used a unit cell to represent the entire volume. We took a µCT scan of a section of the dry biomaterial, segmented and reconstructed it (Mimics, Materialise, Leuven), meshed it (3-matics, Materialise), and then used a Boolean operator to subtract it from an idealized cylinder to represent the pores where flow of fluid would occur (Figure 4A). We then created a microscale model to calculate the permeability of an array of porous membranes and two different types of hydrogels. We used the Navier–Stokes equations to compute the pressure $p$ and the velocity field $u$ for the flow of water in the laminar flow regime

$$\rho \left( u, \nabla \right) u = \nabla \left[ pl + \mu \left( \nabla u + (\nabla u)^T \right) \right]$$

$$\rho \nabla \cdot (u) = 0$$

where $\mu$ and $\rho$ are the dynamic viscosity and density of water (0.001 Pa s and 1000 kg m⁻³, respectively).

For the biomaterial model, we defined the boundary between solid and fluid as a no slip boundary where the fluid velocity is zero ($u = 0$) at the walls. The remaining boundaries were assigned symmetry boundary conditions ($u \cdot n = 0$) (Figure 4B).

We obtained the numerical solution using a direct linear stationary solver in COMSOL. Then we simulated flow through the porous structure (biomaterial or porous membrane), determined the average velocity over the outlet surface area (Figure 4C–E) and calculated the permeability for each material. Finally, we measured the permeability of ventricular tissue experimentally using a custom-built apparatus, as shown in Figure 4F. The apparatus includes a pressure gauge, a sample holder with a circular aperture of radius 5 mm. We measured the flow rate of water through a rat left ventricle at 1 atm and then calculated the permeability $\kappa$ using Darcy’s law

$$\kappa = \frac{\varepsilon \mu u}{\Delta p}$$

where $\varepsilon$ is the porosity of the cardiac tissue, $\mu$ is the dynamic viscosity of water (0.001 Pa s), $u$ is the velocity of water determined by measuring the flow rate of water (0.42 mm s⁻¹) divided by the surface area of the circular aperture (78 mm²), $l$ is the thickness of the cardiac tissue (2 mm), and $\Delta p$ is the applied pressure (1 atm). Table 2 shows the permeability and porosity calculated for the Gelfoam and the porous membrane of different pore sizes.

### 2.4. A simplified Macroscale Model for Design Optimization and Validation with Experimental Data

We repeated the µCT testing described in Figure 2 for varying concentrations of drug analog. We then created a simplified macroscale model in the MultiPhysics Software COMSOL to predict penetration of drug into tissue so that we could alter various device parameters and analyze their effect on drug transport. We modeled diffusion and mass transport of the drug in fluid through the various device components into cardiac tissue using diffusion–convection phenomena. In this approach, we omitted the detailed microstructures of each component, and instead represented the properties of the three porous materials (membrane, biomaterial, and cardiac tissue) with two bulk properties (porosity and permeability) determined from the microscale models described in the previous section. We used Darcy’s law to determine the velocity of the fluid flow $u$ through the porous media, neglecting the effect of gravity, according to the following equation
where \( \Delta p \) is the pressure gradient, and other parameters are as previously described. We created a simple 3D reconstruction of the biomaterial, membrane, and cardiac tissue (Figure 5A).

We defined the exterior surfaces of the biomaterial as the “inlet” and assigned them with pressure \( p_0 \), determined

\[
\textbf{u} = -\frac{\kappa}{\mu} \nabla p
\]

\[
\nabla \cdot (\rho \textbf{u}) = 0
\]

Table 2. Darcy’s Law parameters of biomaterial components of Therepi device for input into in silico model.

|                | Polycarbonate membrane | Gelfoam |
|----------------|------------------------|---------|
| Pore size [\( \mu m \)] | 0.45 0.8 10 Variable |         |
| \( l \) [mm] | 0.02 0.01 0.01 4       |         |
| \( V_0 \) [\( \mu L \)] | 3000 3000 3000 3000    |         |
| \( A \) [mm\(^2\)] | 38.5 38.5 38.5 38.5    |         |
| \( D \) [m\(^2\) s\(^{-1}\)] | \( 7.97 \times 10^{-15} \) | \( 4.12 \times 10^{-14} \) |

\( 4.01 \times 10^{-13} \) 1.38 \( \times 10^{-8} \)
Figure 5. A) Schematic of macroscale model including boundary conditions. B) Example contour plot of drug concentration in COMSOL showing transmural direction. C,E,G) Transmural concentration profiles at different time points for initial drug analog concentrations of 2.5%, 12.5%, and 20% w/v of PMA, respectively. D,F,H) Comparison of experimental versus computational data at each drug analog concentration.
experimentally by measuring the force when the device is filled with fluid. We defined the endocardial (inner) surface of the cardiac tissue as the "outlet" with no pressure. We prescribed the epicardial (outer) boundaries of the cardiac tissue with no flow conditions across impervious boundaries ($\mathbf{V} \cdot (\mu \mathbf{u}) = 0$).

We then defined the mass transport properties through the diffusion and convection equations in a time-dependent domain as following

$$ \frac{dc_i}{dt} + \nabla \cdot (\mathbf{D}_i c_i) + \mathbf{u} \nabla c_i = R_i $$

(6)

$$ \mathbf{N}_i = - \mathbf{D} \nabla c_i + \mathbf{u} c_i $$

where $c_i$ (mol m$^{-3}$) is the concentration of drugs, $D_i$ (m$^2$ s$^{-1}$) is the diffusion coefficient, $\mathbf{u}$ (m s$^{-1}$) is the velocity vector, $R_i$ (mol m$^{-3}$ s$^{-1}$) is the reaction rate expression, and $N_i$ (mol m$^{-2}$ s$^{-1}$) is the flux vector which is used in boundary conditions and flux computation. To apply the measured diffusion coefficients, we used a rotated coordinate system relative to the $xy$ plane in the global Cartesian coordinate system using (45°, 0°, 0°) Euler angles, and a diagonal $3 \times 3$ matrix with $D_{xx}$, $D_{yy}$, and $D_{zz}$ corresponding to the anisotropic diffusion coefficients measured in the µCT experiments. We assigned the experimentally derived diffusion coefficients of the biomatetial and porous membrane, and assumed they were isotropic. We defined the exterior boundaries of the device, including the porous membrane and hydrogel as inflow with an initial concentration $c_0$. We defined the endocardial surface of the cardiac tissue as outflow with no diffusion ($\mathbf{n} \cdot (-\mathbf{D} \nabla c_i) = 0$) and the lateral boundaries of the cardiac tissue as no flow, with no mass flows in or out of the boundaries ($\mathbf{n} \cdot \mathbf{N}_i = 0$). The transmural concentration profiles at various time points along a line perpendicular to the midpoint of the biomaterial (Figure 5B) are shown in Figure 5C, and Figure 5G for increasing concentrations. We validated the accuracy of the model by showing a good match between maximum drug penetration at different time points to the measured experimental values (Figure 5D,F,H).

2.5. Parameter Study Using the Macroscale Model and Varying Device Parameters

We then conducted a parameter study with the macroscale model to vary drug concentration, presence of membrane, membrane pore size, surface area, device thickness, and device orientation. For each parameter, we described the simulated effect on drug transport and describe our findings below.

2.5.1. Concentration of Drug

Increasing the initial concentration of the drug creates a greater driving force for diffusion. At 11 h, with increasing initial concentration of drug, a greater amount of drug is available to the tissue at depths less than $\approx 0.6$ mm (Figure 6A).

Beyond 0.6 mm, the differences in drug analog availability with respect to initial drug analog concentration are negligible. At 8 days, the difference in the amount of drug analog available at depths up to $\approx 3.0$ mm is more pronounced (Figure 7A). Interestingly, in the condition with 2.5% PMA as the initial concentration of drug analog, the concentration gradient dissipates and there is a greater amount of drug available to the tissue from $\approx 1.7$ to $3.0$ mm compared to the profile observed in the simulation condition with 12.5% PMA as the initial drug analog concentration. As expected, these observations indicate that with increasing initial drug concentration, there is a greater concentration gradient and therefore, the flux of drug going into the tissue. The initial concentration governs how much drug is available to the tissue up to a certain point; beyond that point in the tissue, the initial drug concentration has negligible effect. This indicates that initial drug dosing should be concerned with making the therapeutic amount of drug available to a limited portion of the myocardial tissue and that increasing initial drug concentration may not help enhance penetration deeper into the tissue.

2.5.2. Membrane and Membrane Pore Size

At 11 h, the concentration profiles are similar for the conditions of no membrane and membrane pore sizes of 0.8 µm and 10 µm (Figure 6B), with a slightly different profile for the 0.45 µm pore size. At 8 days, assuming a wall thickness of 1 cm, the concentration profiles and relative trends are maintained for all conditions (Figure 7) but the drug travels further (≈fivefold) into the wall. At 8 days, the “no membrane” condition showed greater availability of drug in the tissue. At this time point, the effect of membrane pore size is minimal in limiting transport of the drug analog from the device to the tissue, with the exception of slight differences for the 0.45 µm membrane potentially due to lower permeability of this membrane which may be attributed to resistance through the pores.

2.5.3. Device Thickness

Decreasing the device thickness by a factor of 10 did not demonstrate any pronounced effect on penetration or epicardial coverage of the drug at 11 h (Figure 7C). Additionally, at 8 days, a thinner device did not show any difference in penetration compared to the standard device thickness (Figure 7C). This suggests that the device thickness is not a limiting factor to transport of the drug into the myocardial tissue from the device.

2.5.4. Surface Area

Increasing the surface area of the device to 4 or 6.25 mm$^2$ did not enhance penetration into the myocardium at 11 h but when surface area is increased to 16 mm$^2$, the penetration into the myocardial tissue was enhanced (Figure 6D). With an increase in surface area, there was greater availability of the drug analog across the epicardial surface (Figure 6G) relative to the standard device geometry (Figure 6E). At 8 days, the model predicts that devices with increased surface area will enhance penetration into the tissue and allow for greater availability of the drug at...
any given point along the transmural thickness in comparison to the dimensions of the standard device (Figure 7D). Increasing the surface area significantly to 16 mm² enhances the concentration of drug in the myocardium at both 11 h and 8 days.

2.5.5. Device Orientation

Due to the anisotropic nature of the myocardial tissue, the fiber orientation in the tissue governs the direction in which the drug analog primarily spreads. There is greater drug diffusion along the fibers. Device orientation relative to the fibers has a pronounced effect on the surface area of the epicardial surface that the drug analog covers. When the device is placed parallel to the fibers, the drug spreads in an elliptical manner along the principal axis of diffusion, which is marked as a white arrow (Figure 8).

This covers a greater longitudinal area but has limited spread laterally, with respect to the axis of principal diffusion. When the device is placed perpendicular to the fibers, the opposite effect is observed (Figure 8D). For devices oriented
either $\approx 45^\circ$ and $-45^\circ$ with respect to the principal axis of diffusion or, the distribution somewhere in between the two extremes of parallel to fiber orientation and perpendicular to fiber orientation (Figure 8B,C), there is a greater availability of drug laterally, but the diffusion is limited longitudinally, with respect to the axis of principle diffusion. Additionally, the average concentration of drug analog on the epicardial surface is higher at every time point in the case where the device is oriented perpendicular to the axis of principal diffusion (Figure 8E). This suggests that device orientation relative to fiber orientation governs how much of the surface and what portion of the epicardial surface the drug is made available to, as well as how much drug on average is available to the cells at the surface. Depending on the location of the cellular targets of the therapeutic agents, device placement and orientation may play a key role in therapeutic efficacy since often, the ischemic area and border zones of the tissue have different cellular compositions relatively.

### 3. Conclusion

With increasing research and development focused on epicardial drug delivery systems, there remains an unmet need to understand the important parameters that affect epicardial drug delivery. We used a variety of characterization techniques to determine such parameters. Using these experimentally determined parameters, we then developed a model to help predict the effect of different factors on drug distribution on the epicardial surface and into the myocardium of the cardiac tissue. Our model and simulations indicate that the transport of drug from an epicardial drug delivery system to the cardiac tissue is largely governed by the fiber orientation at a shallow angle to the epicardial surface. The drug analog traveled preferentially along the epicardial fibers with limited penetration into the myocardial tissue. In terms of device design, increasing the surface area moderately had limited effect on enhancing penetration but helped increase the surface area of drug analog coverage on shorter time scales. However, larger increases in the surface area had a more pronounced effect on increasing the concentration of drug analog along the transmural thickness at shorter time scales. Factors such as the size and thickness\(^{[5]}\) of the heart tissue and the size of the infarct may need to be considered when determining the surface area of the device, and when scaling up.

Device thickness, membrane porosity, and initial drug analog loading did not have any noticeable effect on enhancing drug analog penetration into the myocardial tissue or epicardial surface area coverage at both short and longer time scales. At longer time scales, increasing the surface area had the most dramatic effect in enhancing penetration compared to other variables. These results indicate that epicardial drug delivery systems may be better suited for immediately delivering therapeutic agents that have cellular targets located near the epicardial surface and that in designing these drug delivery systems, the primary factor to consider is drug distribution on the surface since our model predicts geometry and orientation of the device has a noticeable impact on only this factor. Examples of these types of therapies have gained increasing attention in recent literature.\(^{[18,27,28]}\) To deliver a drug with target receptors

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Figure 7. Parameter study at 8 days, assuming a cardiac transmural wall thickness of 1 cm. Effects of varying parameters on transmural concentration profile: A) initial drug loading, B) membrane and membrane pore size, C) device thickness, and D) surface area.
located deeper in the cardiac tissue, other approaches such as intramyocardial injection of drug-loaded hydrogels may be better suited.[27] Alternatively, epicardial drug delivery systems with microneedles may help allow for immediate availability of the drug to the myocardial tissue.[12]

The simulations and experiments presented here highlight the important role that anisotropic fibers play in influencing mass transport in tissue. In order to build a complete in silico model for evaluation of epicardial drug delivery systems, further work is needed including: i) representation of the vascular

Figure 8. A–D) Contour plots showing drug concentration distribution on the epicardial surface for different orientations of a rectangular epicardial reservoir. E) Average concentration at epicardial surface for various orientations with respect to the principal axis over time.
network and dynamic contraction of the cardiac tissue, although this is hampered by a lack of data on the density of the vasculature in healthy and diseased tissue and the permeability of the drug in the vascular wall; ii) the consumption of the transported drug in the cardiac tissue (in the current study, reaction kinetics were not considered in the absence of accurate binding parameters); iii) longer time scales and a larger domain as the current study only considered 8 days of drug release (previous studies have shown release with constant concentration up to 21 days\cite{18}); iv) exploration of alternative imaging techniques or drug analogs that will permit the use of agents that more closely approximate the transport properties (molecular weights and binding properties) of therapeutic agents than PMA, and (v) no-flux boundary conditions were used to model the edge of the considered domain in order to reduce the computational cost.

Our study qualitatively investigated what factors determine epicardial drug delivery and we have set up a general model and framework to assist with drug delivery device design. This tool can be useful to rapidly iterate through different device concepts and determine which designs for epicardial drug delivery may be optimal and most promising for the ultimate therapeutic goal.

4. Experimental Section

**Pressure Measurements:** To measure the pressure applied to the Gelfoam upon filling or refilling of the Theripei reservoir, the device was placed between two compression plates of a mechanical tester (Instron 3300) and plate separation was adjusted until the surface area of the device.

CT Imaging of Gelfoam: A micro-CT scanner (Scanco) was used to determine the 3D pore geometry of Gelfoam. The Gelfoam was stained using an iodine vapor staining technique for 5 h and scanned on a µCT scanner (Scanco Medical) with a resolution of 3.3 µm. The resulting reconstructions were converted to DICOM images and imported into Mimics (Materialise, Leuven, Belgium) to create a mask, which was then imported into COMSOL Multiphysics commercial finite element software (v5.3).

SEM Images of Porous Membranes: A visual representation of the membrane structure was obtained using scanning electron microscopy (secondary electron mode) at an accelerating voltage of 12–15 kV and imported into COMSOL Multiphysics.

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Conflict of Interest

The authors declare no conflict of interest.

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