Mathematical Modeling of Drug Delivery from Bi-Layered Core-Shell Polymeric Microspheres

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Abstract

Chronic diseases usually require repetitive dosing. Depending on factors such as dosing frequency, mode of administration, and associated costs this can result in poor patient compliance. A better alternative involves using drug delivery systems to reduce the frequency of dosing and extend drug release. However, reaching the market stage is a time-consuming process. In this study, we used two numerical approaches for estimating the values of the critical parameters that govern the diffusion-controlled drug release within bi-layered core-shell microspheres. Specifically, the estimated parameters include burst release, drug diffusion coefficient in two polymers, and the drug partition coefficient. Estimating these parameters provides insight for optimizing device design, guiding experimental efforts, and improving the device's effectiveness. We obtained good agreement between the models and the experimental data. The methods explored in this work apply not only to bi-layered spherical systems but can also be extended to multi-layered spherical systems.

Keywords: polymeric drug delivery, drug release modeling, mechanistic modeling, sustained drug delivery, polycaprolactone, chitosan

Contents

1 Introduction **2**

2 Methods **3**
2.1 Geometry . . . 3
2.2 Model description . . . 3
2.3 Numerical methods . . . 5
2.4 Parameter estimation procedure . . . 5

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3 Results and Discussion **6**
3.1 Model verification . . . 6
3.2 Parameter estimation . . . 6
3.2.1 Drug release from BSA-loaded microspheres . . . 6
3.2.2 Drug release from Bevacizumab-loaded microspheres . . . 8

4 Conclusions **11**

1. Introduction

Wet age-related macular degeneration (wet AMD) is a chronic eye disorder with no cure that can cause permanent vision loss if not treated [1]. Current treatments depend on monthly intravitreal injections of an anti-vascular endothelial growth factor (anti-VEGF) agent. The intravitreal route provides high drug concentration and minimizes systemic side effects [1, 2]. Still, these injections are painful, costly, and repetitive injections can cause severe complications such as retinal detachment or infection [3, 4]. To address this issue, different drug delivery systems (DDSs) have been studied in the last decade and are discussed in different review papers [5, 6, 2, 7]. Recently, anti-VEGF loaded microspheres composed of polycaprolactone (PCL) and chitosan have been studied [8]. *In vitro* experiments performed during six months have shown the viability of this DDS for sustained drug release. However, critical parameters of the device, such as drug diffusion coefficients, burst release, and drug partition coefficient, are not initially known. Mathematical modeling of drug release from DDSs can help estimate these parameters, optimize device design, and reduce the amount of experimental work required. Ultimately, this will result in improving wet AMD treatments.

Several drug release-controlling mechanisms are discussed in the literature [5, 9, 10, 11]. The diffusion-controlled drug release mechanism is characterized by diffusion through the polymer being the rate-limiting step. The drug transfer rate is usually described by Fick's law with constant diffusion coefficients, perfect sink conditions in the medium, and negligible swelling and erosion of the delivery system [10, 11]. The analytical solution to the diffusion problem of single-layered DDSs of different ideal geometries is well known [12, 13, 14, 15, 16, 17]. However, the case of multi-layered DDSs or DDSs with non-ideal geometries is more complicated. Several models have been derived from Fick's law with constant diffusivities in each device layer. For instance, Lu and Chen [18] derived the generalized analytical solution to the dimensionless problem of drug diffusion from a core-shell microparticle using Laplace transforms. This model involved the use of a drug partition coefficient and initial drug in the inner core only.

Similarly, Hadjitheodorou and Kalosakas [19] derived an analytical solution for composite microspheres consisting of an inner core and an outer shell with different diffusion coefficients. This model was derived for the case of sink boundary conditions at the external surface of the sphere while assuming drug concentration continuity at the interface. Kaoui et al. [20] developed a general model for predicting drug release from spherical, multi-layered capsules. At each interface, flux continuity was applied while considering drug partitioning. The model assumed an external medium confined by a finite length. Carr and Pontrelli [21] solved a similar problem by considering that the surrounding medium was significantly larger than the sphere itself.

Ford Versypt and Braatz [22] derived two finite difference discretization schemes for solving the diffusion equation in spherical coordinates for different cases of variable or constant diffusivity. Even though both schemes are stable for the particular case of constant diffusivity, scheme 1 was preferred. This scheme is based on an equivalent alternative form of the PDE equation for Fickian diffusion in spheres. The solution is obtained by approximating the spatial derivatives with central finite differences in the interior of the spherical domain for $0 < r < 1$.

While these previous papers solved the diffusion-controlled drug release problem using fixed values of drug diffusion coefficient in the different layers (or a drug diffusion coefficient ratio between the layers), and partition coefficient, these values are not always known and sometimes it becomes necessary to estimate them. To the best of our knowledge, no papers have dealt with the parameter estimation of multi-layered spherical devices. There have been publications on single-layered devices. For instance, Wang et al. [23] derived a numerical methods approach for estimating unknown parameters in single-layered spherical drug delivery systems by using a non-linear least-squares problem approach. The diffusion problem was solved using the finite volume method. The estimated parameters included: an initial diffusion coefficient which represents the initial burst, a critical time which represents the transition between initial burst and normal diffusion, normal diffusion, and an effective boundary layer which is the region in which the velocity near the boundary of the device goes from zero to a positive number. The procedure was validated using experimental data of the diffusion of prednisolone 21-hemisuccinate sodium salt from spherical devices made of porous poly(2-hydroxyethyl methacrylate) hydrogels. Later, an extension of the model was developed by Mohd-Mahali et al. [24], who considered rotating and flow-through fluid systems surrounding the three-dimensional drug delivery systems and developed the techniques to estimate the same previously unknown parameters as Wang et al. [23].

In this work, we present a couple of numerical approaches based on finite differences and finite elements for solving the drug release problem and estimating the constant drug diffusion coefficient in the chitosan and PCL layer, the initial burst release, and the drug partition coefficient for a diffusion-controlled bi-layered core-shell spherical DDS. The methods applied here can be extended to bi-layered or multi-layered spherical DDSs with appropriate interface conditions.

2. Methods

2.1. Geometry

The particulate system used for testing the models is a drug-loaded core-shell microparticle system developed by Jiang et al. [8]. It consists of a drug-loaded core made of chitosan and a PCL outer layer (Figure 1). The model drugs used were either bovine serum albumin (BSA) or bevacizumab. Chitosan controls the drug release rate due to electrostatic interaction with these negatively charged drugs [8]. In contrast, PCL protects the chitosan core from degradation and therefore helps extending drug release. Information regarding the geometry of chitosan-PCL microspheres can be found in Table 1.

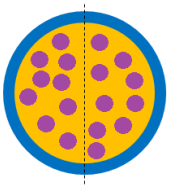

Figure 1: 2D schematic representation of the Chitosan-polycaprolactone microspheres. Blue: polycaprolactone. Yellow: chitosan. Purple: Drug

2.2. Model description

Fick's second law was used to model the unsteady-state diffusion in multiple dimensions without convection:

Table 1: Parameter arbitrary boundaries for chitosan-PCL core-shell microspheres

Parameter	Value	Units
Inner chitosan mean radius	5.10	μm
PCL mean thickness	1.25	μm

$$\frac{\partial C}{\partial t} = D\nabla^2 C \tag{1}$$

where C is the drug concentration, t is time, and D is the constant diffusion coefficients.

For the boundary condition, perfect sink condition at the external surface of the sphere was assumed, meaning that the drug concentration at the border of the device is constant and equal to zero ($c = 0$, meaning that all the drug that is released is immediately being cleared away). Erosion and swelling effects are negligible. The interface condition between the two different polymeric domains is the flux continuity condition while considering drug partitioning:

$$-D_{ch}\frac{dC}{dr}\bigg|_{r=interface} = -D_{PCL}\frac{dC}{dr}\bigg|_{r=interface} \tag{2}$$

Subject to:

$$C_{ch} = \kappa C_{PCL} \tag{3}$$

where C_{ch} is the drug concentration in the chitosan, κ is the partition coefficient, and C_{PCL} is the drug concentration in the PCL. A derivation of the interface boundary conditions used in the MATLAB script can be found in the Appendix.

The initial concentration inside the core is arbitrarily set as $c = 1$ while there is no initial drug at the outer shell ($c = 0$). Furthermore, drug release was calculated in terms of cumulative release:

$$Q(t) = B + (1-B)\left(1 - \frac{\iiint c(\vec{x},t)\,dV}{\iiint c(\vec{x},0)\,dV}\right) \tag{4}$$

where $Q(t)$ is the cumulative percentage of drug released as a function of time, B is the initial burst release, and the last term refers to the fractional amount of drug remaining in the device calculated as the volume-integral of the spatiotemporal distribution of c, where $\vec{x}$ refers to the spatial coordinates.

For the estimation of the parameters like drug diffusion coefficient in chitosan and PCL, burst release, and drug partition coefficient, we used a weighted ordinary least square objective function with the general form:

$$\min_{params}\sum_i w_i[f(params, xdata_i) - ydata_i]^2 = \min_{params}\sum_i \frac{1}{\sigma^2}[f(params, xdata_i) - ydata_i]^2 \tag{5}$$

where i is the index of data points, w_i are the weights at each time point with respect to the standard deviations σ, *params* refers to the parameters to be estimated (D_{ch}, D_{PCL}, κ, and B), $xdata_i$ is the experimental data related to the conditions of the DDS (dimensions, geometry...), and $ydata_i$ is the experimental cumulative drug release data from the work by Jiang et al. [8]. The results presented in this study were obtained for the case of $w_i = 1$.

2.3. Numerical methods

Using two different approaches, we numerically solved Fick's law for drug release from the spherical DDSs under the boundary above and interface conditions. The first approach uses the finite differences method, and the second uses the finite elements method.

We developed the finite differences approach using MATLAB®. Radial symmetry from the center of the microspheres was assumed. The solving procedure uses the method of lines, which transforms the partial differential equation (PDE) into a system of ordinary differential equations (ODEs) by discretizing the spatial domain. The finite difference discretization scheme used was based on scheme 1 from the work of Ford Versypt and Braatz [22]. A central finite differences discretization scheme was applied inside the spherical domain for $0 < r < 1$. A variable α was defined as:

$$\alpha = \frac{D}{R^2} \tag{6}$$

to scale the diffusion coefficient by the outer radius in dimensional form. The resulting ODEs are solved using ode45, a built-in MATLAB® ODE solver. We used a maximum of 200 steps (201 grid points) for defining the microsphere domain. Since the microsphere consists of a chitosan and a PCL layer, the number of grid points in each layer is proportional to the ratio of the chitosan-to-PCL radius. Drug release was calculated in terms of cumulative release (Equation (4)). Furthermore, we used the built-in lsqcurvefit function for estimating the parameters that minimized the weighted least square error (Equation (5)). Since diffusion coefficient values are commonly tiny numbers, we normalized the parameter values inside the parameter estimation function so that we are always estimating a value between 0 and 1. The model allows the estimation of the drug diffusion coefficient in chitosan and PCL, burst release, and partition coefficient. Tolerance is set to 0.001, and the maximum number of function evaluations is 800.

Our finite elements model was developed using COMSOL Multiphysics®. The model geometry is constructed as a 2D axisymmetric structure, which allows us to reduce the 3D problem to a 2D problem by taking advantage of the symmetry about the vertical axis in the 2D plane. The solving procedure involves discretizing the spatial domain into simple geometric elements interconnected at common points to two or more elements. This process results in a system of algebraic equations that must be solved simultaneously. A triangular mesh was used to define the computational domains. The maximum element size allowed was 0.1 mm, while the minimum element size allowed was 2.4×10^{-5} mm. We used the transport of diluted species as the physics package in the software, and drug transport equations were set up independently for each different domain (polymer) present in the drug delivery device. Drug release was calculated in terms of cumulative release (Equation (4)).

Furthermore, we used the built-in global least-square objective function within the optimization module to perform the parameter estimation (Equation (5)). Similar to the finite differences model, this model allows the estimation of the drug diffusion coefficient in chitosan and PCL, burst release, and partition coefficient. A piecewise function was defined to incorporate the standard deviation of the measurements in the model. Tolerance is set to 0.001, with 1000 maximum function evaluations. The parameters to be estimated were scaled to avoid the need to fit really small values.

These two models are compared under the same conditions of drug diffusion coefficients, drug partition coefficient, and burst release, and the drug concentration results at different locations inside the microspheres are used for verification purposes.

2.4. Parameter estimation procedure

To attempt to reach the global minimum of the problem, we implemented a multi-start process with 50 different randomized initial conditions. The initial conditions' values were obtained using a Latin hypercube sampling approach. The parameters' lower and upper boundary limits can be found in Table 2.

Table 2: Parameters for chitosan-PCL core-shell microspheres

Parameter	Lower limit	Upper limit	Units
B	0	100	%
D_{ch}	0	6×10^{-15}	cm^2/s
D_{PCL}	0	7×10^{-12}	cm^2/s
k	0.1	2	-

B: burst release. D_{chi}: drug diffusion coefficient in chitosan. D_{PCL}: drug diffusion coefficient in polycaprolactone. k: partition coefficient.

After finalization of each simulation, we evaluated the resulting error values. We arbitrarily decided a cut-off value where all the simulations with errors below the threshold are considered to be part of the global minimum of the problem. The parameter values obtained for the simulations that reached the global minimum were used to estimate average parameters and their respective standard deviations. Furthermore, the parameters from the simulation with the lowest error value were considered the best model parameters.

3. Results and Discussion

3.1. Model verification

We verified our finite elements model with our finite differences model. To this end, we compared drug concentration at four distinct locations within the chitosan-PCL microspheres. We obtained that the drug concentration profiles in both MATLAB and COMSOL are essentially overlapping at the center of the microsphere (Figure 2a) and at half the chitosan layer (Figure 2b). At initial time points, there is a concentration difference at the interface related to the initial interface condition in both software; however, the concentration profiles quickly converge towards the same values after the algorithms start the solving routine (Figure 2c). This initial difference at the interface might be why there is also a slight difference at half the PCL layer at initial time points. Still, once again the results in both software quickly converge towards the same concentrations (Figure 2d).

3.2. Parameter estimation

After running our optimization algorithms using the experimental data for cumulative drug release from chitosan-PCL core-shell microspheres from Jiang et al. [8], we compared our fitted models with the experimental data for BSA- and bevacizumab-loaded microspheres.

3.2.1. Drug release from BSA-loaded microspheres

Figure 3 shows the final error value after each complete simulation in MATLAB (sorted in decreasing order for visualization purposes). We obtained three different local minima of the problem. By visual inspection and in an arbitrary manner, we decided that any simulation with a final error value below 225 was considered to have achieved the global minimum. The parameters from 36 out of the 50 simulations were used to determine the average parameters of the model with their respective standard deviations. The parameters from the model with the lowest final error value (last point in Figure 3) were used to define the best model.

Table 3 contains the values of the parameters for the average and best models. For the average model, we obtained low standard deviations for burst and BSA diffusion coefficient in chitosan but not for BSA diffusion in PCL and partition coefficient. The results for the model average and the best model are close together except for the case of the BSA diffusion coefficient on PCL, but it is still in the same order of

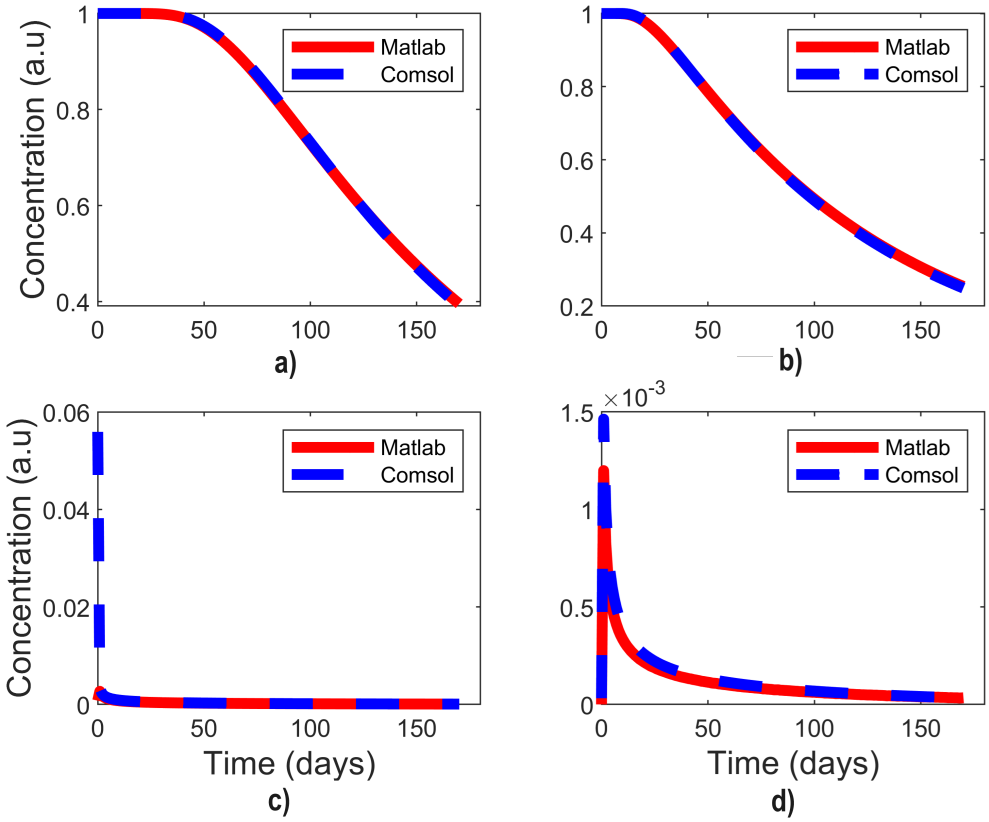

Figure 2: Drug concentration comparison at a) the center of the microspheres, b) half the chitosan layer, c) the PCL-chitosan interface, and d) half the PCL layer.

magnitude. The main difference between the models is in the BSA partition coefficients. For the average model, a value of 1.33 means that the chitosan has a higher drug concentration at the interface than PCL. Still, for the best model the value of 0.77 means that the PCL has a higher drug concentration at the interface than chitosan. The expected result is a value of k>1 since BSA interacts electrostatically with the chitosan, and at the interface, BSA concentration in chitosan should be higher than concentration in PCL. However, the drug partition coefficient value does not significantly impact the drug release profile in our model.

When graphically comparing the average and best models with the experimental data (Figure 4), it can be seen that both models overlap each other. Furthermore, they can describe BSA release from these bi-layered core-shell microspheres. The last experimental data point has a standard error that goes above 100% release, which could reduce the models ability to predict later time points. This is related to the theoretical drug load in the microspheres.

A different error value profile was obtained when solving the BSA-loaded microspheres problem in COMSOL (Figure 5). However, in this case, all the final error values were below the threshold of 225 and, therefore, considered to be part of the global minimum. The parameters from all 50 simulations were used to obtain the average model with its respective standard deviation, and the best model was obtained from the

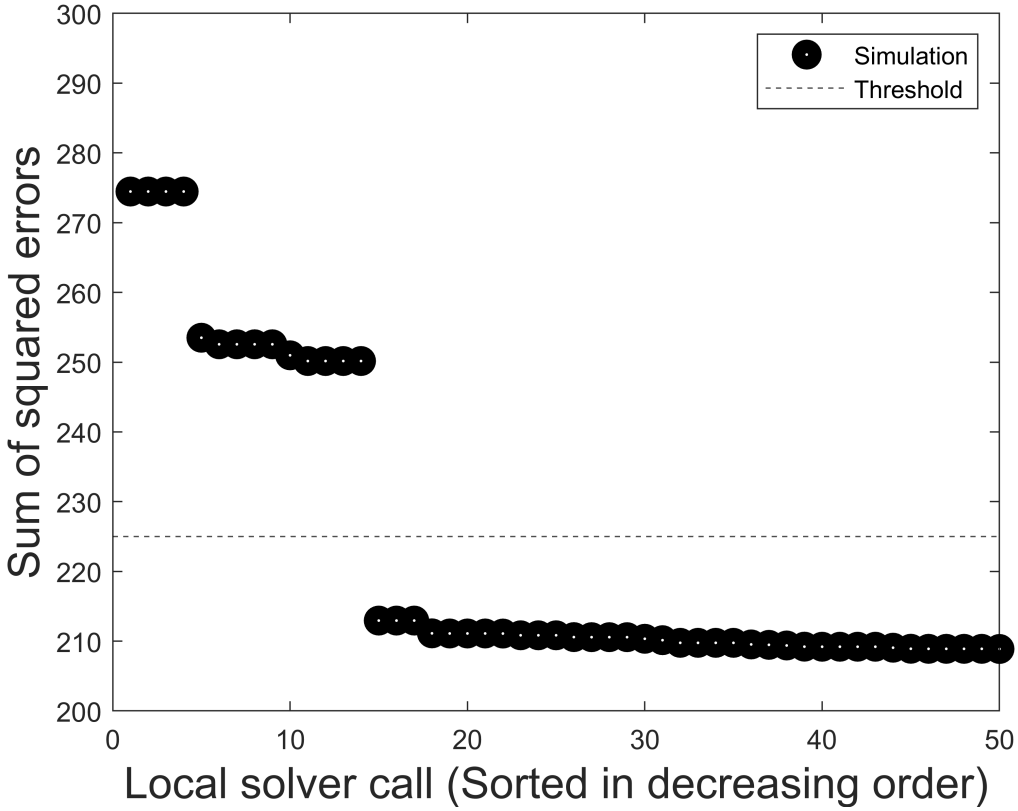

Figure 3: Final error value after each complete simulation in MATLAB

simulation with the lowest error value.

For the case of BSA-release from the bi-layered microspheres using COMSOL, we only obtained a slight standard deviation for the BSA diffusion coefficient in chitosan. In contrast, the rest of the parameters had a more significant standard deviation (Table 4). The results for the model average and the best model are virtually the same, with the exception of the initial burst release. In this case, BSA partition coefficients for both models are in good agreement and have values above unity, suggesting that chitosan has a higher drug concentration at the interface than PCL, which is expected. Compared to MATLAB (Table 3), the average parameters of the COMSOL model are about the same, with a more significant difference on the best models.

Figure 6 shows how both average and best models are close together. Furthermore, both models can accurately predict BSA cumulative release behavior from the bi-layered microspheres.

3.2.2. Drug release from Bevacizumab-loaded microspheres

Figure 7 shows the final error value after each complete MATLAB simulation. Arbitrarily, any simulation with a final error value below 450 was considered to have reached the global minimum. In this case, the final parameters for all 50 simulations were used to obtain the average parameters with its standard deviation for the average model. Additionally, the parameters from the simulation with the lowest final error value were

Table 3: Parameter estimation in MATLAB for BSA-loaded chitosan-PCL core-shell microspheres

Average model ± stdv			**Best model**		
(Error value = 210.15 ± 1.16)			(Error value = 208.88)		
Parameter	**Value**	**Units**	**Parameter**	**Value**	**Units**
B	4.25 ± 0.11	%	B	4.07	%
D_{chi}	$2.90\times10^{-15} \pm 0.01\times10^{-15}$	cm^2/s	D_{chi}	2.91×10^{-15}	cm^2/s
D_{PCL}	$3.58\times10^{-12} \pm 1.45\times10^{-12}$	cm^2/s	D_{PCL}	5.89×10^{-12}	cm^2/s
k	1.33 ± 0.65	-	k	0.77	-

B: burst release. D_{chi}: drug diffusion coefficient in chitosan. D_{PCL}: drug diffusion coefficient in polycaprolactone. k: partition coefficient.

Table 4: Parameter estimation in COMSOL for BSA-loaded chitosan-PCL core-shell microspheres

Average model ± stdv			**Best model**		
(Error value = 207.29 ± 0.64)			(Error value = 206.77)		
Parameter	**Value**	**Units**	**Parameter**	**Value**	**Units**
B	4.34 ± 1.23	%	B	3.84	%
D_{chi}	$2.96\times10^{-15} \pm 0.16\times10^{-15}$	cm^2/s	D_{chi}	2.91×10^{-15}	cm^2/s
D_{PCL}	$3.01\times10^{-12} \pm 1.44\times10^{-12}$	cm^2/s	D_{PCL}	2.92×10^{-12}	cm^2/s
k	1.33 ± 0.54	-	k	1.35	-

B: burst release. D_{chi}: drug diffusion coefficient in chitosan. D_{PCL}: drug diffusion coefficient in polycaprolactone. k: partition coefficient.

used to construct the best model.

For the case of bevacizumab release from the bi-layered microspheres, we got a slight standard deviation for the burst and drug diffusion coefficient values in chitosan (Table 5). But a significantly bigger standard deviation for the cases of drug diffusion coefficient in PCL and drug partition coefficient. Comparing the average model with the best model, the parameter results are close together, except for the drug diffusion coefficient in PCL and the drug partition coefficient. This makes sense because, for the average model, these are also the parameters with the highest standard deviation. Both models resulted in k>1 values, suggesting that at the interface, there is a greater concentration of bevacizumab in chitosan concerning PCL, as expected.

Graphically, it can be observed in Figure 8 that the bevacizumab cumulative release for both the average and the best model are overlapping and that the models can predict bevacizumab release profile from

Table 5: Parameter estimation in MATLAB for bevacizumab-loaded chitosan-PCL core-shell microspheres

Average model ± stdv			**Best model**		
(Error value = 441.14 ± 1.51)			(Error value = 439.74)		
Parameter	**Value**	**Units**	**Parameter**	**Value**	**Units**
B	9.79 ± 0.17	%	B	9.65	%
D_{chi}	$2.60\times10^{-15} \pm 0.01\times10^{-15}$	cm^2/s	D_{chi}	2.60×10^{-15}	cm^2/s
D_{PCL}	$3.21\times10^{-12} \pm 1.49\times10^{-12}$	cm^2/s	D_{PCL}	5.91×10^{-12}	cm^2/s
k	1.38 ± 0.52	-	k	1.80	-

B: burst release. D_{chi}: drug diffusion coefficient in chitosan. D_{PCL}: drug diffusion coefficient in polycaprolactone. k: partition coefficient.

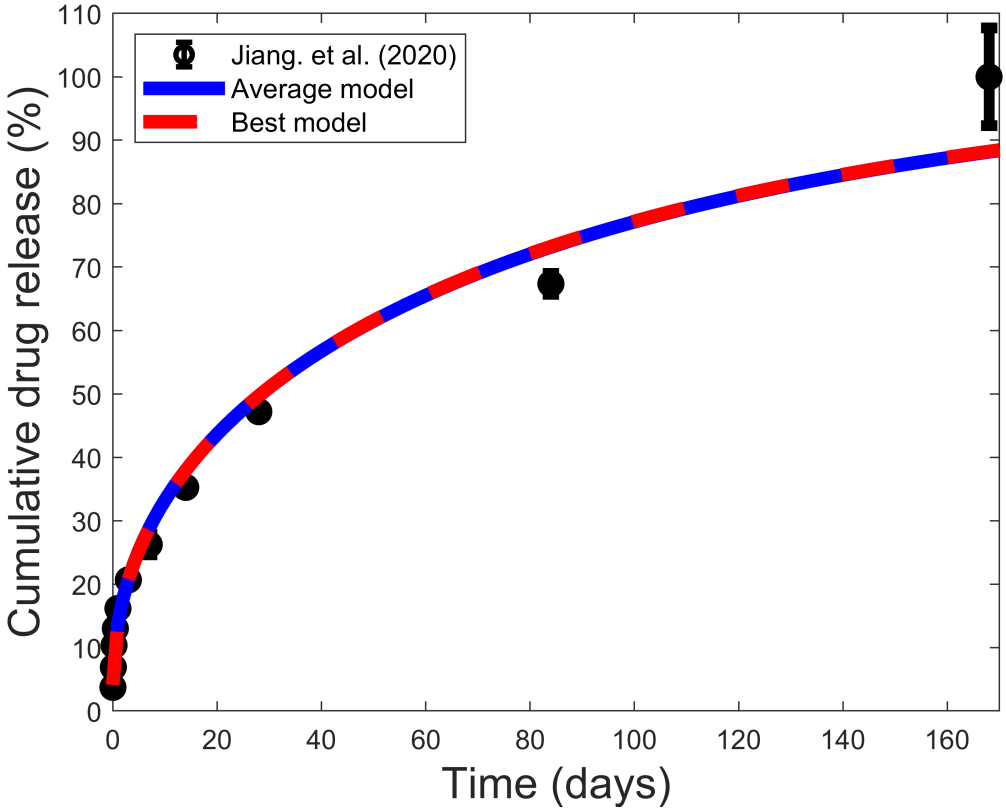

Figure 4: Cumulative drug release comparison from BSA-loaded chitosan-PCL microspheres in MATLAB. Experimental data from from Jiang et al. [8]

the bi-layered microspheres. It is to be noted that the last two data points have high standard deviations, which could explain our higher error values (Table 3) when compared to the errors for the BSA-loaded microspheres (Table 5). This high standard deviation could compromise the efficacy of the model.

Figure 9 shows the final error value after each complete COMSOL simulation. All the simulations with final error values below 450 were considered to be part of the global minimum. Only one simulation was excluded from the average parameter calculation. The remaining parameters were used to obtain the average parameters and the standard deviation for the average model. In contrast, the simulation with the lowest error value was used to obtain the best model.

All our parameter results have negligible standard deviations for the case of bevacizumab release from the bi-layered core-shell microspheres using COMSOL (Table 6). Comparing the average model with the best model, the parameter results are essentially the same, meaning that these parameters were a good fit for the model and representative of the global minimum of the problem. Once again, the partition coefficient value above the unity suggests that the bevacizumab concentration in the chitosan at the interface is greater than the bevacizumab concentration in the PCL, which is expected.

Figure 10 demonstrates that both the average model and the best model overlap, which is expected since

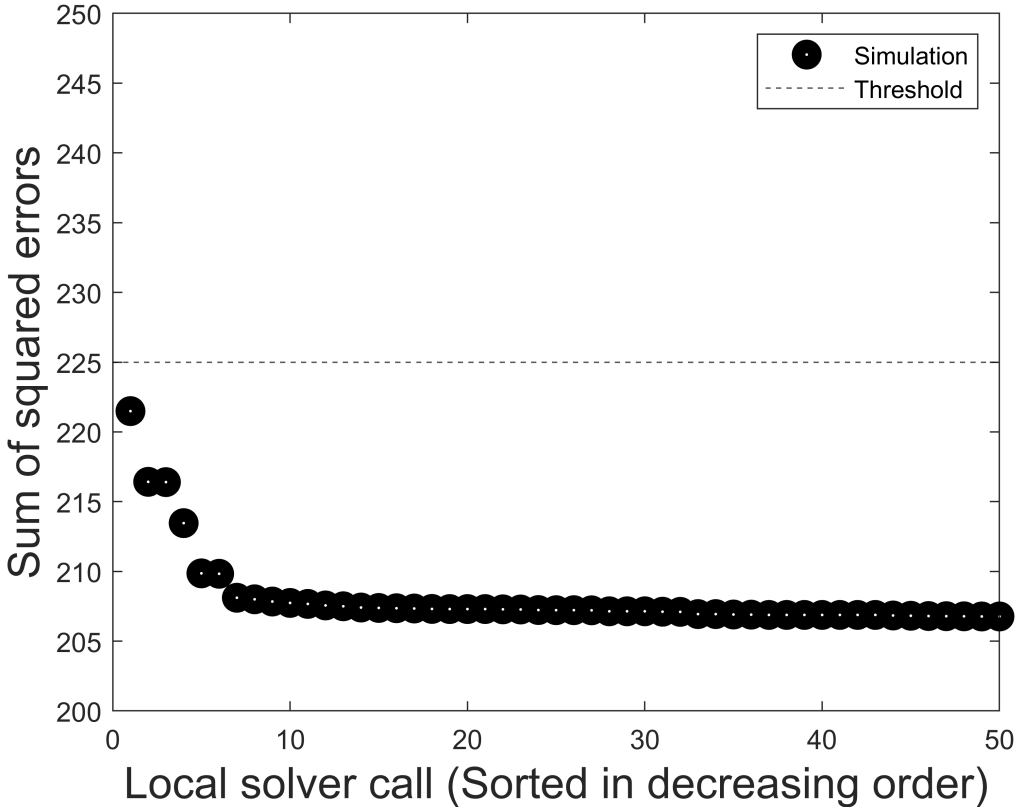

Figure 5: Final error value after each complete simulation in COMSOL

both models essentially present the same parameters. Furthermore, both models can predict bevacizumab release from the bi-layered microspheres. As mentioned before, the last two data points have significant standard deviations, which could explain our higher error values compared to our COMSOL calculations for BSA-release (Figure 4). When comparing MATLAB and COMSOL parameter values, the parameters obtained are similar for burst and drug diffusion coefficient on chitosan but differ in drug diffusion coefficient on PCL and drug partition coefficient. However, both models can predict bevacizumab release behavior from the microspheres.

4. Conclusions

We verified our models by comparing the drug concentration profiles at different locations within the microspheres. The results showed good agreement between both models. However, new data is still required for the validation of our models.

Both finite differences (MATLAB) and finite elements (COMSOL) approaches were able to predict drug release behavior from the BSA- and bevacizumab-loaded microspheres. The average parameter values for both approaches tend to be close. We only performed 50 simulations due to the computational cost,

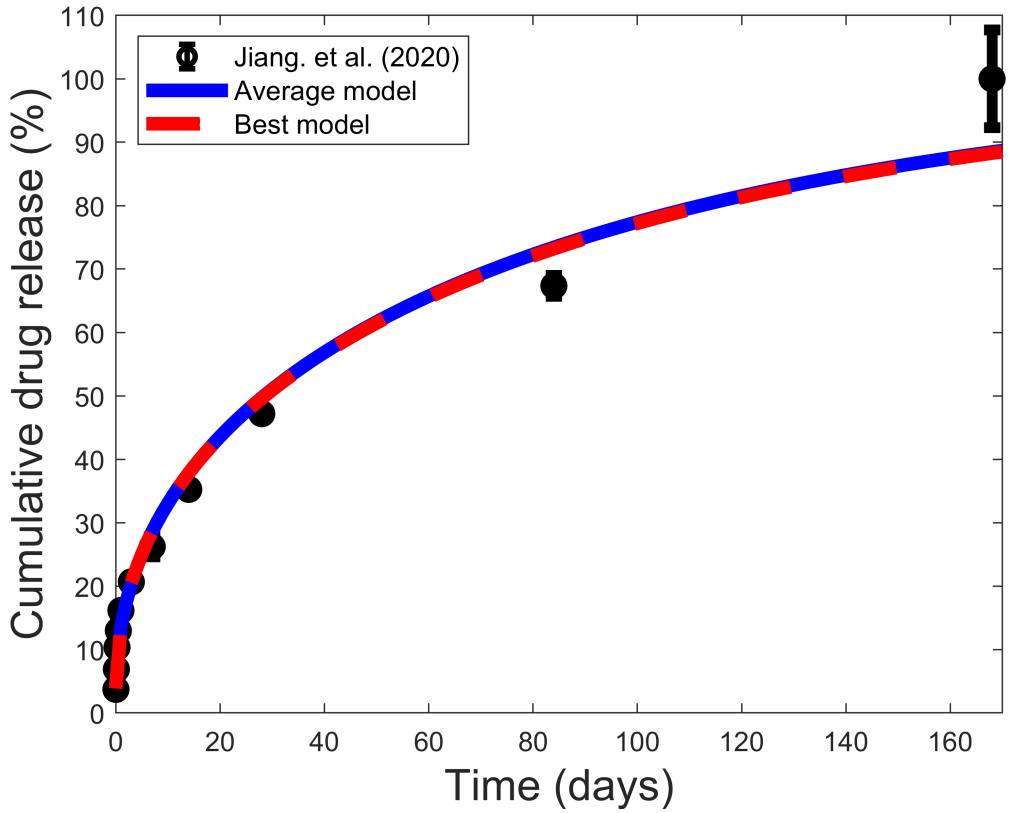

Figure 6: Cumulative drug release comparison from BSA-loaded chitosan-PCL core-shell microspheres in COMSOL. Experimental data from Jiang et al. [8]

but it is expected that the higher the number of simulations, the closer these average models should be. Furthermore, the models tend to be more effective (lower error values) the lower the standard deviations on the experimental data are.

Determining parameters like drug diffusion coefficient in the polymers, burst release, and drug partition coefficient helps to better understand drug release from the bi-layered microspheres. This information can be used to optimize device design computationally (e.g., change the ratio of polymers) to guide experiments and improve wet AMD treatments. The methods described here can be applied to any type of diffusion-controlled bi-layered microsphere and can even be extended to multiple layers to attempt to improve therapies that require long-term release.

Appendix

Interface boundary condition used in the MATLAB script.

$$-D_{ch}\frac{dC}{dr}\bigg|_{r=interface} = -D_{PCL}\frac{dC}{dr}\bigg|_{r=interface} \tag{7}$$

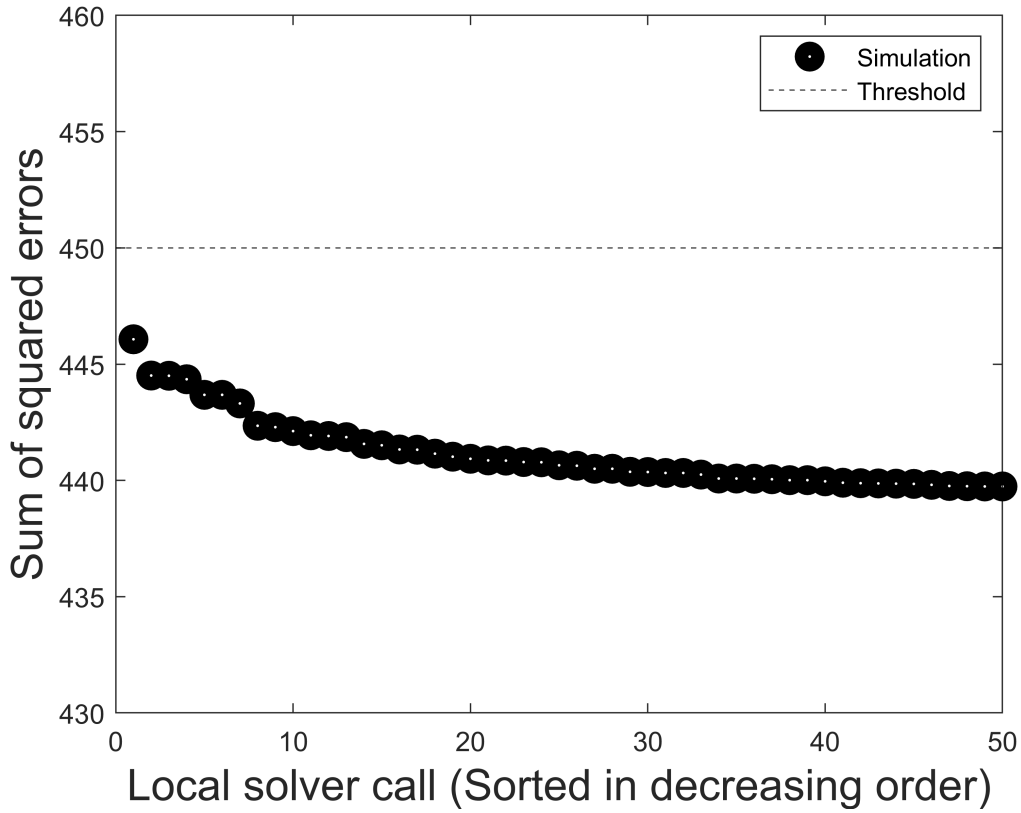

Figure 7: Final error value after each complete simulation in MATLAB

Dividing both sides with respect to the outer radius of the sphere (R) and defining:

$$\alpha = \frac{D}{R^2} \tag{8}$$

We have that:

$$-\alpha_{ch} \frac{dC}{dr}\bigg|_{r=interface} = -\alpha_{PCL} \frac{dC}{dr}\bigg|_{r=interface} \tag{9}$$

At the interface

$$C_{ch} = \kappa C_{PCL} \tag{10}$$

$$\alpha_{ch} \left(\frac{C(rr-1) - \kappa C(rr)}{2\, dr_1} \right) = \alpha_{PCL} \left(\frac{C(rr) - C(rr+1)}{2\, dr_1} \right) \tag{11}$$

$$\frac{\alpha_{ch}}{dr1} \left(C(rr-1) - \kappa C(rr) \right) = \frac{\alpha_{PCL}}{dr2} \left(C(rr) - C(rr+1) \right) \tag{12}$$

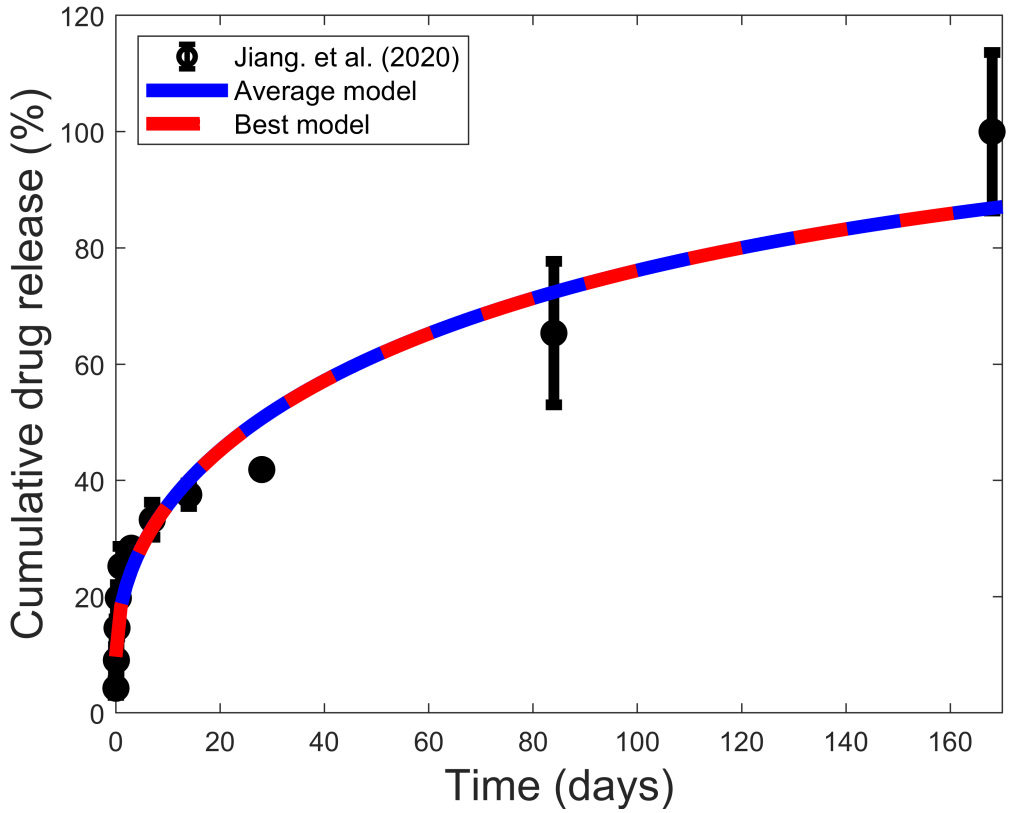

Figure 8: Cumulative drug release comparison from bevacizumab-loaded chitosan-PCL core-shell microspheres in MATLAB. Experimental data from from Jiang et al. [8]

Let

$$\gamma = \frac{\alpha_{PCL}\, dr1}{\alpha_{ch}\, dr2} \tag{13}$$

So that

$$C(rr) = \frac{C(rr-1) + \gamma\, C(rr+1)}{\gamma + \kappa} \tag{14}$$

Applying derivatives with respect to time we have that: So that

$$\frac{dC(rr)}{dt} = \frac{\frac{dC(rr-1)}{dt} + \gamma\, \frac{C(rr+1)}{dt}}{\gamma + \kappa} \tag{15}$$

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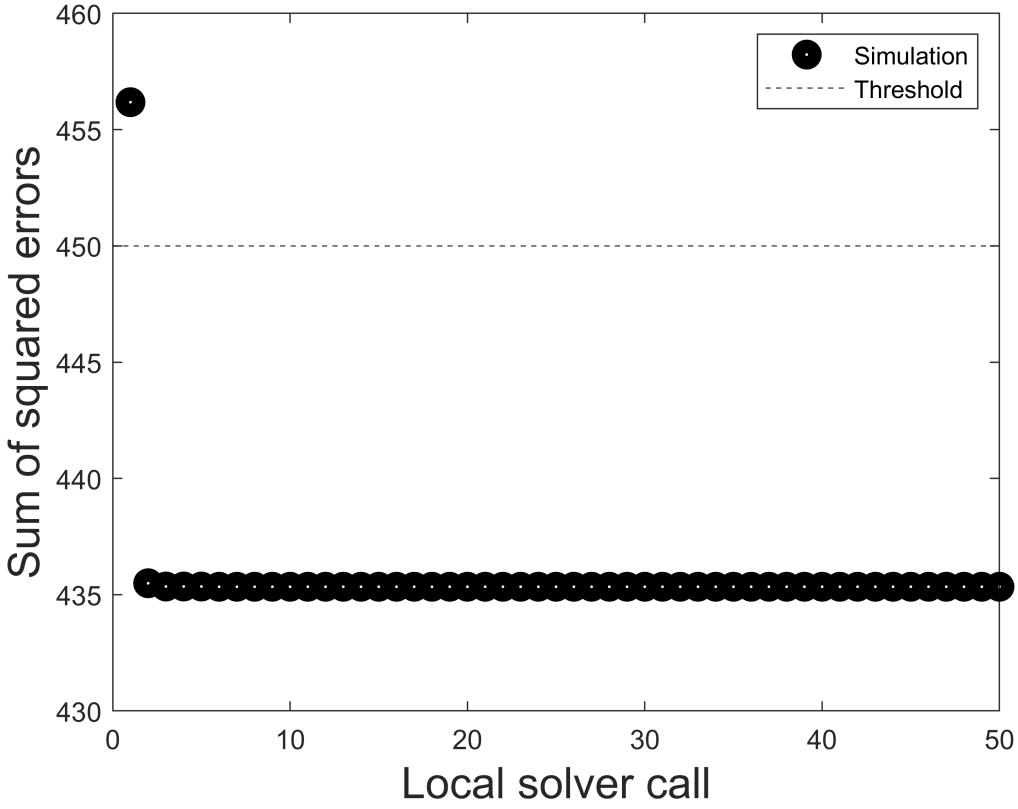

Figure 9: Final error value after each complete simulation in COMSOL

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Table 6: Parameter estimation in COMSOL for bevacizumab-loaded chitosan-PCL core-shell microspheres

Average model ± stdv			**Best model**		
(Error value = 435.34 ± 0.02)			(Error value = 435.34)		
Parameter	**Value**	**Units**	**Parameter**	**Value**	**Units**
B	10.02 ± 0.02	%	B	10.02	%
D_{chi}	$2.57\times10^{-15} \pm 0.004\times10^{-15}$	cm^2/s	D_{chi}	2.57×10^{-15}	cm^2/s
D_{PCL}	$1.06\times10^{-12} \pm 0.003\times10^{-12}$	cm^2/s	D_{PCL}	1.06×10^{-12}	cm^2/s
k	1.06 ± 0.006	-	k	1.05	-

B: burst release. D_{chi}: drug diffusion coefficient in chitosan. D_{PCL}: drug diffusion coefficient in polycaprolactone. k: partition coefficient.

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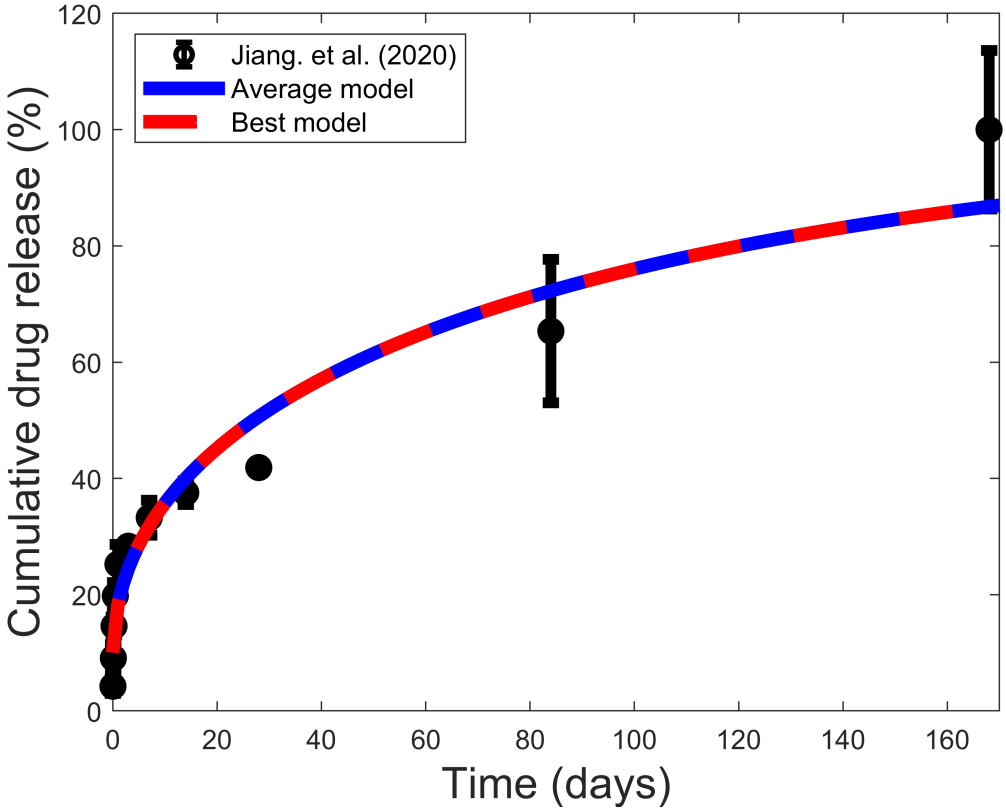

Figure 10: Cumulative drug release comparison from bevacizumab-loaded chitosan-PCL core-shell microspheres in COMSOL. Experimental data from from Jiang et al. [8]

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