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COMPARISON OF COMPUTATIONAL MODELS FOR PREDICTING LEACHING FROM IMPLANTED MEDICAL DEVICES

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INTRODUCTION

Utilization of computational modeling and simulation in medical device development can enable faster development of new products, lower research and development costs, and decrease animal usage. The engineering standard ASME V&V40, "Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices" released in 2018 has made the use of computational modeling more accessible for companies seeking approval or clearance from the US Food and Drug Administration (FDA). Moreover, Regulatory Science Tools (RSTs) and Medical Device Development Tools (MDDTs) approved by the FDA include new computational approaches to aid with submissions that did not exist only a few years ago.

An important aspect of any implanted medical device is biocompatibility, an attribute of which is the need for a device not to release hazardous materials into the body at a level above the safe limit (toxicological threshold). The rate that polymeric components within medical devices leach potentially hazardous materials can be estimated using computational modeling.

In this research, two computational models are developed and compared. The first is a one-component model that predicts the rate that materials are leached from an implanted polymeric medical device using Fickian diffusion equations and a sink boundary condition at the polymer tissue interface. The second model contains two components and adds complexity and clinical relevance by accounting for migration across the polymer tissue interface and diffusion through peri-implant tissue. Differences in the modeling results are compared and the advantages of each approach are identified.

METHODS

Physics based models were developed to calculate the diffusion rate of leachables using Fick's law [1],

$$\frac{\partial C(x,t)}{\partial t} = D_p \nabla^2 C(x,t) \tag{1}$$

where, the concentration of the leachable substance, C, is a function of the position within the polymer, x, and time, t. D_p is the effective (macroscopic) diffusion coefficient of the leachable in the polymer. D_p is scalar and independent of C, x, and t.

The one-component model for the mass release $M(\tau)$ as a fraction of the initial mass of leachable contained within the device M_0 is given by,

$$\frac{M(\tau)}{M_0} = \begin{cases} 2\sqrt{\frac{\tau}{\pi}} & \tau \le 0.2 \\ 1 - \frac{8}{\pi^2} exp\left(-\frac{\tau \pi^2}{4}\right) & \tau > 0.2 \end{cases} \tag{2}$$

$$\tau = \frac{D_p\, t}{L^2} \tag{3}$$

where τ, is a dimensionless time parameter that is scaled by D_p, and half the implant thickness, L.

Leaching from the two-component model is characterized by the equation below [2],

$$\frac{M(\tau,\beta)}{M_0} = \left(\frac{\beta}{1+\beta}\right) 2\sqrt{\tau}\left(\frac{1}{\sqrt{\pi}} - \left(\frac{\beta}{1+\beta}\right) 2 \sum_{n=1}^{\infty}\left[\left(\frac{1-\beta}{1+\beta}\right)^{n-1} ierfc\left(\frac{n}{\sqrt{\tau}}\right)\right]\right) \tag{4}$$

$$\beta = \frac{1}{K_{p:t}} \sqrt{\frac{D_t}{D_p}} \tag{5}$$

where, β, is a dimensionless parameter associated with migration across the polymer-tissue interface and the relative migration rate within the polymer, $K_{p:t}$, is the polymer tissue partition coefficient, and D_t, is the diffusion rate of the leachable within the tissue.

Numerical solutions were developed using custom MATLAB code to characterize a "general medical device". Thus, the solutions presented are applicable to any implanted device that contains polymeric material. Two cases were used as an example 1) the release of Bisphenol A (BPA) from a silicone device and 2) the release of Irganox 1010 from a device made from high density polyethylene (HDPE). The first case is representative of small molecules diffusing through a high diffusivity polymer where $\log_{10} \beta$ = - 1.27. The second case represents the other extreme, a large molecule diffusing through a low diffusivity polymer where $\log_{10} \beta$ = 2.40.

RESULTS

For BPA in silicone the one-component model estimated complete mass release (M/M_0 = 100%) within about 8 hours, but the more complex two-component model only predicted 35.3% mass release in 24 hours (Figure 1a). For Irganox 1010 in HDPE the one-component model and two-component model have visibly identical results with the first line being totally covered by the second (Figure 1b). Both models predict a mass release of 0.15% of the total mass in the first 24 hours.

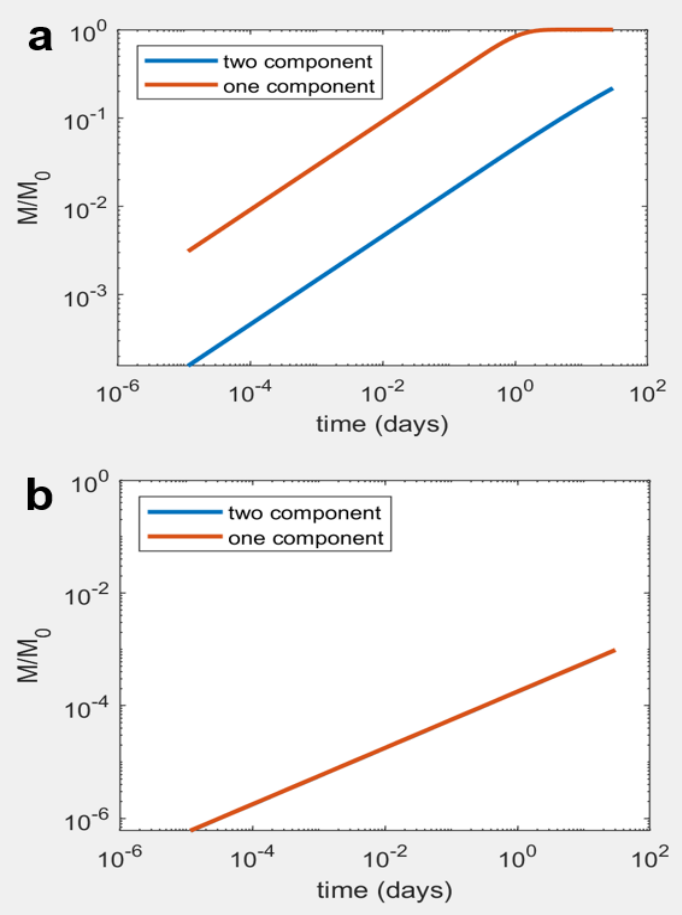

Figure 1: Comparison of model results for cumulative mass release of BPA in silicone (a) and Irganox 1010 in HDPE (b).

Figure 2 shows the difference in predicted mass release using the two models to be indistinguishable over much of the clinically relevant input parameter range (Deep blue area on the top portion). However, when the value of β was small, large differences were observed in the predicted mass release, exceeding four orders of magnitude in some instances.

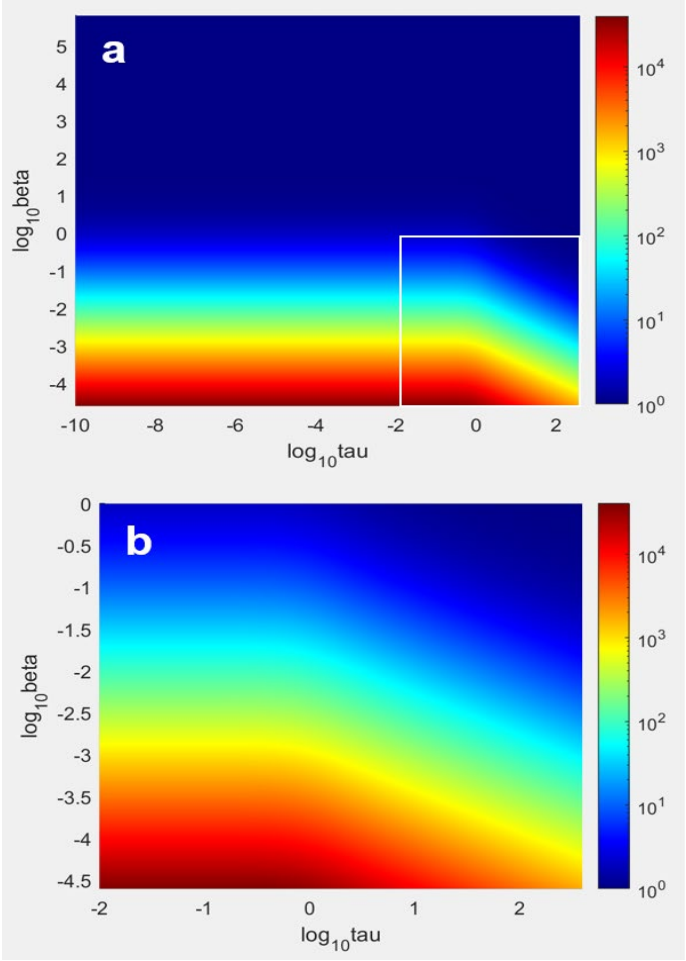

Figure 2: The ratio of predicted mass release (one-component model / two-component model) is shown over the typical range of input parameter values (a) and in a close-up section (b).

DISCUSSION

The findings imply that the one-component model may be sufficient to predict the mass release in cases like Irganox 1010 in HDPE because the two models yield essentially the same result. This effect was also observed in general for other cases where values of β are high. Thus, in these cases, it may not be beneficial to apply the more complex model when the simpler model predicts the same outcome.

However, in the case of BPA in silicone, mass release predicted by the one-component model exceeded the two-component model by an order of magnitude. When clinically relevant predictions of mass release are desired, use of the more complex two-component model may be warranted.

ACKNOWLEDGEMENTS

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