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Tissue Diffusion and Two Component Computational Model to Predict Leaching from Medical Devices

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INTRODUCTION

Implanted polymeric medical devices can pose a risk to human health when they contain potentially hazardous materials that leach into the body. Historically, extraction experiments and animal studies have been used to estimate the amount of material released. However, these approaches are changing. Fueled by increases in computational capabilities, computer models can now be used to predict the amount of material released over time. These simulations can complement traditional extraction studies and yield several benefits for regulatory science. First, the models can be used to simulate a more realistic environment than the harsh conditions used in extraction studies. Second, because the models contain system specific input parameters, they can be easily adapted to other polymer types or leachable chemicals making it easy to analyze a multitude of different systems. Third, once the models are developed and validated, simulations can often be run in seconds saving the weeks or months needed for extraction studies. This can help medical device companies to accelerate new product development getting new devices to market faster. Finally, reducing the effort needed to meet regulatory requirements will reduce overall product development costs.

The FDA has already developed regulatory science tools for rapid risk assessments of color additives in medical devices. These tools use physics-based models to predict the amount of material that may be released from an implanted polymeric medical device. In this research, models will be extended beyond a one component system (implant only) to a two-component system that also includes the surrounding tissue.

METHODS

A two-component mathematical model was developed to characterize the migration of leachable chemicals from an implanted polymeric device into the surrounding tissue (Figure 1). The model assumes that the leachable chemical is homogeneously distributed throughout the implant and that the implant will remain structurally consistent throughout the duration of the simulation (i.e., no degradation or swelling). Human tissue surrounding the implant was also modeled. Tissue was assumed to be quasi-static with consistent material parameters over the duration of the simulation. The mathematical model estimates the amount of material released over a time period of one day (24 hours). When this quantity is less than the allowable daily dose for the leachable chemical, the risk associated with potential exposure to the chemical is considered acceptable.

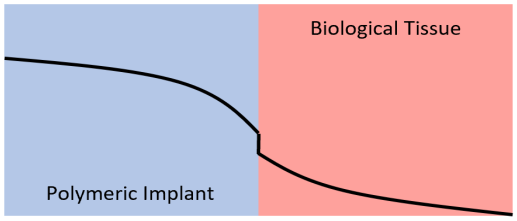

Figure 1: Two-component model shows diffusion through the implant (blue), across the partition, and into the surrounding tissue (red).

Fick's law was used to predict diffusion through the implant and the tissue.

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

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 polymer-tissue partition coefficient, K, was used to predict migration across the polymer-tissue interface. Due to differences in hydrophilicity/lipophilicity, the migrating chemical can have a different affinity for the polymer than the tissue which can lead to a step change in concentration at the interface. Our model utilizes equations originally developed by Gandek to characterize migration of potentially hazardous

materials into food from its surrounding packaging [1]. The amount of material release, M_τ is, given by,

$$M_\tau(\tau) = \left[\frac{2\beta}{1+\beta}\right]\sqrt{\frac{\tau}{\pi}}\left\{1 - \frac{2\beta}{1+\beta}\sum_{n=1}^{\infty}\left[\frac{1-\beta}{1+\beta}\right]^{n-1}\left[e^{\left(\frac{-n^2}{\tau}\right)} - \frac{n\sqrt{\pi}}{\sqrt{\tau}}erfc\left[\frac{n}{\sqrt{\tau}}\right]\right]\right\} \quad (2)$$

$$\tau = \frac{D_p\, t}{L^2} \quad (3) \qquad \beta = K\sqrt{\frac{D_t}{D_p}} \quad (4)$$

where, τ is a dimensionless time parameter, β is a dimensionless parameter that consists of the partition coefficient, K, and the tissue and polymer diffusion coefficients D_t and D_p. Values for D_p for various chemical-polymer combinations were obtained from FDA databases and polymer tissue partition coefficients were previously developed by the co-authors [2]. Tissue diffusion coefficients were determined through literature review. Searches on Scopus, SciFinder, and Google Scholar were utilized. Forward and backward snowballing was also used to expand the search. Models were verified by comparing results to those developed by Crank [3].

$$M(\tau) = \begin{cases} 2M_0\sqrt{\tau/\pi} & \tau \le 0.2 \\ M_0\left(1 - 8\exp\left[-\tau\pi^2/4\right]/\pi^2\right) & \tau > 0.2 \end{cases} \quad (5)$$

Equations 2 and 5 are identical models with different boundary conditions that converge to the same solution at low values of K and high D_t. While it is not feasible to analyze all possible combinations of polymer types, leachable chemicals, and tissue types, several cases were considered that represent a broad range of input parameter combinations. Furthermore, results over the expected range of parameter values were calculated.

RESULTS

Tissue diffusion values were found for 307 different combinations of chemicals and tissues (Figure 2). These were grouped into barrier tissues (red) and non-barrier tissues (blue). Because an implanted device is often located against cut tissue the higher diffusion rates associated with non-barrier tissues were used for the model.

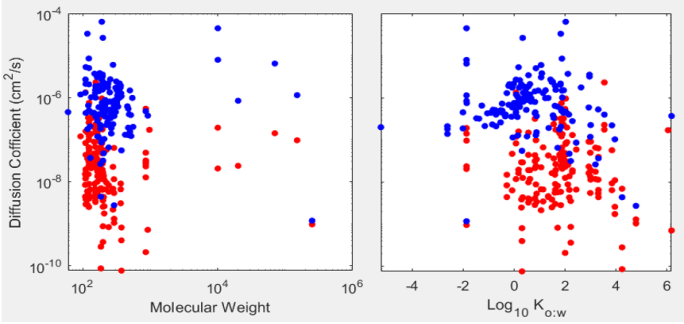

Figure 2: Tissue diffusion data as a function of molecular weight and octanol-water partition coefficient (hydrophobicity)

Table 1 shows the mean value by group and the two inner quartiles (25% and 75%). The 5% and 95% values were estimated from these inner quartiles, but values are only estimates because there is no confirmation that the distribution is normal.

Table 1: Diffusion for barrier and non-barrier tissues (x10^{-6} cm^2/s)

Tissue Type	5%	25%	mean	75%	95%
Barrier	0.0010	0.0057	0.0201	0.0612	0.3387
Non-Barrier	0.1145	0.3510	0.6500	1.6657	5.1055

Using the values for K, D_t and D_p, the results of equation 2 were calculated. Large variability in D_p led to large variability in τ causing it to range in value from 10^{-13} to 10^{1}. Similarly, β spans a large range from 10^{-3} to 10^{9}. This yields material release quantities that span over 20 orders of magnitude.

One of the main objectives of the two component model was to determine conditions where use of the more complex model (Eq. 2) yields more clinically relevant results than the simpler one component model (Eq. 5). Several cases were considered. The case that yielded the greatest difference (1), several intermediate combinations (2 – 6), and the case that yielded the smallest difference (7). Results showed that for case 1, the one-component model could overestimate material release by as much as 445 times (Figure 4). Several intermediate cases are also shown in the figure. For case 7 (not shown), there was no difference in results between the one and two component models.

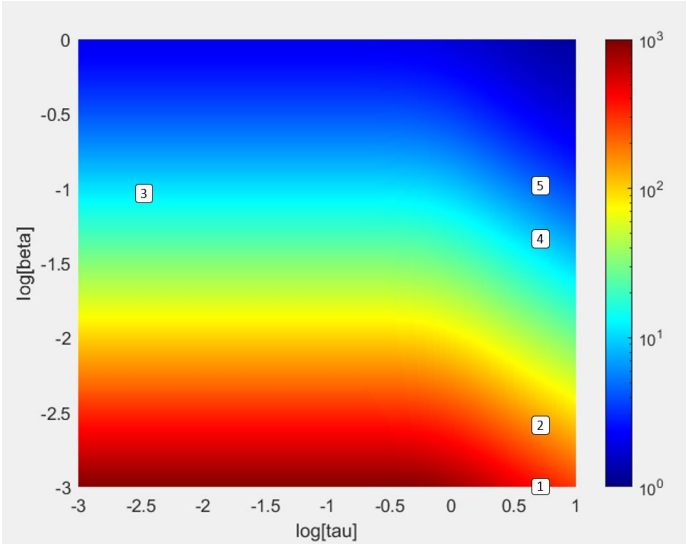

Figure 4: Ratio of one-component to two-component models. Results for case 1-5, respectively; 445, 188, 13.4, 12.6, 5.8

DISCUSSION

When analyzed over a large range of values, the more complex two-component model predicted lower quantities of leached material than the more conservative one component model. Differences in predictions could imply that the more clinically relevant two component model should be adopted. However, when clinically relevant values for K, D_t and D_p are used, it was apparent that the conditions where the two-component model is needed is limited. Conditions where this occurs include migration through high diffusion rate polymers such as silicones, hydrophobic leachables that have reduced transport across the implant-tissue barrier, and tissues with lower chemical diffusion rates. Overall, these findings have enhanced our understanding of chemical migration across multicomponent systems.

ACKNOWLEDGEMENTS

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