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Mathematical Modeling of Triamcinolone Acetonide Drug Release from the I-vation™ Intravitreal Implant (A Controlled Release Platform)

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***Abstract*—In-vitro drug release of triamcinolone acetonide from the I-vation™ implant can be controlled and tuned by varying its formulation ingredients. These release characteristics can be modeled using a parabolic partial differential equation to describe one dimensional Fickian drug diffusion in a durable polymer matrix.**

I. Introduction

THE I-VATION™ implant is an intra-ocular drug delivery platform. It consists of three key components; a nonferrous metallic scaffold in the shape of a helix, a cap that is attached to the helix, and a drug loaded polymer coating that encapsulates the helix. The helix design facilitates ease of implantation into the Pars Plana region of the eye. When fully implanted the bottom of the cap is seated on the sclera, the coated helix is immersed in the vitreous fluid, and the top of the cap is covered by the conjunctiva. The design is integral to maximizing the drug payload that can be delivered while maintaining the ability to discontinue treatment by removing the implant. A picture of an I-vation™ Intravitreal Implant can be seen in figure 1.

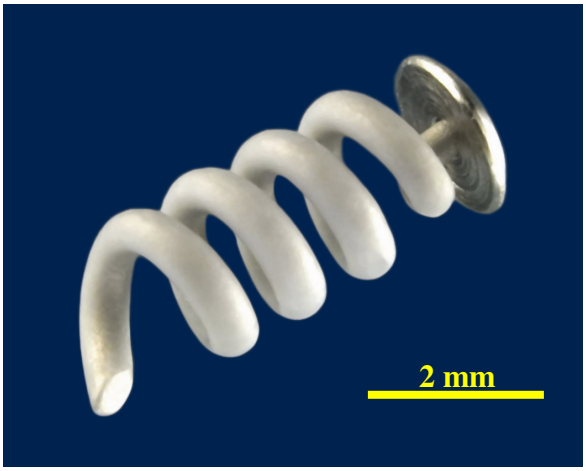

Fig. 1. I-vation™ Intravitreal Drug Delivery Platform

In principle the I-vation implant can be coated with many different types of polymers and many different types of drugs. Also, depending on a variety of factors, the platform has the ability to deliver drug for a year or more. This paper focuses on triamcinolone acetonide delivery and modeling its release from the Bravo™ class of polymers developed by SurModics, Inc.

The Bravo Drug Delivery Polymer Matrix is a durable coating technology designed for the site-specific delivery of low molecular weight hydrophobic drugs. The Bravo matrix, the drug delivery system used on the first-to-market drug-eluting coronary stent, is a proprietary blend of poly-butyl methacrylate (PBMA) and polyethylene vinylacetate (PEVA) polymers. By varying the ratios of the constituent polymers in the coating, drug delivery rates and mechanical properties can be controlled.

Triamcinolone acetonide (TA) is a synthetic corticosteroid small molecule hydrophobic drug. It is an anti-inflammatory drug that is sometimes administered through intravitreal injections in off label use to treat macular degeneration. It has a molecular weight of 434.5 g/mol and a solubility of ~10 µg/mL in Phosphate Buffer Solution (PBS) (37ºC, pH 7.4). The molecular structure of TA can be seen in figure 2.

Mathematical modeling the release characteristics of TA

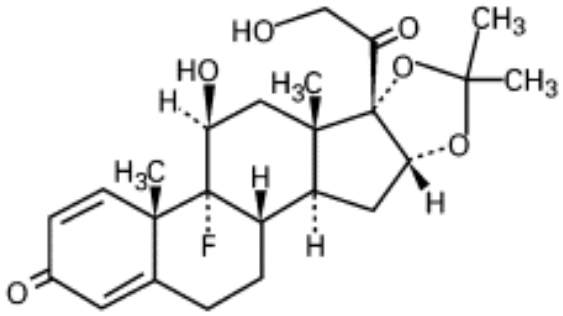

Fig. 2. Triamcinolone Acetonide ($C_{24}H_{31}FO_6$)

from the I-vation implant is useful because it allows for the following activities.

- Early prediction of long term release behavior
- Elucidation of drug release mechanisms
- Expediting formulation optimization
- Developing in-vitro to in-vivo drug release correlations
- Pharmacokinetic modeling

These activities are important because drug release to the target tissue must be tailored so the localized concentration of the pharmaceutical is in the therapeutic window.[1] The implantable drug delivery devices must release the active ingredient to the target tissue such that the drug concentration stays below the toxicity limit but is high

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enough to have a pharmacological effect. Also, the release must be sustained long enough to make the implantable dosage form more convenient from a patient compliance perspective.

II. Experimental Methods

I-vation implants were manufactured using SurModics, Inc. proprietary coating processes. Three different coating formulations were prepared. The formulations contained 100 µg, 500 µg, and 925 µg of drug respectively.

In-vitro drug release data was obtained using a time course elution method designed to maintain the product near sink conditions for mass transfer. I-vation TA implants were immersed in individual vials containing 4 mL of PBS (37ºC, pH 7.4). The individual vials were stored in a heated orbital shaker at 37ºC. At predetermined intervals fresh aliquots of PBS were exchanged with the resident elution PBS aliquots in the vials. Each resident elution PBS aliquot was assayed for drug content via UV-VIS spectroscopy (λ = 242 nm). Cumulative drug elution curves were generated by summing the amount of drug released into the individual drug elution aliquots for each independent implant over the time course of the experiment.

III. Physical Analysis and Model Development

A. Physical Analysis

Figure 3 shows a cross section of an individual I-vation implant and how the coating conforms to the helical scaffold.

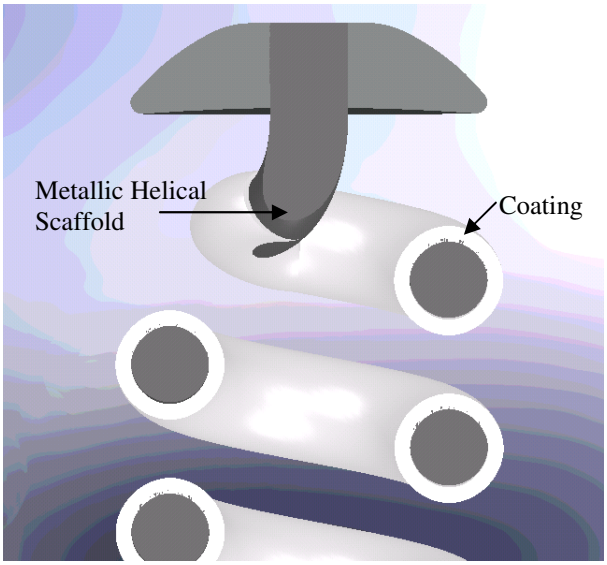

Fig. 3. CAD Drawing of Cross Sectioned I-vation Implant

The geometry of the coating is such that it encapsulates the helical scaffold. The mathematical model developed for this paper use cylindrical coordinates taking advantage of the circular geometry.

B. Mass Transport Dynamics

Immediately after the I-vation implant is placed in PBS solution any free drug on the surface that is not encapsulated in polymer begins to dissolve. During this process water begins to slowly penetrate into the coating matrix dissolving drug and acting like a transport medium through which more drug can move. This general process of mass transport from high concentration to low concentration through a stagnant polymer matrix can be described mathematically using Fick's Second Law of Diffusion.[2]

$$\frac{\partial C_{TA}}{\partial t} = D_{TA}\nabla^2 C \tag{1}$$

The model developed uses cylindrical coordinates and the Θ and z dependencies were removed because of symmetry. The simplified version of equation 1 follows.

$$\frac{\partial C_{TA}}{\partial t} = \frac{1}{r}\left[\frac{\partial}{\partial r}\left(rD_{TA}\frac{\partial C_{TA}}{\partial r}\right)\right], \quad R_1 < r < R_2 \tag{2}$$

Where D_{TA} is the effective diffusivity of TA in the coating matrix, R_1 is the radius at the scaffold/coating interface, and R_2 is the radius at the coating PBS interface.

Initially, within the coating matrix, the drug concentration is at a maximum and it is constant throughout the coating.

$$C_{TA}(r, t=0) = C_{TA}^{Init} \tag{3}$$

At the scaffold/coating interface there is a no flux boundary condition as the drug can not penetrate the metallic scaffold.

$$r = R_1 : \frac{\partial C_{TA}}{\partial r} = 0, (t > 0) \tag{4}$$

At the coating/PBS boundary there is mass flux equality.

$$r = R_2 : D_{TA}\left[\frac{\partial C_{TA}}{\partial r}\right]_{(R_2,t)} = K_M(K \cdot C_{TA}[R_2, t] - C_{TA}^{PBS}) \tag{5}$$

Where K_M is a mass transfer coefficient and K is a TA coating matrix/PBS partition coefficient.[3]

C. Mathematics and Model Simplification

Nondimensionalization and scaling were used to simplify the model, initial condition, and boundary conditions. The following scaling factors were used. Note: * Indicates dimensionless variables.

$$C_{TA}(r,t) = C_{TA}^{Init} \cdot c_{TA}^{*}(r^{*}, t^{*}) \tag{6}$$

$$t = \frac{\Delta R^2}{D_{TA}} \cdot t^{*} \quad \text{where,} \quad \Delta R = R_2 - R_1 \tag{7}$$

$$r = r^{*}\Delta R + R_1 \tag{8}$$

$$\varepsilon = \frac{\Delta R}{R_1} \tag{9}$$

After applying the scaling factors and expanding the partial derivative with respect to r* the following dimensionless model was obtained.

$$\frac{\partial c_{TA}^*}{\partial t^*} = \frac{\varepsilon}{\varepsilon \cdot r^* + 1}\frac{\partial c_{TA}^*}{\partial r^*} + \frac{\partial^2 c_{TA}^*}{\partial r^{*2}}, \quad 0 < r^* < 1 \qquad (10)$$

With initial condition,

$$c_{TA}^*(r^*, t^* = 0) = 1 \qquad (11)$$

and the following boundary conditions. Note: It is assumed the implant is maintained under sink conditions for mass transfer thus C^{PBS}_{TA} in equation 5 has been set to 0.

$$r^* = 0 : \frac{\partial c_{TA}^*}{\partial r^*} = 0, (t^* > 0) \qquad (12)$$

$$r^* = 1 : \frac{\partial c_{TA}^*}{\partial r} = Biot_M \cdot c_{TA}^*[1, t > 0] \qquad (13)$$

The following table shows the key parameters that were used to model the release characteristics for I-vation TA.

Table I
Key Parameters

Symbol	Quantity	Units
D_{TA}	Effective TA Diffusivity	$\frac{cm^2}{day}$
$Biot_M \# = \frac{K_M K \Delta R}{D_{TA}}$	Ratio of external mass transfer to internal mass transfer	None
$\varepsilon = \frac{\Delta R}{R_1}$	Ratio of coating thickness to scaffold inner radius	None
M^0_{TA}	Initial drug loading	mcg

D. Mathematics, Model Simulation, and Parameter Estimation

The dimensionless concentration was expanded using a power series asymptotic expansion in terms of ε and substituted into equation 10.[4] The resulting parabolic partial differential equation was grouped in terms of ε and solved to O(1) accuracy. Differential equation solving was accomplished using the "pdepe" function in MATLAB. An iterative error minimization algorithm was employed using the "lsqnonlin" function in MATLAB to fit the data and extract optimized model parameters that give the best agreement between model data and experimental data. Model parameters were extracted using 30 days or less of experimental data. Figure 4 shows a flow chart of the data optimization technique.

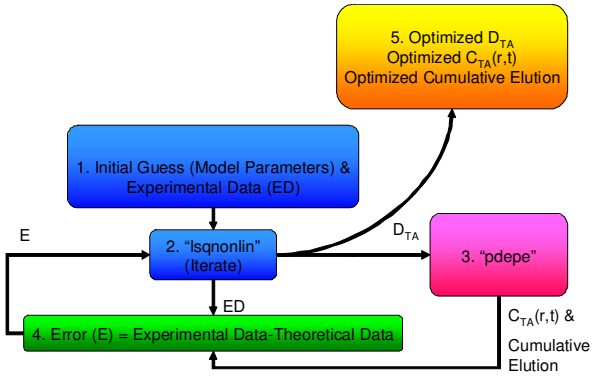

Fig. 4. Data Optimization Technique

E. Theoretical Cumulative Elution

The theoretical cumulative elution (CE_{TA}) was calculated at each experimental data time point by subtracting the theoretical amount of drug left in the coating (M_{TA}) from the theoretical initial drug load (M^0_{TA}). An expression for this can be seen below.

$$CE^t_{TA} = M^0_{TA} - M_{TA} \qquad (14)$$

$$= M^0_{TA}\left(\int_0^1 c_{TA}^*[r^*, 0]dr^* - \int_0^1 c_{TA}^*[r^*, t^*]dr^*\right) \qquad (15)$$

IV. Results

A. Prediction of Long Term Behavior

The overlay of all three formulas with model predictions can be seen in figure 5.

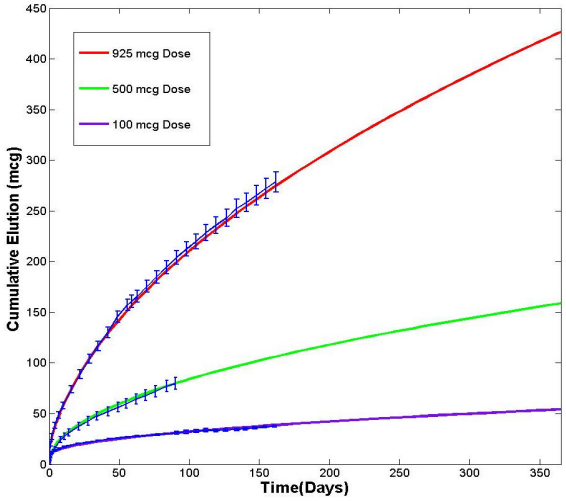

Fig. 5. Overlay of three TA doses including experimental data and model data. (n = 7 for all doses, error bars represent +/- 1 standard deviation)

As can be seen the release rate of TA can be controlled over a broad range of release rates by varying the composition of the coating. There is very good agreement between the model data and the experimental data. Plots such as these allow for prediction of long term drug release with a minimum amount of experimental data.

Another interesting way to prepare and analyze the data is to look at the plot of elution rate vs. time. This is the derivative of the cumulative elution plot and it is also the total mass flux of drug out of the coating per day over time. The elution rate is akin to the dosing regimen for other drug products. See figure 6 for the elution rate vs. time.

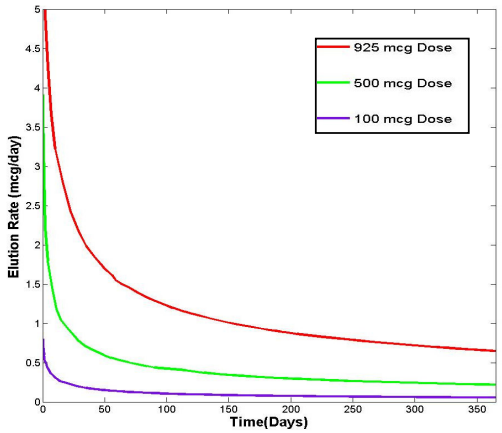

Fig. 6. TA Elution Rate vs. time

As is characteristic of unsteady diffusion limited release, the rate is ever changing as it starts out high and quickly decreases to a quasi-steady level.

Table II shows the model parameters that were determined for each formula.

Table II
Model Parameters

Formula (M^0_{TA})	D_{TA}	$\frac{K_M K \Delta R}{D_{TA}} = Biot_M\ \#$	$\varepsilon = \frac{\Delta R}{R_1}$
100 mcg	1.19E-7	5.04	0.33
500 mcg	4.46E-8	4.04	0.33
925 mcg	2.05E-7	1.32	0.44

V. Discussion

A. Key Parameters and their Effect on Modeling

The key parameters shown in Table II influence the slope, curvature, and the maximum amount of drug released on the cumulative elution curve.

The diffusivity of TA (D_{TA}) in the polymer matrix is a measure of how fast the drug moves in the coating. Some of the factors that can influence this are; drug molecular weight, drug affinity for coating matrix, coating microstructure/porosity, drug/polymer phase separation, hydrophilicity of excipients, drug polymorph form, and polymer Tg. In general the larger the diffusivity the faster the drug release.

The mass transfer biot number ($Biot_M$ #) is a dimensionless quantity that arises from nondimensionalizing the model. This number is a ratio of external mass transfer to internal mass transfer. Some of the factors that influence the individual variables that make up this number include; elution media turbulence, elution media temperature, elution media composition, and the factors listed previously for the diffusivity.

Epsilon (ε) is a dimensionless quantity comprised of the ratio of the average coating thickness to average inner scaffold radius. The values for ε used in the model were based on the actual measured geometry of I-vation implant. The importance of this variable arises from the power series expansion of the dimensionless concentration of TA in the coating. The smaller the value ε becomes the more justified the model becomes in terms of solving it to O(1) accuracy.

The initial drug load (M^0_{TA}) is an important variable in setting the maximum drug that can be eluted from the coating matrix. This sets an upper bound or asymptote on the cumulative elution curve. It also plays a role in determining the rate of drug release as similar coating thicknesses with higher drug loading are more concentrated and have a higher driving force for mass transer.

B. Model Limitations and Future Work

The model developed generally describes diffusive mass transport in durable coating matrices. This model may not be applicable to polymer matrices that biodegrade or bioerode quickly as they would likely display biphasic or multiphasic character.[5]

This model can easily be augmented to incorporate reactive terms and/or biodegradation terms to more accurately characterize systems for which it would apply.

Lastly, the data extracted from this model can be used as input data to phamacokinetic modeling simulations such as tissue compartment models to predict the concentrations of drug in tissues of interest.

VI. Conclusion

An unsteady state diffusive model has been developed and utilized to characterize the cumulative release of triamcinolone acetonide from the I-vation intravitreal implant. The model data adequately fits the experimental data and extrapolates to longer times for which there is no experimental data. Utilizing these principles can increase the efficiency of the product development process and decrease the time to market for other controlled drug delivery systems.

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