A Pharmacokinetics Model for Injection-Delivered Subcutaneous Drug Deposits

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Version: 1.0
(March 10, 2017)

Abstract

In this technical report, we present a hybrid theoretical-empirical model to describe and support the design of the exposure profiles for subcutaneously delivered drugs that form a solid deposit in subcutaneous tissue. Our primary goal is to develop approaches that are practical and predictive (*e.g.*, relationships between model parameters and injection parameters). Our model is a two-compartment model involving transport of drug through a porous medium (subcutaneous tissue), first-order elimination kinetics, and the Noyes-Whitney equation for dissolution rate. By solving the evolution equations, we derive expressions for the time-dependence of the plasma concentration and mass of the drug deposit. We then analyze these solutions to develop approaches for determining model parameters, characterizing the subcutaneous transport process, and providing physical interpretations that could potentially be useful to guide the design of injection protocols.

Key Technical Results

- Physical models for absorption, elimination and dissolution.
- Closed-form solutions for plasma concentration and mass of drug deposit.
- Analysis method for estimating model parameters.
- Analysis method for determining the mechanism of transport through subcutaneous tissue.
- Empirical model for effective surface area of drug deposit in terms of injection control parameters.
- Interpretation of fitted model parameters for effective surface area in terms of geometric properties of drug deposit.
- Predictive (empirical) model for depletion time of drug deposit.

Introduction

Subcutaneous administration of drugs to patients provides various advantages over oral and intravenous delivery mechanisms. However, to be reliable and controllable, it is important to have a practical framework for understanding the pharmacokinetics of subcutaneous drug delivery.

In this technical report, we develop a hybrid theoretical-empirical pharmacokinetic model for a subcutaneously delivered drug that forms a solid deposit in the subcutaneous tissue. We use a two-compartment model based on

- a model of the subcutaneous tissue as a porous medium,
- first-order elimination kinetics, and
- the Noyes-Whitney equation for the drug dissolution rate.

By solving the evolution equations, we derive closed-form expressions for the time-dependence of the plasma concentration and mass of the drug deposit. We then analyze these solutions to develop approaches for determining model parameters, characterizing the subcutaneous transport process, and providing physical interpretations that could potentially be useful to guide the design of injection protocols.

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Notation

- k_A: absorption rate coefficient for diffusion-dominated subcutaneous transport
- C: concentration of drug in plasma
- C_{inject}: concentration of drug in injection
- C_{SC}: concentration of drug in subcutaneous tissue surrounding drug deposit
- C_{steady}: concentration of drug in plasma at steady state
- $t_{depleted}$: deposit depletion time
- D: diffusion coefficient of drug
- k_D: dissolution rate coefficient (empirical)
- C_S: drug solubility
- A: effective surface area of drug deposit
- $A^\dagger$: effective surface area of drug deposit (scaled by physical constants)
- k_E: elimination rate coefficient
- m_0: initial mass of drug in deposit
- m: mass of drug in deposit
- α, β, γ: miscellaneous model fitting coefficients
- L: thickness of drug dissolution boundary layer
- t: time
- Q: volumetric flow rate of fluid through subcutaneous tissue
- $Q^\dagger$: volumetric flow rate of fluid through subcutaneous tissue normalized by volume of plasma in circulatory system
- V_{plasma}: volume of plasma in circulatory system
- V_{inject}: volume of drug injection

Model Equations

Two-Compartment Model

We model the transport of drug from the subcutaneous drug deposit to the plasma using a two-compartment model with compartments representing (i) the drug deposit and (ii) the plasma. The flow of drug through these compartments from administration through elimination can be modeled as a three stage process.

1. Drug in the deposit dissolves into the subcutaneous tissue.
2. Dissolved drug is transported from the subcutaneous tissue to the plasma.
3. Drug is eliminated from the plasma.

The basic equations governing the amount of drug in the two compartments can be written as

$$\frac{dC}{dt} = (\text{absorption rate}) - (\text{elimination rate}) \tag{1}$$

$$\frac{dm}{dt} = -(\text{dissolution rate}) \tag{2}$$

where m, C, and t are, respectively, the plasma concentration of drug, the mass of drug in the deposit, and time.

Absorption Rate

For the absorption rate, we propose a formula based on a model of the subcutaneous tissue as a fluid-filled porous medium. The formula represents transport through the fluid phase driven by a combination of two mechanisms: (i) advection and (ii) diffusion.

In the case of advection-dominated transport, the absorption rate would be given by the product of the drug concentration in the subcutaneous tissue , C_{SC}, and the volumetric fluid flow rate, Q, from drug deposit through the subcutaneous tissue to the vessels of the circulatory system. Treating the subcutaneous tissue as a porous medium, Q can be modeled by Darcy's law [4], which relates the volumetric fluid flow rate to the pressure drop between the inlet and outlet, geometric factors (*e.g.*, cross-sectional area to flow) and intrisic properties of the fluid (*i.e.*, viscosity) and porous medium (*e.g.*, permeability). Note that Q is *independent* of the plasma concentration of drug. Therefore, we can model absorption rate as

$$(\text{absorption rate}) = \frac{QC_{SC}}{V_{plasma}} = Q^{\dagger}C_{SC}, \tag{3}$$

where V_{plasma} is the effective volume of fluid in the circulatory system and $Q^{\dagger}$ is defined as the normalized volumetric flow rate, Q/V_{plasma}, out of the subcutaneous tissue and implicitly encapsulates the complexities of the fluid flow through the subcutaneous tissue.

In the case of diffusion-dominated transport, the absorption rate would be given by a formula of the form:

$$(\text{absorption rate}) = k_A \left(C_{SC} - C\right), \tag{4}$$

where k_A is a coefficient relating the absorption rate to the difference in the subcutaneous tissue and plasma drug concentrations[1].

In the the general case, the transport through the subcutaneous tissue would be a combination of both advection and diffusion, so the absorption rate would be given by

$$(\text{absorption rate}) = Q^{\dagger}C_{SC} + k_A \left(C_{SC} - C\right), \tag{5}$$

[1]This formula arises because, at steady state the drug concentration profile in the diffusion region satisfies Laplace's equation [5, 7]. In the situation where there the diffusion region is defined by two non-intersecting boundaries (*e.g.*, the boundary of the drug deposit and boundary of the vessels of the lympatic and cirulatory systems), the rate that material is transported through the diffusion region is equal to the integrated flux through either one of the boundaries. When the concentration takes on a fixed value for each boundary, the resulting rate of material transport is always, as a result of the linearity of Laplace's equation, linearly related to the difference in the concentrations on the two boundaries.

where $Q^\dagger$ and k_A are, respectively, the coefficients for the advection and diffusion contributions to transport through the subcutaneous layer[2]. It can be shown that equation (5) reduces to equations (3) and (4) in the advection-dominated and diffusion-dominated limits, respectively[3].

It is important to note that there are still many open questions about transport through subcutaneous tissue [8]. Equations (3), (4) and (5) provide three possible formulas that are useful for empirical modeling and may yield useful qualitative insights.

Elimination Rate

For the elimination rate, we use the standard first-order elimination model [9]:

$$(\text{elimination rate}) = -k_E C. \tag{6}$$

Dissolution Rate

To model the drug dissolution process, we use the Noyes-Whitney equation [1]:

$$\frac{dm}{dt} = -\frac{D}{L} A \left(C_S - C_{SC}\right), \tag{7}$$

where D is the diffusion coefficient of the drug, L is the thickness of the diffusion layer, A is the surface area of the drug deposit, C_S is the concentration of the drug at the surface of the deposit (within the diffusion boundary layer), and C_{SC} is the concentration of drug within the subcutaneous tissue (outside of the diffusion boundary layer). Assuming a saturated solution of drug at the surface of the deposit, C_S is equal to the solubility of the drug.

Because parameters in the equation (7) are sensitive to the experimental conditions (*e.g.*, roughness of the solid surface, *etc.*), it may be difficult to apply it in practice except under ideal conditions. However, the equation may still be useful if treated as a purely empirical relationship:

$$\frac{dm}{dt} = -k_D A \left(C_S - C_{SC}\right), \tag{8}$$

where k_D is an effective dissolution coefficient that accounts for real-world physical complexities (*e.g.*, geometric irregularities and complicated fluid flows).

It is important to note that the dissolution rate using either equation is independent of the plasma concentration, C. Therefore, assuming that the timescale for dissolution is sufficiently small compared to the timescale of plasma concentration variations[4], the dissolution rate is effectively constant with respect to the plasma concentration equations.

[2] There are several equivalent formulas that combine advection and diffusion transport. For instance, it is possible to express the absorption rate where the advection term is the product of $Q^\dagger$ and the plasma concentration, C, instead of the concentration in the subcutaneous tissue, C_{SC}:

$$(\text{absorption rate}) = Q^\dagger C + k_A^* \left(C_{SC} - C\right).$$

Note that the absorption rate formula remains the sum of an advection term and a diffusion term. We need only adjust the coefficients multiplying the driving forces $Q^\dagger$ and $(C_{SC} - C)$. For the case above, C and k_A are replaced by C_{SC} and $k_A^* = k_A + Q^\dagger$, respectively.

[3] Intuitively, when advection dominates, the diffusion term becomes negligible so that equation (5) becomes equation (3). Similarly, when diffusion dominates, the advection term, $Q^\dagger C_{SC}$, becomes negligible so that equation (5) becomes equation (4).

[4] This can be verified using an asymptotic analysis of the model equations after non-dimensionalization and identification of small parameters [2, 6].

Model Analysis

By combining the expressions for absorption, elimination and dissolution rates with the evolution equations (1) and (2), we can derive differential equations for the plasma concentration and mass of the drug deposit. All of the absorption, elimination and dissolution models presented lead to linear, constant coefficient differential equations that can be solved analytically [3]. The resulting solutions are straightforward to analyze and fit with experimentally obtained plasma concentration profiles.

Plasma Concentration

Advection-Dominated Subcutaneous Transport

When transport through the subcutaneous tissue is advection dominated, the plasma concentration equation is

$$\frac{dC}{dt} = Q^{\dagger} C_{SC} - k_E C. \tag{9}$$

Solving this equation assuming an initial concentration of 0, we find that

$$C(t) = \frac{Q^{\dagger} C_{SC}}{k_E} \left(1 - e^{-k_E t}\right). \tag{10}$$

In the long-time limit, the plasma concentration reaches a steady state value of $Q^{\dagger} C_{SC}/k_E$.

Diffusion-Dominated Subcutaneous Transport

When transport through the subcutaneous tissue is diffusion dominated, the plasma concentration equation is

$$\frac{dC}{dt} = k_A \left(C_{SC} - C\right) - k_E C = k_A C_{SC} - \left(k_E + k_A\right) C. \tag{11}$$

Solving this equation assuming an initial concentration of 0, we find that

$$C(t) = \frac{k_A C_{SC}}{k_E + k_A} \left(1 - e^{-(k_E + k_A)t}\right). \tag{12}$$

In the long-time limit, the plasma concentration reaches a steady state value of $k_A C_{SC} / \left(k_E + k_A\right)$.

General Advection-Diffusion Subcutaneous Transport

When transport through the subcutaneous tissue involves both advection and diffusion, the plasma concentration equation is

$$\frac{dC}{dt} = Q^{\dagger} C_{SC} + k_A \left(C_{SC} - C\right) - k_E C = \left(Q^{\dagger} + k_A\right) C_{SC} - \left(k_E + k_A\right) C. \tag{13}$$

Solving this equation assuming an initial concentration of 0, we find that

$$C(t) = \frac{\left(Q^{\dagger} + k_A\right) C_{SC}}{k_E + k_A} \left(1 - e^{-(k_E + k_A)t}\right). \tag{14}$$

In the long-time limit, the plasma concentration reaches a steady state value of $\left(Q^{\dagger} + k_A\right) C_{SC} / \left(k_E + k_A\right)$.

Plasma Concentration After Drug Deposit Depleted

After the subcutaneous drug deposit is fully depleted, the plasma concentration equation is given by

$$\frac{dC}{dt} = -k_E C, \tag{15}$$

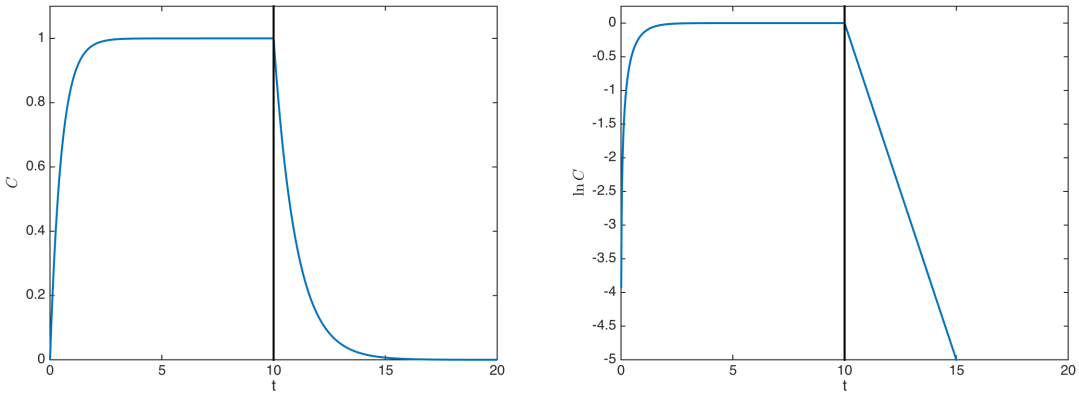
which is standard first-order elimination [9]. Solving this equation, we find that

$$C(t) = C\left(t_{depleted}\right) e^{-k_E\left(t - t_{depleted}\right)}. \tag{16}$$

After the subcutaneous deposit becomes depleted, the plasma concentration exponentially decays to zero. Assuming that the deposit takes sufficiently long to become depleted, the plasma concentration immediately after depletion $C\left(t_{depleted}\right)$ is equal to the steady state plasma concentration before depletion. For advection-dominated subcutaneous transport, $C\left(t_{depleted}\right) = Q^{\dagger} C_{SC}/k_E$. For diffusion-dominated subcutaneous transport, $C\left(t_{depleted}\right) = k_A C_{SC}/\left(k_E + k_A\right)$. For general advection-diffusion subcutaneous transport, $C\left(t_{depleted}\right) = \left(Q^{\dagger} + k_A\right) C_{SC}/\left(k_E + k_A\right)$.

Plasma Concentration Profiles

For deposits that are large enough to allow the plasma concentration to reach steady state, typical concentration profiles are shown below in Figures 1a and 1b.



(a) (b)

Figure 1: Plasma concentration (left) and logarithm of plasma concentration (right) profiles. The black vertical line indicates the time that the drug deposit becomes fully depleted.

Mass of Drug Deposit

Equation (8) describes the consumption rate of the drug deposit. As noted in earlier, we expect that dissolution occurs much faster than changes in the plasma concentration. Therefore, the dissolution rate is effectively constant so that equation (8) can be integrated to obtain

$$m(t) = m_0 - k_D A\left(C_S - C_{SC}\right) t. \tag{17}$$

Using this result, we can relate the total amount of administered drug to the deposit depletion time $t_{depleted}$ (because the mass of drug at $t_{depleted}$ is 0):

$$m_0 = k_D A\left(C_S - C_{SC}\right) t_{depleted}. \tag{18}$$

Applications to Analysis of Experimental Data

Using the results from the previous section, we develop approaches for analyzing experimental data.

Estimation of Elimination Rate Coefficient

Taking the logarithm of equation (16), we find that

$$\ln\left(C(t)\right) = -k_E\left(t - t_{depleted}\right) + C^{\dagger}, \tag{19}$$

where $C^{\dagger} = \ln\left(C(t_{depleted})\right)$ is a constant. From this equation, we see that we can estimate the elimination rate coefficient, k_E, from the slope of the plasma concentration profile in the region after the drug deposit has been depleted (see Figure 2).

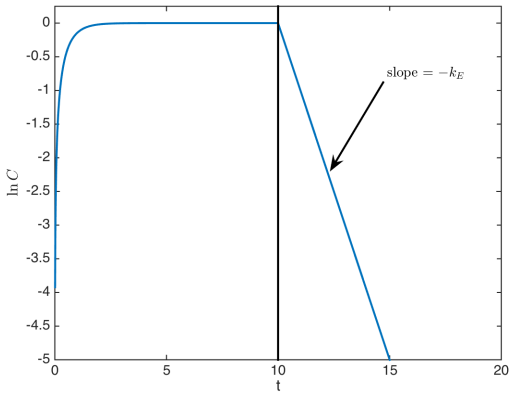


Figure 2

Figure 3: Logarithm of plasma concentration as a function of time. k_E may be estimated as minus the slope of the concentration profile after the deposit becomes depleted.

Determination of Transport Mechanism in Subcutaneous Tissue

To determine the mechanism of drug tranpsort in the subcutaneous tissue surrounding the drug deposit, we begin by noting that equations (10), (12), and (14) can all be rearranged into the form

$$\ln\left(1 - \frac{C(t)}{C_{steady}}\right) = -\gamma t, \tag{20}$$

where C_{steady} is the steady state plasma concentration before the drug deposit becomes depleted and γ is a constant that depends on whether diffusion plays a significant role in transport through the subcutaneous tissue. For advection-dominated subcutaneous transport, $\gamma = k_E$. For transport with a strong diffusion contribution, $\gamma = k_E + k_A$.

From equation (20), we see that we can estimate γ from the slope of the plot of $\ln\left(1 - \frac{C(t)}{C_{steady}}\right)$ vs. time in the region before the plasma concentration reaches steady state (see Figure 4). If γ is close to k_E, transport through the subcutaneous tissue is advection-dominated. Otherwise, diffusion plays an important role in transport through the subcutaneous tissue.

Design of Exposure Profile

For injection-delivered drugs, the controllable parameters are the injection concentration C_{inject}, the injection volume V_{inject}, and the injection protocol. Because the depletion time of the drug deposit $t_{depleted}$ plays a

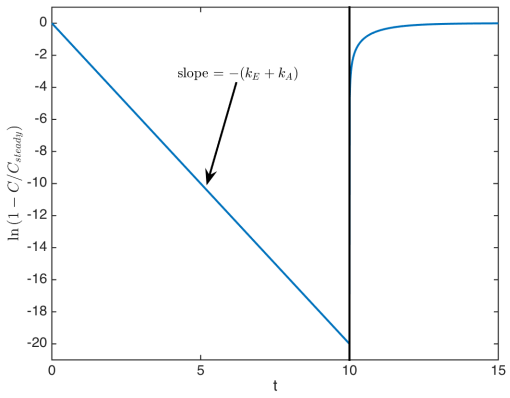


Figure 4

Figure 5: Plot of the logarithm of one minus the plasma concentration (scaled by the steady state concentration) as a function of time. $k_E + k_A$ may be estimated as minus the slope of the curve before the deposit becomes depleted.

key role in the design of the exposure profile, it would be useful to a have predictive model of $t_{depleted}$ as a function of the control parameters C_{inject} and V_{inject}.

In this section, we develop an empirical model for the effective surface area of the drug deposit in terms of the control parameters. In our discussion, we assume that the injection protocol is fixed so that the injection concentration and volume are the only control parameters. To understand the impact of variations to the injection protocol, we could apply the following analysis to data collected for each injection protocol and compare the resulting injection protocol-dependent empirical models.

Empirical Model for Effective Area of Drug Deposit

From equation (18), we see that the effective area of the drug deposit is an important factor in determining the time until the deposit is depleted. Therefore, it would be useful to develop a model for the effective area as a function of the injection concentration and volume. Because (i) area and volume are both geometric quantities and (ii) the initial mass of drug is the product of C_{inject} and V_{inject}, a reasonable ansatz for the functional form of the effective area is

$$A = \alpha C_{inject}^{\beta} V_{inject}^{\gamma} \tag{21}$$

where α, β and γ are fitting parameters. For curve fitting purposes, it is convenient to transform equation (21) into a linear equation by taking logarithms:

$$\ln A = \beta \ln C_{inject} + \gamma \ln V_{inject} + \alpha^*, \tag{22}$$

where $\alpha^* = \ln \alpha$. To further facilitate curve fitting, we define a scaled effective surface area $A^\dagger$ that includes the physical constants from equation (8) that relate surface area to dissolution rate:

$$A^\dagger = k_D \left(C_S - C_{SC}\right) A. \tag{23}$$

In terms of $A^\dagger$, equation (22) becomes

$$\ln A^\dagger = \beta \ln C_{inject} + \gamma \ln V_{inject} + \alpha^\dagger, \tag{24}$$

where the physical constants have been incorporated into $\alpha^\dagger = \alpha^* + \ln k_D + \ln\left(C_S - C_{SC}\right)$.

To estimate the the parameters in equation (24), we calculate $A^\dagger$ for each experimental condition (C_{inject}, V_{inject}) and perform a linear regression with $\ln A^\dagger$ as the independent variable and $\ln C_{inject}$ and $\ln V_{inject}$ as the dependent variables.

Interpretation of Fitting Parameter Estimates

If a linear regression of equation (24) yields a good fit, the fitting parameters β and γ can provide insight into the nature of the deposit formed after injection. Several interesting cases include:

- $\beta \approx \gamma$. The effective surface area depends only on the total mass of drug (because $m_0 = C_{inject}V_{inject}$). $A \propto m_0^{\beta}$.
- $\beta \approx 0$. The effective surface area is independent of the injection concentration.
- $\gamma \approx 0$. The effective surface area is independent of the injection volume.
- $\gamma \approx 1$. The effective surface area is proportional to the injection volume, which suggests that thickness of the drug deposit is independent of the injection volume and may be determined by the physical properties of the subcutaneous layer.
- $\gamma \approx 2/3$. The effective surface area is varies as injection volume to the 2/3 power, which suggests that the geometry of the deposit is not constrained by the physical properties subcutaneous layer (*e.g.*, spherical deposit).

We could potentially use these insights into the nature of the drug deposit to engineer the injection protocol and better control the effective surface area.

Empirical Predictive Model of Deposit Depletion Time

To derive an empirical predictive model for the deposit depletion time, we can combine equations (18) and (24) to obtain

$$\begin{aligned} t_{depleted} &= \frac{m_0}{k_D\left(C_S - C_{SC}\right)A} \\ &= \frac{C_{inject}V_{inject}}{k_D\left(C_S - C_{SC}\right)A} \\ &= \exp\left(-\alpha^{\dagger}\right) C_{inject}^{1-\beta} V_{inject}^{1-\gamma}. \end{aligned} \tag{25}$$

Assuming that linear regression gives a fit for equation (24) and that there are no modifications to the injection protocol, equation (25) with fitted parameters can be used to estimate the depletion time of the drug deposit.

Summary and Conclusions

In this technical report, we have developed a hybrid theoretical-empirical model to describe and support the design of the exposure profiles for subcutaneously delivered drugs that form a solid deposit in the subcutaneous tissue. To model the plasma concentration profile, we used a two-compartment model based on

- a model of the subcutaneous tissue as a porous medium and
- first-order elimination kinetics.

We modeled dissolution of the drug deposit using the Noyes-Whitney equation. By solving the evolution equations (assuming that plasma concentration is the slowest evolving process), we derived expressions for the time-dependence of the plasma concentration and mass of the drug deposit. We then analyzed these solutions to develop approaches for determining model parameters, characterizing the subcutaneous transport process, and providing physical interpretations that could potentially be useful to guide the design of injection protocols.

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