

Supplementary Information

1. Transport Models

1.1. Zero-Order Model

For zero-order release kinetics, the dissolution of a drug molecule is only a function of time. This model holds true only in the case of very slow drug release. Zero-Order release is therefore modeled as follows:

$$M_0^{\text{gel}} - M_t^{\text{gel}} = k_0 t \quad (1)$$

where M_0^{gel} is the initial concentration of drug present in the drug molecule, M_t^{gel} is the concentration of drug in the drug molecule at time t , and k_0 is the Zero-Order release constant with units of concentration per time.

1.2. First-Order Model

Typically utilized to describe the adsorption and/or elimination of certain drugs, the First-Order model is derived from First-Order release kinetics, which states that the change in concentration with respect to change in time is dependent only on concentration:

$$\frac{dM^{\text{gel}}}{dt} = -kM^{\text{gel}} \quad (2)$$

where M^{gel} is the concentration of drug in the drug molecule and k is the First-Order release constant. Integrating Equation (2) yields the following:

$$\ln\left(\frac{M_0^{\text{gel}}}{M_t^{\text{gel}}}\right) = kt \quad (3)$$

where M_0^{gel} is the initial concentration of drug in the drug formulation and M_t^{gel} is the concentration of drug in the drug formulation at time t .

1.3. Higuchi Model

A descriptive mathematical model for drug dissolution from matrix systems was not developed until 1961 by Higuchi [1]. The model was initially derived for planar systems; however it has since been modified for use with different geometries and porous systems. The most familiar form of the Higuchi model is the simplified Higuchi model, which relates drug concentration to the square root of time:

$$M_t^{\text{gel}} = k_H t^{1/2} \quad (4)$$

where M_t^{gel} is the concentration of drug in the drug matrix at time t and K_H is the Higuchi dissolution constant.

Many assumptions follow with the use of this model however: (i) the drug concentration in the matrix is initially much higher than the solubility of the drug; (ii) edge effects are negligible, so diffusion is unidirectional; (iii) the thickness of the dosage form is much larger than the size of the drug molecules; (iv) the swelling and dissolution of the matrix is negligible; (v) the diffusivity of the drug is constant; (vi) and perfect sink conditions are attained in the release environment [1]. A perfect

sink condition is such that the total dissolution of the drug molecule in solution yields a resulting concentration that is much lower than that of saturation (typically 1/3 of saturation).

1.4. Hixson-Crowell Cube Root Model

For systems in which the surface area and diameter of the drug matrix change with time, the Hixson-Crowell model can be used. In 1931, Hixson and Crowell discovered that a group of particles' regular area is proportional to the cube root of its volume [2]. This relationship can thus be used to derive the following:

$$W_0^{\text{gel}^{1/3}} - W_t^{\text{gel}^{1/3}} = \kappa t \quad (5)$$

where W_0^{gel} is the mass of the drug molecule initially, W_t^{gel} is the mass of the drug molecule at time t , and κ is a constant incorporating the relationship between the surface area and the volume of the drug molecule.

1.5. Korsmeyer-Peppas Model

The Korsmeyer-Peppas Model was developed to specifically model the release of a drug molecule from a polymeric matrix, such as a hydrogel. Korsmeyer *et al.* developed the following Equation [3]:

$$\frac{M_t^{\text{sol}}}{M_\infty^{\text{sol}}} = k_{\text{KP}} t^n \quad (6)$$

where M_t^{sol} is the concentration of the drug in the release solution at time t , M_∞^{sol} is the equilibrium concentration of drug in the release solution, k_{KP} is the drug release rate constant, and n is the diffusional exponent.

2. Figures and Tables

2.1. Calibration Curves

Figure S1. Calcium ion concentration ladder.

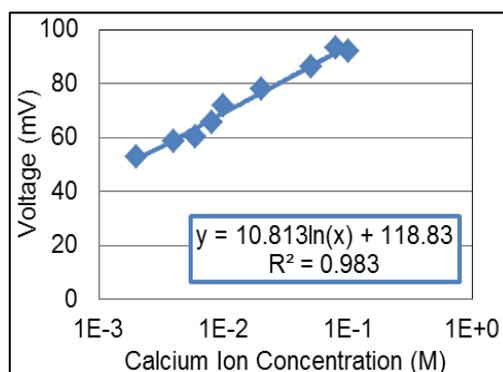
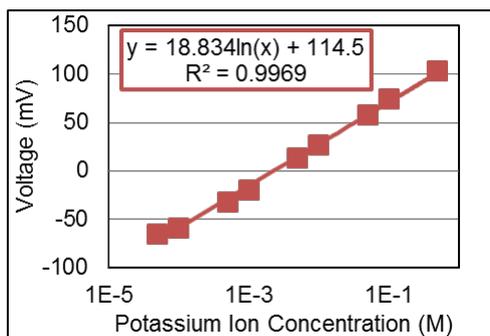


Figure S2. Potassium ion concentration ladder.



2.2. Fit Parameters

Figure 3. Calculated Korsmeyer-Peppas constants, k_{KP} , from Equation 6 for calcium (◆) and potassium (■) at varying TEGDA concentrations.

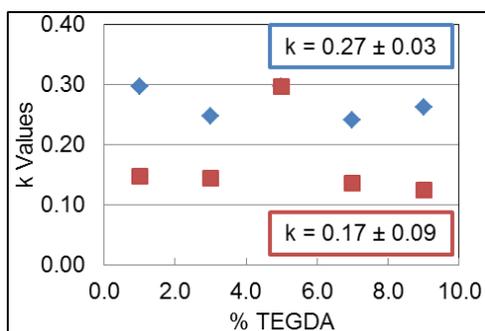


Table 1. Calculated Korsmeyer-Peppas constants, k_{KP} , for calcium (blue) and potassium (red) at varying TEGDA concentrations. Error bars represent 95% confidence intervals.

| %TEGDA | 1.0 | 3.0 | 5.0 | 7.0 | 9.0 |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|
| k | 0.30 ± 0.09 | 0.25 ± 0.13 | 0.30 ± 0.08 | 0.24 ± 0.09 | 0.26 ± 0.12 |
| | 0.15 ± 0.84 | 0.14 ± 0.11 | 0.30 ± 0.32 | 0.14 ± 0.02 | 0.12 ± 0.08 |

Figure 4. Calculated diffusion coefficients, n , from Equation (6) for calcium (◆) and potassium (■) at varying TEGDA concentrations.

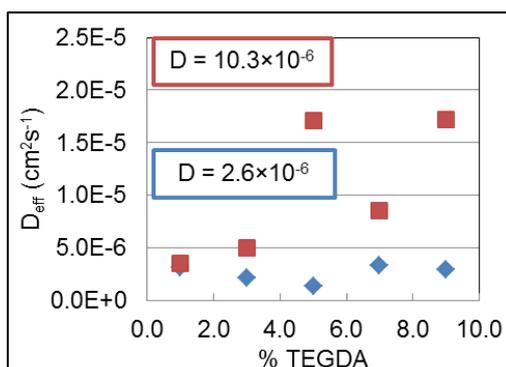


Table 2. Calculated effective diffusivities, D_{eff} , for calcium (**blue**) and potassium (**red**) at varying TEGDA concentrations. Error bars represent 95% confidence intervals.

| % TEGDA | 1.0 | 3.0 | 5.0 | 7.0 | 9.0 |
|------------------|--|--|--|--|---|
| D_{eff} | 03.2×10^{-6} $\pm 11 \times 10^{-6}$ | 2.2×10^{-6} $\pm 5.9 \times 10^{-6}$ | 1.5×10^{-6} $\pm 2.7 \times 10^{-6}$ | 3.4×10^{-6} $\pm 4.5 \times 10^{-6}$ | 3.0×10^{-6} $\pm 2.05 \times 10^{-6}$ |
| | 3.5×10^{-6} $\pm 31 \times 10^{-6}$ | 5.1×10^{-6} $\pm 14 \times 10^{-6}$ | 17×10^{-6} $\pm 35 \times 10^{-6}$ | 8.6×10^{-6} $\pm 4.2 \times 10^{-6}$ | 17×10^{-6} $\pm 37 \times 10^{-6}$ |

Figure 5. Calculated diffusion coefficients, n , determined using values from the Korsmeyer-Peppas model for calcium (\blacklozenge) and potassium (\blacksquare) at varying TEGDA concentrations.

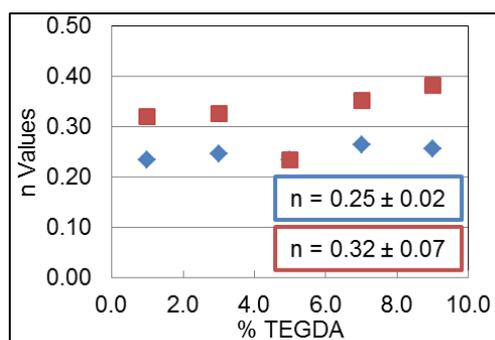


Table 3. Calculated diffusion coefficients, n , for calcium (**blue**) and potassium (**red**) at varying TEGDA concentrations. Error bars represent 95% confidence intervals.

| % TEGDA | 1.0 | 3.0 | 5.0 | 7.0 | 9.0 |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|
| n | 0.24 ± 0.11 | 0.25 ± 0.12 | 0.24 ± 0.07 | 0.27 ± 0.04 | 0.26 ± 0.05 |
| | 0.32 ± 0.90 | 0.33 ± 0.16 | 0.24 ± 0.36 | 0.35 ± 0.03 | 0.38 ± 0.18 |

Reference

- Omidian, H.; Park, K. Introduction to Hydrogels. In *Biomedical Applications of Hydrogels Handbook*; Springer: New York, NY, 2010; pp. 1–16.
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- Peppas, N.A.; Merrill, E.W. Crosslinked poly(vinyl alcohol) hydrogels as swollen elastic networks. *J. Appl. Polym. Sci.* **1977**, *21*, 1763–1770.