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DIFFUSION OF PROTEINS THROUGH THE HYDROGEL MATRICES

Aim

To determine the diffusivity of the proteins through the hydrogel matrices

Objective

To employ a fitting algorithm to the release profiles of proteins having different molecular weights

Software Required

MATLAB

Theory

Hydrogels have proved to be an optimal biomaterial in drug delivery applications requiring controlled-release, in which a single dose of drug administered maintains a desired concentration within the blood circulation for reasonable periods of time for therapeutic efficacy. A three dimensional structure composed of chemically and physically cross-linked polymer chains, hydrogels are often characterized with good water imbibing abilities that allow the polymer structure to swell extensively by absorbing biological fluids ten to twenty times their molecular weight. The cross-linkage renders the gel insoluble in water through ionic interactions and hydrogen bonding. Also, the hydrogel mimics biological tissues relatively well, inducing minimal immune-responses from hosts and thus demonstrating an excellent biocompatibility. Porous in structure, drugs can be concentrated or trapped within the polymer and released through diffusion mechanisms based on zero-order kinetics. The inherent properties of the hydrogel, drug-polymer interactions, amount of entrapped drug, and drug solubility determine the diffusion kinetics, duration and rate of solute release from the hydrogel.

Diffusion-controlled is the most widely applicable mechanism for describing the drug release from the hydrogels. Fick's laws of diffusion with either constant or variable diffusion coefficients is commonly used in modeling the diffusion-controlled release. The diffusion-controlled system consists of reservoir and matrix systems. A reservoir delivery system comprises a drug core entrapped in a spherical, cylindrical, and slab-like-shaped reservoir, which is in turn encapsulated within a hydrogel membrane. In order to ensure drug delivery at a constant rate, the drug can be concentrated in the center of the device such that the concentration gradient across the membrane is maintained zero. The matrix system features a drug dispersed uniformly throughout the entire hydrogel lying within another bigger polymer structure, rather than isolated and encapsulated within a separate reservoir in the center. Mesh size (also known as the correlation length, ξ) is defined as the linear distance between two adjacent crosslinks and is a key structural parameter for hydrogel-based drug carriers.

Consequently, understanding the relationship between mesh size and solute size is critical for the design of carriers for controlled release of therapeutics. Most frequently, hydrogel mesh size is measured using equilibrium swelling theory or rubber elasticity theory. Drug permeates the macromolecular mesh or water filled pores into the exterior of the hydrogel and blood stream.

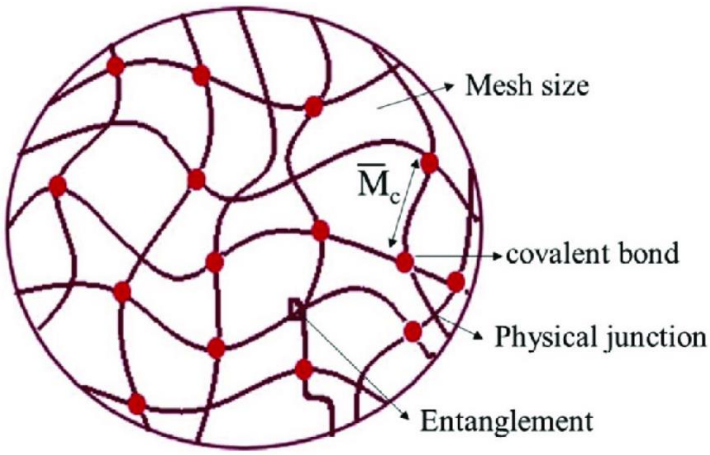

Figure 1. Structure of a Hydrogel

The cumulative drug release fraction is the ratio of the amount of solute molecules released from the hydrogel patch up to any time t (M_t) to the amount of solute molecules released after infinite time (M_∞). It can be calculated using the following equation:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left(\frac{-D(2n+1)^2\pi^2 t}{4 \times L^2}\right) \quad (1)$$

where n is a symbolic variable used for the summation from 0 to infinity and t is a symbolic variable for time. D denotes the diffusion coefficient of the solute and L refers to the thickness of the hydrogel patch.

Methodology

The patch is made of polyethylene glycol (PEG) hydrogel having a molecular weight of 10,000 g/mol. Insulin (5,700 g/mol) and Trypsin inhibitor (20,000 g/mol) are the two proteins diffusing the hydrogel matrix. The length of the patch is regarded as 4 cm.

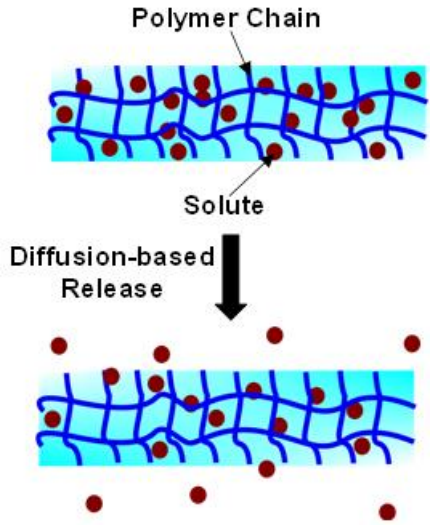

Figure 2. Schematic Representation of the Protein Encapsulated PEG Hydrogel Patch

The experimental diffusion data of the above proteins are as follows:

Table 1. Diffusion of Insulin from the PEG 10000 Hydrogel

Diffusion Time (h)	Cumulative Drug Release Fraction
0.09320175	0.66315789
0.18725241	0.86578947
0.48210243	0.92894737
0.98687748	0.97368421
1.48666525	0.98947368
1.99197085	0.99473684

Table 2. Diffusion of Trypsin Inhibitor from the PEG 10000 Hydrogel

Diffusion Time (h)	Cumulative Drug Release Fraction
0.109256962	0.64198895
0.205797973	0.756906077
0.511431829	0.913812155
1.001904261	0.973480663
1.50550607	0.991160221
1.999862192	0.993370166

The fitting algorithm has been developed to tune the value of D to minimize the fitting error with the equation (1). Interior-point method-based optimization algorithm has been used to solve the nonlinear convex optimization problems.

Code

```
global Time Diffusion_Fraction

A = [];
```

```
b = [];
Aeq = [];
beq = [];
lb = 1e-8;
ub = 1e-4;
nonlcon = [];
options = optimoptions('fmincon','Display','iter');
D0 = 5e-6;
D = fmincon(@costfun,D0,A,b,Aeq,beq,lb,ub,nonlcon,options);

syms n t

L= 0.04;
f_1(t)=(8/((2*n+1)^2*pi^2))*exp((-D*(2*n+1)^2*pi^2*t)/(4*L^2));
M_1(t)=1-symsum(f_1(t),n,0,Inf);
T=exp([0:0.2:ceil(log(7200))]);
mt_minf_1=double(M_1(T));


figure()
xlabel('Time (hours)','Interpreter','latex')
ylabel('$$M_{t}/M_{\infty} (\%)$$','Interpreter','latex');
set (gca,'FontSize', 16)
hold on
p = plot(Time,100*Diffusion_Fraction,"ko ");
p.MarkerFaceColor = [0 0 0];
p.MarkerSize = 8;
plot(T/3600,100*mt_minf_1,'r','LineWidth',1)
legend('Trypsin Inhibitor', 'Fitted Data','Interpreter','latex');
text_show = ['$$D = ' num2str(round(D/1e-6,2)) ' \times 10^{-6} cm^{2}/s$$'];
text(1,30,text_show, 'Interpreter','latex', 'FontSize', 16)
box on;
hold off
%%%%%
function cost = costfun(D)
global Time Diffusion_Fraction
syms n t
L= 0.04;
f_1(t)=(8/((2*n+1)^2*pi^2))*exp((-D*(2*n+1)^2*pi^2*t)/(4*L^2));
M_1(t)=1-symsum(f_1(t),n,0,Inf);
T=3600*Time;
mt_minf_1=double(M_1(T));
output = mt_minf_1';
cost = 1e4*sum((Diffusion_Fraction' - output).^2);
end
```

Results

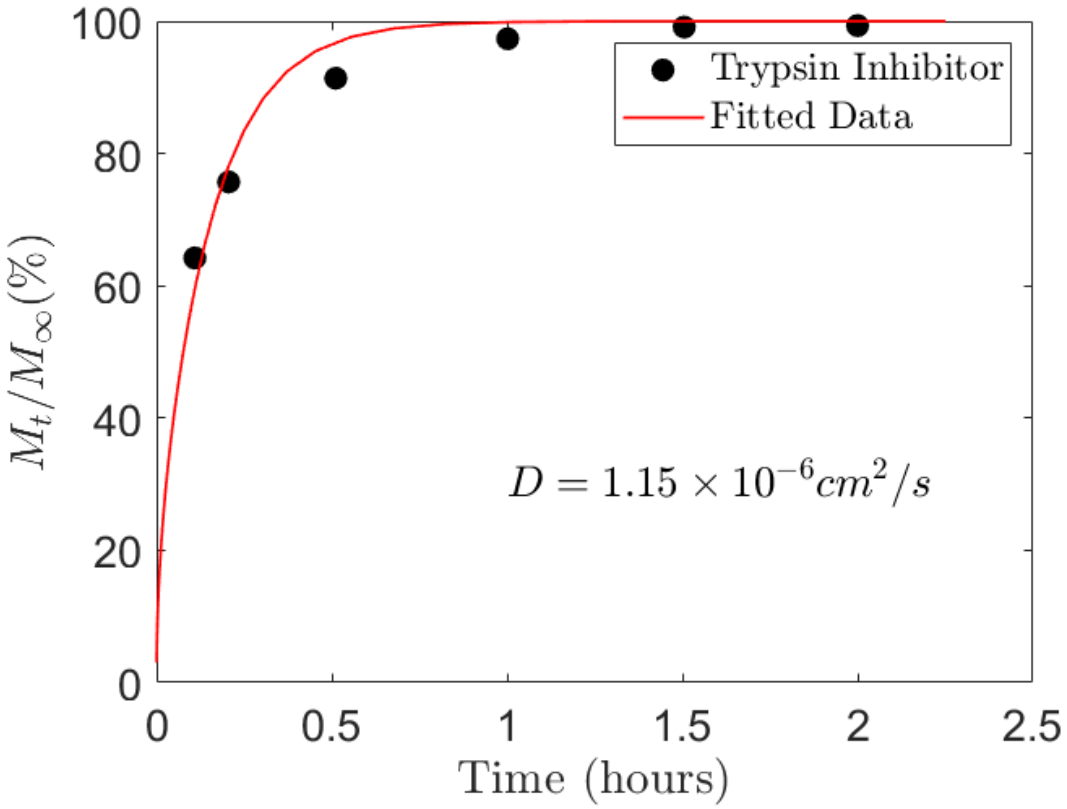

Figure 3. Release profile of Trypsin Inhibitor from PEG 10k hydrogel

Observations

- The diffusion coefficient of the proteins can be estimated from the fitting algorithm
- The diffusivity of a solute is inversely proportional to its molecular weight

Conclusion

Proper network design of hydrogels is important for tuning the drug release rates. The fitting algorithm utilized in this study aids in the determination of the diffusion coefficients of the drugs from the experimental data.