Diffusion in Polymers
and Applications in the Development of Controlled Release Systems

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CONTROLLED RELEASE: Art or Science?
CONTROLLED RELEASE

DIFFUSION-CONTROLLED
Matrix Systems
Membrane Reservoirs

CHEMICALLY-ACTIVATED
Biodegradable Polymers
Pendant Chain Chemistry

SOLVENT-ACTIVATED
Swellable Gels
Osmotic Systems

PULSATILE
pH- or Temperature- Sensitive
Electric or Ultrasonic
Multi-Compartmental
Challenges in Drug Delivery in the New Millenium:
The Future of Drug Delivery and Controlled Release Formulations

- Pressure from generic companies stifles research on more conventional forms
- Yet, work on modified cellulose derivatives, chitosans, PEO and PEG will continue
- Promising new systems for targeting or novel medical treatments
- Protein delivery with patient preferred formulations
- Intracellular delivery
- Bionanotechnology
- Systems for diagnosis, recognition and treatment

Diffusion in Controlled Release Systems

• Controlled Release Systems Function Because a Bioactive Agent Diffuses Through a Polymer Carrier

• Drug (Peptide, Protein) Diffusion Through Polymer Carrier is the Main Mechanism of Controlled Release
Fick’s Law of Diffusion

This Law Describes Transport of a Drug (or Other Bioactive Agent) Through a Polymer Carrier of a Controlled Release Device

In its Differential Form

\[ J_1 = -D_{1P} \frac{dc}{dz} \]

- \( J_1 \): Drug Flux (mol/cm\(^2\)\(\cdot\)s)
- \( c \): Drug Concentration (mol/cm\(^3\))
- \( z \): Position in Device (cm)
Fick’s Law of Diffusion

• In its Integrated Form

\[ J_1 = -D_{1p} K \frac{\Delta c}{\delta} \]

\[ \delta \]  Device Thickness (cm)

\[ K \]  Partition Coefficient
Fick’s Second Law of Diffusion

This Law Applies to Unsteady State Problems, i.e., when We Wish to Know how Drug Concentration Changes with Time

\[ \frac{\partial c_1}{\partial t} = D_{1P} \frac{\partial^2 c_1}{\partial z^2} \]
Fick’s Second Law of Diffusion

Usual Assumptions

- Constant $D_{1P}$
- One-Dimensional Diffusion
- Constant Boundaries (No Swelling)

Parameters Describing the Magnitude of Solute Transport

I. Diffusion Coefficient \( D \)

II. Permeability Coefficient \( P \)

where

\[
P = \frac{D K}{\delta}
\]

and \( K \) is the Partition Coefficient (Solubility)
Application of Diffusion to Membrane-controlled Release Systems
Membrane-controlled Release Systems

Membrane Structure

Membranes may be Classified as

I. Macroporous Membranes
   - Large Pores (d of 0.1 – 1.0 µm)
   - Tortuous, Irregular Diffusion Path

II. Microporous Membranes
    - Small Pores (d of 100 – 500 Å)
    - Polymer Structure may Affect Size

III. Non-Porous (Gel) Membranes
    - Molecular Size “Pores” (d of 20 – 100 Å)
    - Polymer Structure is Important
Membrane Controlled Release Systems

Membrane Preparation Techniques
I. Molding or Extrusion
II. Casting of Polymer Solution
III. Monomer Reaction in a Casting Apparatus
IV. Reaction Injection Molding
Membrane Modification and Treatment

I. Uniaxial or Multiaxial Orientation

It Increases the Strength of the Membrane by Introducing of Crystallites

II. Heat Treatment (Annealing Above $T_g$)

It Induces Crystallinity, Increases Strength but Decreases Drug Diffusion Coefficient
Membrane Modification and Treatment

III. Secondary Reactions

Usually Surface Reactions Which Alter the Drug Solubility (Partition Coefficient)

IV. Multilaminate Structures

By Combining Several Membranes Together one may Achieve Desirable Diffusional Characteristics
Membrane-Type Controlled Release Devices

• Previous Fundamental Studies can be Used for the Development of Important Controlled Release Systems

• Such Devices Include Systems for:
  - Ocular Therapy
  - Contraception
  - Transdermal Applications
  - Other Uses
I. Ocular Therapy

Ocusert® (Alza Corporation, a J&J Company)

- Historical Reservoir System Made of Ethylene-Vinyl Acetate (EVAc) Copolymer

- It was Available in Two Different Loadings 20 µg/h and 40 µg/h

- Active Agent: Pilocarpine
I. Ocular Therapy

Ocusert® (Alza Corporation)

*In Vitro* Release Rates for Pilocarpine Ocular Therapeutic Systems
II. Contraception
Progestasert® (Alza Corporation)

- Historical Reservoir System Made of EVAc Copolymer
- Release Rate of 65 µg/day for a Year
- Active Agent: Progesterone
II. Contraception

Progestasert® (Alza Corporation)

*In Vivo* Release Rate of the Progestasert Intrauterine Progesterone Delivery System
III. Transdermal Systems
Delivery of Scopolamine, Nitroglycerine, etc.

Schematic diagram of a transdermal drug delivery system for controlled release of scopolamine.
Some Other Transdermal Systems That Function As Membrane Controlled Release Systems

- Estraderm®
  Administers Estradiol to Relieve Menopausal Symptoms (Novartis)
  Available in Three Dosage Strengths
  Twice-Weekly Application Recommended

- Catapres-TTS®
  Administers Clonidine for Treatment of High Blood Pressure
Some Other Transdermal Systems That Function As Membrane Controlled Release Systems

- Transderm-Scop®
  Administers Scopolamine for Prevention of Motion Sickness (Novartis)

- TTS-Fentanyl
  Administers Fentanyl for Treatment of Pain (Alza)
Drug Transport in Membrane Systems

Film (Slab)

\[ J = -D \frac{dc}{dx} \]

Integrate Between the Two Sides of Membrane to Get

\[ J = D \frac{\Delta c}{\ell} \]

Where \( \ell \) is the Membrane Thickness
To Relate Concentration in Membrane ,$c'$ , to Concentration in Bulk Phase ,$c$ , Use Partition Coefficient $K$

$$K = \frac{c'}{c}$$
Then

\[ J = \frac{1}{A} \cdot \frac{dM_t}{dt} = \frac{DK\Delta c}{\ell} \]

Or

\[ \frac{dM_t}{dt} = A \frac{DK\Delta c}{\ell} \]
This Equation Shows that the Drug Release Rate is Independent of Time, i.e. the Release Kinetics is of Zero-Order
If one Integrates this Expression, one Obtains

\[
\frac{dM_t}{dt} = A \cdot \frac{DK\Delta c}{\ell}
\]

\[
M_t = A \cdot \frac{DK\Delta c}{\ell} \cdot t
\]
Conclusions

Amount of Drug Released from Device per Unit Time is a Function of (and can be controlled by)

- Area \( A \)
- Diffusion Coefficient \( D \)
- Partition Coefficient \( K \)
- Concentration Difference \( \Delta c \)
- Thickness \( l \)
Similar Expressions are Obtained for Cylinders and Spheres

Cylinder

\[
\frac{dM_t}{dt} = A \cdot \frac{DK\Delta c}{\ell_n \frac{r_0}{r_i}}
\]

\[
M_t = A \cdot \frac{DK\Delta c}{\ell_n \frac{r_0}{r_i}} \cdot t
\]
Sphere

\[
\frac{dM}{dt} = 4\pi \frac{DK\Delta c}{r_0 \cdot r_i} \left[ \frac{r_0 - r_i}{r_0 \cdot r_i} \right] = M_t = 4\pi \frac{DK\Delta c}{r_0 \cdot r_i} \cdot t
\]

Note that the Ratio of \( r_0 / r_i \) is also a Controlling Factor Here
Release in Finite Release Volume

Reservoir of Volume $V_1$ Separated by Sink of Volume $V_2$

At $t = 0$ \hspace{1em} $M_{1t} = M_\infty$

At $t = t$ \hspace{1em} $M_{1t} + M_{2t} = M_\infty$

\[
\frac{dM_{1t}}{dt} = -\frac{M_\infty ADK}{V_1 \ell} \exp\left\{-\frac{DKA}{\ell} \left[ \frac{1}{V_1} + \frac{1}{V_2} \right] t \right\}
\]

\[\begin{align*}
V_1 & \quad V_2 \\
M_t^{(1)} & \quad M_t^{(2)} \\
& \quad S
\end{align*}\]
Effect of System History on Initial Release Kinetics of Membrane Devices

I. Time-Lag Effect

- It Appears When a Membrane System is Used Shortly After Preparation
- It is Characterized by an Induction Period for Release of Drug

\[
M_t = A \frac{DK\Delta c}{\ell} \left( t - \frac{l^2}{6D} \right)
\]
Effect of System History on Initial Release Kinetics of Membrane Devices

II. Burst Effect

• It Appears When a Membrane System is Used Long After Preparation

• It is Characterized by a Sudden Fast Release of Drug

\[ M_t = A \frac{DK\Delta c}{l} \left( t + \frac{l^2}{3D} \right) \]
Drug Diffusion Coefficients in Real Release Problems


- Only Rarely can the Drug Diffusion Coefficient be Considered Constant (very Dilute Solutions, Quasi-Equilibrium Systems)

- Diffusion Coefficient is Concentration-Dependent
Drug Diffusion Coefficients in Real Release Problems

Fujita Analysis

\[ D_i = D_{io} \exp \left[ -\beta_1 \left[ c_i - c_o \right] \right] \]

This equation describes the Influence of Drug Concentration, \( c_i \)
Drug Diffusion Coefficients in Real Release Problems

• Fujita Analysis

\[ D_i = D_{io} \exp \left[ -\beta_2 \left[ c_o - c_i \right] \right] \]

This equation describes the influence of diluent concentration, \( c_i \).
Typical Problems Encountered in Testing of Controlled Release Devices

- Non-Constant Diffusion Coefficient Due to Large Drug Loading
- Non-Constant Diffusion Coefficient Due to Solvent Incorporation in Polymer Carrier
- Three-Dimensional Geometric Shapes (e.g., Tablet Analysis) Analyzed with One-Dimensional Solutions
- Increase or Decrease in Carrier Size Due to Solvent Transport
- Multicomponent Transport Instead of Single Drug Diffusion
Polymer Structural Effects on Diffusion Coefficient

Degree of Crosslinking

Screening Effect of Polymer Network
Swellable Hydrogel Systems

Drug released by diffusion;
Rate controlled by gel mesh space, $\xi$, and polymer relaxation
Diffusion in Semicrystalline Polymers

Crystals are Barriers for Diffusion

\[ D_{ic} = D_{ia} \frac{\nu_a}{\psi} \]

Detour and Blocking Effects in the Amorphous Phase of the Crystalline Polymer Solid. The Impermeable Crystals are Shadowed. The Diffusion Path Marked by the Broken Line is Blocked at \( a \) for Large Penetrant Molecule.
Diffusion in Porous Systems

Peptide Release From Porous Polymers

Porous Systems Are Produced By

• Compression of Microparticles of Particles And Peptide
• Dispersion of Peptide in Polymer Solution and Evaporation of Solvent

Peptide Release From Porous Polymers

Preparation of Sustained Release Polymers

1. Wash polymer in alcohol
2. Dry
3. Dissolve polymer in methylene chloride
4. Add dry protein powder
5. Cast at -80°C
6. Dry at -20°C
7. Dry at 20°C
8. Activate with physiological saline

Matrix Preparation - Sintering Method

Step 1: Dry at 100°C
Step 2: Heat in SF6 gas atmosphere
Step 3: Heat in SF6 gas atmosphere

Preparation of Ethylene-Vinyl Acetate Copolymer (EVAc) Matrices by Solvent Casting.

Preparation of EVAc Matrices by Sintering.
Schematic of Pores Through which a Diffusing Drug Molecule Must Pass. Bulging Pores are Connected via Narrow Channels. Due to the Narrowness of the Channel, the Molecule has a Difficult Time Finding its Way into the Next Pore.
Kinetics of Release for Bovine Serum Albumin (BSA) from EVAc Matrices at Various Drug Loadings and Particle Sizes. Abscissa is Square Root of Time. Ordinate is Cumulative Fraction of Incorporated BSA that is Released.

Loading = 0.10, particle size range = 150-180µm
Loading = 0.10, particle size range = 300-125µm
Loading = 0.30, particle size range = 150-180µm
Loading = 0.30, particle size range = 300-125µm
Loading = 0.50, particle size range = 150-180µm
Schematic of EVAc – Polypeptide Matrices before Release

a. Low Loading – Most Drug is Trapped by Surrounding Polymer.
b. High Loading – almost all Drug is Connected to Surface via Other Drug Particles, and is therefore Releasable.
Experimental Techniques for Determination of Solute Diffusion Coefficient Through Polymers

- Diffusion and Permeation Cells
- Interferometry
- NMR Spectroscopy
Diffusion Cells

Membrane Supports and Membrane Mounting

Other Diffusion Cells Such As The Franz and The Side-By-Side Cells can be Used
Determination of the Permeability Coefficient

Permeability coefficients are determined from the concentration data obtained from the permeation studies using the following equation

$$\ln \left( \frac{2c_t}{c_0} - 1 \right) = \frac{2A}{V} Pt$$

where $c_t$, $c_0$ are the solute concentrations in the donor cell at time, $t$, and in the receptor cell at time zero.

$A$ is the effective area for permeation.

$V$ is the volume of each half cell.

$P$ is the permeability coefficient.
Determination of the Partition Coefficient

• A polymer disk with known volume is placed in a drug solution with known concentration for three days.
• The final concentration of the drug solution is determined, and the partition coefficient is calculated from the following equation
Determination of the Partition Coefficient

\[ K_d = \frac{c_m}{c_s} = \frac{(c_0 V_0 - c_e V_e)}{V_m} \]

or

\[ K_d = \frac{(c_0 - c_e)}{c_e} \frac{V_s}{V_m} \]

where \( c_m, c_s \) = Concentration in the membrane, solution
\( c_0, c_e \) = Initial, equilibrium solution concentration
\( V_m, V_s \) = Volume of the membrane, solution
Determination of Drug Diffusion Coefficient

In General Diffusion Through Polymers Can be Described by Fick’s Law With Diffusion Coefficient $D_{\text{eff}}$, where

$$D_{\text{eff}} = D_{\text{sw}} \frac{\varepsilon K}{\tau}$$

$D_{\text{sw}}$  Peptide Diffusion Coefficient Through Water-Filled Pores
$\varepsilon$  Void Fraction (Porosity)
$\tau$  Tortuosity
Determination of Drug Diffusion Coefficient

\[ K_r \] Restriction Coefficient Dependent upon the Ratio \( \lambda \) where

\[ \lambda = \frac{r_s}{r_p} \]

\( r_s \) Peptide Radius

\( r_p \) Average Pore Radius
Permeability of Hydrogels

The Solute Diffusion Coefficient Varies with the Degree of Swelling for a Number of Solute Species

Normalized Diffusion Coefficient of Various Solutes as a Function of the Hydration Factor \((Q_m^{-1})^{-1}\) for Various Cellulose-Based Membranes.


Adjusting the Drug Flux Through Polymers

- Change of the Polymer Structure (Crosslinking, Crystallinity)
- Change Of Thickness (Multilaminate Systems)
- Change Of Barriers (Porosity)
- Change Of Solubility (Plasticizers)
Additional Information

See recent references attached