Controlled Release

Reservoir-Membrane Systems

Overview

- History
- Membrane devices with constant release rate
- Diffusion cell experiments with first order release
- Burst and lag effects in membrane systems
- Diffusion coefficients
- Membrane materials
- Applications of membrane systems

Components of membrane systems

- Mechanism: diffusion-controlled
- Driving force: ?C across membrane
- Medium: polymer membrane or liquid-filled pores
- Resistance: function of film thickness, diffusivity of solute in medium
- Membrane usually interfaces with biological site. Biocompatibility may be important.

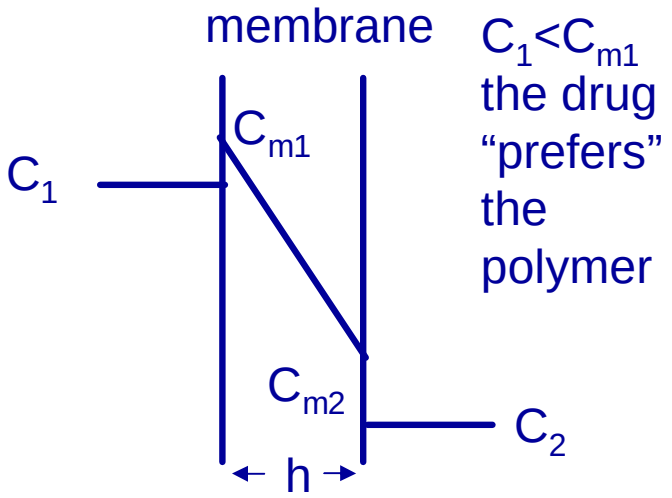
History of Membrane Systems

- Folkman and Long (1966 patent)
- Folkman studied effect of thyroid hormone on heart block
- Folkman needed non-inflammatory vehicle for extended release of hormone
- Long performed a photographic study of turbulence induced by artificial Si rubber heart valves
- Long noticed that certain dyes permeated Si rubber

History (continued)

- Folkman and Long tested diffusion of dyes and drugs across Si tube walls.
  - Observed that oil-soluble, low MW (<1000) dyes permeated membrane
  - Observed that water-soluble, high MW dyes did not.
- This was the beginning of a research EXPLOSION!
- First CR device (late 1960s) was use of hormones for contraception, which has now been widely studied.

Theory



- Fick's First Law

$$J = -D\frac{dCm}{dx} = -D\left[\frac{C_{m2} - C_{m1}}{h}\right]$$

- Relate C_{m1} and C_{m2} to surrounding concentrations

$$K_{m1} = \frac{C_{m1}}{C_1} \qquad K_{m2} = \frac{C_{m2}}{C_2}$$

- Rewrite Flux

$$J == -DK_m\left[\frac{C_2 - C_1}{h}\right]$$

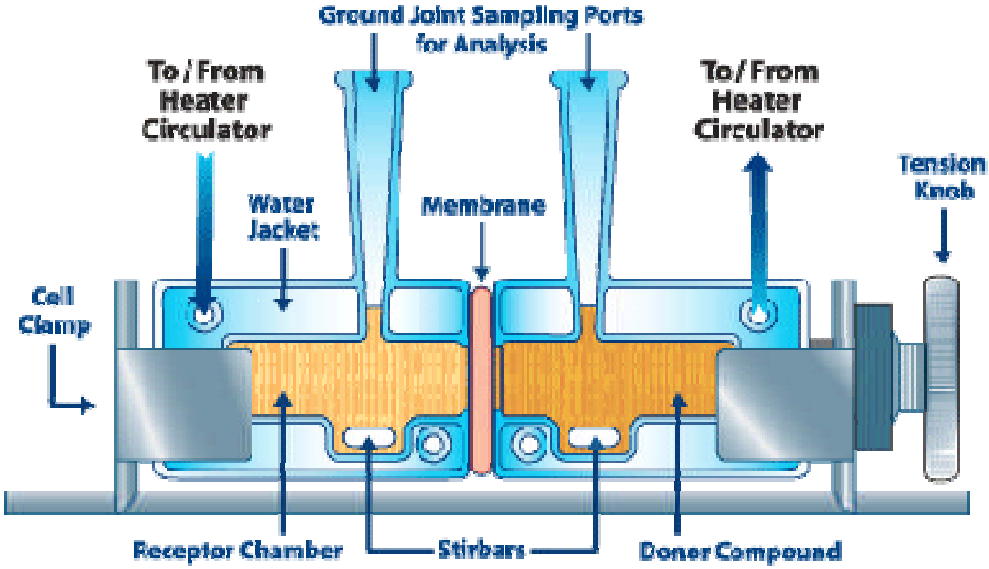
- Body acts as a sink (C_2 ~ 0)

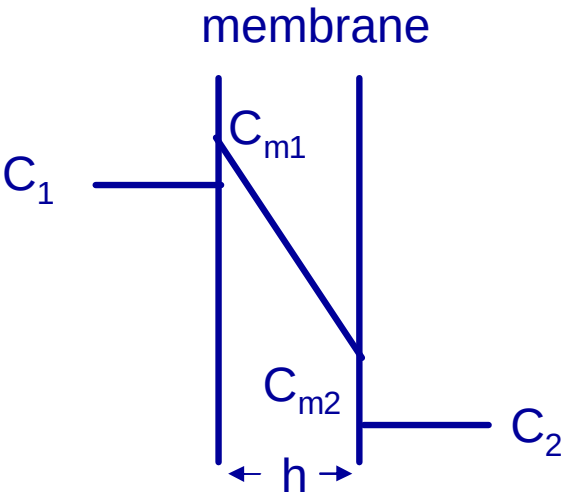
$$J \cong DK_m\left[\frac{C_1}{h}\right]$$

- Constant rate can be achieved if C_1 is kept constant.

What if C_1 is not constant?

- Common situation in diffusion cell
  - Drug is depleted from reservoir (1)
  - Drug accumulates in receiver (2)





Diffusion cell: Derivation of $M_1(t)$

- Fick's Law

$$J = -D\frac{dCm}{dx} = -DK_m\left[\frac{C_2 - C_1}{h}\right]$$

- USS Mass Balance

$$J = -\frac{V_1}{A}\frac{dC_1}{dt} = \frac{V_2}{A}\frac{dC_2}{dt}$$

$$\frac{d(C_1 - C_2)}{dt} = -AJ\left[\frac{1}{V_1} + \frac{1}{V_2}\right]$$

- Combine USSMB with Fick's Law

$$\frac{d(C_1 - C_2)}{dt} = -\frac{ADK}{l}(C_1 - C_2)\left[\frac{1}{V_1} + \frac{1}{V_2}\right]$$

- Rearrange

$$\frac{d(C_1 - C_2)}{(C_1 - C_2)} = -\frac{ADK}{l}\left[\frac{1}{V_1} + \frac{1}{V_2}\right]dt$$

Diffusion cell

- Integrate with IC: C_1-C_2= C_1^0-C_2^0

$$\ln\left[\frac{(C_1 - C_2)}{(C_1^0 - C_2^0)}\right] = -\frac{ADK}{l}\left[\frac{1}{V_1} + \frac{1}{V_2}\right]t$$

  - Apply mass balance

$$M_1 + M_2 = M_1^0$$

  - Substitute

$$M_1 = C_1 V_1$$

$$M_2 = C_2 V_2$$

Diffusion cell

- Rearrange (see details)

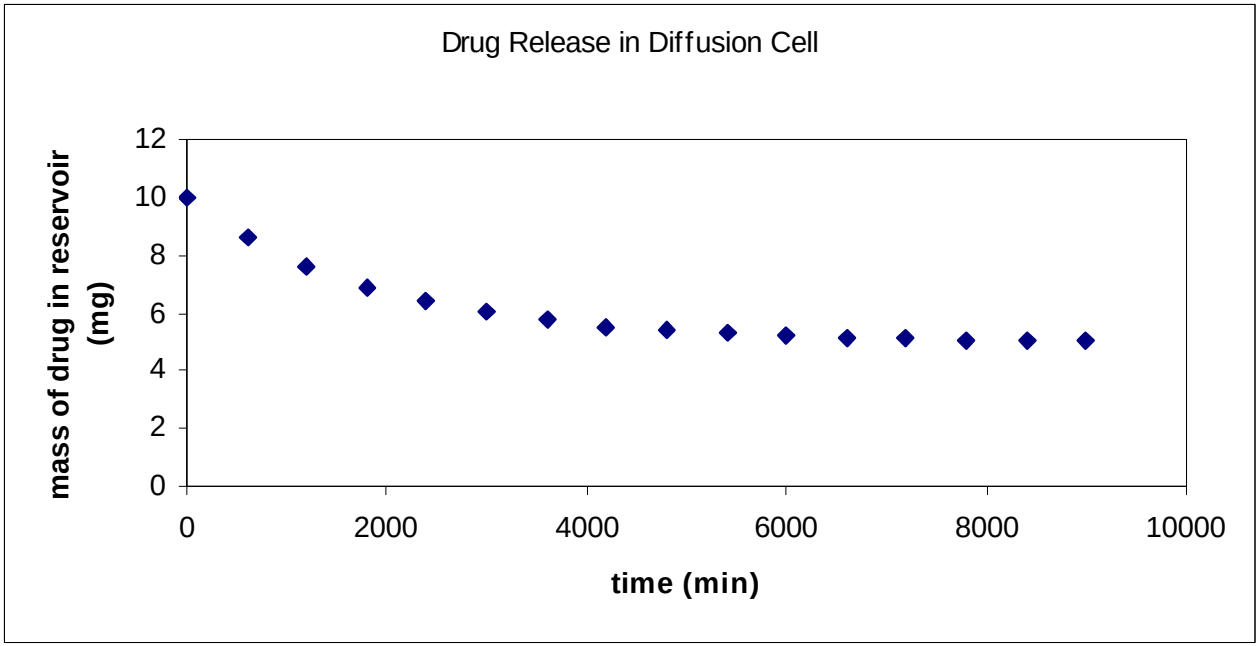
$$M_1 = \frac{M_1^0}{V_1 + V_2}\left\{V_2 \exp\left(\frac{-ADK(V_1 + V_2)t}{lV_1V_2}\right) + V_1\right\}$$

- Differentiate to find release rate

$$\frac{dM_1}{dt} = \frac{-M_1^0 ADK}{lV_1}\left\{\exp\left(\frac{-ADK(V_1 + V_2)t}{lV_1V_2}\right)\right\}$$

- First Order Release Rate

Release profile for diffusion cell



Data Analysis

- Diffusion Cell Experiment provides data for C_1 vs t
- Rearrange equation for M_1

$$\frac{M_1(V_1+V_2)}{M_1^0} - V_1 = \left\{ V_2 \exp\left(\frac{-ADK(V_1+V_2)t}{lV_1V_2} \right) \right\}$$

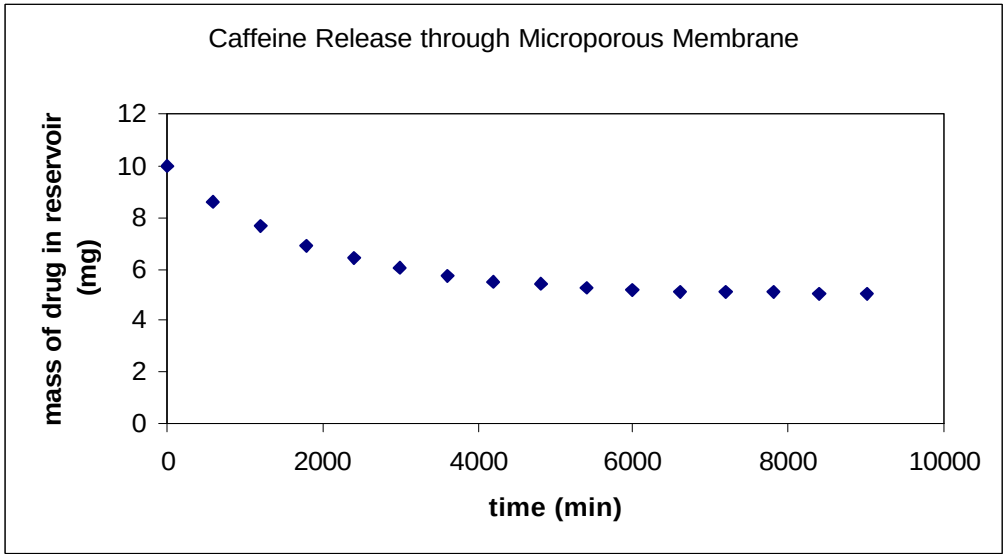
- Taking natural log of both sides results in linearized eqn

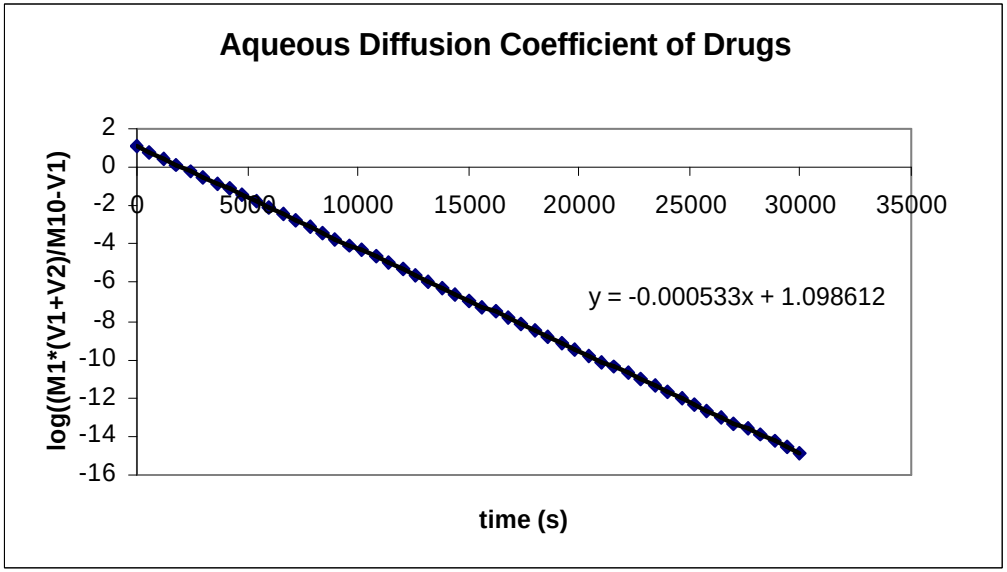
$$\ln\left(\frac{M_1(V_1+V_2)}{M_1^0} - V_1 \right)_1 = \ln(V_2) + \left(\frac{-ADK(V_1+V_2)t}{lV_1V_2} \right)$$

$$y = b + mx$$

Graphing diffusion cell data

- Experiment:
  - L=2.5x10^{-3} cm
  - V_1=V_2=3 cm^3
  - A = 2 cm^2
  - K = 1 (water-filled pores)
- Analysis
- m = -0.000533s^{-1}
- m = $\left(\frac{-ADK(V_1+V_2)}{lV_1V_2}\right)$
- Solve for D
- D=1.0 x 10^{-6} cm^2/s

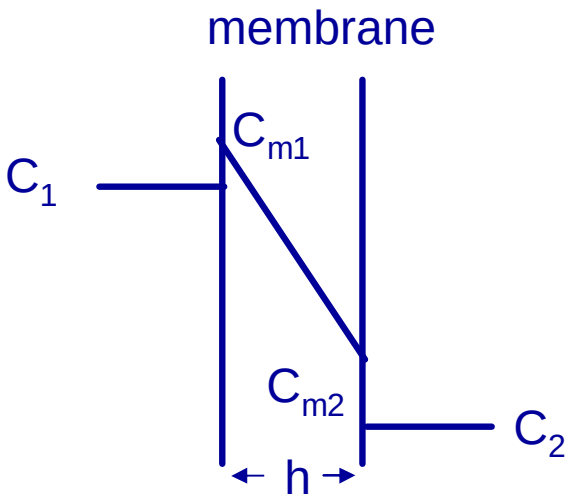




Burst and Lag Effects

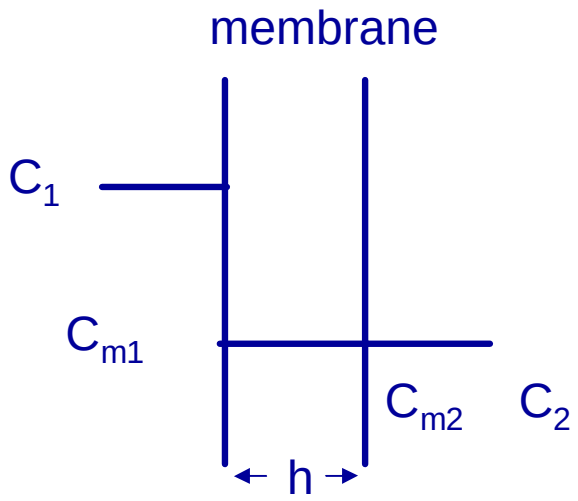
- Previous analysis was based on steady-state flux in membrane

$$J = -D\frac{dCm}{dx} = -D\left[\frac{C_{m2} - C_{m1}}{h}\right]$$



Burst and Lag

- Lag

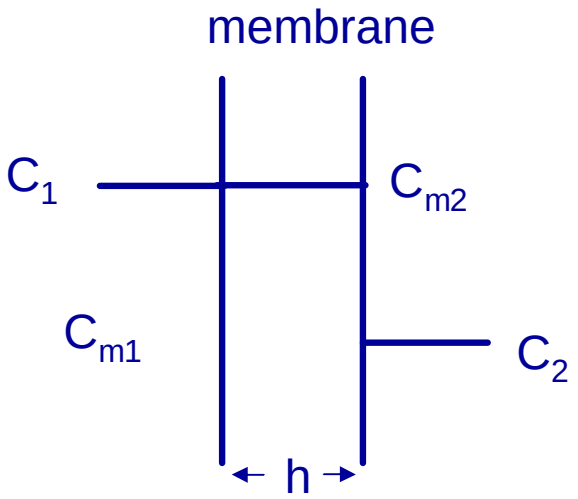


Membrane exposed to reservoir at t=0

Initially no drug in membrane

Takes time to build up SS concentration gradient

- Burst



Device stored before use

Initial concentration of drug in membrane = C_1

Takes time for drug to desorb and achieve SS concentration gradient

Lag Time & Burst Effect

Equations for the amount of drug released after SS is attained in the membrane:

- Lag

$$M_2^{SS} = \frac{ADKC_1}{l}\left(t - \frac{l^2}{6D}\right)$$

- Burst

$$M_2^{SS} = \frac{ADKC_1}{l}\left(t + \frac{l^2}{3D}\right)$$

- Equations result from solving transport eqns. (Fick's 2nd Law) for USS diffusion with relevant ICs; then taking limit as t ? 8
- These equations are for C1=const; C2=0

Burst and Lag Effects

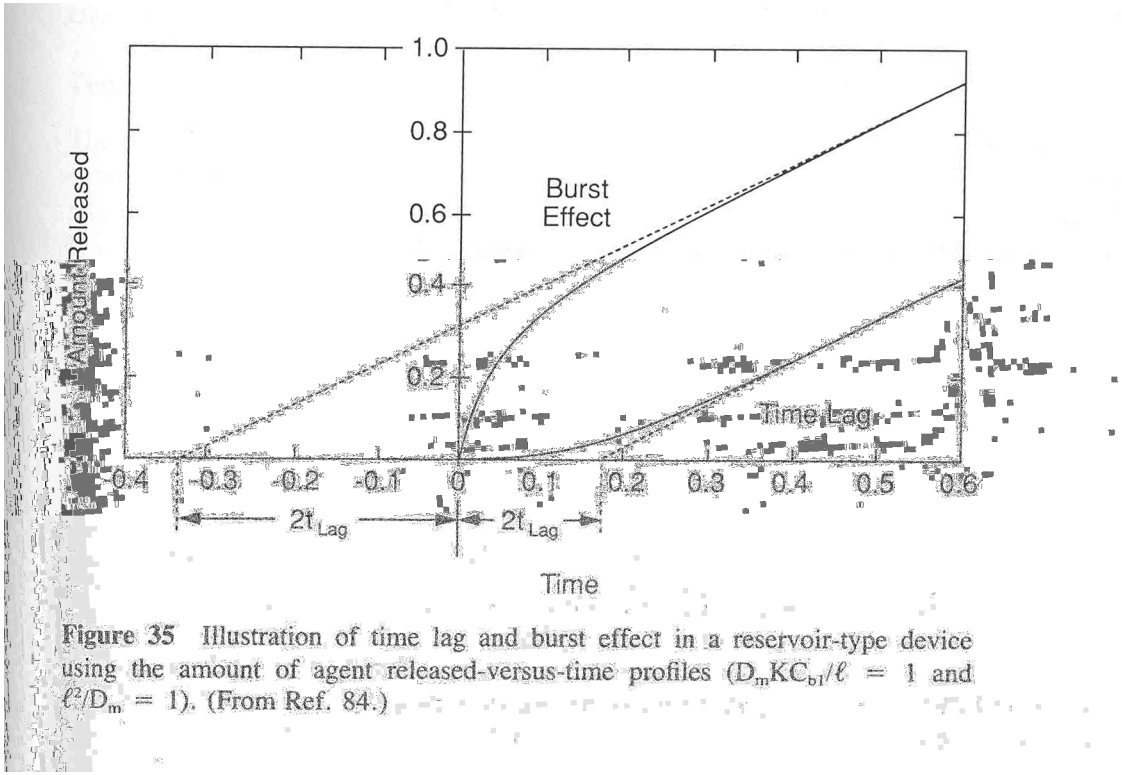


Figure 35 Illustration of time lag and burst effect in a reservoir-type device using the amount of agent released-versus-time profiles ($D_m KC_{b1}/\ell = 1$ and $\ell^2/D_m = 1$). (From Ref. 84.)

The lag time is the time required for the solute to appear on the receiver side. It is also the time required to attain a SS concentration profile in the membrane

Lag

$$M_2 = \frac{ADKC_1}{l}\left(t - \frac{l^2}{6D}\right)$$

$$\text{slope of M vs t} = \frac{ADKC_1}{l}$$

$$\text{x-intercept} = -l^2/6D = -t_{lag}$$

Burst

$$M_2 = \frac{ADKC_1}{l}\left(t + \frac{l^2}{3D}\right)$$

$$\text{slope of } M_2 \text{ vs t} = \frac{ADKC_1}{l}$$

Effect of lag and burst

- Membrane thickness 100 microns
- $D = 1 \times 10^{-7}\ cm^2/s$
- Calculate Lag time and Burst time
- Repeat for $D = 1 \times 10^{-9}\ cm^2/s$

D	$= 1 \times 10^{-7}\ cm^2/s$	D	$= 1 \times 10^{-9}\ cm^2/s$
t_{lag}	$= 2.7$ min	t_{lag}	$= 277$ min
t_{burst}	$= 5.5$ min	t_{burst}	$= 555$ min

Diffusivity values for polymers

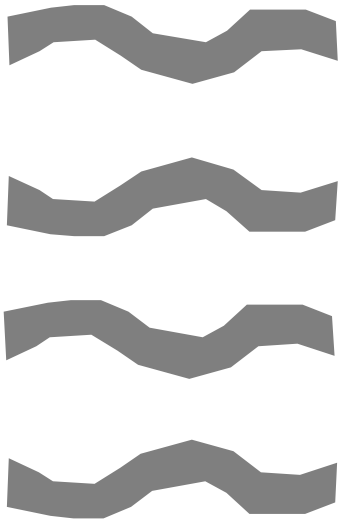
- Function of MW
  - Greater dependence for solute in polymers than for solute in liquids.
  - For drugs with <400 MW
    - In water: 10^{-6} cm^2/s<D<10^{-4} cm^2/s
      - Weak dependence on MW
    - In rubbery polymer: 10^{-11} cm^2/s<D<10^{-4} cm^2/s
      - MW is somewhat important
    - In glassy polymer: 10^{-14} cm^2/s<D<10^{-5} cm^2/s
      - Polymer is very stiff and rigid. Strong dependence on MW

Diffusion through microporous membranes

- Molecules move through liquid-filled pores
- Small molecules do not experience hindered diffusion

$$D_{eff} = \frac{De}{t}$$

- Porosity $0 < e < 1$
- Tortuosity typically $1 < t < 5$
  - pathlength is longer than membrane thickness



Membrane materials

- Silicone (Silastic – Dow Corning)
- EVA – Ethylene Vinyl Acetate
  - EVAc- Ethylene Vinyl Acetate copolymer
- Entrapped fluids
  - Hydrogels and microporous membranes

Silicone membranes

- Biocompatible and sterilizible
- High permeability to many steroids
- Low permeability to ionized species
- Fick's law is valid for many compounds
- D is on the order of 10^{-6}
  - High compared to many polymers

Applications of Silicone membranes

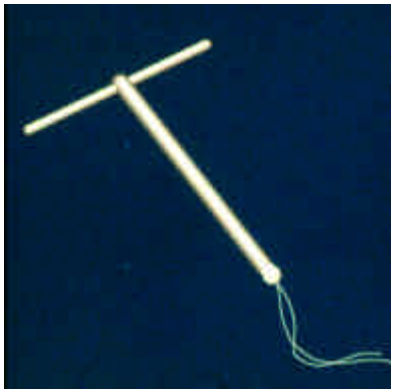
- 5 year contraceptive
- Transderm Nitro patch: 0.843 mg/cm^2/day

EVA Membrane Systems

- Advantages over silicone
  - Lower permeability to non-polar compounds offers better rate control
  - Easier processing and formation of thermoplastic
    - Extrusion, injection molding, film casting
  - Co-polymers can effect big changes in properties
    - Flexibility, permeability, strength

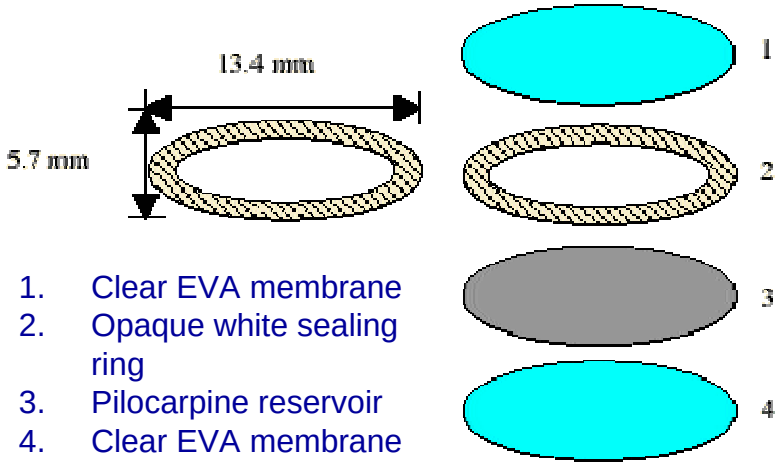
Examples of EVA Systems

- Progestasert
  - Progesterone contraceptive by ALZA
  - Intrauterine device, 65 mcg per day for 400 days
  - Silicone T-shaped tube with 35 mg drug in Si oil



Examples of EVA Systems

- Ocusert
  - Pilocarpine glaucoma treatment system by ALZA
  - Thin, flexible “contacts” behind eyelid
  - Use once a week; replaces drops 4 times per day
  - Releases 20 or 40 mcg per hour
  - Contains 5-11 mg pilocarpine
  - Sterilized by irradiation



1. Clear EVA membrane
2. Opaque white sealing ring
3. Pilocarpine reservoir
4. Clear EVA membrane

  - Oval shape, 6 mm x 13 mm x 0.5 mm
  - Thin EVA membranes 100 microns thick

Hydrogel systems

- Hydrophilic monomers that make cross-linked networks which hold water
  - Great ease of synthesis
  - Wide range of properties
  - D depends on cross-linking agent and water content

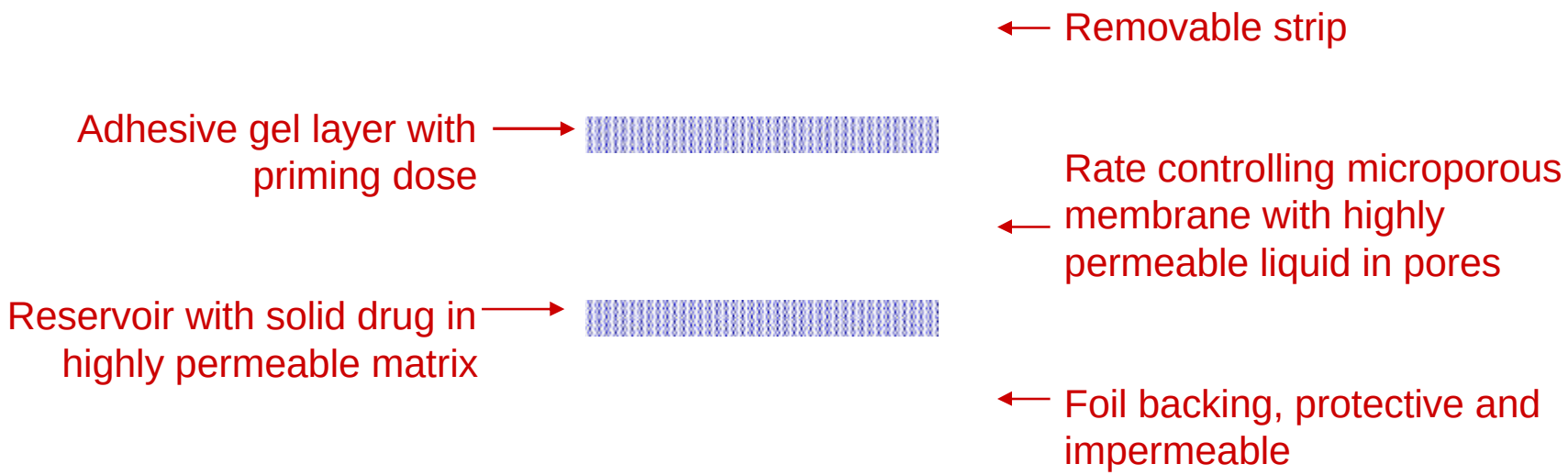
Applications of hydrogels membrane systems

- Fluoride salts in the mough
  - 0.2 – 1.0 mg/day for 6 months
- Narcotic agonist – cyclazocine
  - Prevents opiate effect and is used in rehabilitation
- Anticancer pouches for direct placement on tumors

Applications of microporous membranes

- Microporous Membranes – used in many biomedical applications
  - Blood oxygenation, dialysis, wound dressings, drug delivery
- Drug Delivery Applications
  - Transderm Scop® (scopolamine) —Introduced in 1981 for motion-sickness. Microporous polypropylene membrane. (Alza-Ciba Geigy)
  - Transderm-Nitro® (nitroglycerin) — For angina patients. Alternative to the brief effects of sublingual nitroglycerin and the messiness of nitroglycerin ointment. Microporous EVA membrane. (Alza-Ciba Geigy)
  - Catapres-TTS® (clonidine) — Once-a week patch for hypertension replaces up to four daily oral doses. Uses microporous polypropylene membrane. (Alza-Boehringer/Ingelheim)
  - Estraderm® (estradiol) —Twice-weekly, convenient estrogen replacement therapy. Avoids first pass and therefore uses only a fraction of the drug used in the oral therapy. Uses microporous polypropylene membrane. (Alze-Ciba Geigy)
  - Duragesic® (fentanyl) —Introduced in 1991 for management of chronic pain via opioid analgesia. Uses microporous polyethylene membrane. (Alza)
  - NicoDerm® CQ® (nicotine)—smoking-cessation aid in multiple dosage strengths offering maximum control of the drug delivery rate. Uses microporous polypropylene membrane. (Alza-GSK)
  - Testoderm® and Testoderm® —Introduced in 1994 and 1998, respectively, for hormone replacement therapy in men with a deficiency or absence of testosterone. Microporous EVAc membrane. (Alza-Lederle)

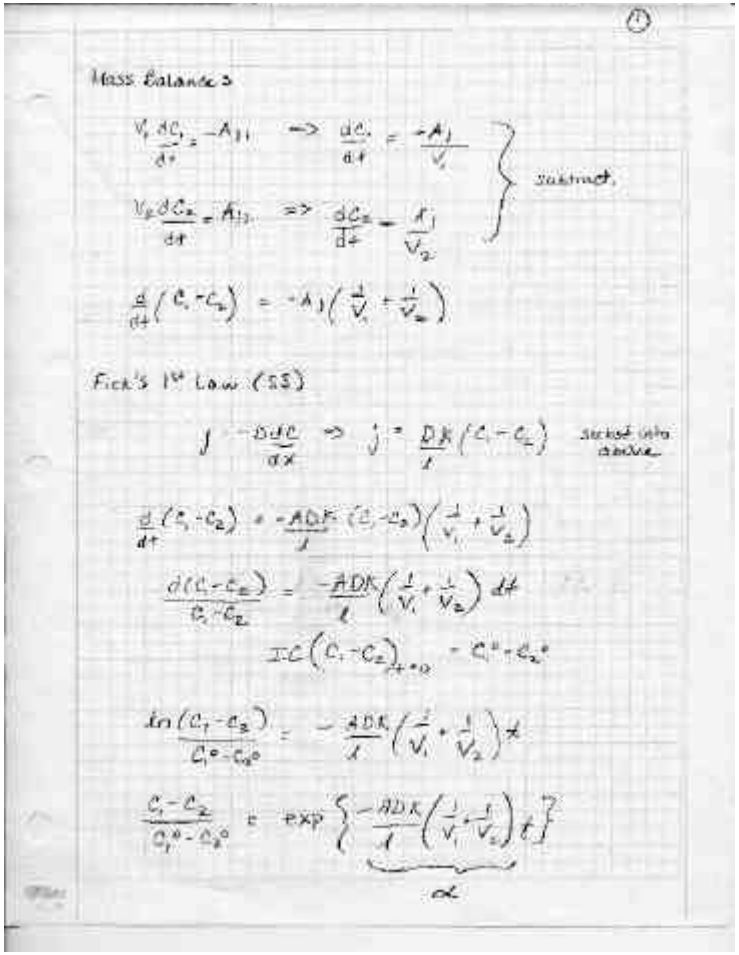
ALZA's Transderm Scop

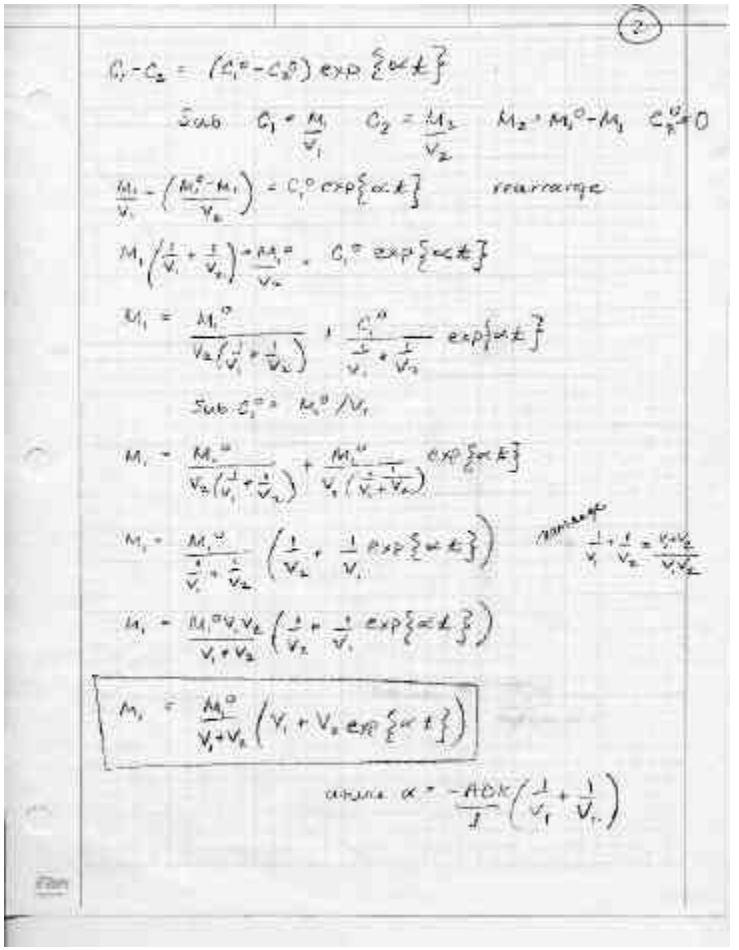


- Controlled release form maintains low conc of drug, reduces side effects
- 2.5 cm^2 area
- 200 mcg priming dose
- 10 mcg/h for 72 h steady state delivery

Diffusion Cell Equations

- Derivation of $M_1(t)$





Burst and Lag effects

TEMPORAL IDIOSYNCRASIES

Although a controlled-release device is generally designed to achieve zero-order kinetics, the initial release rates of an actual device are often higher or lower than steady state value, depending on the history of the device. These phenomena are termed temporal idiosyncrasies. The two common phenomena associated with the storage history are time lag and burst effect.

The mathematical expression for the burst effect and the time lag can be derived from the release kinetics. In this section, studies will focus on a reservoir device having a membrane of thickness ℓ. The typical permeation conditions to be studied in this section are that one face of the membrane at $x = 0$ contacts with a bulk solution of constant concentration $C_{s,1}$, and the other face at $x = \ell$ contacts with another bulk solution of constant concentration $C_{s,2}$. Provided that the membrane is initially at a uniform concentration KC_M, the cumulative amount of diffusant M_t which has passed through the membrane at time t is expressed by the following polynomial [66]:

$$M_t = AD_m(KC_{s,1} - KC_{s,2})\frac{t}{\ell} + \frac{2A\ell}{\pi^2}\sum_{n=1}^{\infty}\frac{KC_{s,1}\cos n\pi - KC_{s,2}}{n^2}\left[1 - \exp\left(-\frac{D_m n^2\pi^2 t}{\ell^2}\right)\right] - \frac{4AKC_M\ell}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{(2n-1)^2}\left[1 - \exp\left(-\frac{D_m(2n+1)^2\pi^2 t}{4\ell^2}\right)\right] \quad (199)$$

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The mathematical expressions for the time lag and burst effects can be deduced from Eq. (199), as described below.

Time Lag

When a membrane-type controlled-release device is used immediately after it is manufactured, the membrane is theoretically free of drug. It will require some time to establish the concentration gradient within the membrane before the drug molecules can emerge from the surface of the device. It can be conceived that both $C_{s,0}$ and $C_{s,\ell}$ are essentially zero. In this case, Eq. (199) reduces to

$$\frac{M_t}{A\ell KC_0} = \frac{D_m t}{\ell^2} - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(-\frac{D_m n^2\pi^2 t}{\ell^2}\right) \quad (200)$$

where the following relationship has been used in the derivation:

$$\sum_{n=1}^{\infty}\frac{\cos n\pi}{n^2} = -\frac{\pi^2}{12} \quad (201)$$

The asymptotic line for Eq. (200) can be obtained by letting $t \to \infty$, as given by [84]:

$$M_t = \frac{AD_m KC_0}{\ell}\left(t - \frac{\ell^2}{6D_m}\right) \quad (202)$$

The intercept of Eq. (202) on the time axis is equal to $\ell^2/6D_m$, which is termed the lag time.

Burst Effect

For the case of the burst effect, the device has been stored for some time before use, during which the agent gradually permeates through the membrane and eventually saturates the entire membrane. When it is placed in a desorbing environment, some of the agent in the membrane is released at a high initial rate. In this case, $C_{s\ell}$ is initially equal to $C_{s,0}$, whereas C_{s0} is equal to zero. Equation (199) can be simplified as

$$\frac{M_t}{A\ell KC_M} = \frac{D_m t}{\ell^2} - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(-\frac{D_m n^2\pi^2 t}{\ell^2}\right) + \frac{1}{2} - \frac{4}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(-\frac{D_m(2n+1)^2\pi^2 t}{\ell^2}\right) \quad (203)$$

where the following relationship has been used for the derivation:

$$\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2} = \frac{\pi^2}{8} \quad (204)$$

The asymptotic line for Eq. (203) can be obtained by letting $t \to \infty$, giving [84]

$$M_t = \frac{AD_m KC_M}{\ell}\left(t - \frac{\ell^2}{3D_m}\right) \quad (205)$$

Similar sets of equations for spherical and cylindrical membrane geometries are well established [66].

Ref. Kydonieus, A. Treatise on Controlled Drug Delivery