3.051J/20.340J

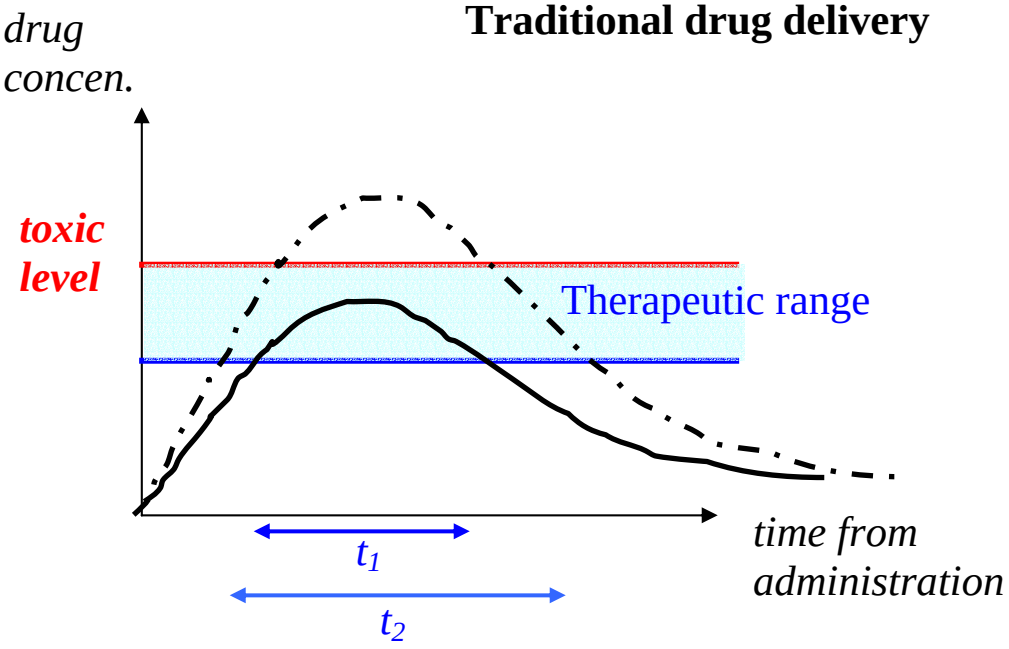
Lecture 19
Drug Delivery: Controlled Release

What do we mean by "controlled" release?

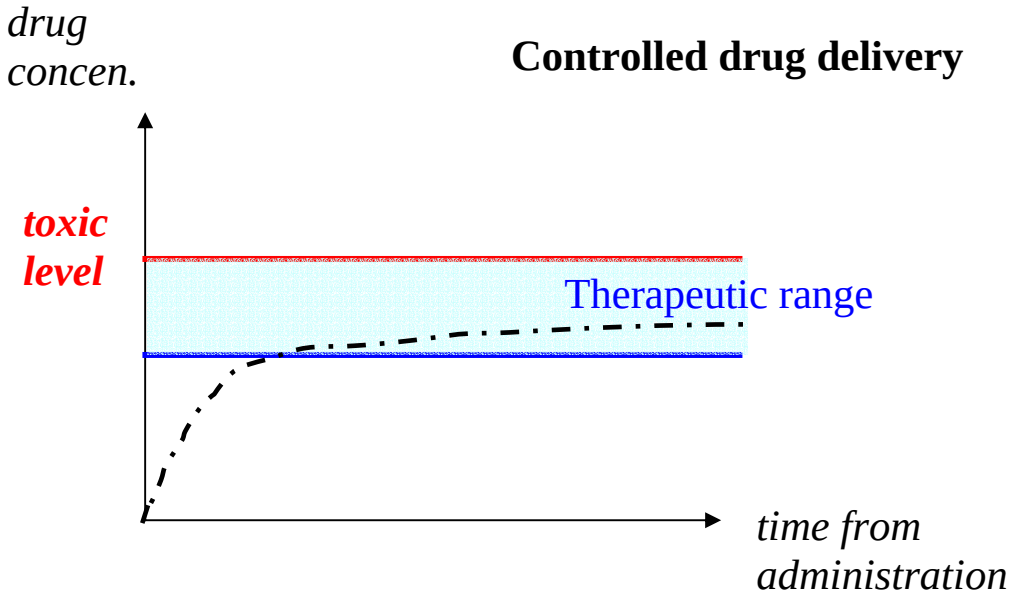
Control of: **1. delivery rate**
2. site of release/activity

Need for Control

Traditional drug delivery



longer period of dose efficacy = toxicity risk



Types of Devices

1. Diffusion Controlled Delivery Devices

- Monolithic Devices
- Membrane Controlled Devices
- Osmotic Pressure Devices
- Swelling-Controlled Devices

2. Chemically Controlled Approaches

- Matrix Erosion
- Combined Erosion/Diffusion
- Drug Covalently Attached to Polymer
- Desorption of Adsorbed Drug

3. Electronic/Externally Controlled Devices

1. Diffusion Controlled Devices

a) Monolithic Devices

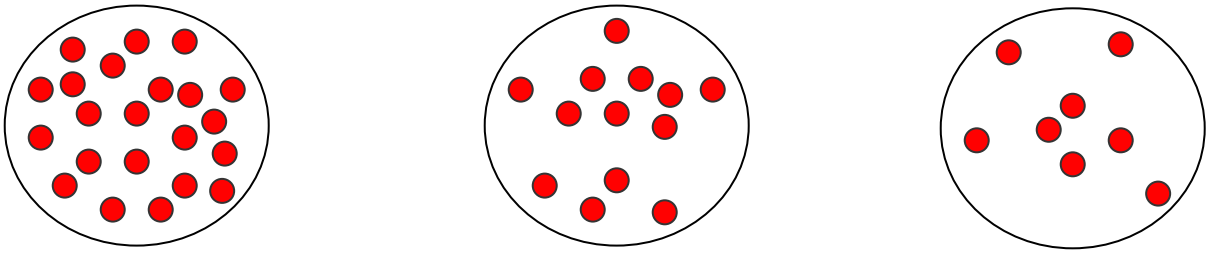
Drug is released by diffusion out of a polymer matrix

Release rate depends on initial drug concentration

i) Case of $C_0 < C_s$

(drug concentration C_0 is below solubility limit in matrix C_s)

$\Rightarrow$ Diffusion through matrix limits the release rate



t_0 t_1 t_2

How can we control release rate?

Rate control by **choice of matrix**:

glassy matrix: $D \sim 10^{-10}$-10^{-12} cm^2/s
rubbery matrix: $D \sim 10^{-6}$-10^{-7} cm^2/s

Quantifying drug release

Governed by Fick's Laws.

For 1D: The drug flux J is: $J = -D\frac{dC}{dx}$

The change in drug concentration with time is: $\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$

We want to calculate:

- dM_t/dt = release rate
- M_t = amount released after time t

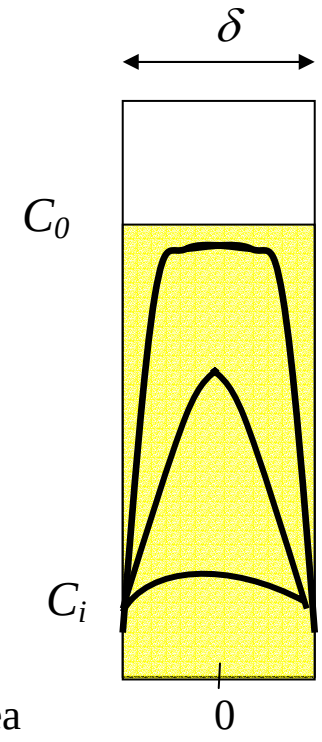
$\Rightarrow$ Solve Fick's 2nd law with initial & boundary conditions.

Example: For a 1D slab loaded at an initial concentration of C_0, with drug concentration in solution resulting in constant surface concentration of C_i.

I.C.: $C(x,0) = C_0$

B.C. 1: $\left.\frac{\partial C}{\partial x}\right|_{x=0,t} = 0$

B.C. 2: $C(\delta/2,t) = C_i$



Solve for $C(x,t)$

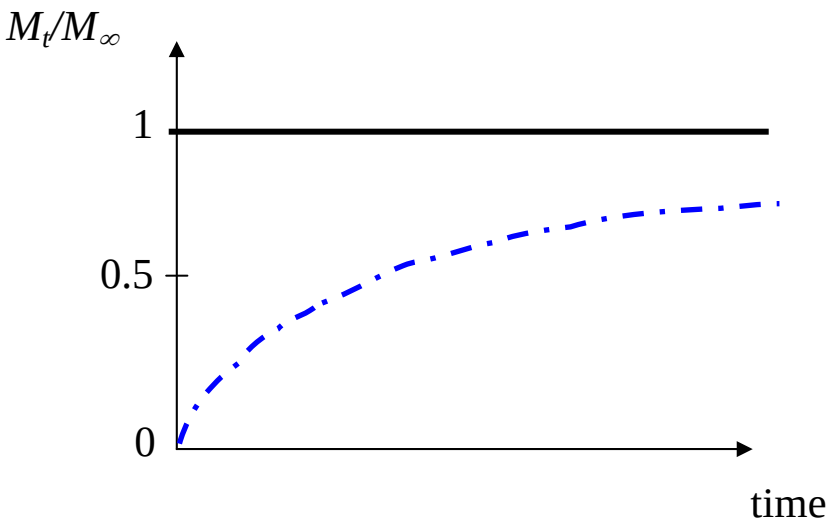
$$\frac{dM_t}{Adt} = -D\left.\frac{dC(x,t)}{dx}\right|_{x=\delta/2} \Rightarrow M_t$$

A = cross-sectional area

The amount of drug released is given by the series solution:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D(2n+1)^2 \pi^2}{\delta^2} t\right]$$

where: M_∞ = amount of drug released at long times
(e.g., total amt of drug: $M_\infty = C_0 A \delta$)
δ = slab thickness



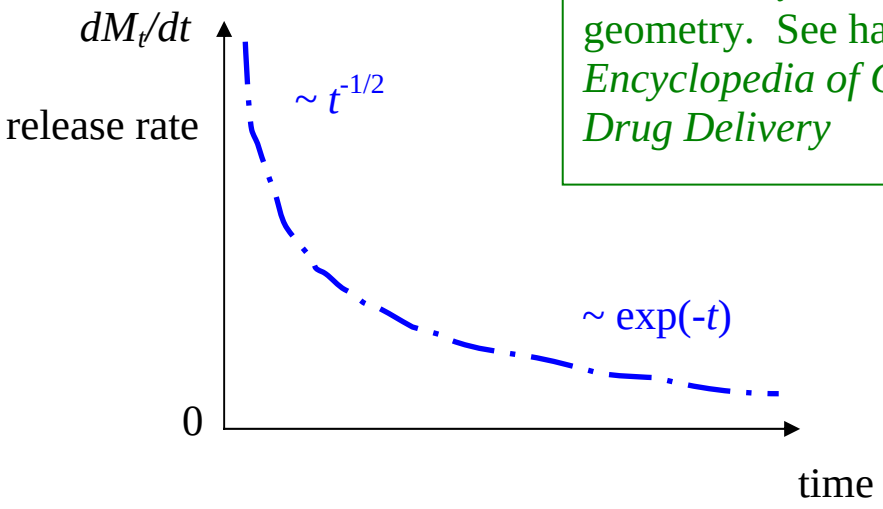
Release rate (from derivative)**:**

$$\frac{dM_t}{dt} = 2M_\infty \left[\frac{D}{\pi \delta^2 t}\right]^{1/2}$$

short times: ~ $t^{-1/2}$

$$\frac{dM_t}{dt} = \frac{8DM_\infty}{\delta^2} \exp\left[\frac{-\pi^2 Dt}{\delta^2}\right]$$

long times: exponential decay



NOTE: dM_t/dt and M_t depend on geometry. See handout from *Encyclopedia of Controlled Drug Delivery*

ii) **Case of $C_0 > C_s$**
(drug concentration above solubility limit in matrix)

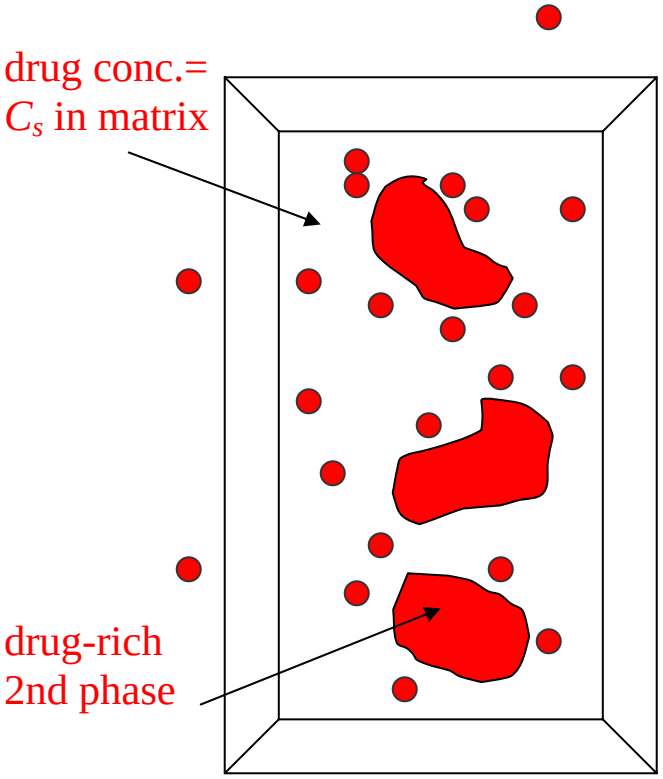
$\Rightarrow$ Drug dissolution in polymer matrix limits release rate

Higuchi model: assumes $C_i = 0$

$$M_t = A\left[DC_s\left(2C_0 - C_s\right)t\right]^{1/2}$$

$$\frac{dM_t}{dt} = \frac{A}{2}\left[DC_s\left(2C_0 - C_s\right)\right]^{1/2} t^{-1/2}$$

where A = surface area of the slab



For $C_s << C_0$:

$$\frac{dM_t}{dt} = \frac{A}{2}\left[\frac{2DC_sC_0}{t}\right]^{1/2}$$

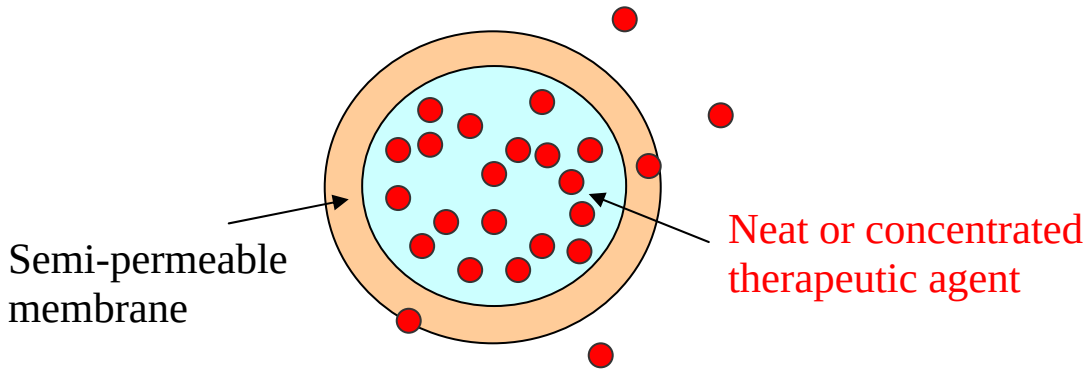
How can we control release rate?

b) Membrane Controlled Devices

Drug release is controlled by a **semi-permeable membrane**

$\Rightarrow$ Diffusion through membrane limits the release rate

Advantage: ***A constant flux device!***



Release rate thru membrane described by Fick's 1st law.

For 1D:

$$J = \frac{dM_t}{Adt} = -D\frac{dC}{dx}$$

Typical flux units: g/cm^{2}s

i) Nonporous semi-permeable membranes

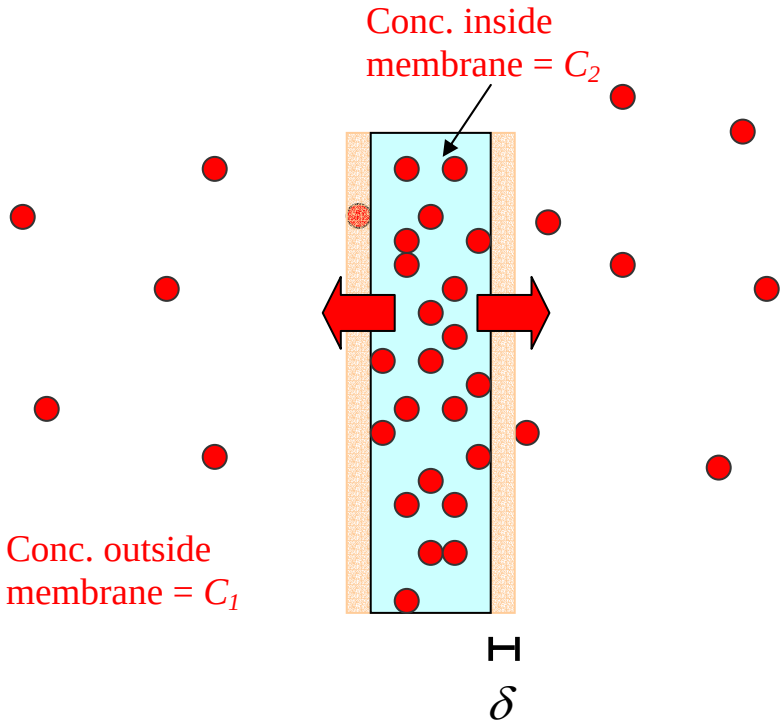
⇒ Drug diffusion through swollen polymer membrane

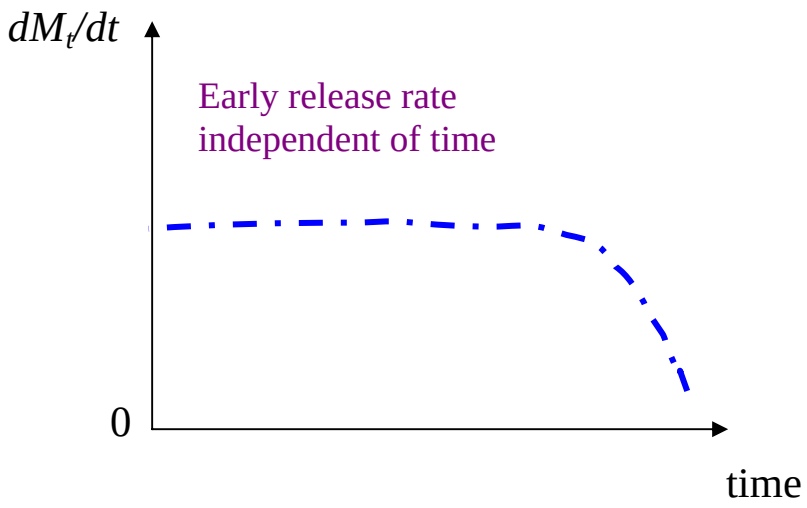
$$\frac{dM_t}{dt} = \frac{DKA}{\delta}(C_2 - C_1)$$

$$M_t = \frac{DKA}{\delta}(C_2 - C_1)t$$

K = membrane "partition" coefficient (unitless metric of drug solubility in membrane)

Which D is referred to?





Is this release profile advantageous?

ii) Porous semi-permeable membranes

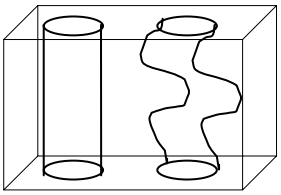
⇒ Drug diffusion through membrane pores

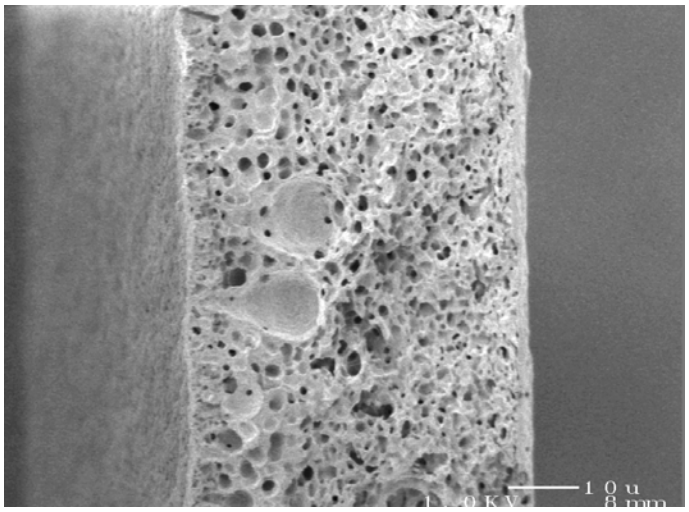
Requires replacing D by D_{eff}:

$$D_{eff} = \frac{D_{pore}\varepsilon}{\tau}$$

ε = porosity $0 < \varepsilon < 1$

τ = tortuosity $\tau \geq 1$

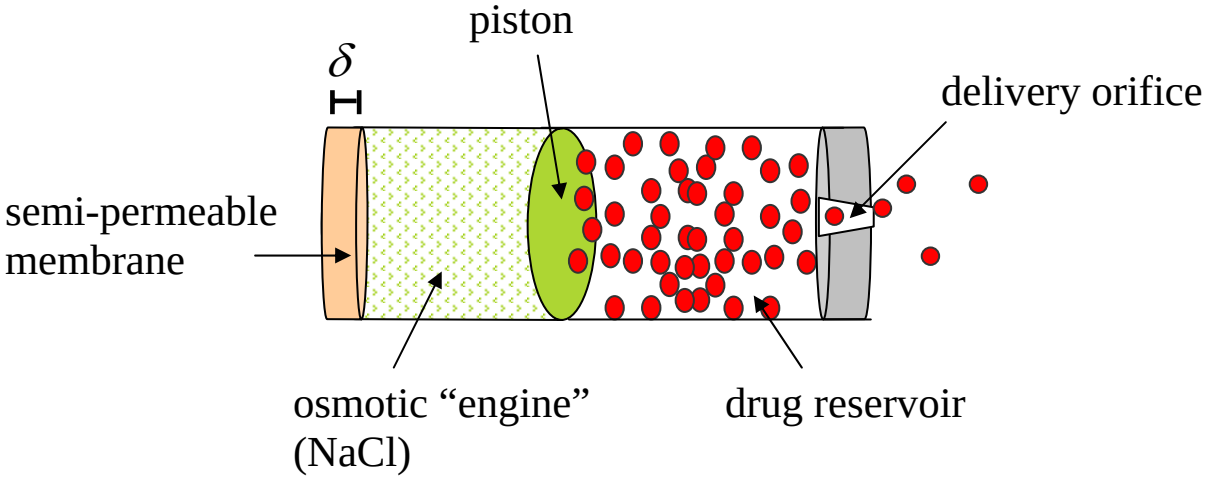




Cross-section of porous semi-permeable membrane

c) Osmotic Pressure Devices

Osmotic pressure build-up from water in-flux across semi-permeable membrane forces drug release through orifice



http://www.alza.com/alza/duros

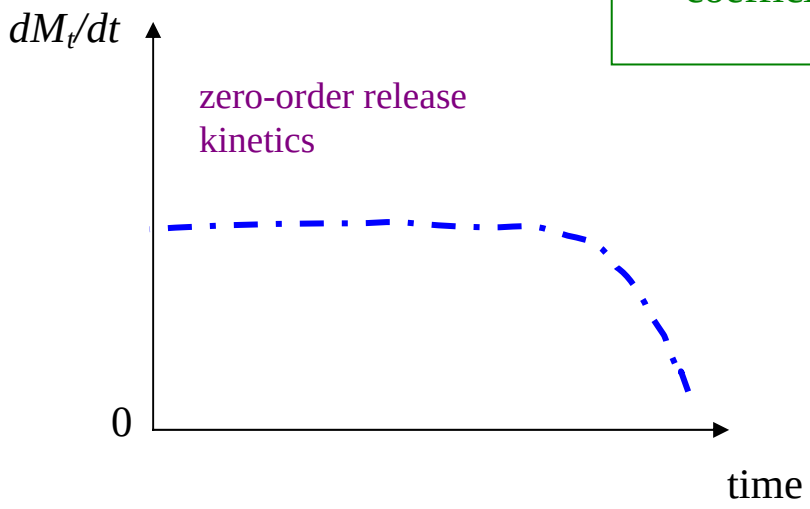
Ex: DUROS Implant (ALZA)

- Ti housing, 4mm × 45 mm
- ~ 1 year duration
- in use for prostate cancer therapy

Release rate proportional to change in volume of drug reservoir:

$$\frac{dM_t}{dt} = \frac{dV}{dt}C = \frac{Ak\Delta\pi C}{\delta}$$

A= membrane area
Δπ = osmotic pressure differential
C = drug concentration in reservoir
k= membrane permeability coefficient (~10^{-6}-10^{-7}g/cm/s)



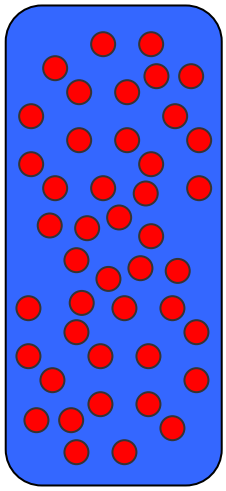
Controlled Release via Solute Choice for Osmotic Engine (Δπ)

Solute	Osmotic Pressure (atm)
body tissue	7
NaCl	356
KCl	245
sucrose	150
dextrose	82
potassium sulfate	39

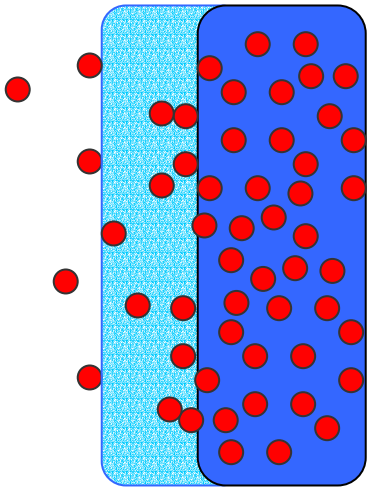
d) Swelling Controlled Devices

- Drug dispersed in a glassy, hydrophilic matrix
- Swelling in aqueous medium allows drug release

glassy polymer matrix with dispersed drug

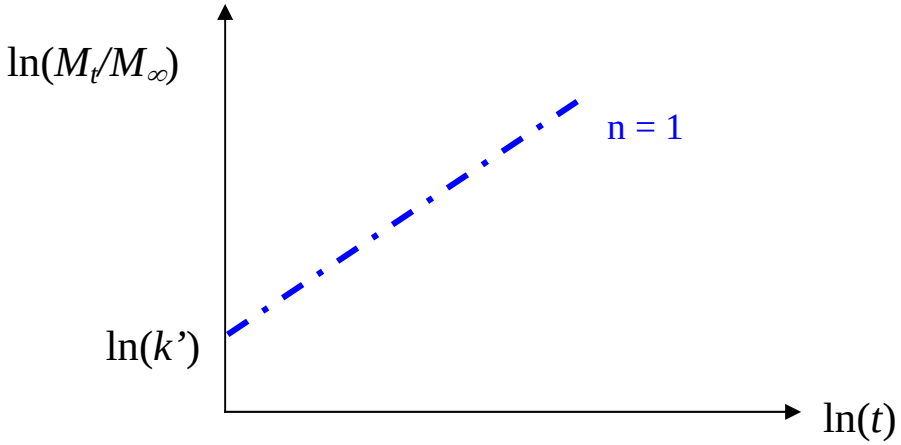


H_2O swelling provides mobility for drug release



Complex release kinetics: modeled by fitting experimental data to power law expression.

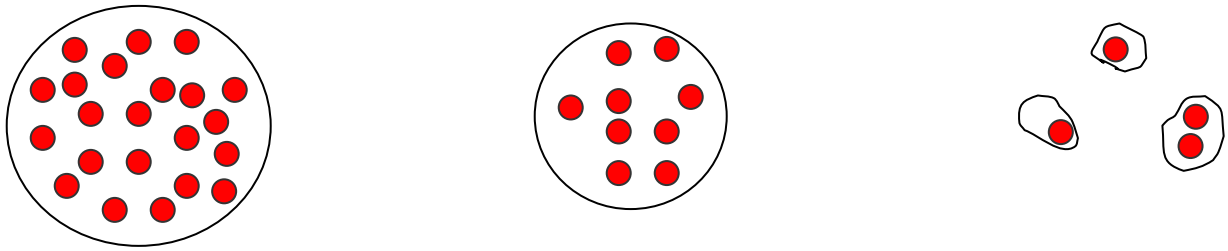
$$\frac{M_t}{M_\infty} = k' t^n$$



2. Chemically Controlled Approaches

a) Eroding Monolithic Device

Drug is incorporated into a **bioerodible or dissolvable** polymer **matrix**



t_0 **t_1** **t_2**

i) Surface Erosion Devices

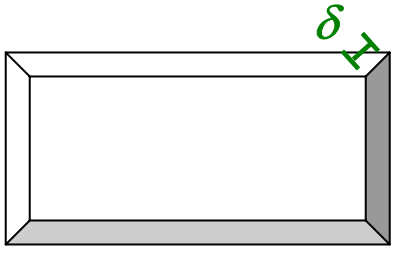
$$\frac{dM_t}{dt} = k_e A_e$$

release rate = strong function of device geometry

A_e = instant surface area
k_e = rxn or dissolution rate const.

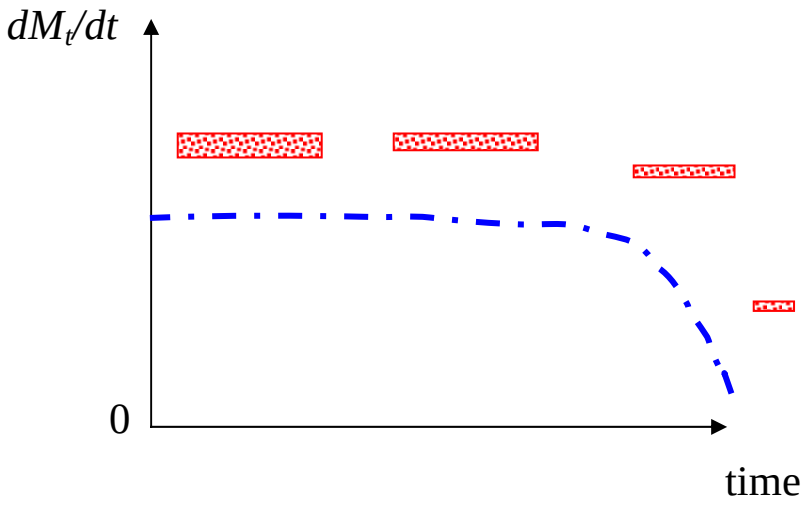
For a slab:

$$A_e \approx \frac{2M_\infty}{C_0 \delta} \approx const$$



$$\frac{dM_t}{dt} = \frac{2k_e M_\infty}{C_0 \delta}$$

$\Rightarrow$ ***zero-order release kinetics***



For other geometries, A_e is a function of time:

$$\frac{dM_t}{dt} = k_e A_e(t)$$

For various geometries, the solution to this expression is:

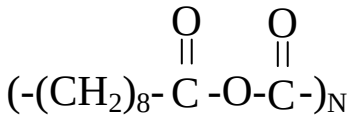
$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_e t}{C_0 \frac{\delta}{2}}\right]^n$$

Geometry	δ	*n*
slab	thickness	1
cylinder	diameter	2
sphere	diameter	3

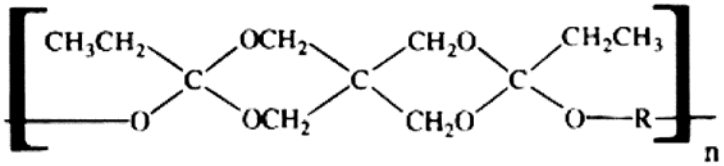
Matrix Examples:

- polyanhydrides

poly(sebacic acid anyhydride)



- poly ortho esters *DETOSU*



where R = $(CH_2)_5$

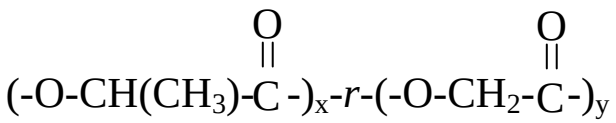
ii) Bulk Erosion Devices

- uniform hydrolysis of bulk matrix polymer
- hydrolysis rate vs. drug diffusion controls release rate

$$\frac{dM_t}{dt} \sim t^n \qquad \Rightarrow n = -1/2 \text{ drug diffusion limited}$$

Matrix Example:

poly(lactide-co-glycolide)

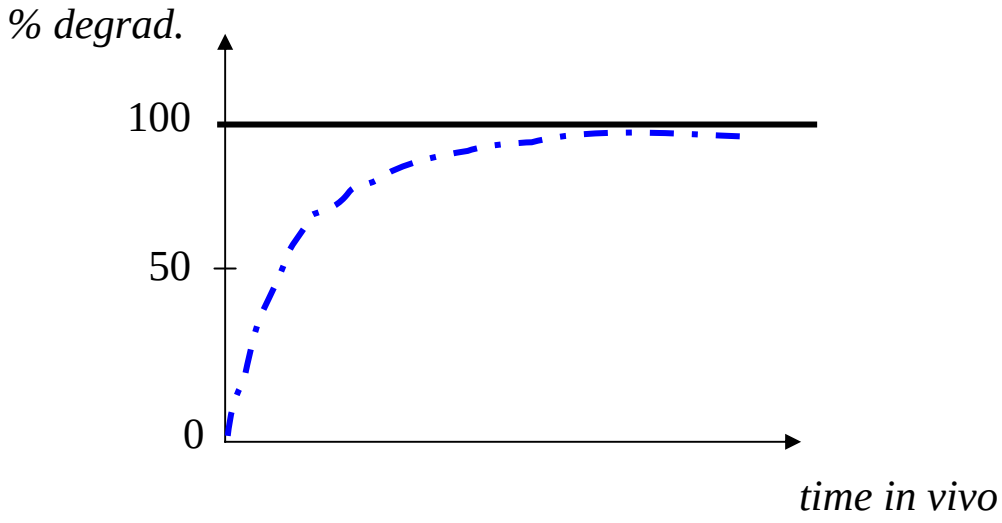


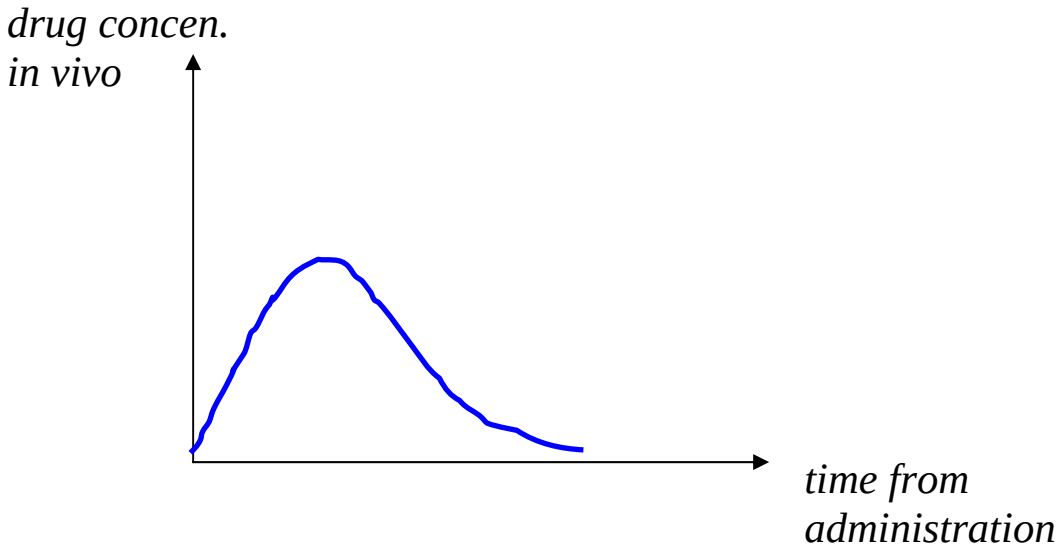
lactic acid glycolic acid

iii) Pulsed release systems

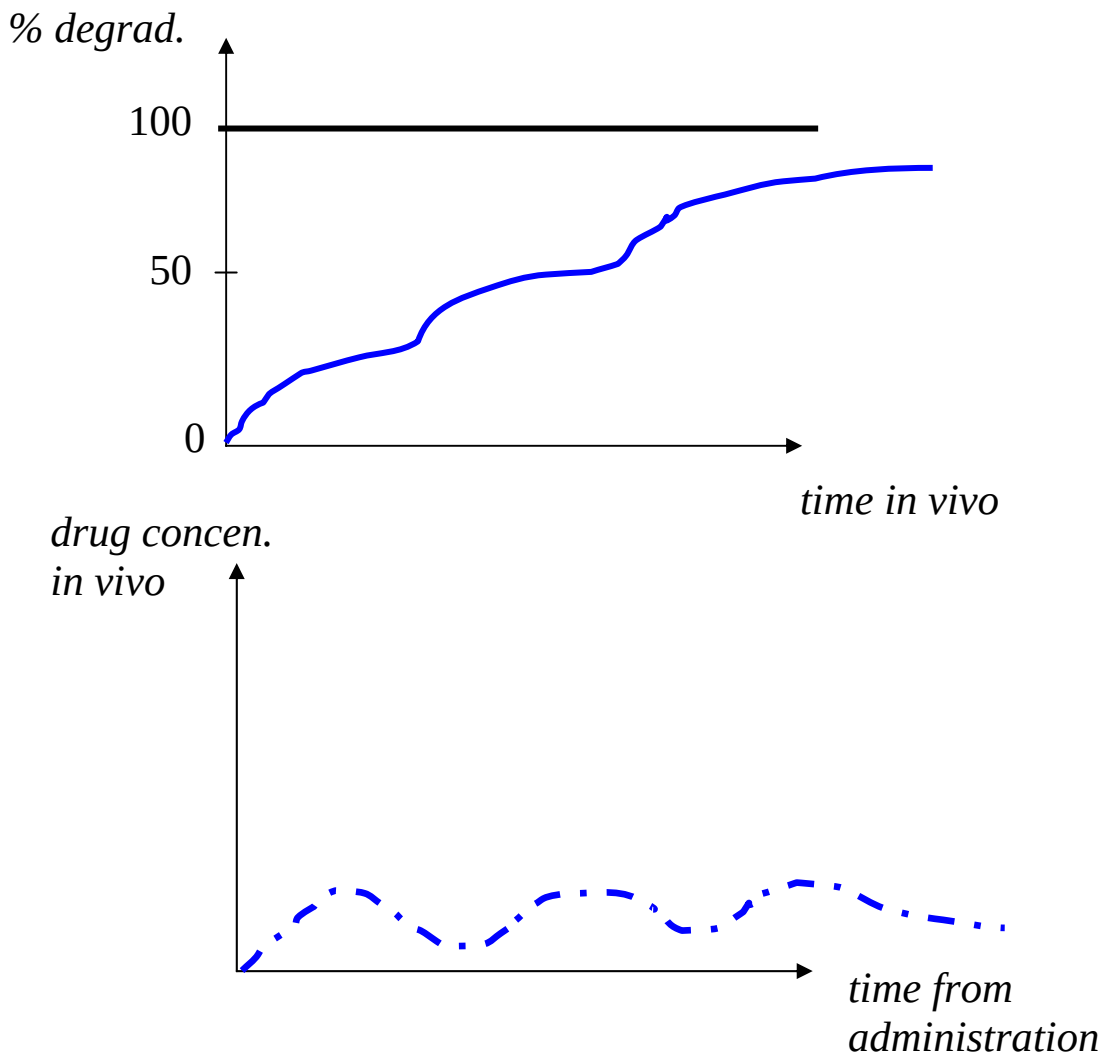
Mixture of eroding particles with different degradation rates

Degradation Profile for Single Eroding Component (schematic)





Degradation Profile for Mixture of Components (ex., microspheres)



Applications Example: "one shot" vaccines with multiple antigens

TT tetanus toxoid
DT diptheria toxoid
HBSA hepatitis B surface antigen
SEB staphylococcal enterotoxoid B

Vaccines stimulate Ab production

⇒ How can we achieve different degradation rates?

Factors influencing degradation:

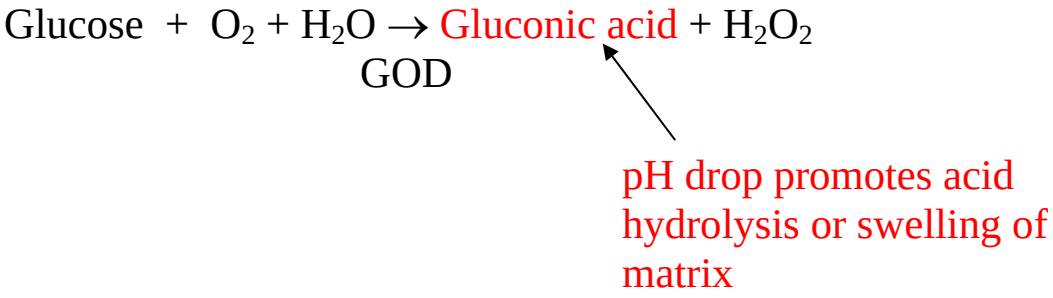
- Composition (e.g., PLGA copolymer LA:GA ratio)
- Geometry

iv) Regulated systems

Incorporate a component that responds to the *in vivo* environment

- Enzyme that catalyzes degradation in presence of a substrate

Example: GOD-regulated insulin release



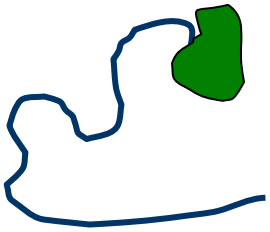
b) Polymer-Drug Conjugates

Therapeutic agent is covalently or ionically bound to a polymer through a cleavable bond

Purposes:

- increase resistance to proteolysis (protein drugs)
- reduce antigenicity/immunogenicity
- prolong plasma circulation lifetime
- enhance water solubility of hydrophobic agents
- reduce toxicity

Example 1: Therapeutic proteins tethered to polyethylene glycol (PEG)



protein

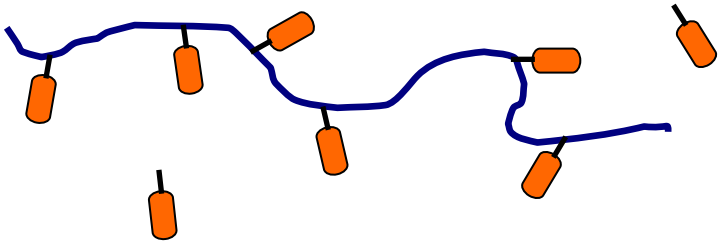
⇒ ***Increases intravascular lifetime—why?***

PEG

Some clinical systems:

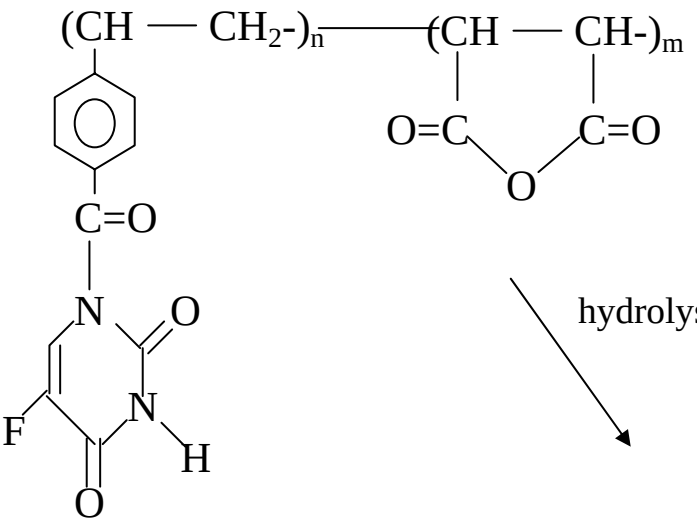
- PEG-adenosine deaminase (FDA appr. immunodeficiency therapy)
- PEG-asparaginase (FDA appr. for lymphoblastic leukemia)
- PEG-hemoglobin
- PEG-interluekin 2
- PEG-alpha interferon
- PEG-colony stimulating factor

Example 2: Chemotherapeutic agent attached to water-soluble or hydrolysable backbone

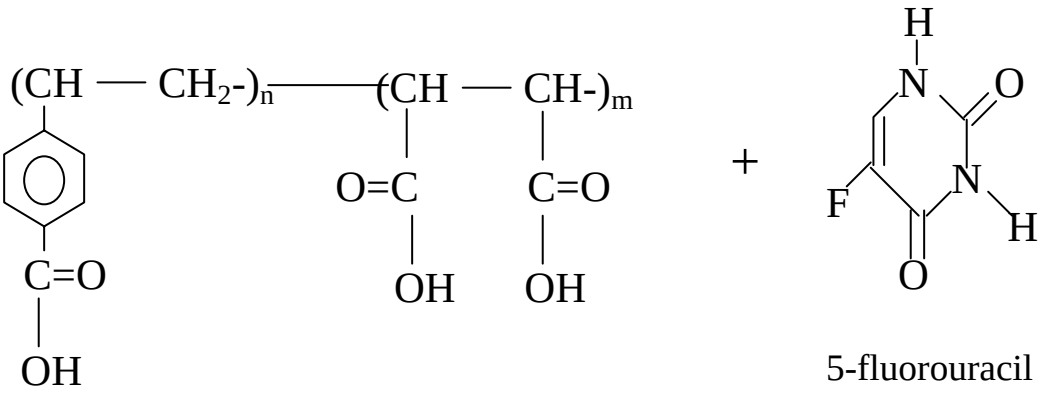


vinyl benzyl fluorouracil

maleic anhydride



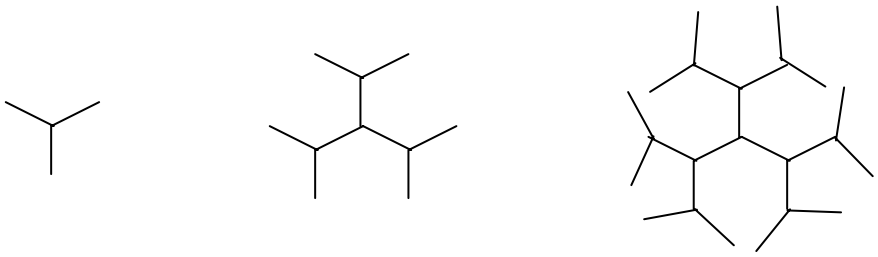
hydrolysis



5-fluorouracil

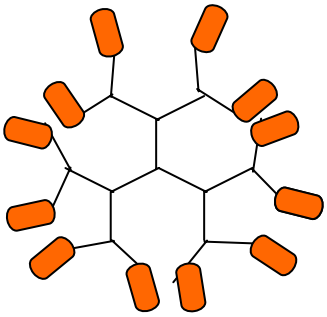
Example 3: Dendrimer Drug Conjugates (early development)

Dendrimers – sequentially synthesized, hyperbranched macromolecules

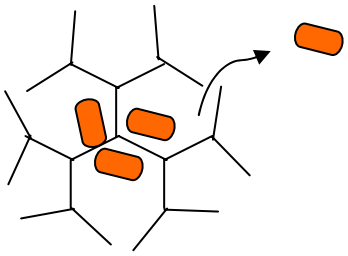


1st generation 2nd generation 3rd generation

Two strategies for controlled drug delivery



drug-conjugated chain ends



Drug-filled core (diffusion-controlled)

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