Controlled Release Theory

Last time:	tailoring the structure of degradable polymers Fundamental concepts in controlled release
Today:	Theory of degradable polymer-based controlled release
Reading:	Charlier et al., 'Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations,' *Int. J. Pharm*. **200**, 115-120 (2000)

ANNOUNCEMENTS:

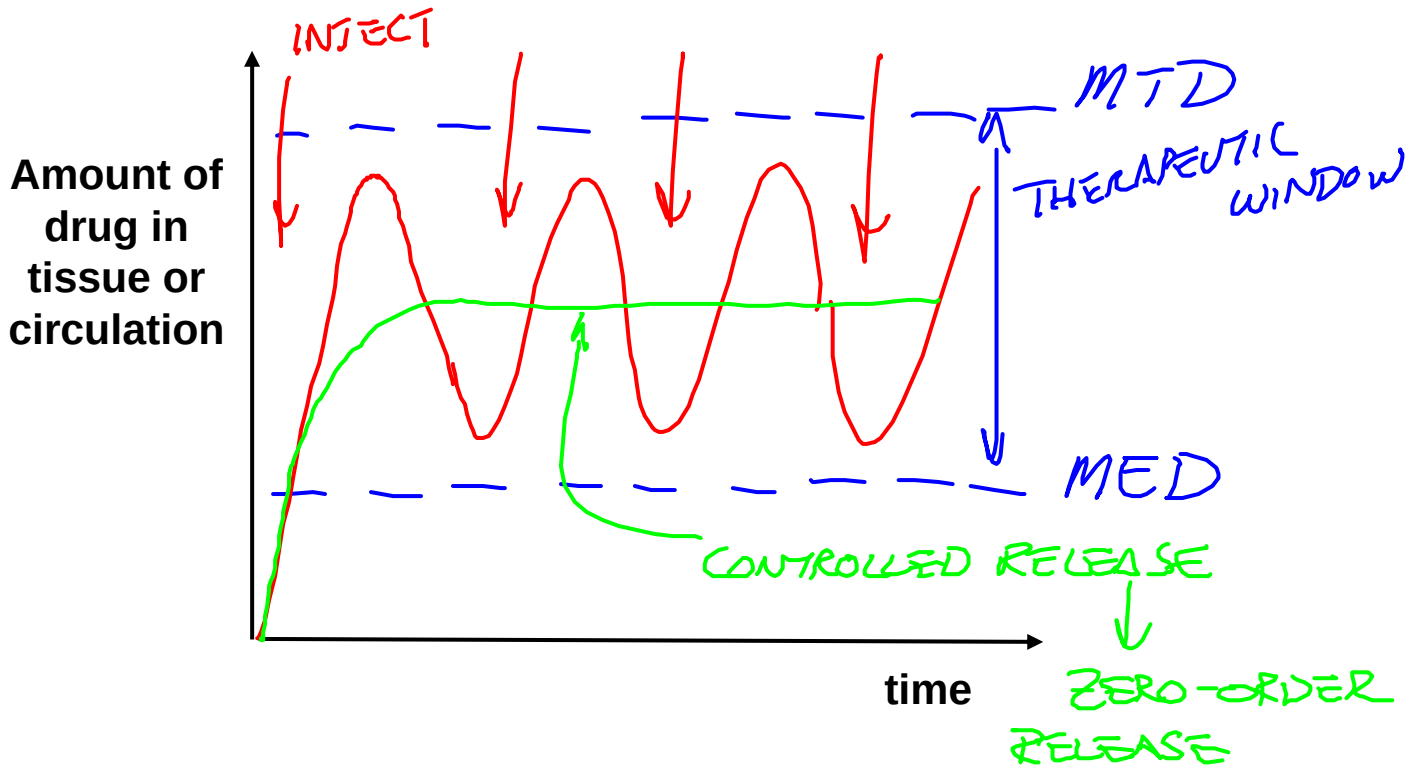
PS 1 DUE 5pm

PS 2 POSTED TOMORROW, DUE 1 WEEK LATER

Last time

Therapeutic index: tailoring materials to provide release kinetics matching the 'therapeutic window'

Bolus drug injection:

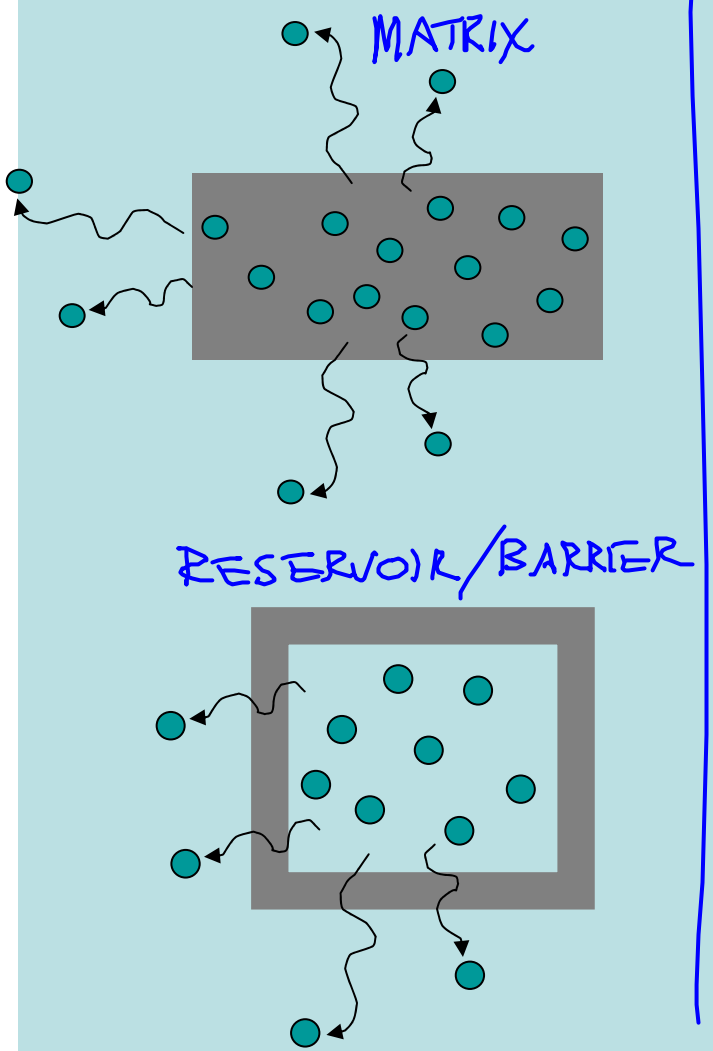


Mechanisms of controlled release

OVERVIEW OF MECHANISMS:

- DIFFUSION-BASED RELEASE
  - → WATER INFLUX-CONTROLLED RELEASE
- ERODING MATRIX
- REGULATED/TRIGGERED RELEASE

Drug diffusion-controlled release



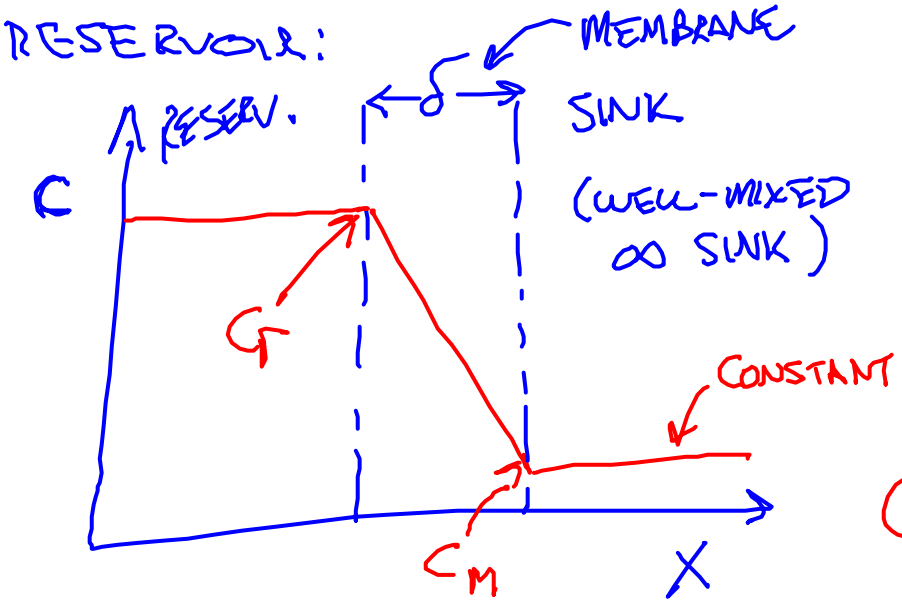
Advantage:

- WELL-DEFINED KINETICS
  - ↓
  - MODEL RIGOROUSLY

Disadvantages:

- NON-DEGRADABLE MATERIALS
- DIFFUSION OF MACROMOLECULES TOO SLOW TO BE USEFUL
- DANGER OF 'DOSE DUMPING' IN RESERVOIR SYSTEMS

Release kinetics for diffusion-controlled release



FICK'S FIRST LAW:

$$J = \text{FLUX} = \frac{\text{MASS DIFF}}{A \cdot \text{TIME}} = -D\frac{\partial C}{\partial x}$$

$$J = \frac{dQ}{dt}\frac{1}{A}$$

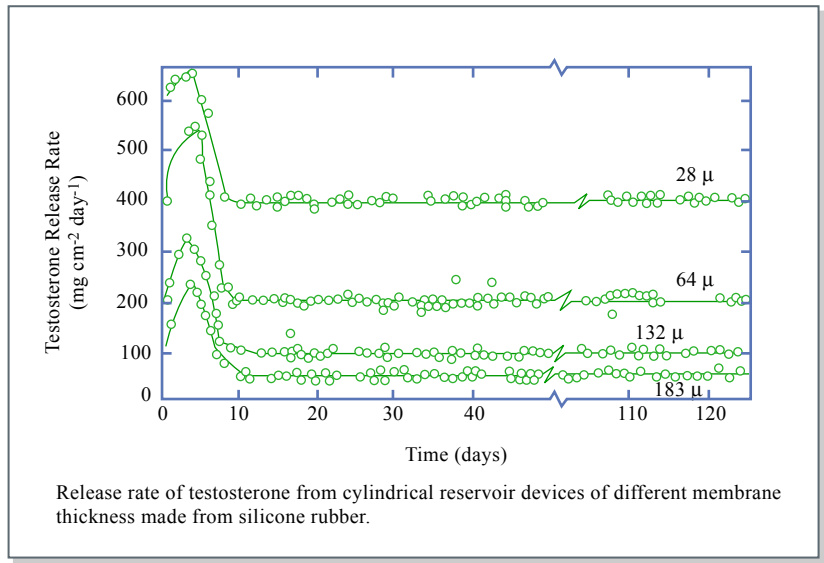
Q = MASS OF DRUG A = SURF. AREA OF MEMBRANE

$$\frac{dQ}{dt} = \frac{AD}{\delta}(C_r - C_m)$$

↓ TOTAL AMOUNT RELEASED AT TIME t:

$$Q(t) = \frac{AD}{\delta}(C_r - C_m)t$$

$$\frac{dQ}{dt} = \text{CONSTANT! (ZERO-ORDER)}$$



Release rate of testosterone from cylindrical reservoir devices of different membrane thickness made from silicone rubber.

Figure by MIT OCW.

Release kinetics for diffusion-controlled release

MATRIX:

FICK'S 2ND LAW: $\frac{\partial c}{\partial t} = \nabla(D\nabla c)$

DRUG DISSOLVED IN MATRIX, NEGLECTING "END" EFFECTS:

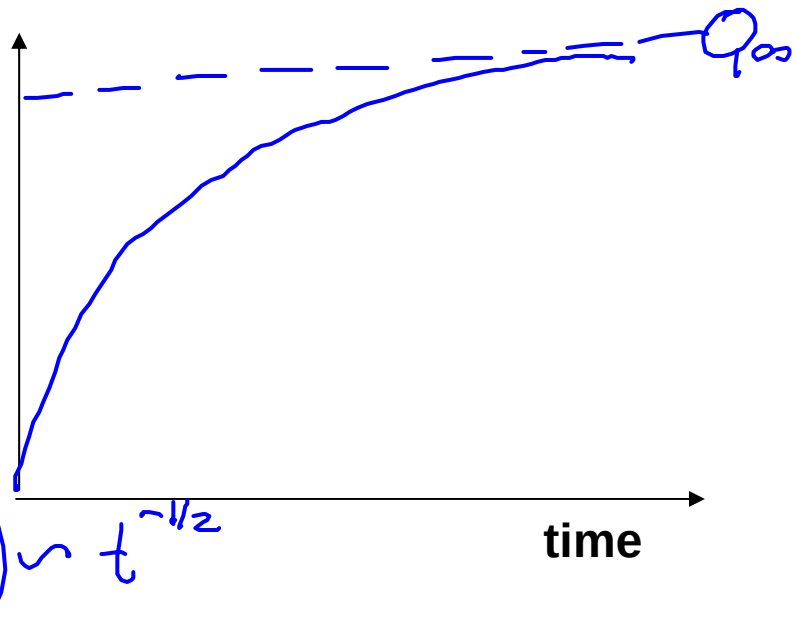
$$\frac{Q}{Q_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left(-\frac{D(2n+1)^2\pi^2 t}{\delta^2}\right)$$

Q: AMOUNT RELEASED AT $t = \infty$

"SHORT TIMES" $\left(0 < \frac{Q}{Q_\infty} \leq 0.6\right)$

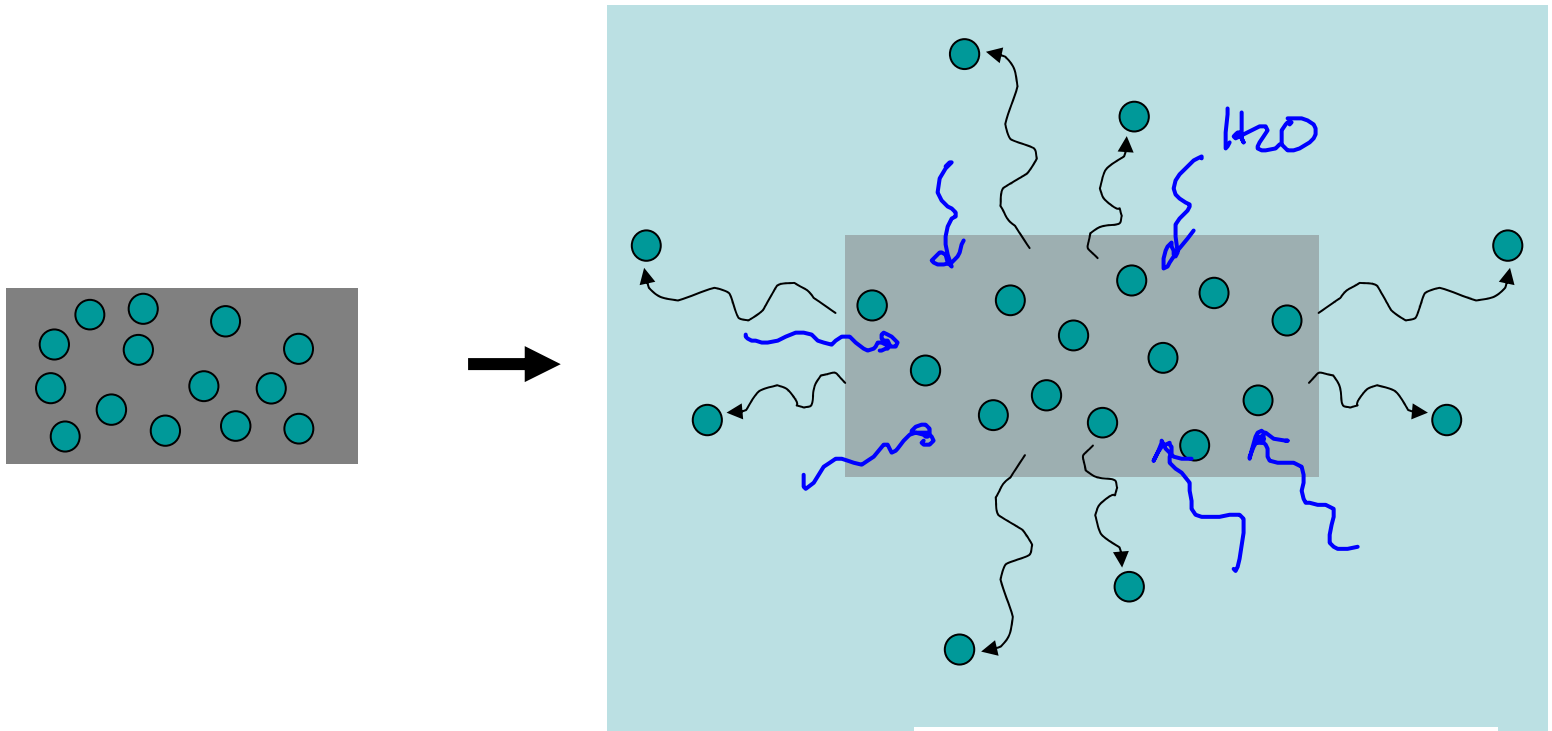
$$\frac{Q}{Q_\infty} \simeq 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2}$$

RATE: $\left(\frac{dQ}{dt}\right) \sim t^{-1/2}$

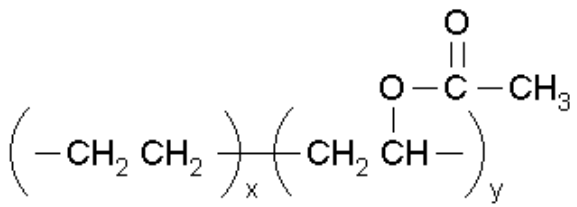


Water-influx controlled release

HYDROPHILIC MOLECULES RELEASED BY H_2O SWELLS THE MATRIX



Example: poly(ethylene-co-vinyl acetate)

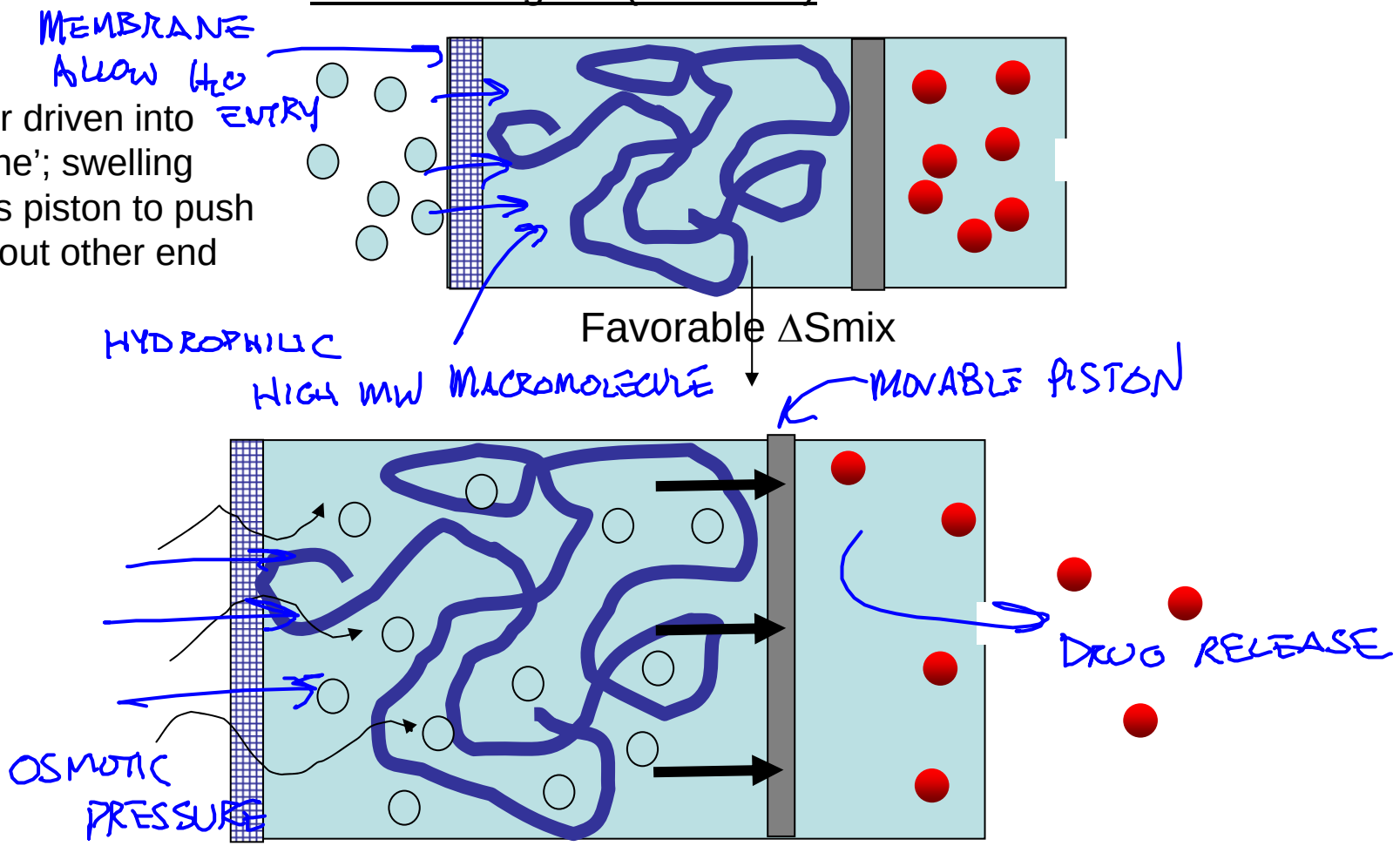


Regulated/triggered release: mechanical

RELEASE HAPPENS IN RESPONSE TO A STIMULUS — PROGRAMMED / EXTERNAL

Osmotic engine: (one form)

Water driven into 'engine'; swelling drives piston to push drug out other end



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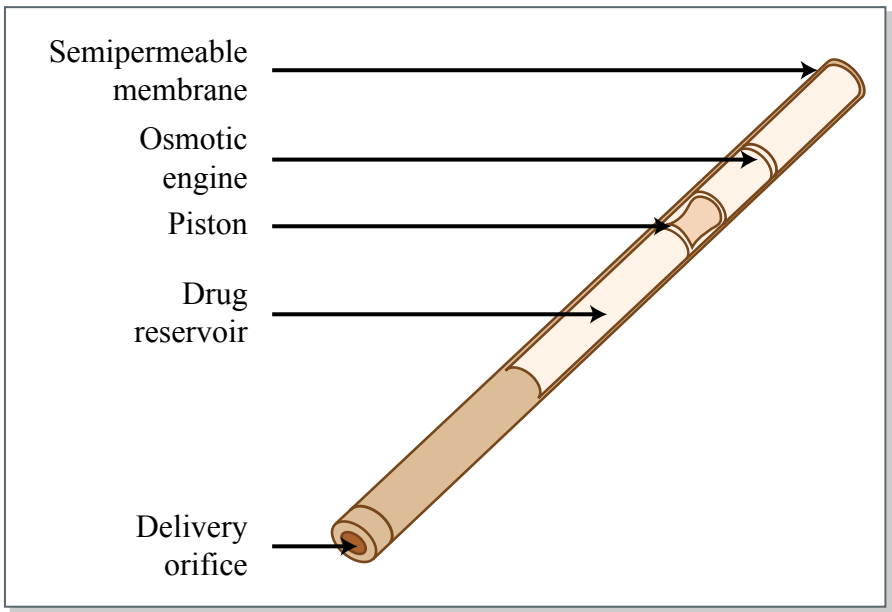


Figure by MIT OCW.

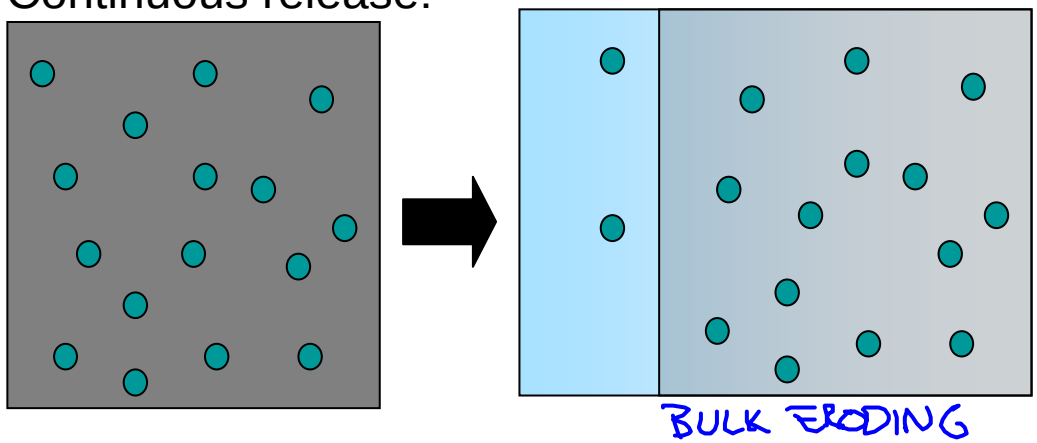
Designed to provide continuous release of drugs up to one year

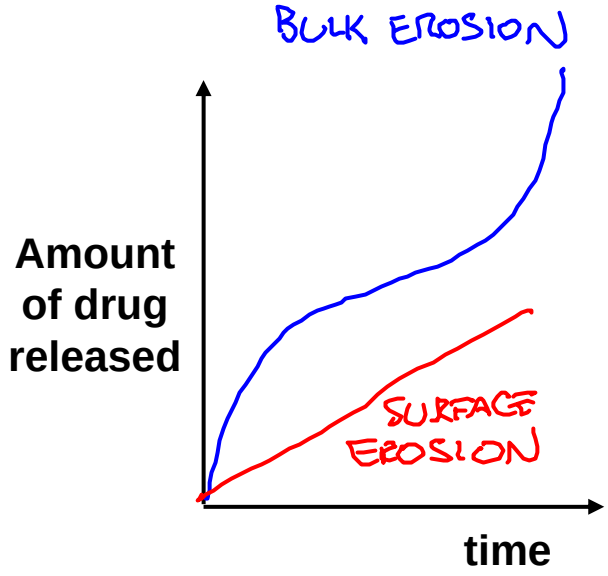
SEMI-ZERO ORDER RELEASE ACHIEVABLE

Titanium rod casing

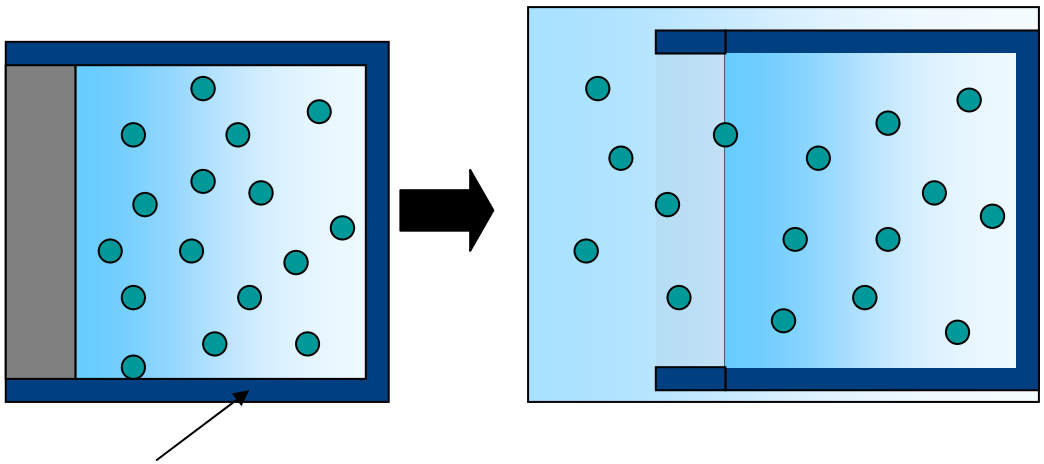
eroding matrix

Continuous release:

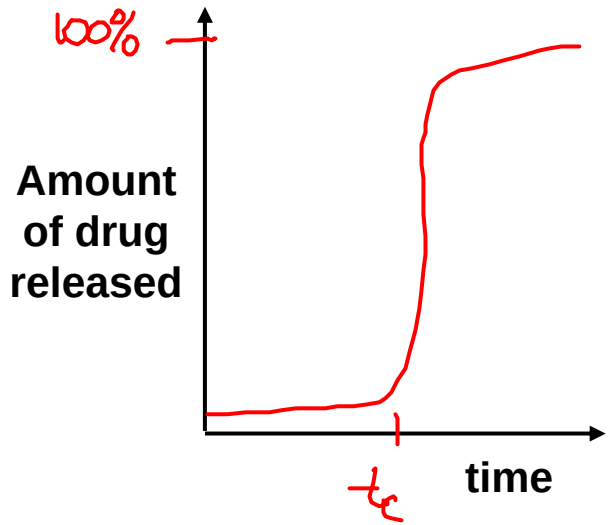




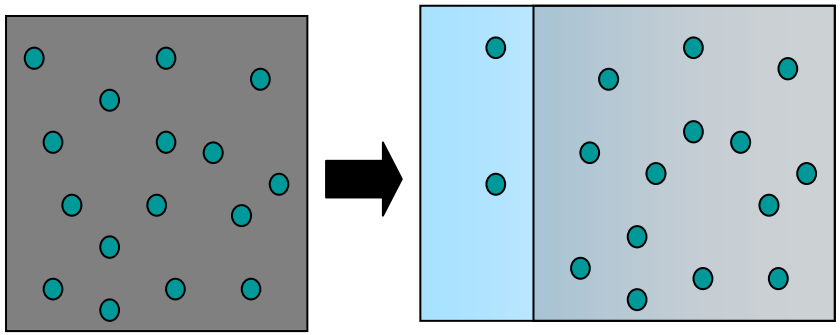
burst release:



Non-erodible capsule

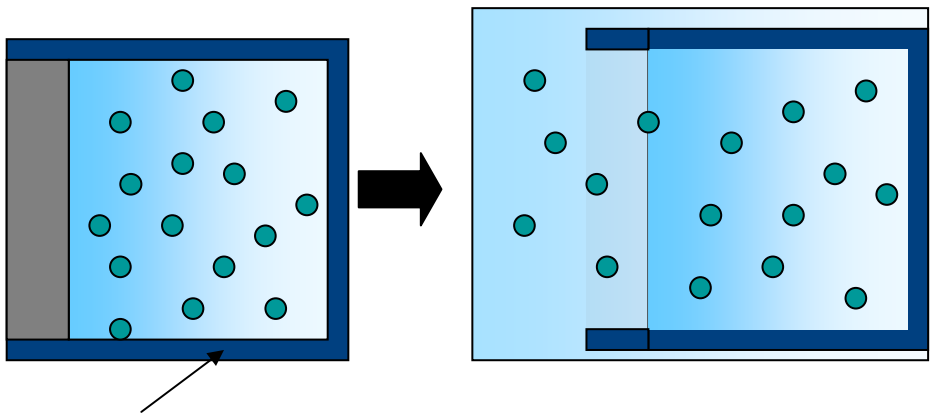


eroding matrix



Advantages:

- CAN BE INJECTABLE AND DEGRADABLE
- LOW DANGER OF DOSE DUMPING RELATIVE TO RESERVOIR DEVICE

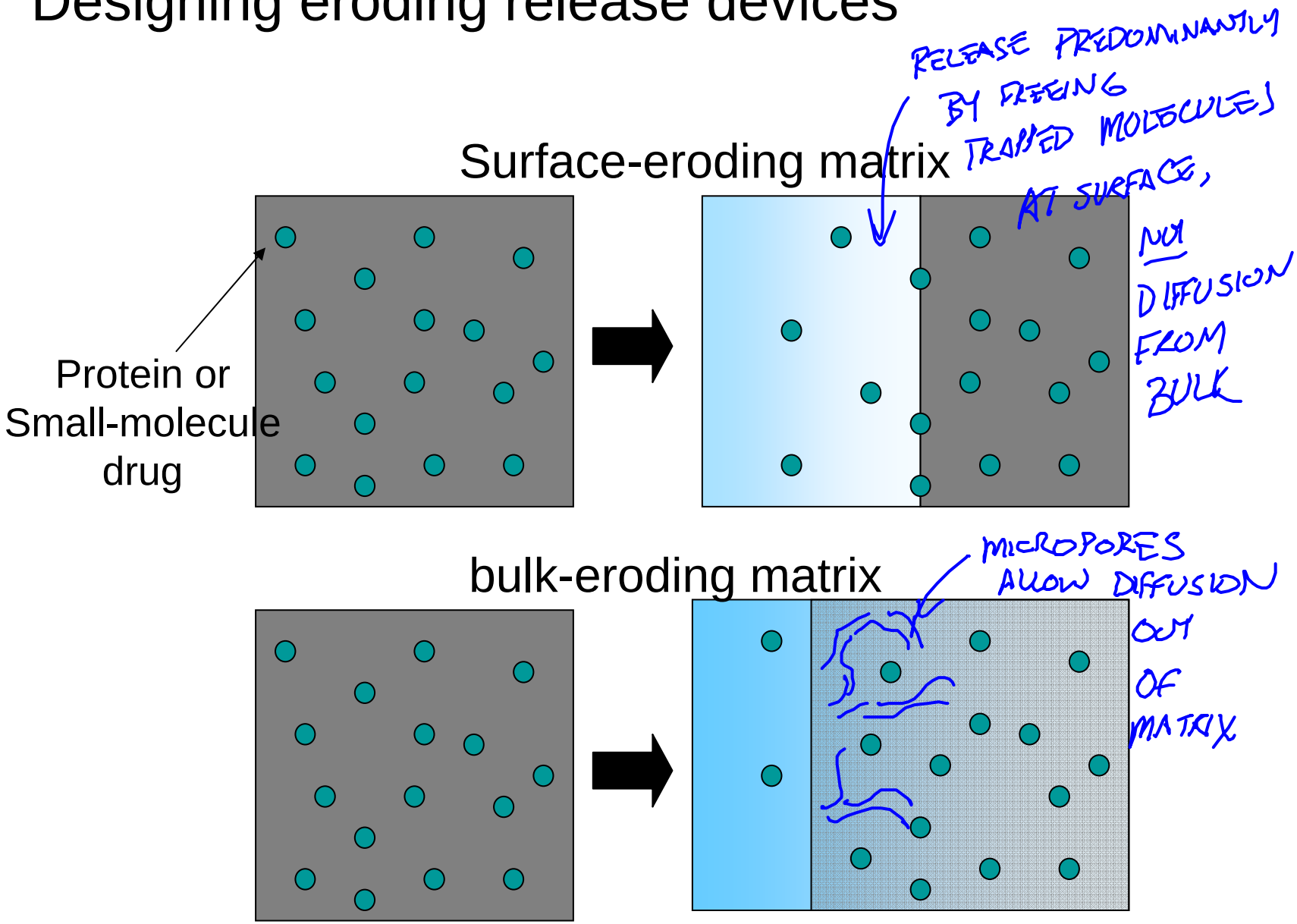


Non-erodible capsule

Disadvantages:

- OFTEN DIFFICULT TO STOP THERAPY UNTIL EROSION IS COMPLETE
- RELEASE WILL VARY W/ TIME, FOR BULK EROSION

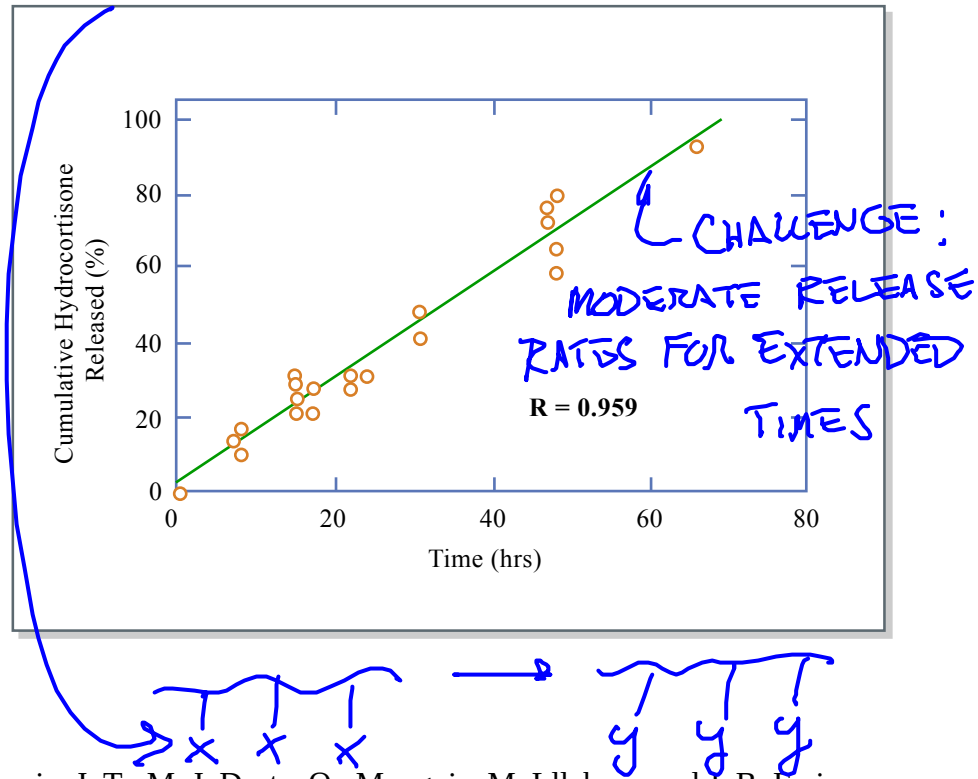
Designing eroding release devices



Typical release profiles

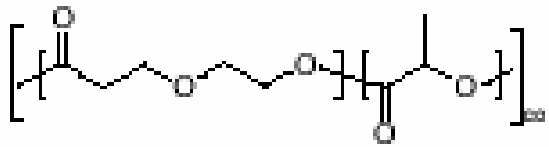
Surface-eroding matrix

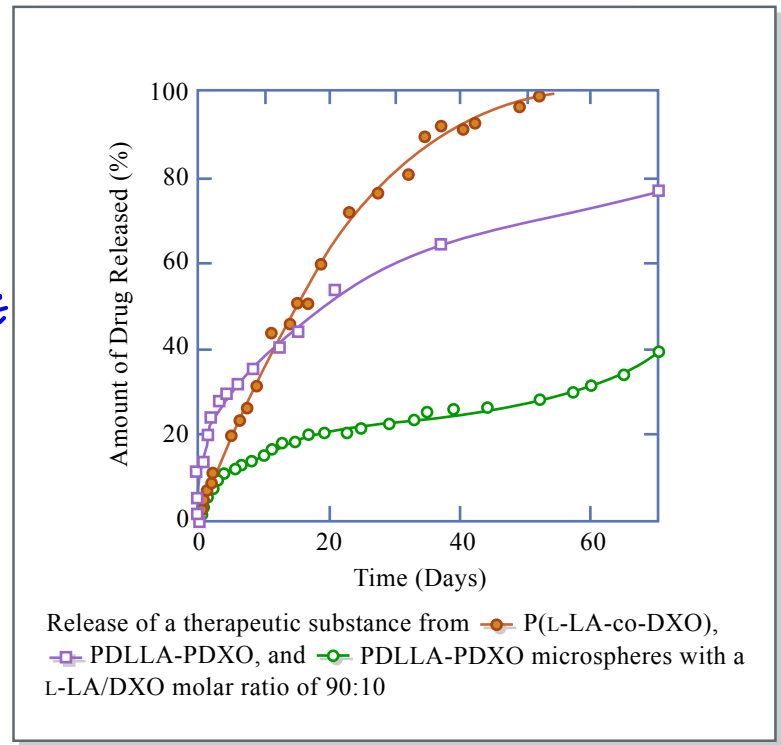
Poly(methyl vinyl ether-co maleic anhydride)



Bulk-eroding matrix

Poly(dioxepanone-co-lactide)

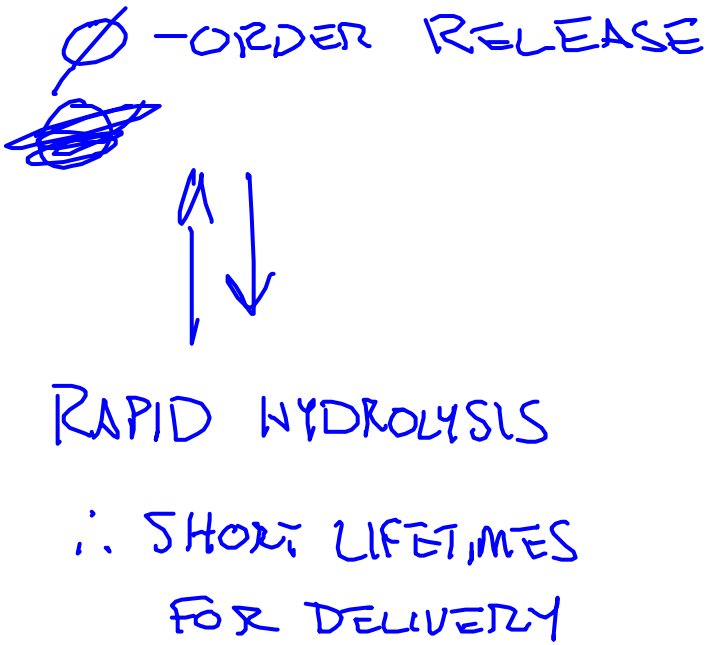




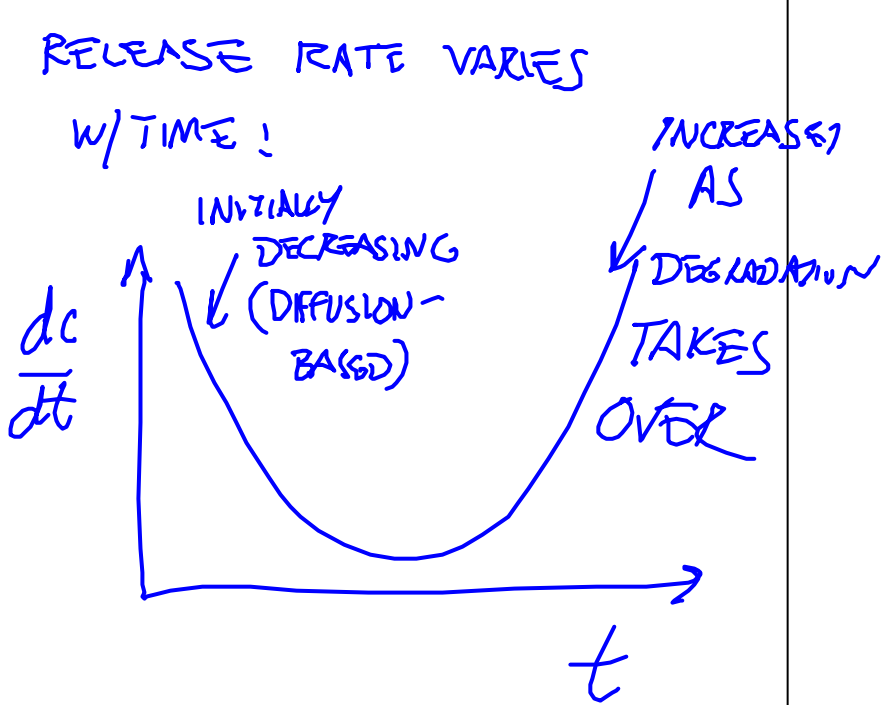
Garcia, J. T., M J. Dorta, O. Munguia, M. Lllabres, and J. B. Farina. "Biodegradable Laminar Implants for Sustained Release of Recombinant Human Growth Hormone." *Biomaterials* 23 (2002): 4759-4764.

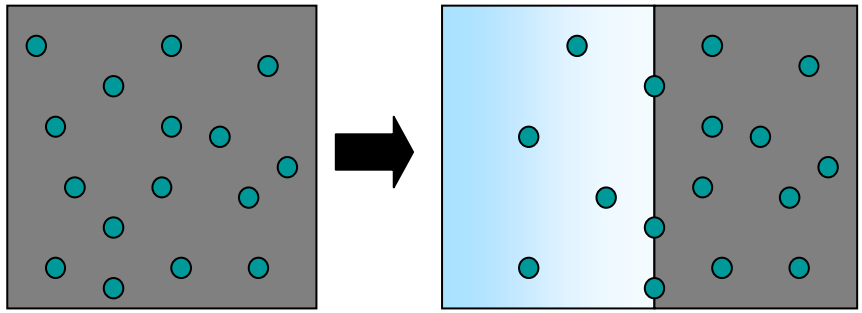
Characteristics of surface vs. bulk-eroding controlled release: (why not always use surface-eroding polymers?)

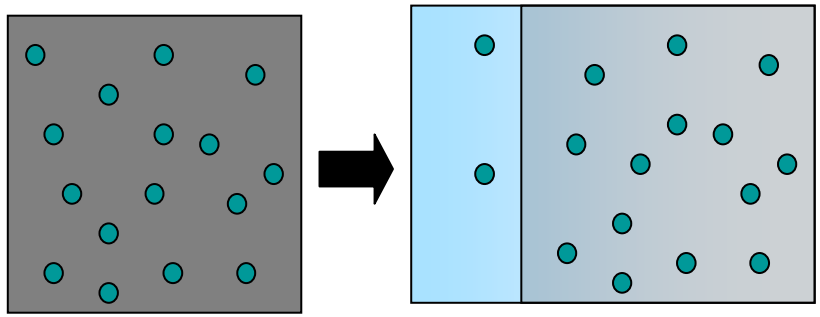
surface erosion:



bulk erosion







Surface-eroding matrix

Poly(methyl vinyl ether-co maleic anhydride)

Bulk-eroding matrix

Poly(dioxepanone-co-lactide)

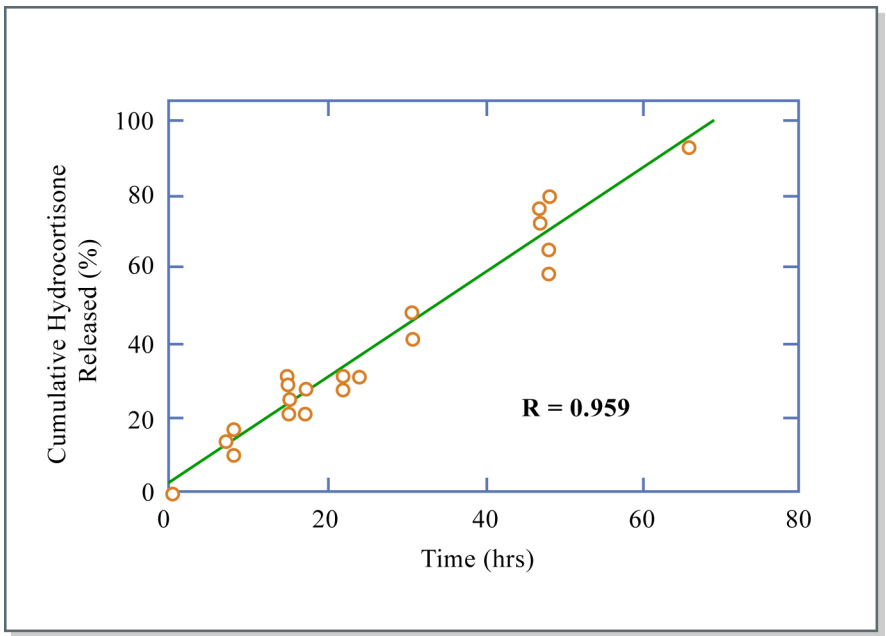


Figure by MIT OCW.

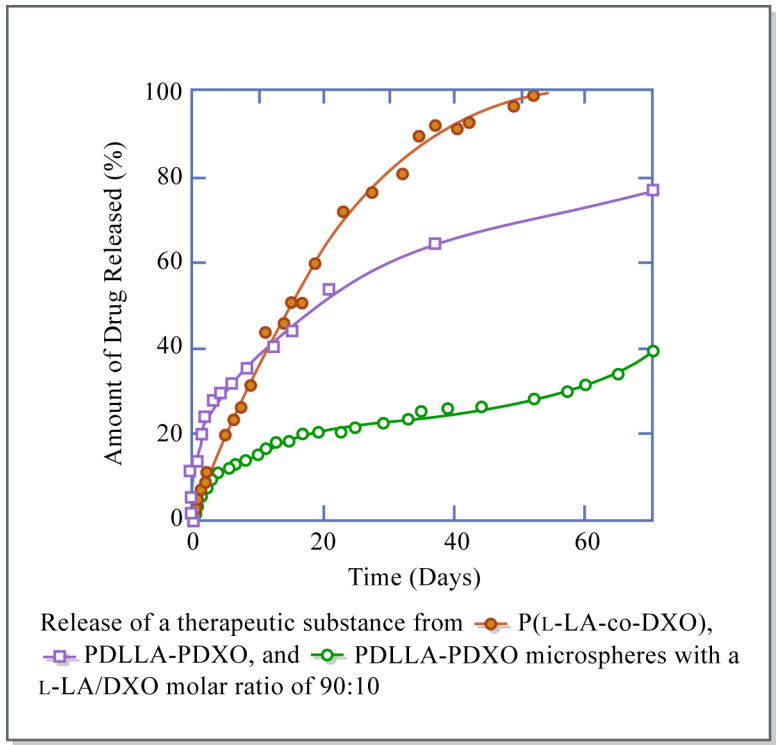
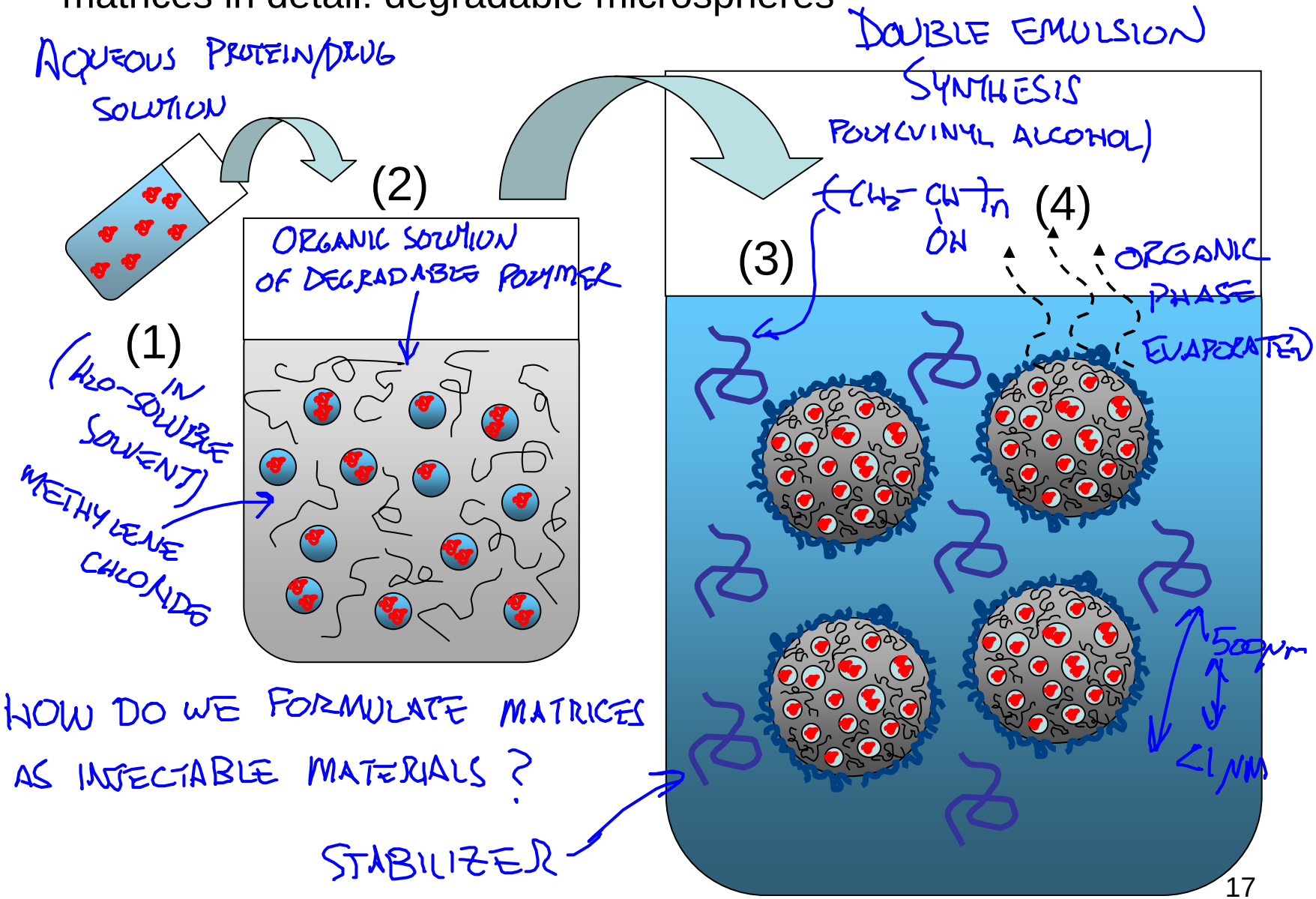


Figure by MIT OCW.

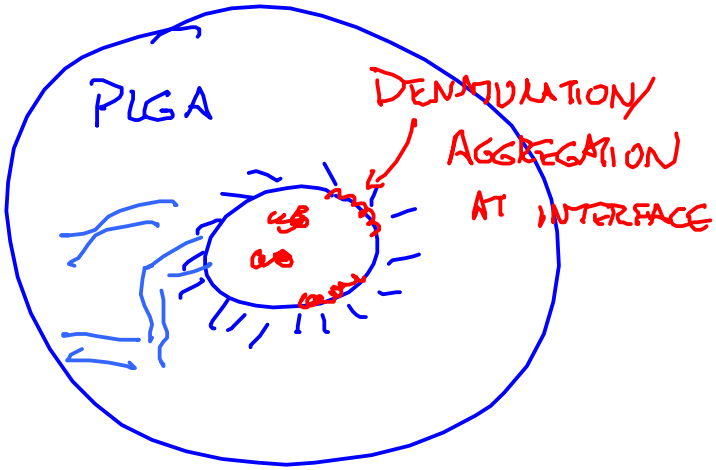
Examination of one approach to drug delivery using eroding matrices in detail: degradable microspheres



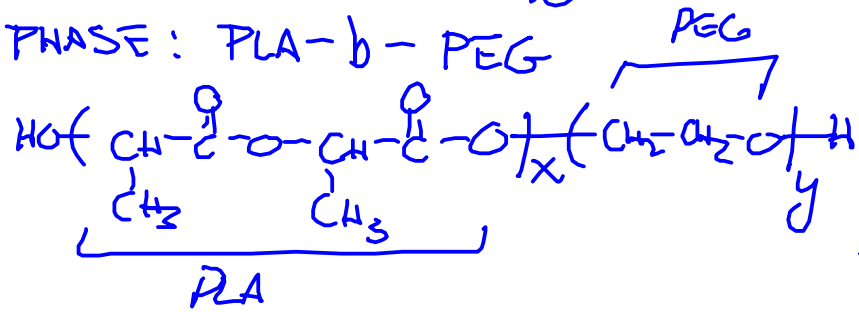
Limiting factors: pH gradients within degradable devices

Fu, K., D. W. Pack, A. M. Klibanov, and R. Langer. “Visual Evidence of Acidic Environment within Degrading Poly(lactic-co-glycolicacid) (PLGA) Microspheres.” *Pharm Res.* 17, no. 1 (January 2000): 100-6.

Limiting factors: Contact with hydrophobic surfaces/organic interfaces

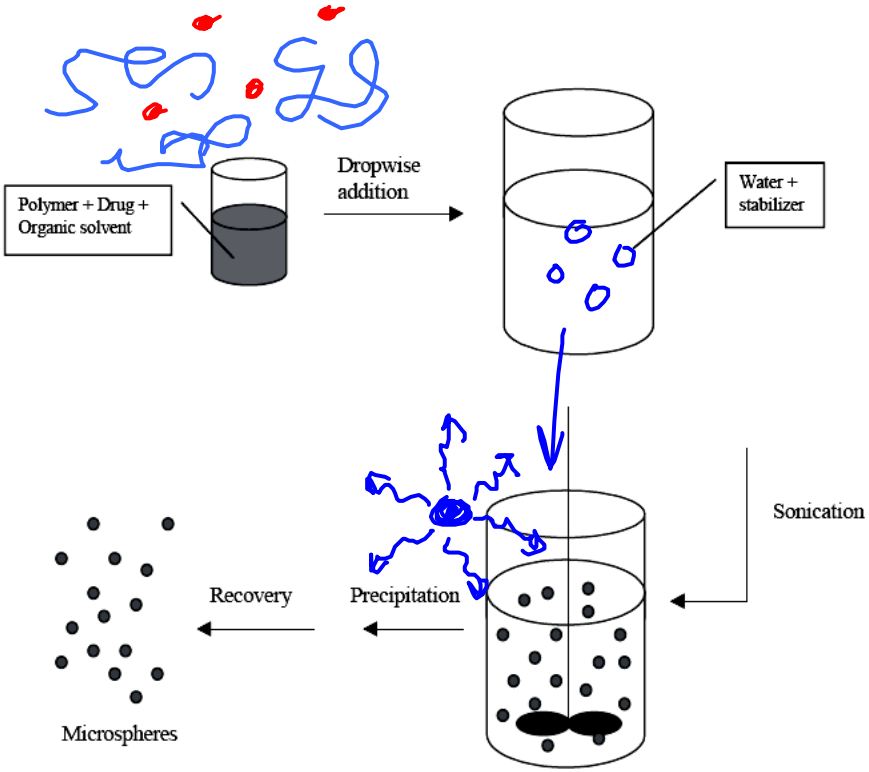


ADD AMPHIPHILIC BLOCK COPOLYMER TO ORGANIC PHASE: PLA-b-PEG



Quellec et al. *J Biomed Mater Res* 42 45-54 (1998)

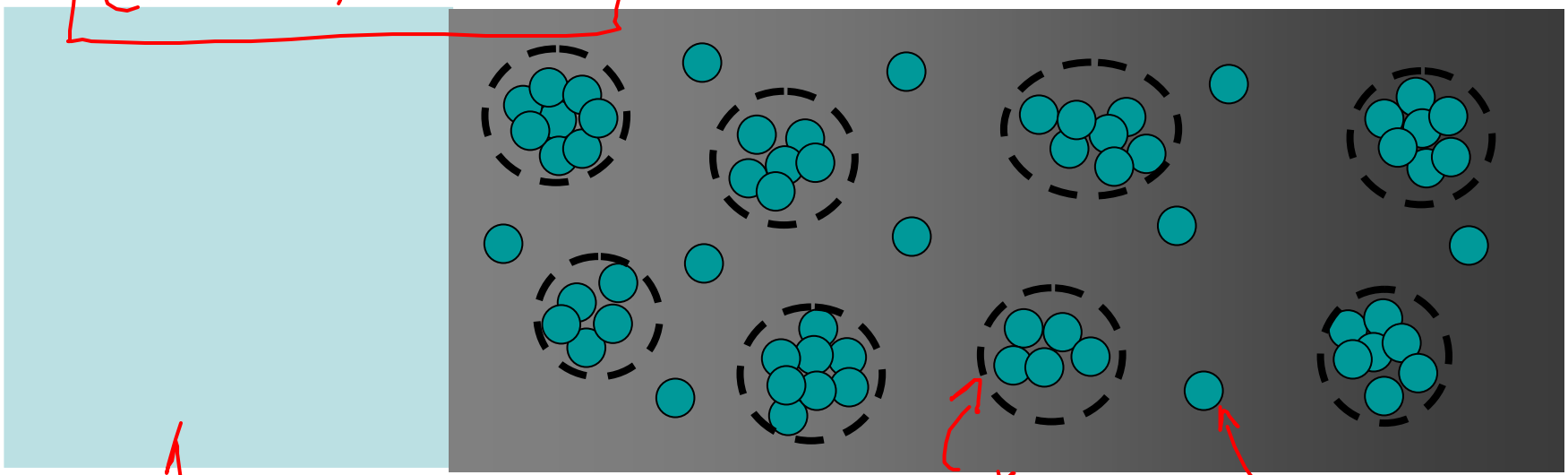
Modeling an important controlled release system: single emulsion encapsulation of small molecule drugs in degradable polymers



(Edlund 2002)

Faisant N., J. Siepmann, and J. P. Benoit. “PLGA-based Microparticles: Elucidation of Mechanisms and a New, Simple Mathematical Model Quantifying Drug Release." *Eur. J Pharm Sci.* 15, no.4 (May 2002): 355-66.

Theory of controlled release from degradable solids: physical basis of the model



(Charlier et al. 2000)

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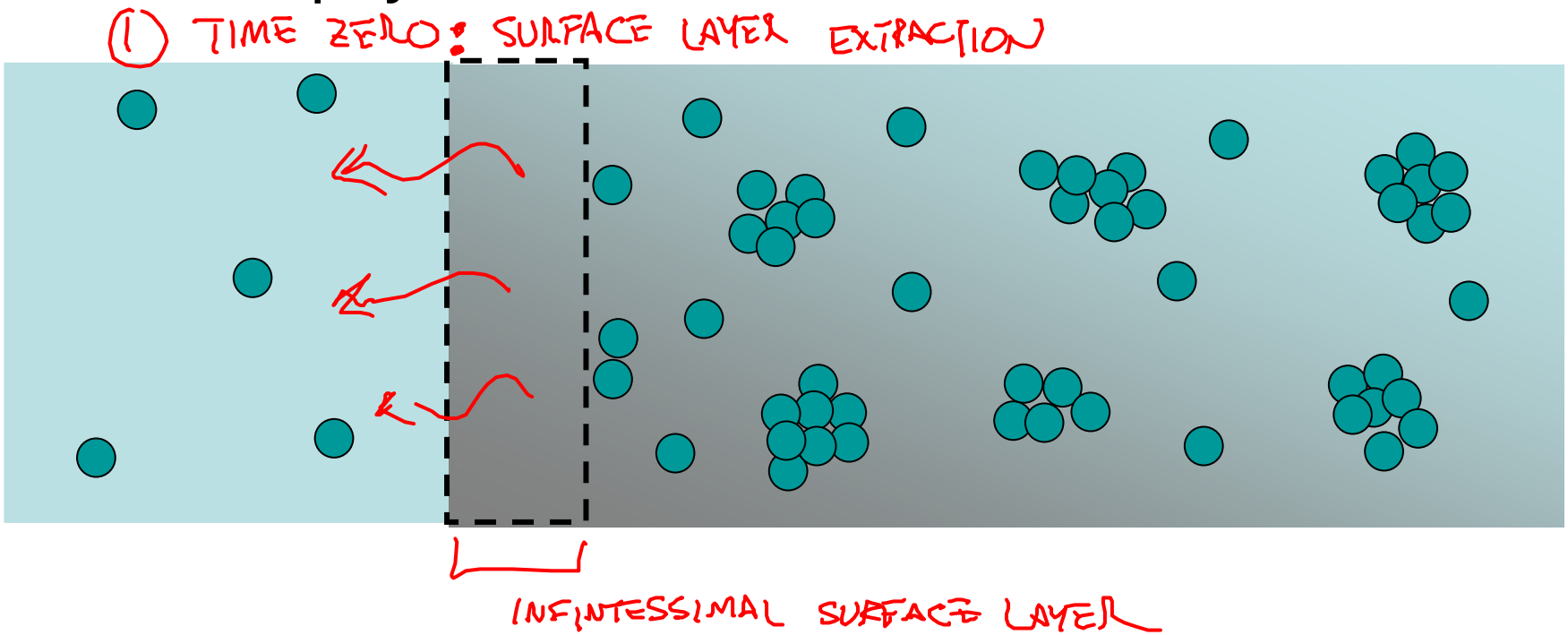

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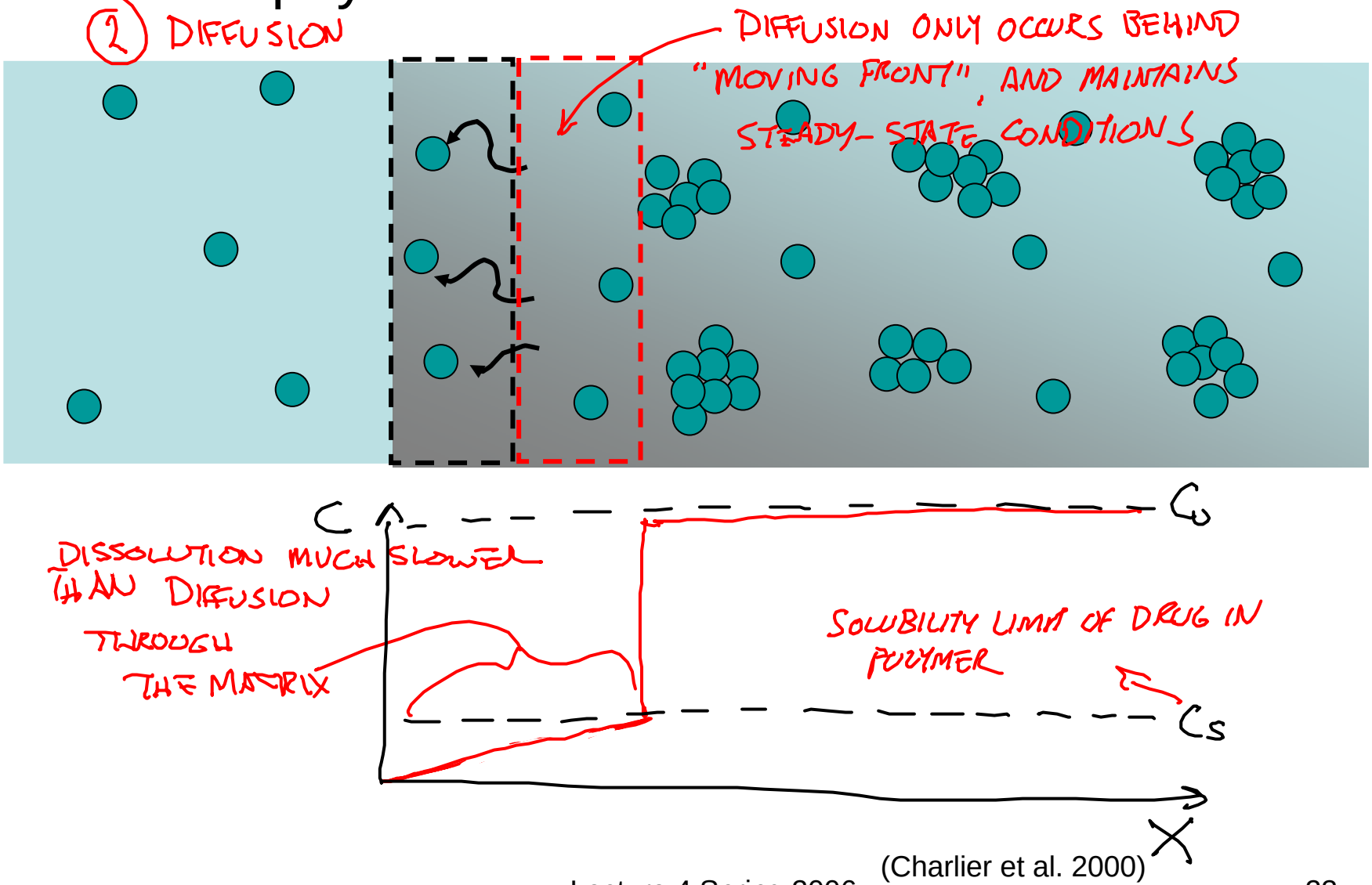
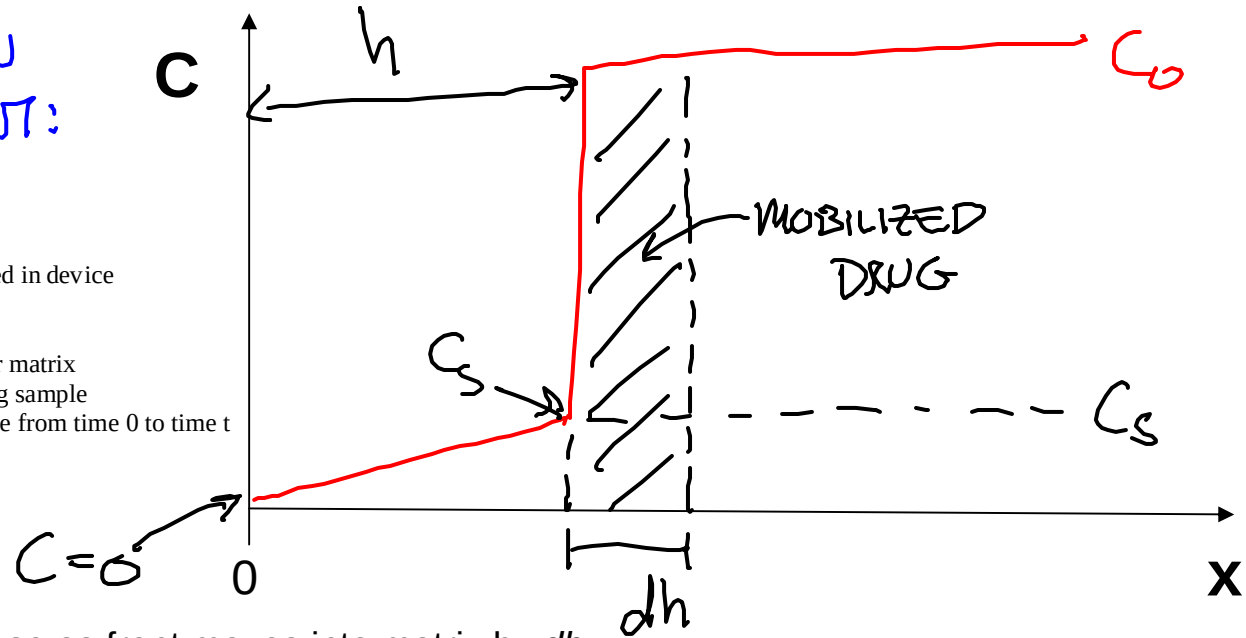


(Charlier et al. 2000)

MOTION OF DIFFUSION FRONT:

1. List of parameters:

A	device surface area
Cs	concentration of drug soluble in matrix
C_0	initial concentration of drug encapsulated in device
M(t)	molecular weight of matrix at time t
M_0	initial molecular weight of matrix
D	Diffusion coefficient of drug in polymer matrix
h	thickness of diffusion region in releasing sample
Q(t)	total mass of drug released from dispersed phase from time 0 to time t



Amount of drug freed to diffuse as front moves into matrix by *dh*:

$$\boxed{I} \quad dQ = C_0 A dh$$

Fick's first law in pseudo-steady-state diffusion region:

$$J = \frac{\text{MASS DRUG}}{\text{A-TIME}} = \frac{1}{A}\frac{dQ}{dt} = -D\frac{dc}{dx} = -D\frac{(0 - C_s)}{h}$$

$$\frac{1}{A}\frac{dQ}{dt} = \frac{DC_s}{h} \qquad \boxed{II} \quad \therefore dQ = \frac{A}{h} DC_s dt$$

Diffusion-controlled release for *nondegradable* solid: Higuchi equation

$$\boxed{I}\quad dQ = C_0 A\, dh$$

$$\boxed{II}\quad dQ = \frac{A}{h} D C_s\, dt \qquad h \rightarrow h = h(t)$$

ASSUMING NON-DEGRADABLE MATRIX!

MASS BALANCE:

$$C_0 A\, dh = \frac{A}{h} D C_s\, dt$$

$$h'\, dh' = D\frac{C_s}{C_0}\, dt$$

$$\int_0^{h(t)} h'\, dh' = \int_0^t D\frac{C_s}{C_0}\, dt$$

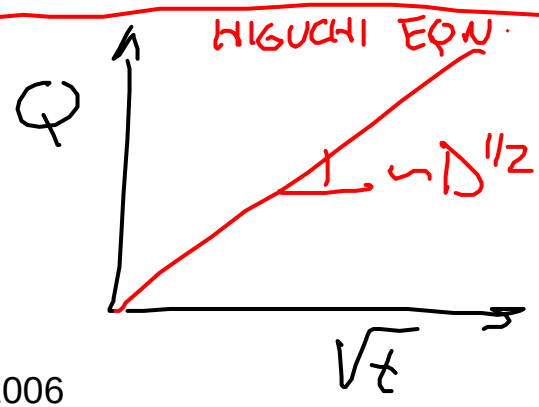
$$\boxed{\frac{h^2(t)}{2} = \frac{D C_s t}{C_0}}$$

PLUG INTO $\boxed{II}$:

$$dQ = \frac{A D C_s\, dt}{\left(2 D \frac{C_s}{C_0} t\right)^{1/2}}$$

$$\boxed{Q(t) = 2^{1/2} A D^{1/2} C_s^{1/2} C_0^{1/2} t^{1/2}}$$

HIGUCHI EQN.



Further Reading

1. Kumamoto, T. et al. Induction of tumor-specific protective immunity by in situ Langerhans cell vaccine. *Nat Biotechnol* **20**, 64-9 (2002).
2. Dash, P. R. & Seymour, L. W. in *Biomedical Polymers and Polymer Therapeutics* (eds. Chiellini, E., Sunamoto, J., Migliaresi, C., Ottenbrite, R. M. & Cohn, D.) 341-370 (Kluwer, New York, 2001).
3. Baldwin, S. P. & Saltzman, W. M. Materials for protein delivery in tissue engineering. *Adv Drug Deliv Rev* **33**, 71-86 (1998).
4. Okada, H. et al. Drug delivery using biodegradable microspheres. *J. Contr. Rel.* **121**, 121-129 (1994).
5. Santini Jr, J. T., Richards, A. C., Scheidt, R., Cima, M. J. & Langer, R. Microchips as Controlled Drug-Delivery Devices. *Angew Chem Int Ed Engl* **39**, 2396-2407 (2000).
6. Garcia, J. T., Dorta, M. J., Munguia, O., Llabres, M. & Farina, J. B. Biodegradable laminar implants for sustained release of recombinant human growth hormone. *Biomaterials* **23**, 4759-4764 (2002).
7. Jiang, G., Woo, B. H., Kang, F., Singh, J. & DeLuca, P. P. Assessment of protein release kinetics, stability and protein polymer interaction of lysozyme encapsulated poly(D,L-lactide-co-glycolide) microspheres. *J Control Release* **79**, 137-45 (2002).
8. Edlund, U. & Albertsson, A.-C. Degradable polymer microspheres for controlled drug delivery. *Advances in Polymer Science* **157**, 67-112 (2002).
9. Siepmann, J. & Gopferich, A. Mathematical modeling of bioerodible, polymeric drug delivery systems. *Adv Drug Deliv Rev* **48**, 229-47 (2001).
10. Charlier, A., Leclerc, B. & Couarraze, G. Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations. *Int J Pharm* **200**, 115-20 (2000).
11. Fan, L. T. & Singh, S. K. *Controlled Release: A Quantitative Treatment* (eds. Cantow, H.-J. et al.) (Springer-Verlag, New York, 1989).