Tuning degradation through molecular structure/ Controlled Release Devices

Last time:	factors controlling polymer degradation and erosion theory of polymer erosion
Today:	degradable solid polymer molecular design fundamental concepts of controlled release devices and applications controlled release devices based on degradable polymers
Reading:	•W.M. Saltzman and W.L. Olbricht, 'Building drug delivery into tissue engineering, Nat. Rev. Drug Disc. 1, 177-186 (2002) •W.M. Saltzman 'Drug administration and effectiveness,' from Drug Delivery: Engineering Principles for Drug Therapy, (2001)

Announcements:

Last time

Bulk vs. surface erosion: how do we predict it?

Bulk erosion **Surface erosion**

Figures removed for copyright reasons.
Please see:

Fig. 8(b) in Lu, L., C. A. Garcia, and A. G. Mikos. "In Vitro Degradation of Thin Poly(DL-lactic-co-glycolic acid) Films." *J Bio Med Mater Res* 46 (1999): 236-44.

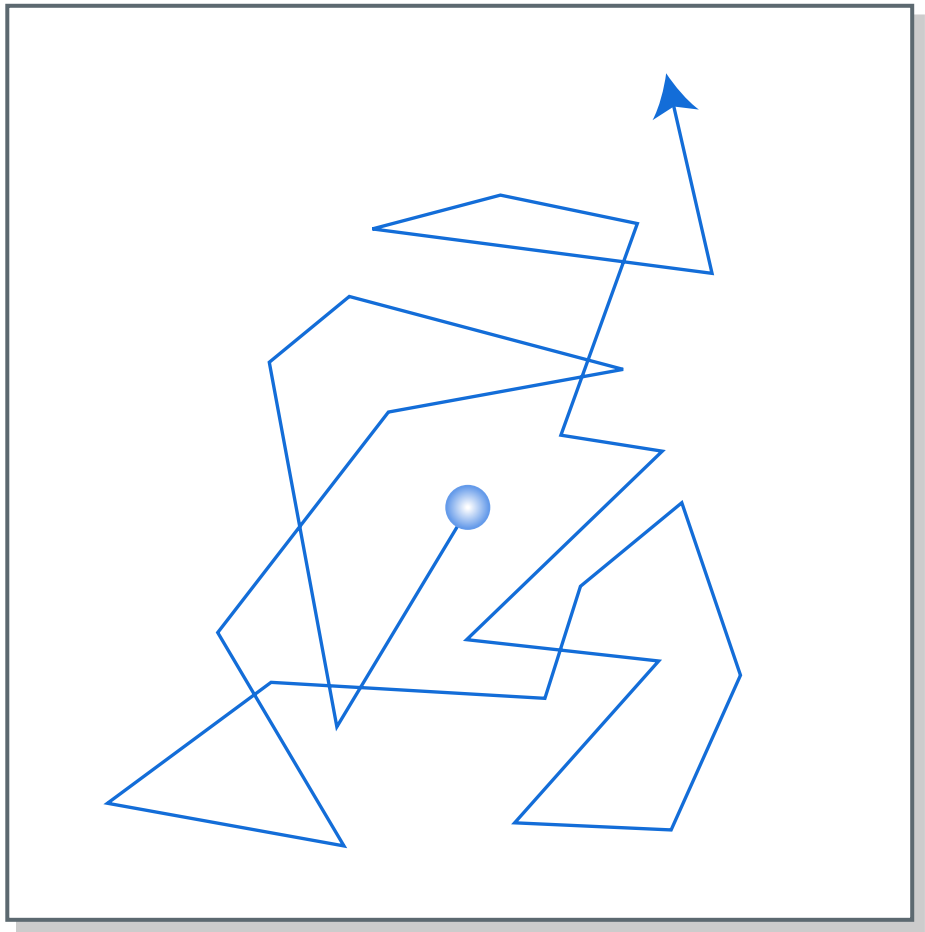
Images of Surface Erosion removed due to copyright restrictions.

Fig. 6(d) in Agrawal, C. M., and K. A. Athanasiou. "Technique to Control pH in Vicinity of Biodegrading PLA-PGA Implants." *J Biomed Mater Res* 38 (1997): 105-14.

Göpferich theory of polymer erosion

- If polymer is initially water-insoluble, and hydrolysis is the only mechanism of degradation, then two *rates* dominate erosion behavior:

Rate of water diffusion into polymer matrix



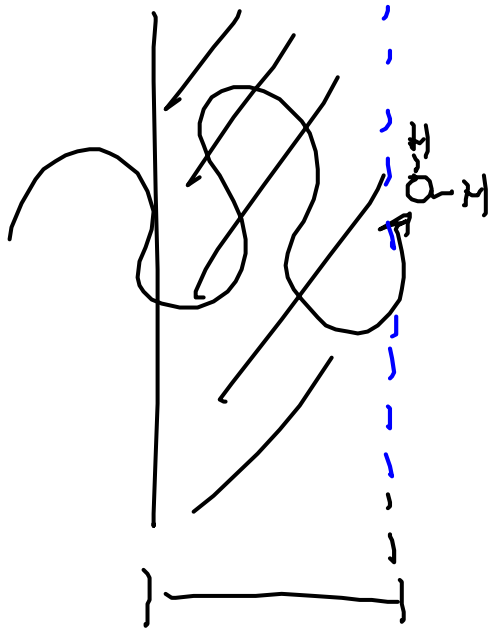
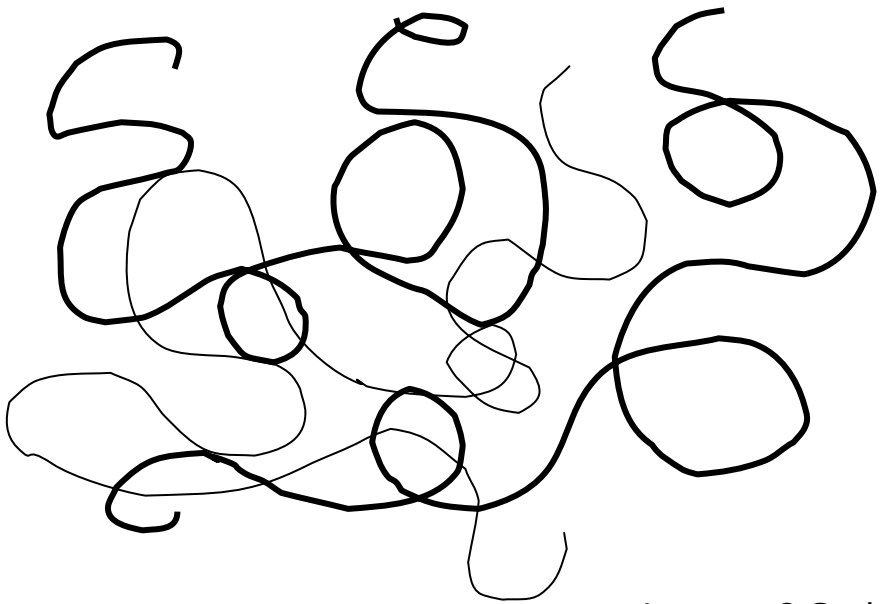


Figure by MIT OCW.

After Atkins, P. *The Elements of Physical Chemistry*. New York, NY: W. H. Freeman, 1997.

Rate of chain cleavage



Rate of chain cleavage

$p(t) = ke^{-kt}$

Mean lifetime of one bond:

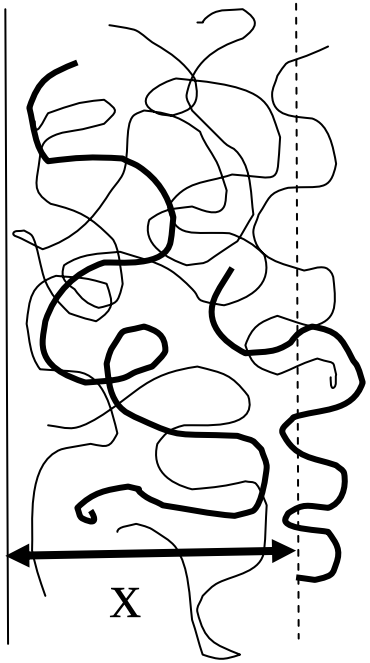
…this is the mean time I need to wait to observe one bond I am watching be broken.

Rate of chain cleavage

Mean lifetime of *n* bonds:

Rate of chain cleavage

Mean lifetime of *n* bonds:



How many bonds in a depth x?

Comparison of water diffusion rate to bond lysis rate allows the qualitative mechanism to be predicted:

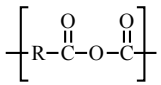
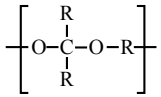
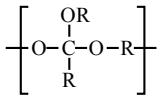
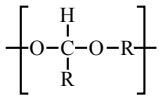
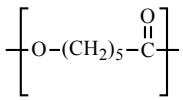
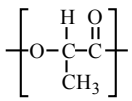
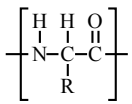
ε = erosion number $\equiv \dfrac{t_{DIFF}}{t_c(n)}$

$\varepsilon >> 1$

ε ~1 change in erosion mechanism

$\varepsilon << 1$

Erosion parameters of degradable polymers

Chemical Structure	Polymer	$\lambda(s^{-1})$	ε^a	$L_{critical}^b$
	Poly(anhydrides)	1.9×10^{-3} Ref. [30]	11,515	75 µm
	Poly(ketal)	6.4×10^{-5} Ref. [30]	387	0.4 mm
	Poly(ortho esters)	4.8×10^{-5} Ref. [30]	291	0.6 mm
	Poly(acetal)	2.7×10^{-8} Ref. [30]	0.16	2.4 cm
	Poly(e-caprolactone)	9.7×10^{-8} Ref. [31]	0.1	1.3 cm
	Poly(α-hydroxy-esters)	6.6×10^{-9} Ref. [30]	4.0×10^{-2}	7.4 cm
	Poly(amides)	2.6×10^{-13} Ref. [30]	1.5×10^{-6}	13.4 m

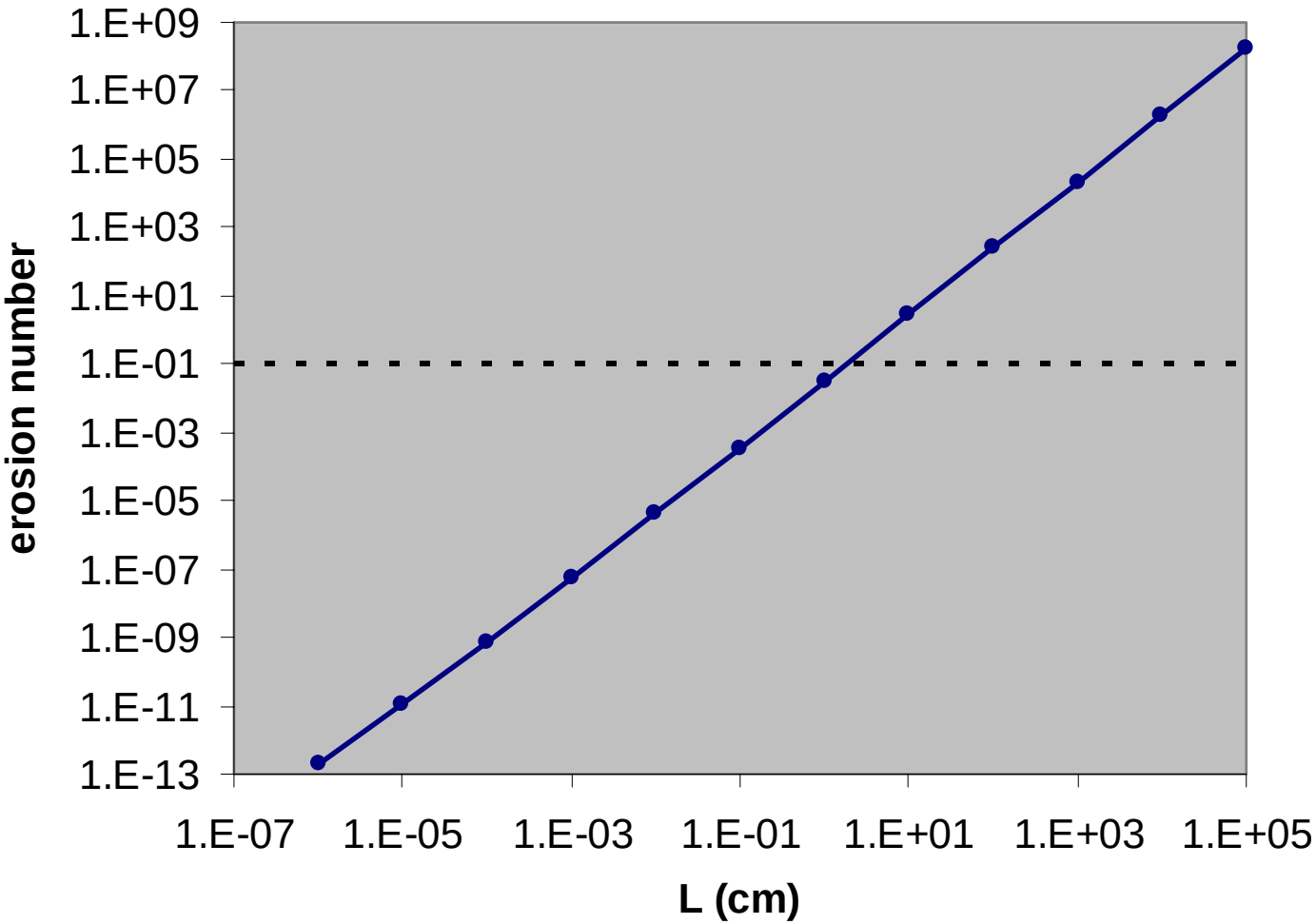
[a]For a 1cm thick device, $D = 10^{-8} cm^2 s^{-1}$ (estimated from Ref. [32]) and in $\left[\sqrt[3]{\overline{M}_n/N_A(N-1)\rho}\right] = -16.5$.

[b]$D = 10^{-8} cm^2 s^{-1}$ (estimated from Ref. [32]) and in $\left[\sqrt[3]{\overline{M}_n/N_A(N-1)\rho}\right] = -16.5$.

Estimated values of ε and $L_{critical}$ for selected degradable polymers

Figure by MIT OCW.

Dependence of erosion number on device dimensions



Testing the theory: experimental switch of a bulk-eroding polymer to a surface-eroding mechanism

PLA and PLGA degradation at pH 7.4: (bulk erosion)

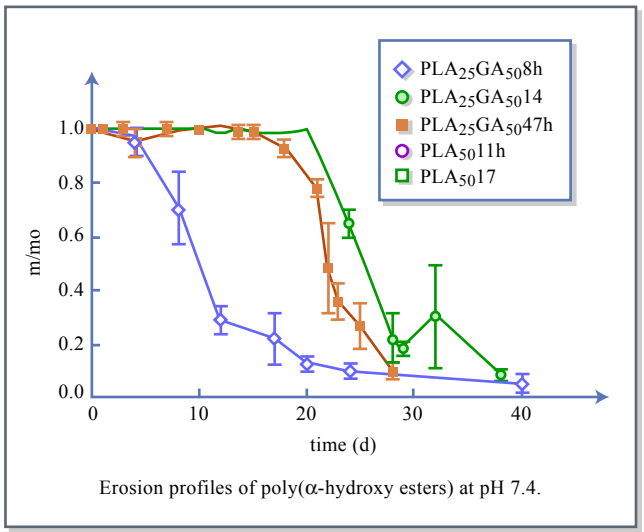


Figure by MIT OCW.

PLA and PLGA degradation at pH 12: (surface erosion)

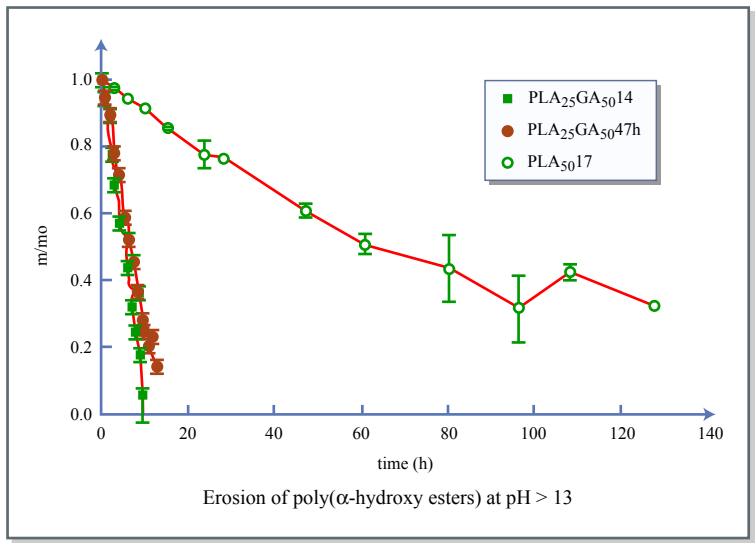


Figure by MIT OCW.

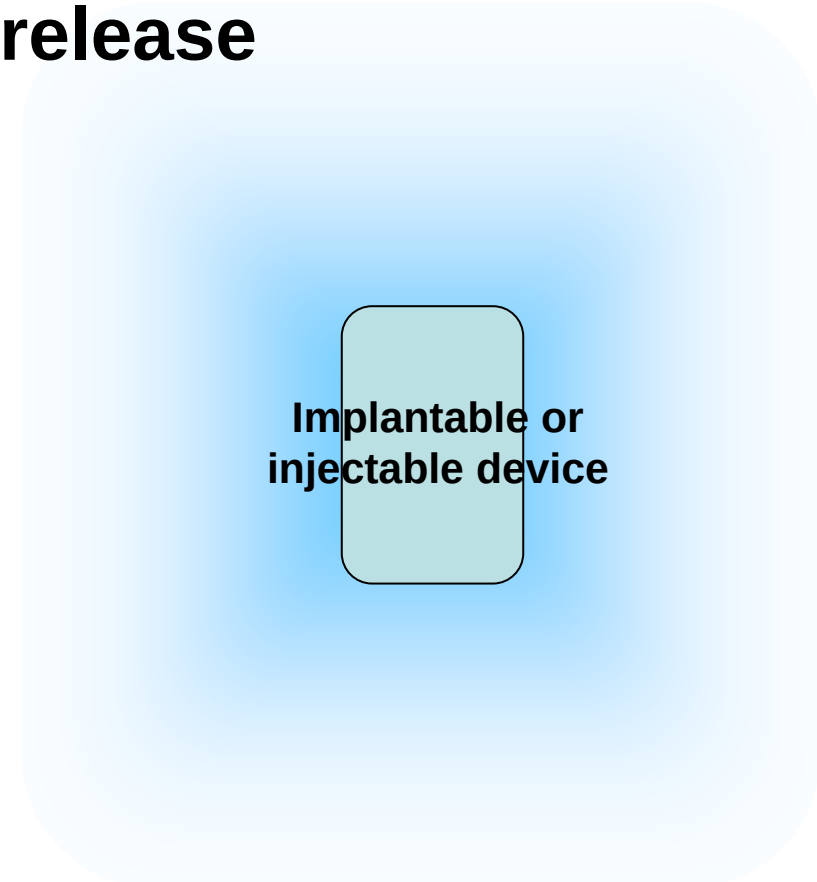
(SEM shown earlier confirms surface erosion mechanism)

Control over polymer degradation by molecular architecture

Controlling molecular architecture: self-assembly

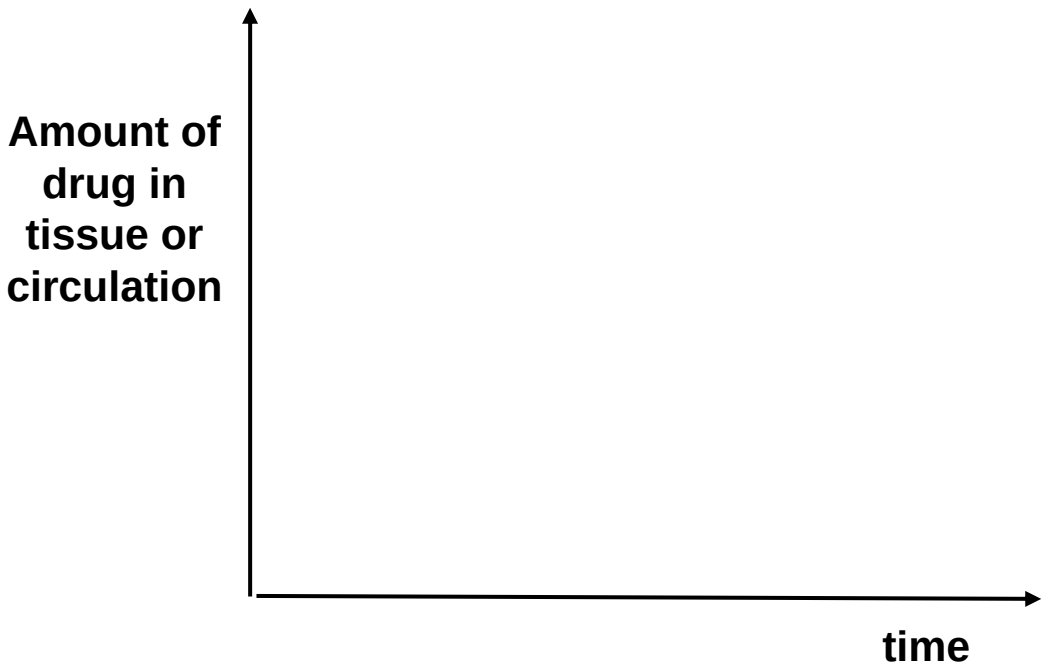
Concepts in controlled release

Application of degradable solid polymers to controlled release



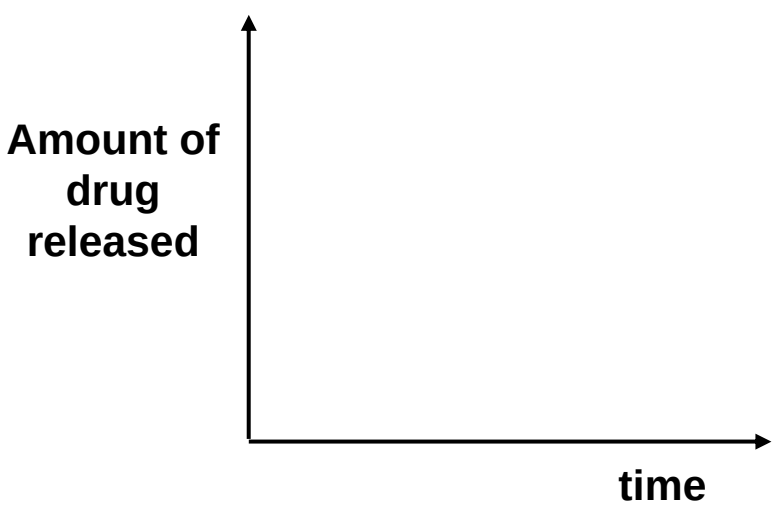
Therapeutic index: tailoring materials to provide release kinetics matching the ‘therapeutic window’

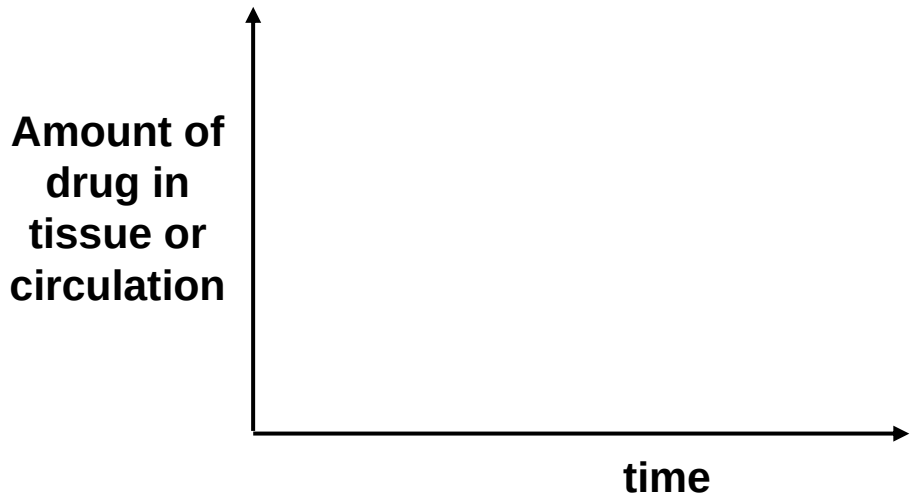
Bolus drug injection:



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

Objective of controlled release:



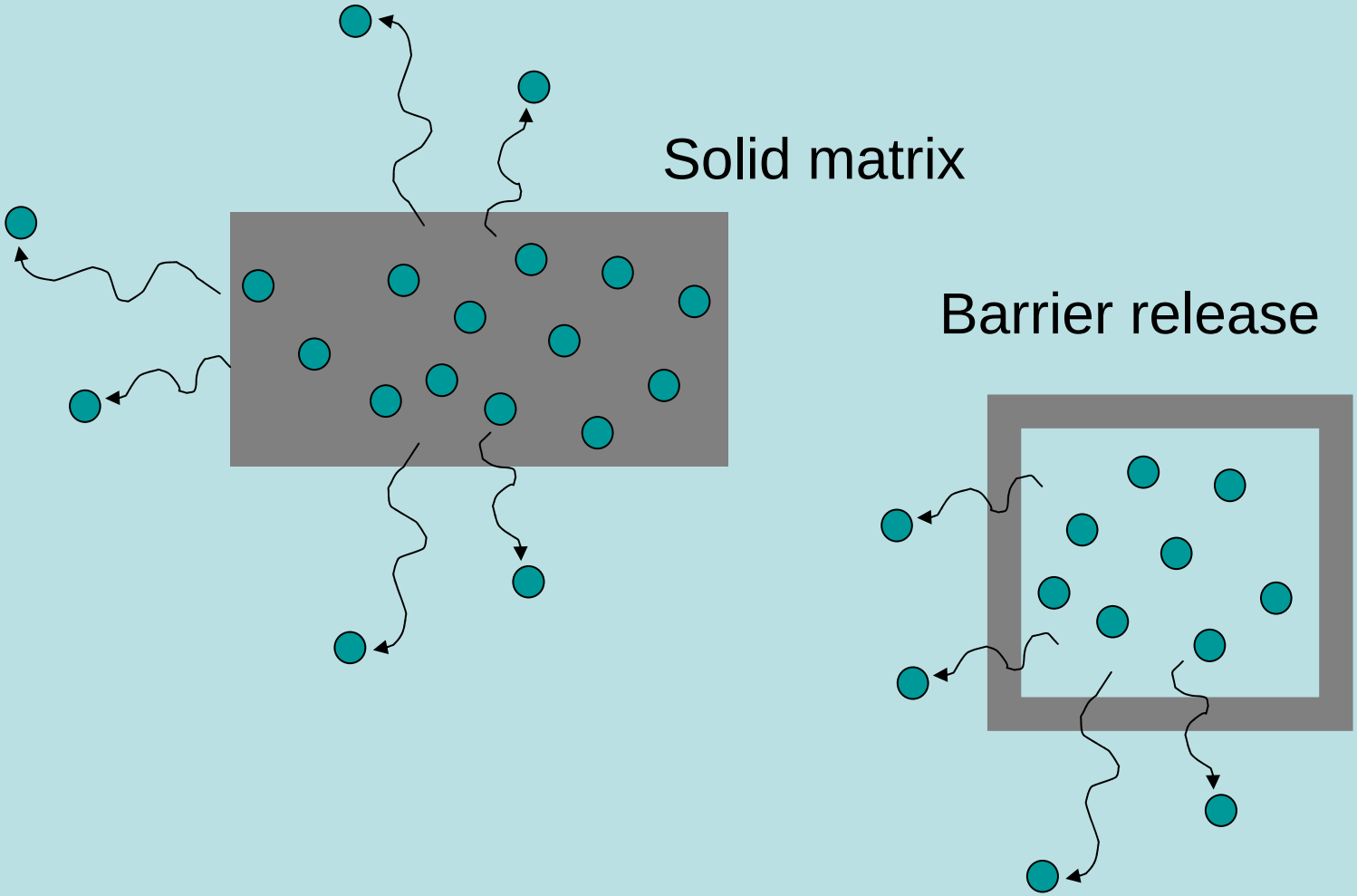


Example applications of controlled release

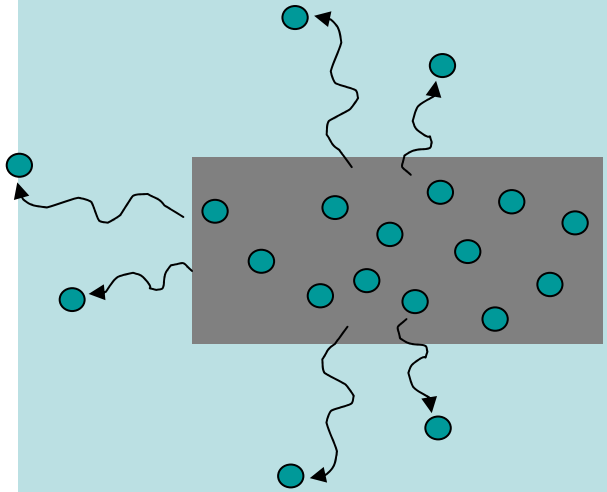
Application	**Examples**	**Active concentration of cargo**
Provide missing soluble factors promoting cell differentiation, growth, survival, or other functions	Replace deficient human growth hormone in children	1-10 pM; Hormones 5-10 nM
Sustained or modulated delivery of a therapeutic drug	Release of anti-cancer drugs at site of tumors to induce cancer cell apoptosis, ocular drugs for treatment of glaucoma, contraceptive drugs, antimalarial drugs	varies
Create gradients of a molecule *in situ*	Chemoattraction of immune cells to antigen depot for vaccinesk[1]	1-50 pM
One time procedure (e.g. injection) with multiple dose delivery	Pulsatile release of antigen for vaccines	10-100 µg antigen
Gene therapy	Correction of cystic fibrosis gene defect, correction of adenosine deaminase deficiency (ADA-SCID) in lymphocytes, replace defective gene in Duchenne muscular dystrophy, cancer immunotherapy[2]	1-20 µg DNA

Delivery site
Oral (delivery via digestive tract)
Sublinguinal (under tongue)
Rectal
Parenteral • intramuscular • peritoneal (gut) • subcutaneous (under skin)
Ocular

Drug diffusion-controlled release

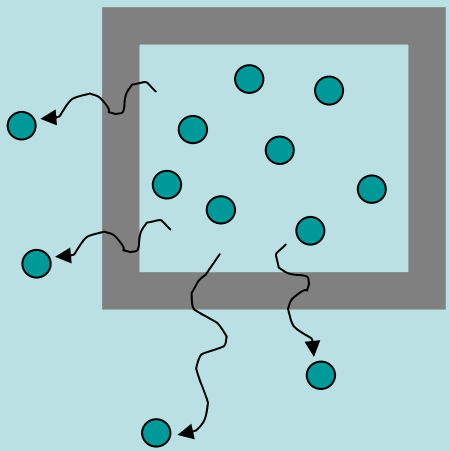


Drug diffusion-controlled release



Advantage:

Disadvantages:



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).