Controlled Release Theory

Last time: tailoring the structure of degradable polymers
Fundamental concepts in controlled release

Today: Theory of degradable polymer-based controlled release

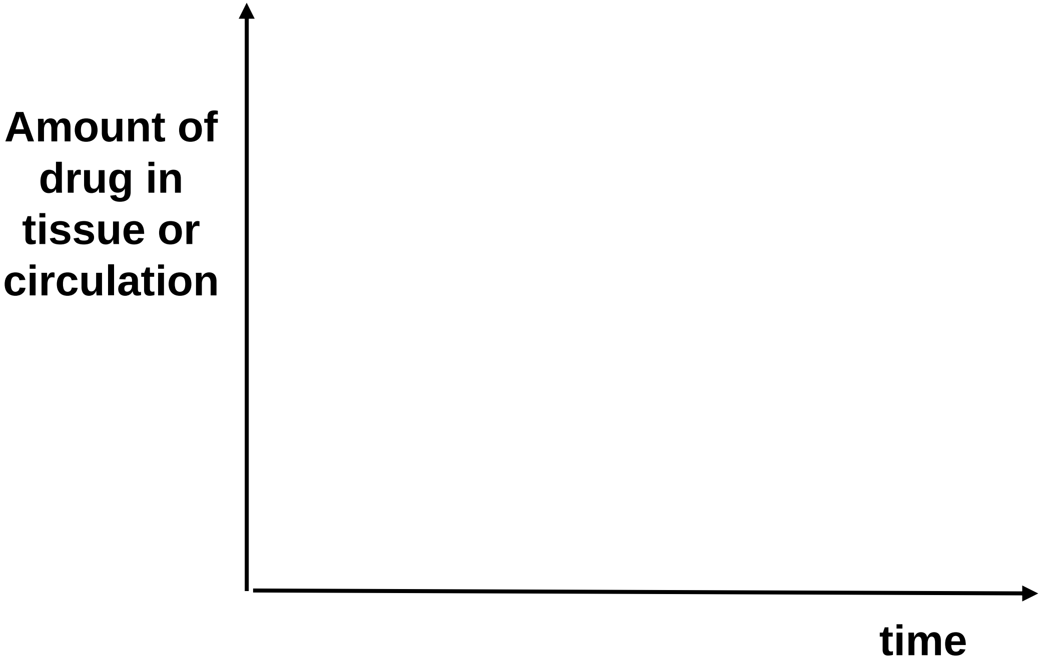
Reading: Charlier et al., 'Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations,' *Int. J. Pharm*. **200**, 115-120 (2000)

ANNOUNCEMENTS:

Last time

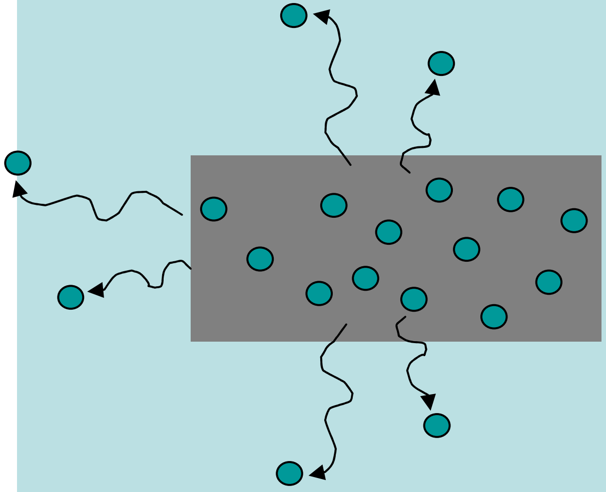
Therapeutic index: tailoring materials to provide release kinetics matching the 'therapeutic window'

Bolus drug injection:



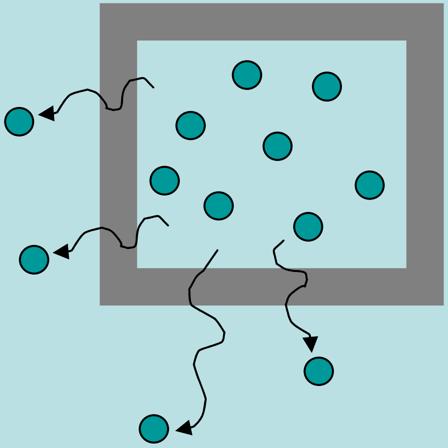
Mechanisms of controlled release

Drug diffusion-controlled release

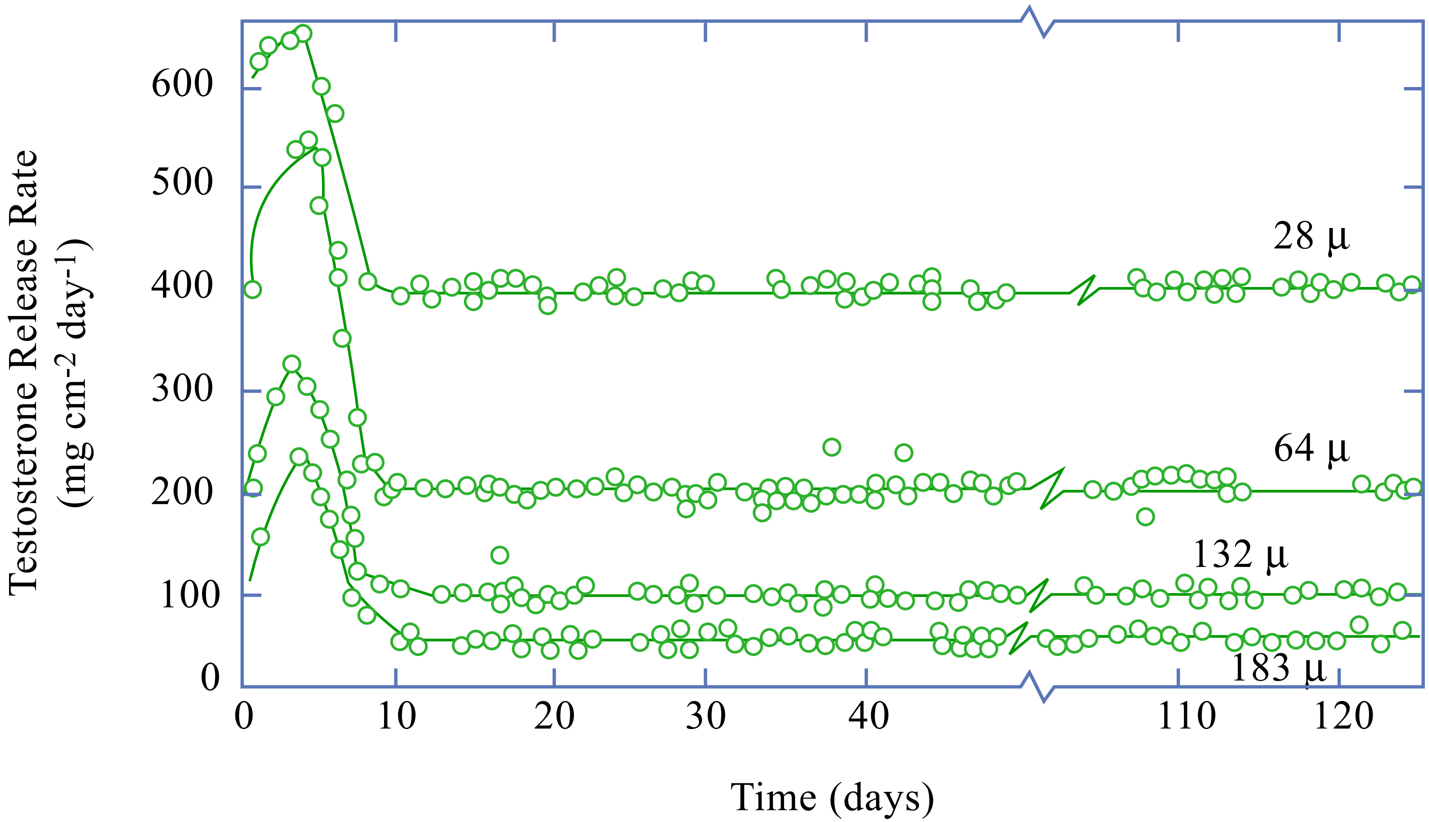


Advantage:

Disadvantages:



Release kinetics for diffusion-controlled release

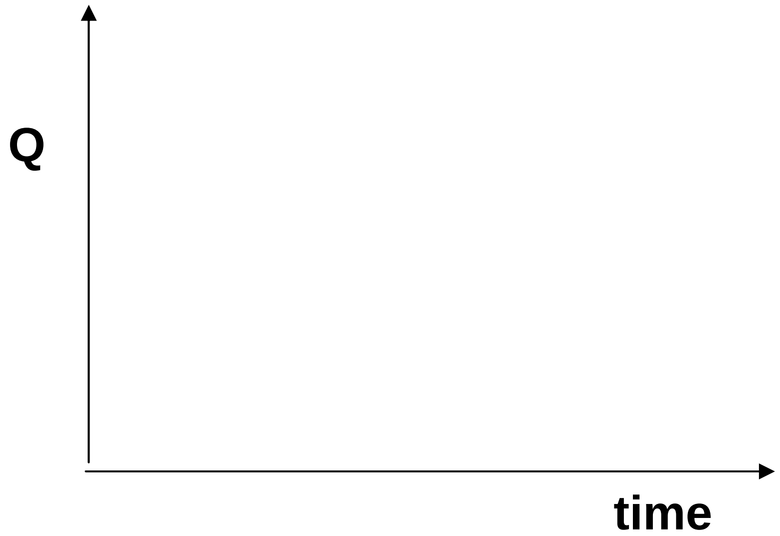


Release rate of testosterone from cylindrical reservoir devices of different membrane thickness made from silicone rubber.

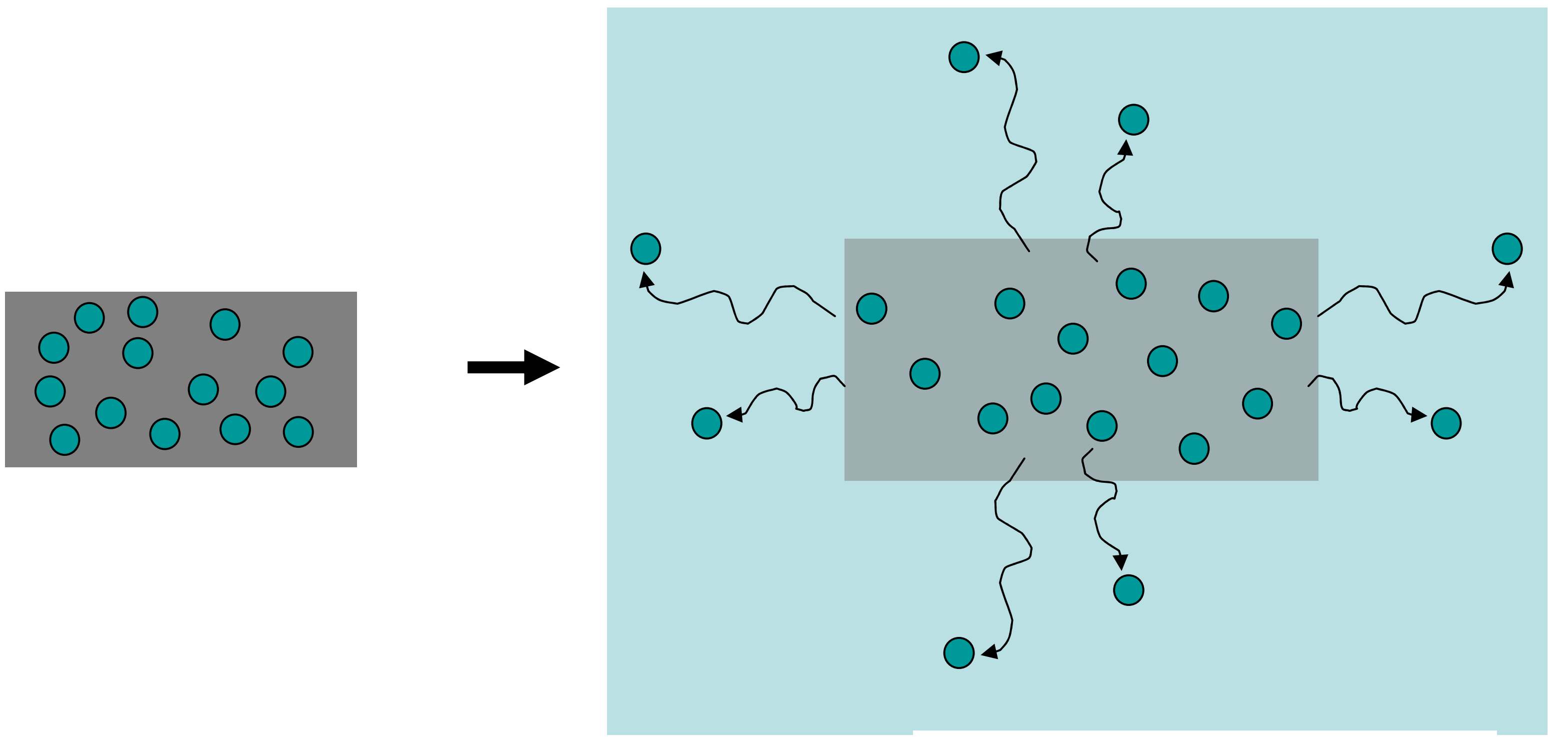
Figure by MIT OCW.

(Fan and Singh, 1989)

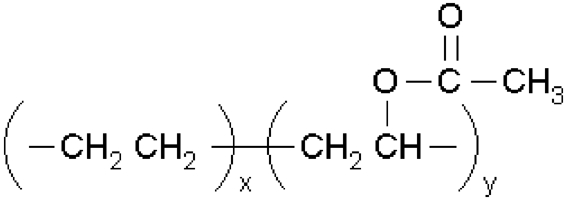
Release kinetics for diffusion-controlled release



Water-influx controlled release



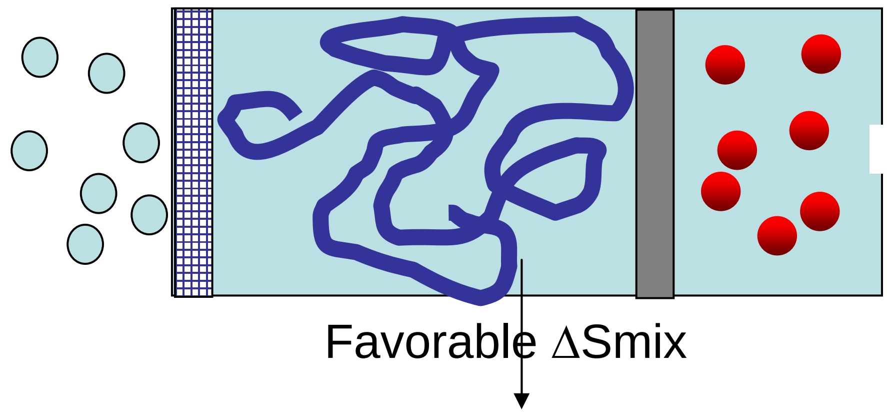
Example: poly(ethylene-co-vinyl acetate)

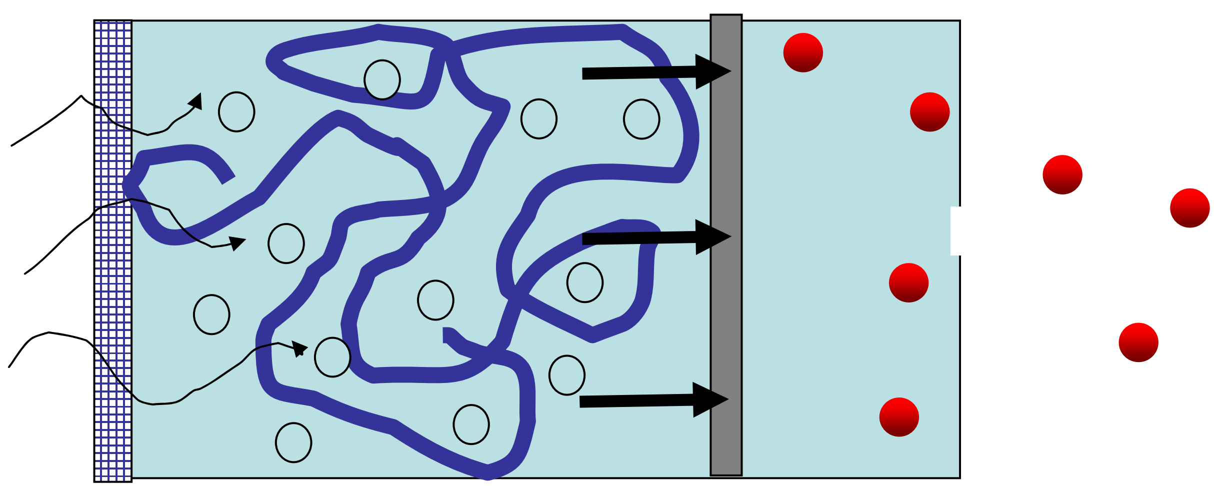


Regulated/triggered release: mechanical

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

<u>Osmotic engine: (one form)</u>





Regulated/triggered release: mechanical

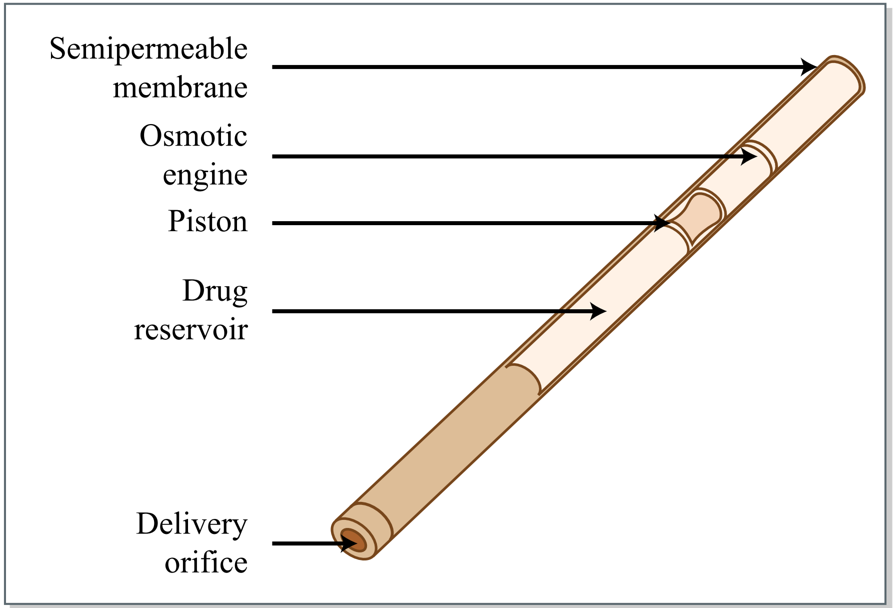


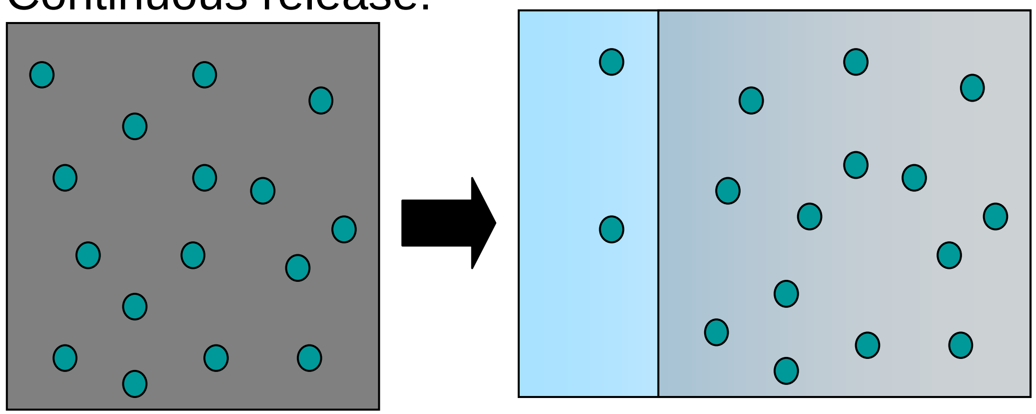
Figure by MIT OCW.

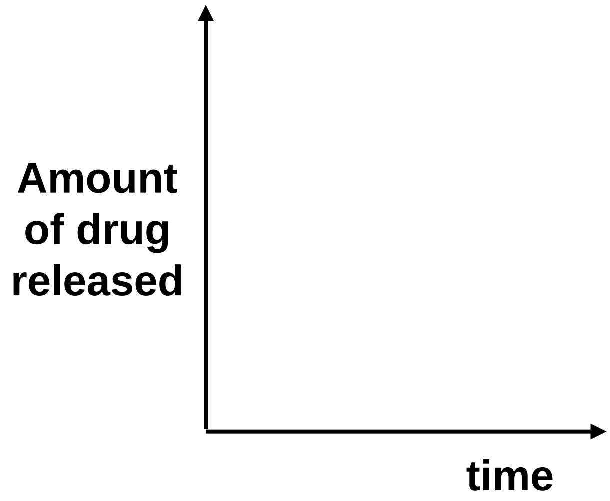
Titanium rod casing

Designed to provide continuous release of drugs up to one year

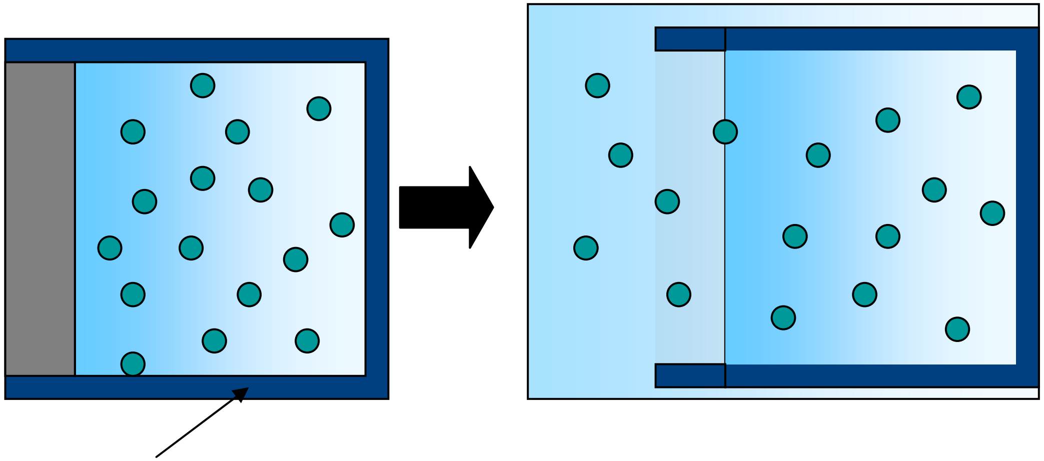
eroding matrix

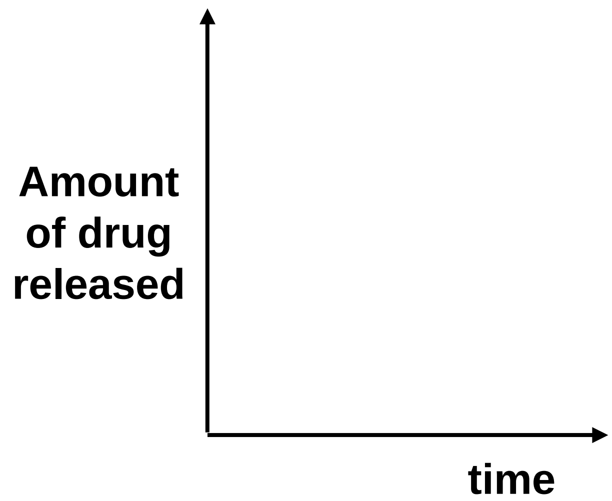
Continuous release:





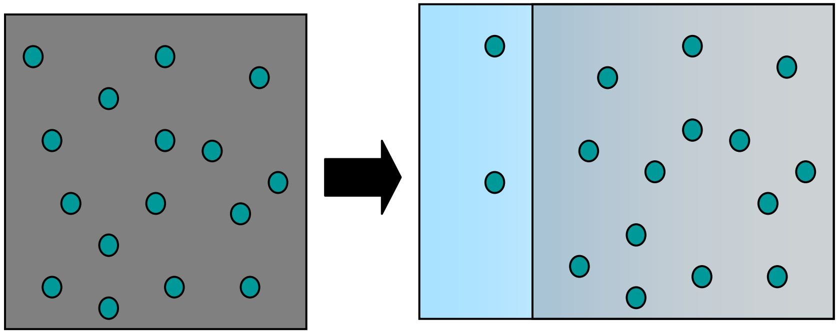
burst release:





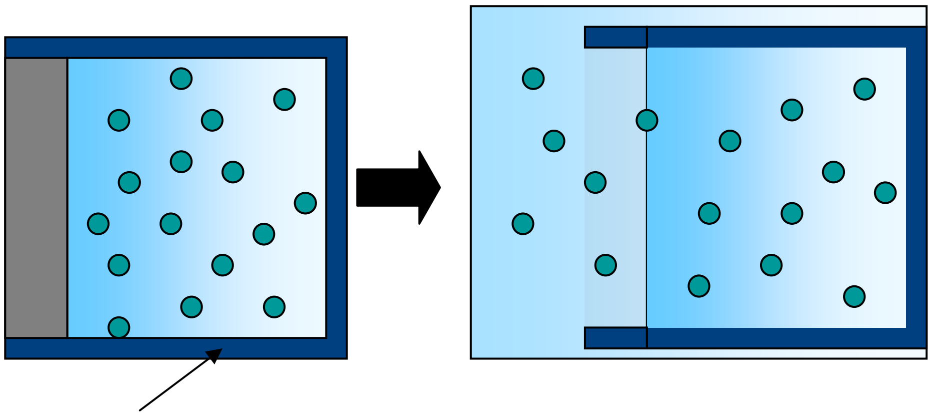
Non-erodible capsule

eroding matrix



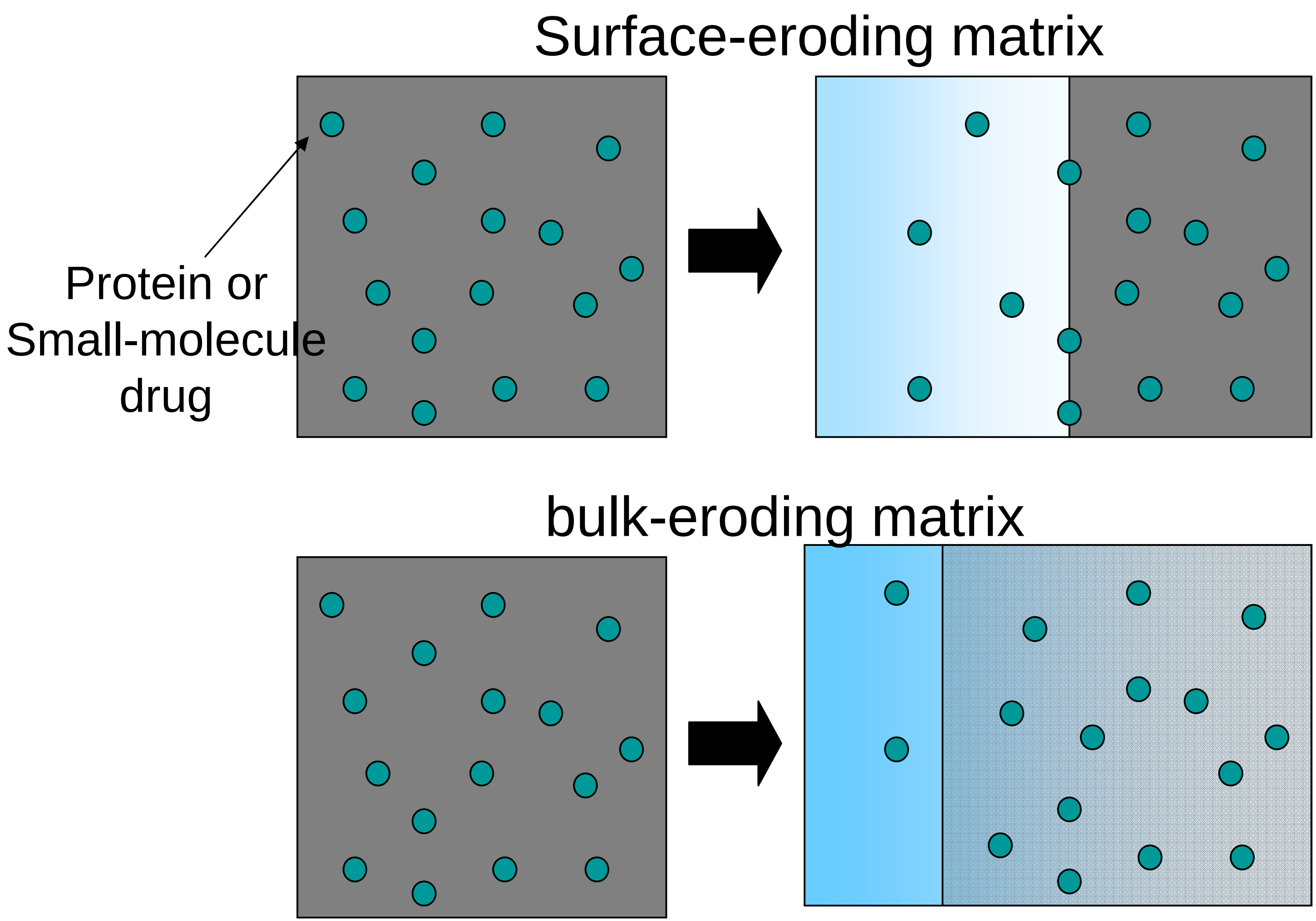
Advantages:

Disadvantages:



Non-erodible capsule

Designing eroding release devices



Typical release profiles

Surface-eroding matrix

Poly(methyl vinyl ether-co maleic anhydride)

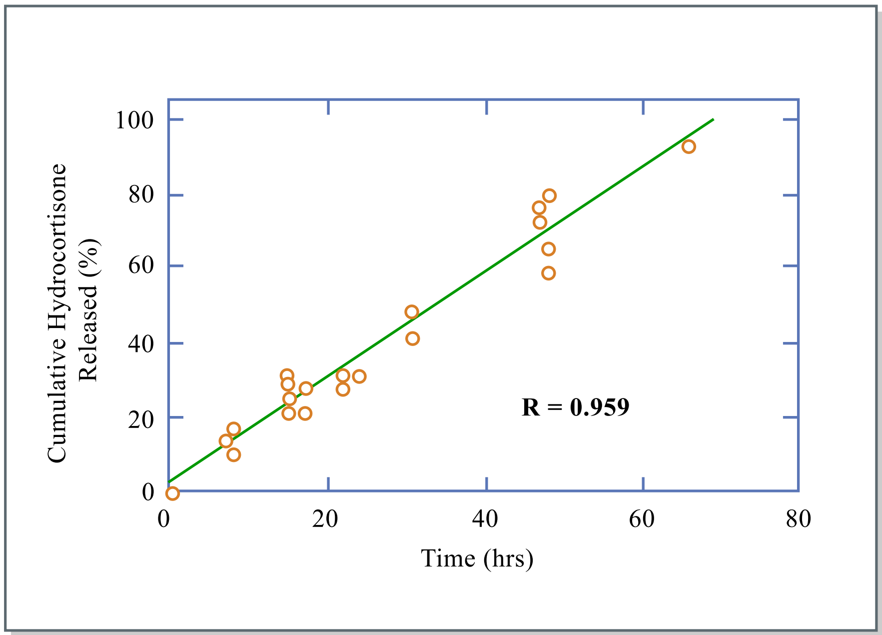
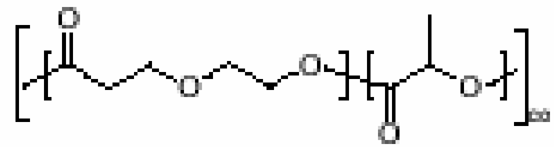
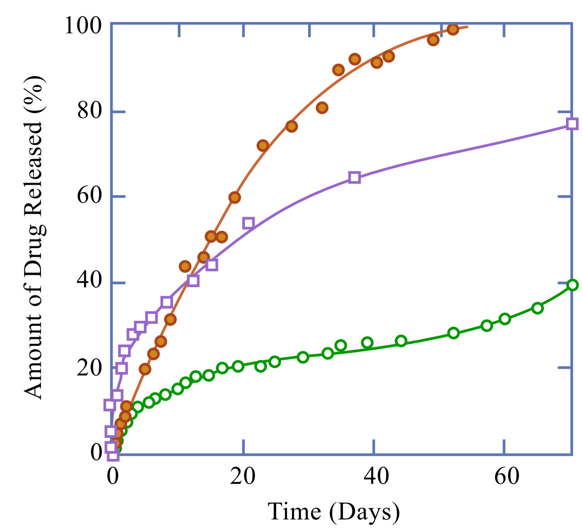


Figure by MIT OCW.

Bulk-eroding matrix

Poly(dioxepanone-co-lactide)





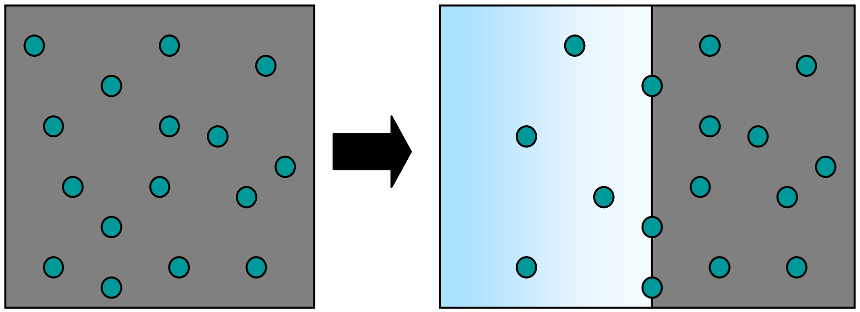
Release of a therapeutic substance from P(L-LA-co-DXO), PDLLA-PDXO, and PDLLA-PDXO microspheres with a L-LA/DXO molar ratio of 90:10

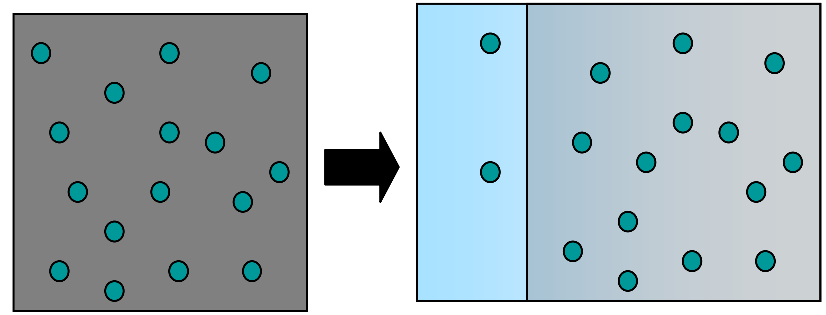
Figure by MIT OCW.

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?)

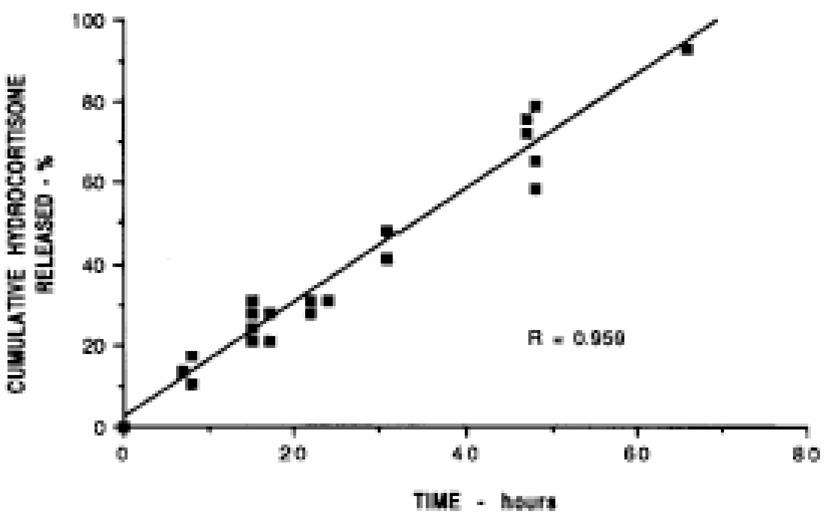
surface erosion:	bulk erosion





Surface-eroding matrix

Poly(methyl vinyl ether-co maleic anhydride)



Bulk-eroding matrix

Poly(dioxepanone-co-lactide)

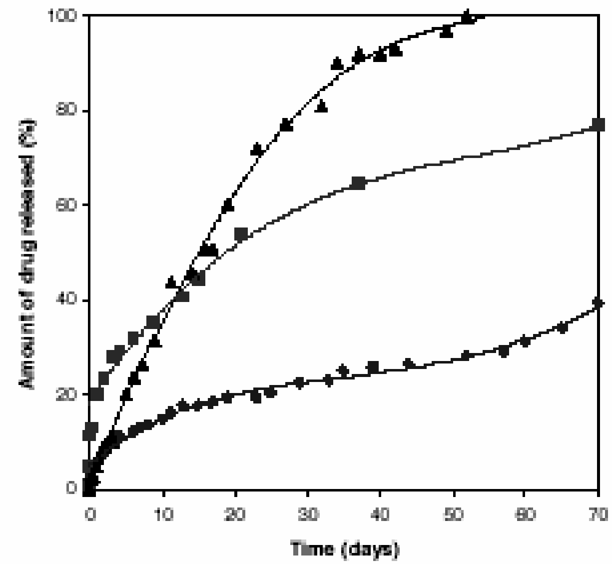
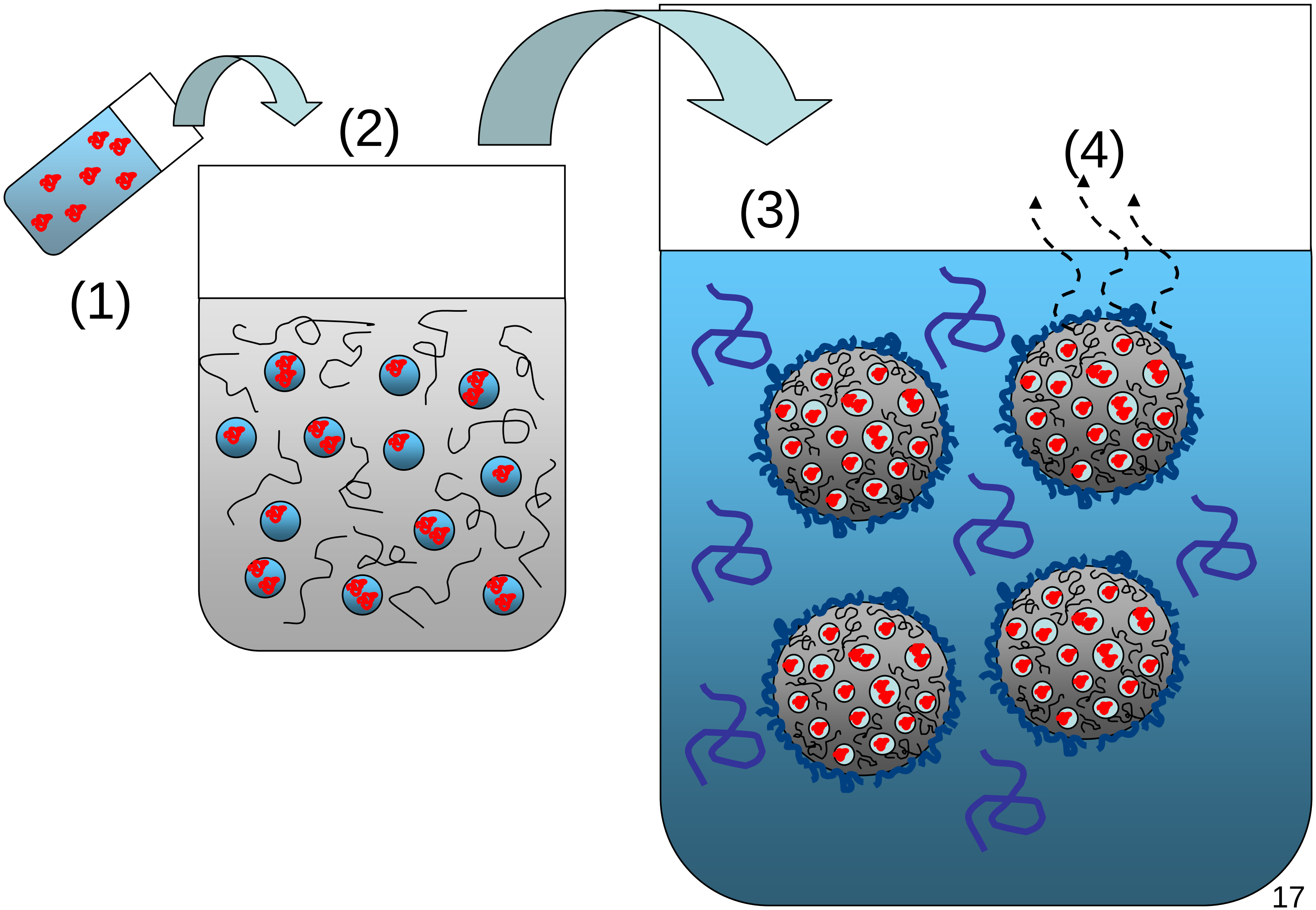


Fig. 14. Release of a therapeutic substance from (▲▲) P(L-LA-co-DXO), (■■) PDLLA-PDXO, and (●●) PLLA-PDXO microspheres with a L-LA/DXO molar ratio of 90:10

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

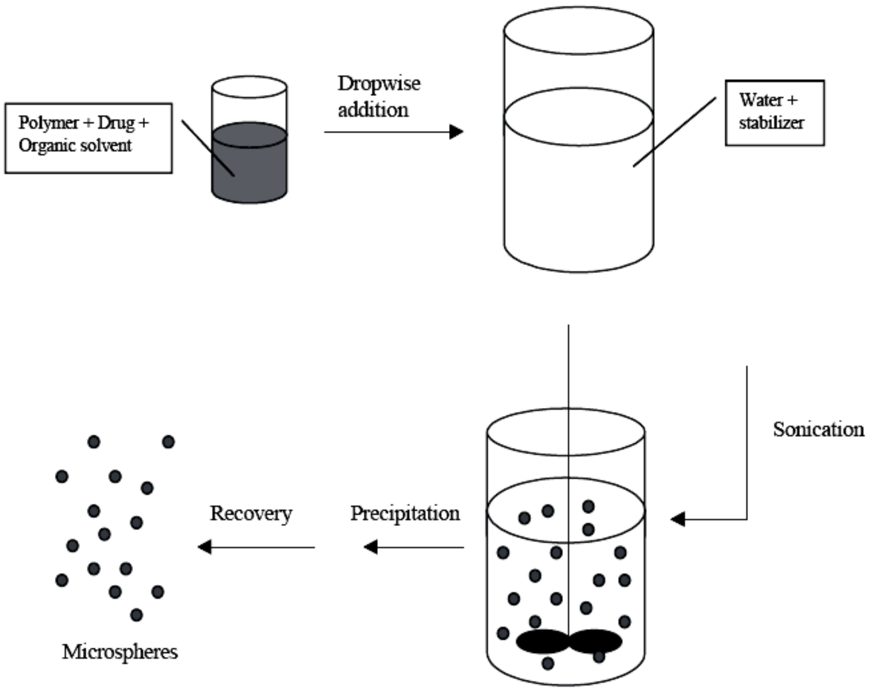


imiting factors: pH gradients within degradable devices

Fu, K., D. W. Pack, A. M. Klibanov, 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

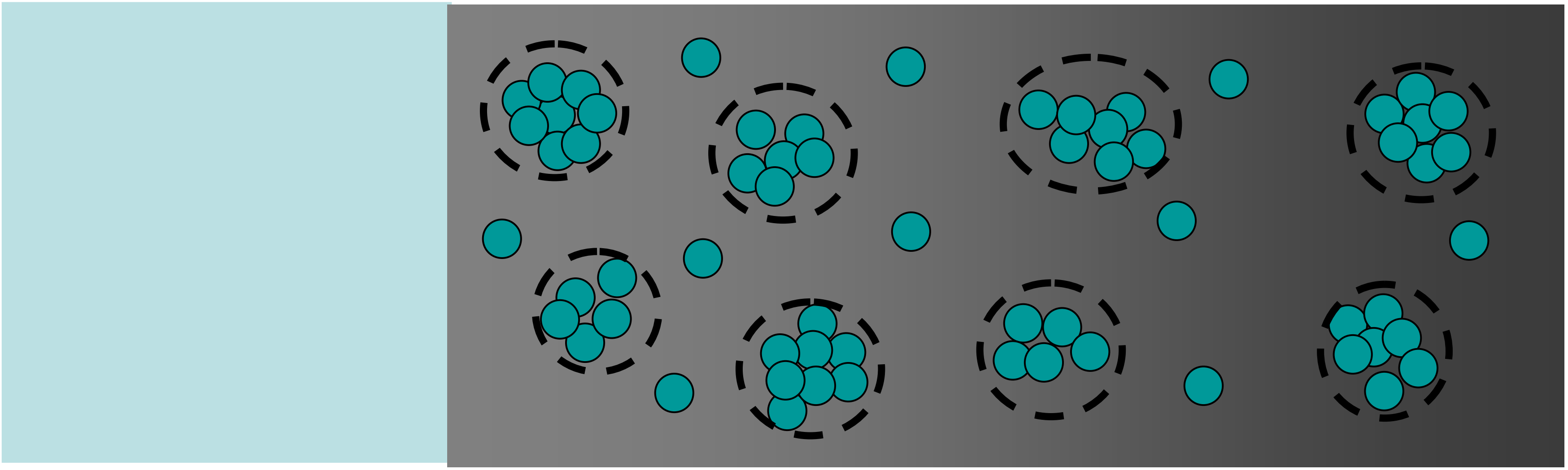
Modeling an important controlled release system: single emulsion encapsulation of small molecule drugs in degradable polymers



(Edlund 2002)

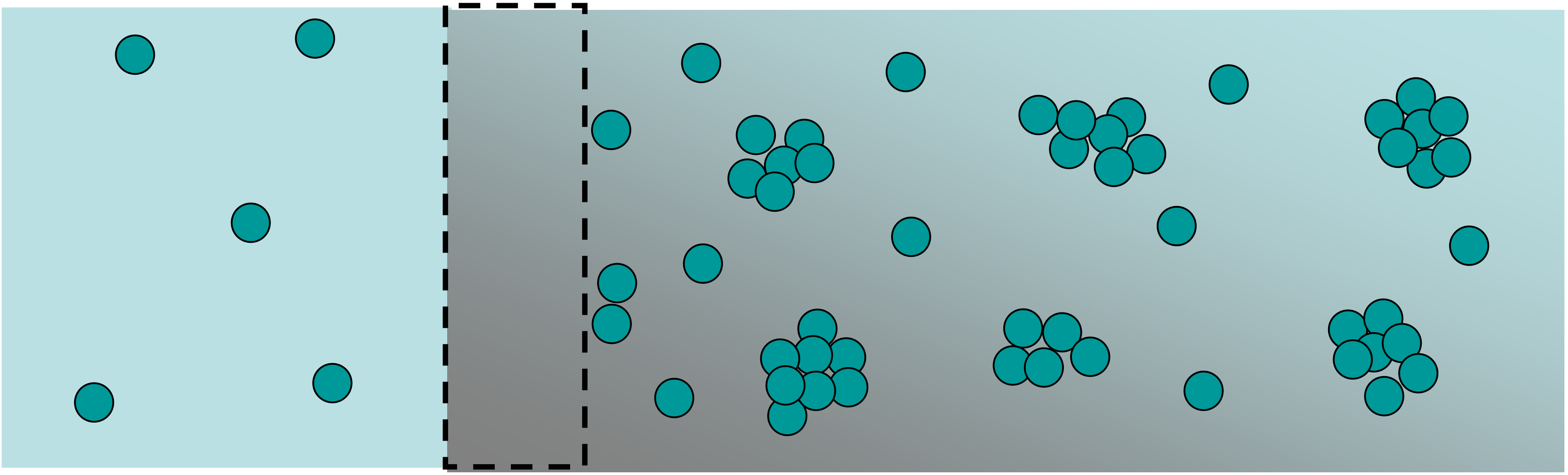
Faisant N., J. Siepmann, and J. P. Benoit. “PLGA-based Microparticles: Elucidation of Mechanisms and a New, Simple Mathematical Model Quantifying Drug Release." *Eur. J Pharm Sci.* 15, no.4 (May 2002): 355-66.

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



(Charlier et al. 2000)

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



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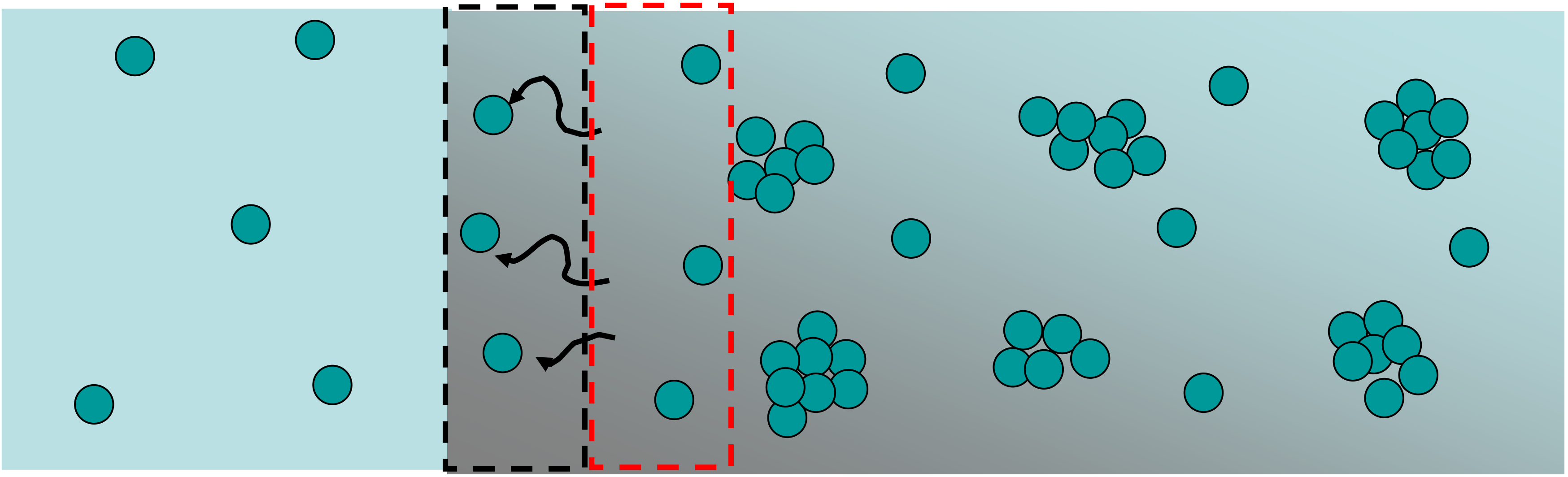
Theory of controlled release from degradable solids: physical basis of the model



(Charlier et al. 2000)

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*:

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

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

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).