Lecture 1: Molecular Design and Synthesis of Biomaterials I: Biodegradable Solid Polymeric Materials

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Today:	course overview and administrative details Intro to concepts covered Chemistry and physical chemistry of biodegradable polymeric solids
Hand-outs:	course syllabus Course administrative details
Reading:	"Third-Generation Biomedical Materials," L.L. Hench and J.M. Polak, *Science* **295**, 1014 (2002) Ratner, 64-72 Ratner 243-259
Supplementary Reading:	Young and Lovell, 'Introduction to Polymers,' Ch.4 Polymer Structure

Course Overview

Definition of Biomaterials for this course:

Materials *designed* for application to problems in biological engineering or biotechnology. This includes materials comprised of purely 'synthetic' or 'natural'/'biological' components, but will focus primarily on hybrid materials that make are composed of both.

-not 'off the shelf'
-our objective is to cover the chemistry and physics of these materials

How can biomaterials solve problems in Biological Engineering?

1. Model systems for studying biology
   a. Both *in vitro* and *in vivo* models ***(SLIDE)***
   (Lauffenburger/Griffith labs[1]:)

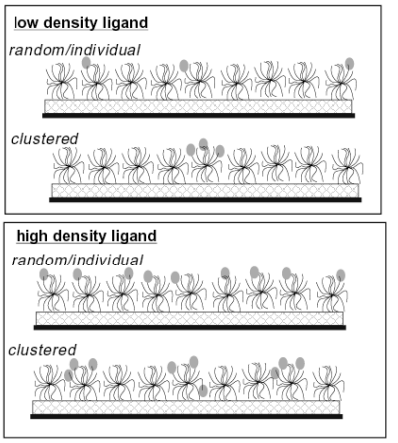
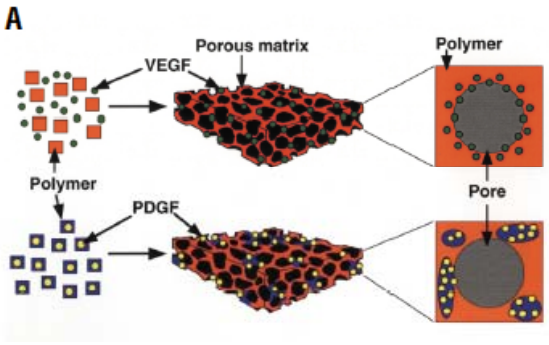
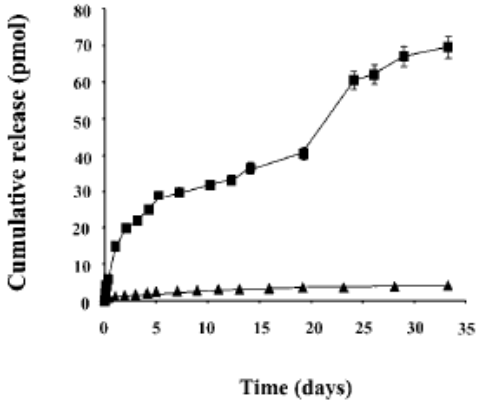


Fig. 1. Schematic illustration of star polymer as a tether to present ligand (shaded oval) in a manner in which the total average concentration (top versus bottom) and the spatial distribution, from homogeneous to highly clustered (left to right), can be independently varied.

2. Therapeutic devices ***(SLIDE)***
    a. Drug delivery
        1. small molecules, peptides, and proteins, and DNA (gene therapy)
    b. tissue engineering/regenerative medicine





(Mooney[2])

3. Analytical devices
    a. Biosensors
        1. glucose sensors
        2. toxin detection
    b.

…or something in between (1), (2), and (3): ***(SLIDE)***

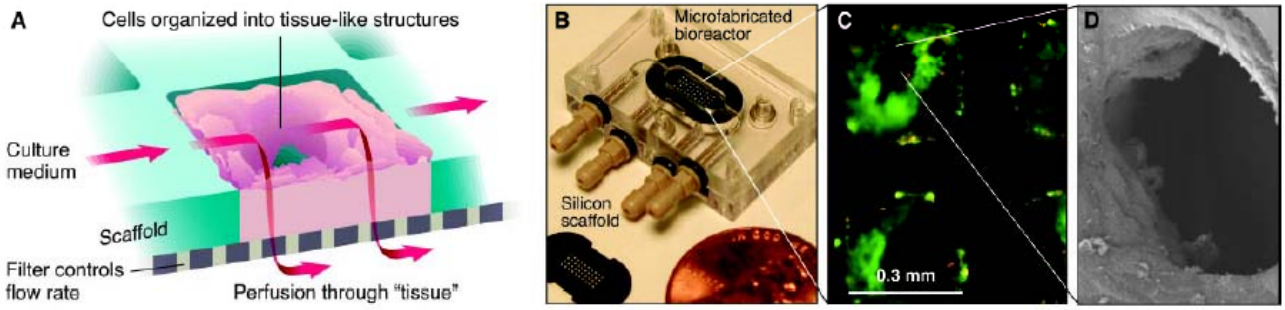


Fig. 2. A microfabricated bioreactor for perfusing 3D liver tissue engineered in vitro (*54*, *55*). (**A**) A cross section showing tissue aggregates growing attached to the inside walls of the narrow channels of the silicon-chip scaffold. Culture medium flows across the top of the scaffold as well as through the narrow channels, enabling tissue aggregates to extract oxygen and nutrients. The design of the scaffold promotes self-assembly of the cells into tissues. (**B**) A bioreactor containing a 0.2-mm-thick silicon-chip scaffold etched with 0.3-mm-diameter channels. (**C**) Hepatocytes seeded onto the scaffold of the bioreactor attach to the walls of the channels (four channels are shown) and reorganize to form 3D structures that are reminiscent of liver cords. Bile canaliculi and tight junctions can be seen with high-power microscopy (*54*, *55*). Live cells are green and dead cells are red as visualized with the calcein AM/ethidium homodimer stain. (**D**) Scanning electron micrograph showing vessel-like structures assembled from endothelial cells at the fluid-tissue interface in the bioreactor channels. [Illustration: Preston Morrighan]

(Prof. Giffith's lab[3])

Overview of topics and viewpoint (syllabus summary) *(SLIDE)*

1. Biodegradable polymeric solids
2. Controlled release from solid polymers
3. hydrogels
4. bioceramics and biocomposites
5. hybrid biological/synthetic molecules
6. stimuli-responsive biomaterials

-we'll try to remain complementary to other biomaterials courses:
2.79J/3.96J/BE.441J Biomaterials-Tissue Interactions
BE.342 Molecular Structure of Biological Materials

Course administration

- 2 dates when there is no class – out of town
- Course grading
  - Weekly problem sets
  - 3 1-hour exams
  - term projects
- website
- office hours
- discuss term projects

Materials that can be used *in vivo*

Basic considerations

- Many applications require to materials to function inside the body: ***(SLIDE)***
  - Mechanical implants
    - Artificial hips, artificial hearts, pacemakers, etc.
  - Drug delivery
    - Injected or implanted devices
  - Tissue engineering
    - Delivery of cells
    - In vivo tissue engineering: materials that guide invading cells into proper position and function
  - Biosensors
    - In situ measurements of pH, molecule concentrations, etc.

If a device is to be applied in vivo, what characteristics must it have in addition to fulfilling the device requirements?

-non-toxic (acute or chronic), non-carcinogenic, non-mutagenic, and non-allergenic

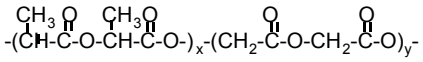
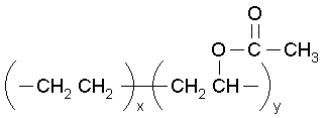
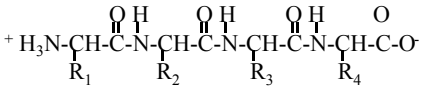
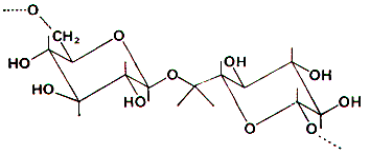
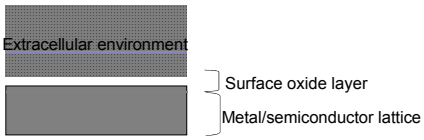
- Toxicity of synthetic materials
  - Few generalities can be made, typically determined by empirical studies
  - Cost and time involved in developing new biomaterials extremely high
  - Industry and clinicians further motivated by fear of malpractice cases
    - E.g., the case of silicone breast implants
    - A very small number of FDA-approved materials has been intensively studied due to this hurdle

-biodegradable, bioeliminible, or removable

- biodegradable: breaks down into metabolic products (most attractive) - mechanisms?
  - Hydrolysis
  - Enzymatic action
- bioeliminible: dissolves into low molecular weight compounds that can be excreted by natural pathways
- removable: a retrieveable implant (least attractive)

- FDA APPROVAL…

Examples:

Biodegradable	Bioeliminible	Removable
Poly(lactide-co-glycolide) [PLGA]	**poly(ethylene glycol) ^{4} < 10KD**	**poly(ethylene-co-vinyl acetate)**
	$-(CH_2\text{-}CH_2\text{-}O)_n-$	
Polypeptides	**dextran**	**metal/semiconductor devices**
		

Characteristics of materials from each category:

Hydrophilic or hydrophobic Chemically unstable in water	hydrophilic (water soluble) chemically stable in water	hydrophobic/insoluble chemically stable in water

Biodegradable Solid Polymeric Materials

Our definition: Biodegradable = solid polymer reduced to soluble fragments that are either excretable or metabolized under physiological conditions (saline environement, pH 7.4, 37°C)

Why biodegradable?

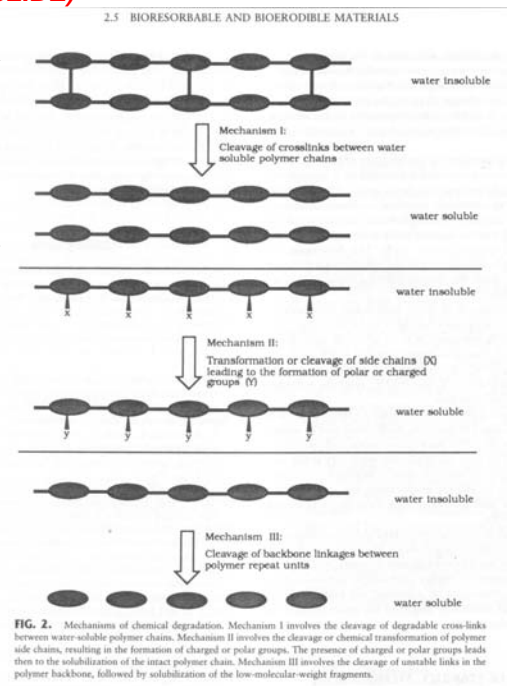
- Generally desirability of one-time surgeries where a device does not need to be retrieved after living out its useful lifetime

1. Temporary needs
   a. E.g. fill and support bone defect until natural bone grows back (TE)
   b. Provide drug delivery until a condition is corrected
2. Avoid chronic inflammation and long-term complications
   e.g. loosening in artificial hip
3. Limited alternatives in eliminable materials devices
   poly(ethylene glycol)
   dextran

First use of biodegradable sutures: 1962 PGA
Produced by American Cyanamid Co. under name Dexon™
Vicryl introduced in 1966 (PLGA)
Arch. Surg. **93**, 839 (1966)

Chemistry of biodegradable solid polymers

Pathways of solid polymer erosion *(SLIDE)*



Used for biodegradable hydrogels

I

II

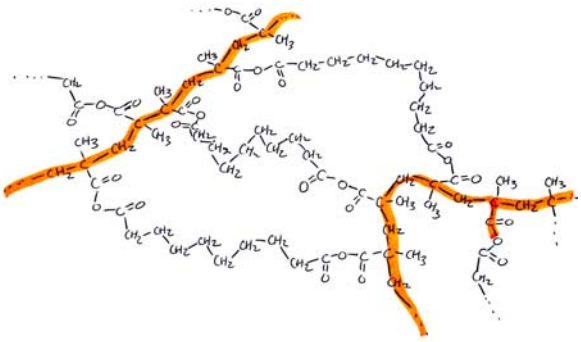
Main mechanism exploited in solid polymers

III

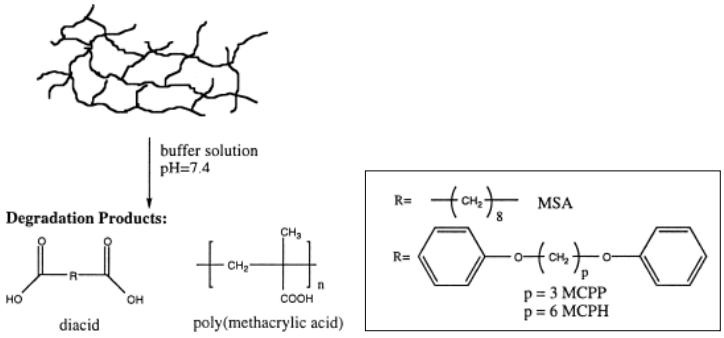
(Ratner, *Biomaterials Science*)

Example Materials- Common hydrolytically unstable linkages:

Mechanism I:

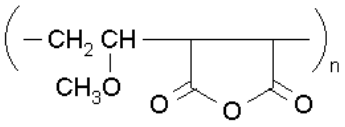


Crosslinked polyanhydrides[5-7]:



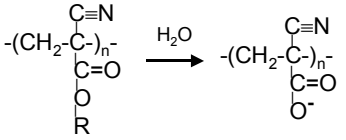
Mechanism II:

- Poly(methyl vinyl ether-co-maleic anhydride) -> carboxyl group generation[8]



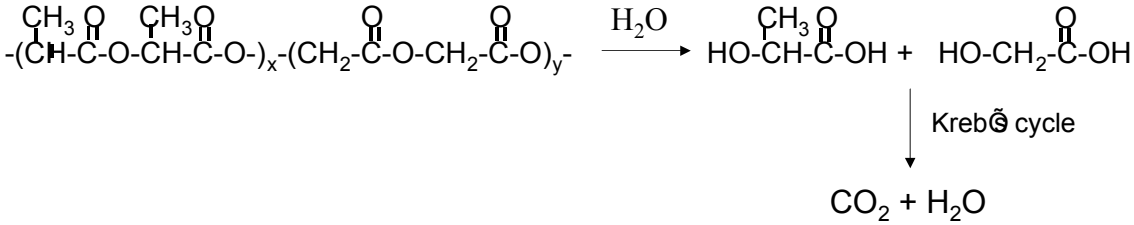
ionizes to 2 carboxyl groups

- Poly(alkyl cyanoacrylates)

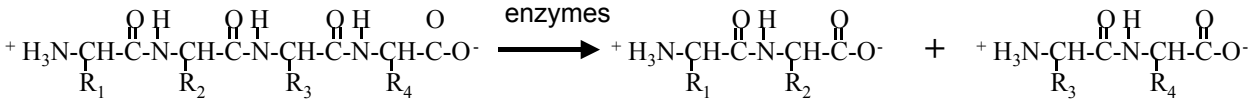


Mechanism III:

- poly(α-hydroxy, β-hydroxy esters)
  - acid or base catalyzed

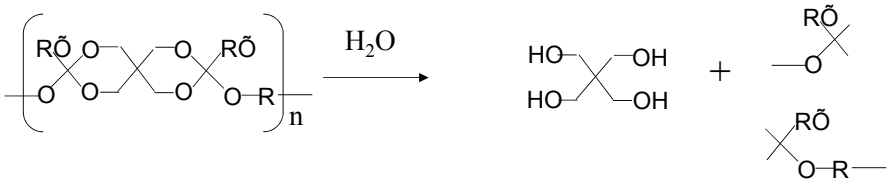


- polyamides
  - e.g. polypeptide hydrolysis



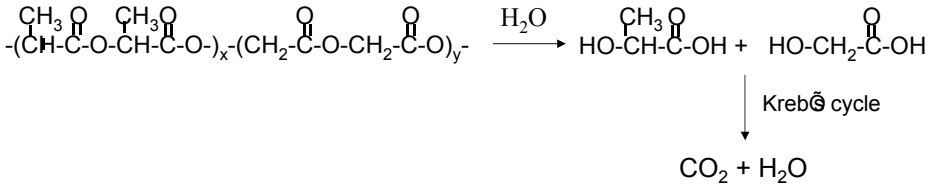
- polyanhydrides

- poly(ortho esters) (SKIP?)



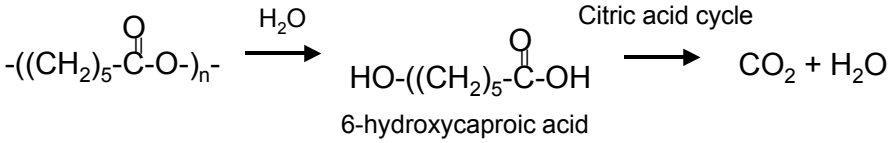
Medically-applied polymers are chosen for metabolizable or excretable final degradation products:

PLGA:

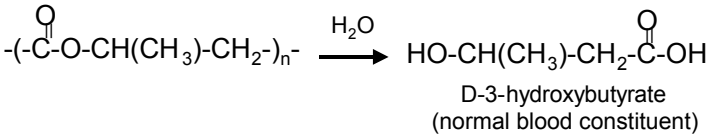


Kreb's cycle = citric acid cycle (conversion of pyruvate from glycolytic cycle into energy)
(D.H. Lewis in "Biodegradable polymers as drug delivery systems," 1990 p. 1-41 M. Chasin, ed.)

PCL:

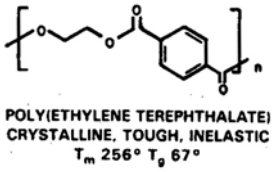


poly(hydroxybutyrate):



Holmes, Phys. Technol. 16, 32 (1985)

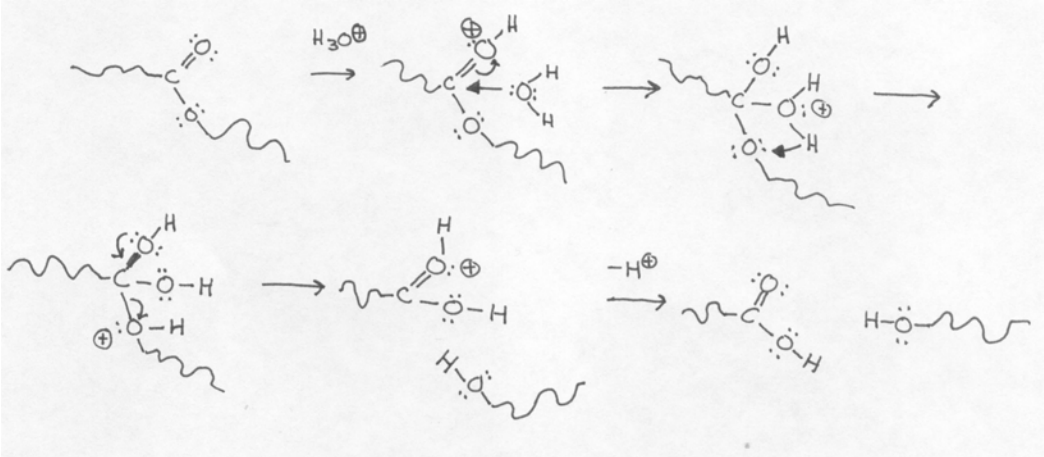
- What doesn't work?
  - e.g. poly(ethylene terephthalate) (PET) – used for soda bottles
    - breaks down to aromatic oligomers which form deposits in body
    - therefore more than just a hydrolysis-susceptible bond is needed!



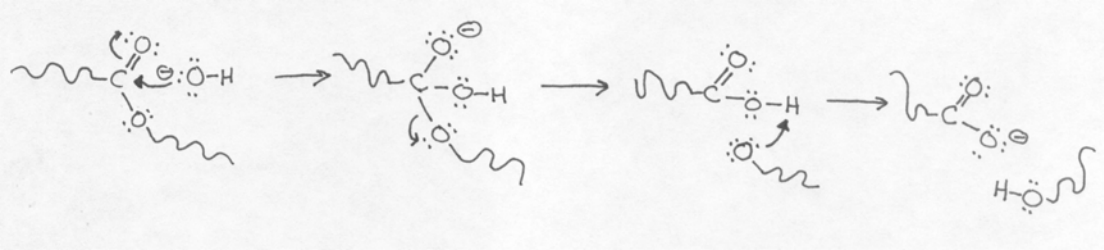
Mechanisms of Hydrolysis

One example, for polyesters:[9]

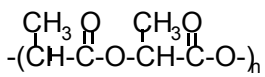
Acid-catalyzed hydrolysis:

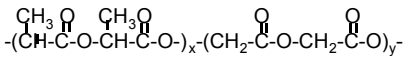
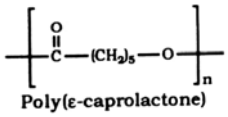
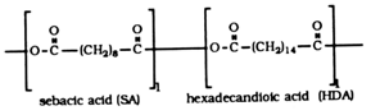
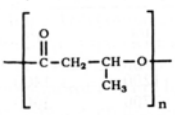
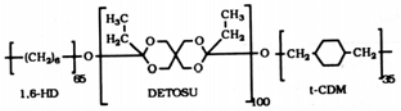
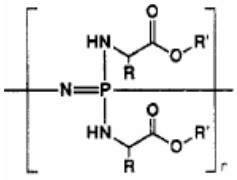


Base-catalyzed hydrolysis (saponification):



Example Structures, Properties, and Applications: (solid polymers, not water soluble) *(SLIDE)*

Polymer (class)	***Structure***	***Current Applications***
Polylactide: (polyester) Poly(L-lactide) [PLLA] Poly(D,L-lactide) [PDLLA] • Monomer can be obtained from fermentation of corn • First investigated by Carothers (DuPont) in 30s[10]		• Resorbable sutures • bone fixtures • tissue engineering scaffolds for bone[11], liver, nerve • PDLLA – Atrix laboratories in situ precipitation for scaffolds • Drug delivery (various)

Poly(lactide-co-glycolide) (polyester)		• Controlled release devices (protein and small molecule drugs)[12] • Tissue engineering scaffolds • Drug delivery (various) • Gene delivery
Poly(ε-caprolactone) [PCL] (polyester)	 Poly(ε-caprolactone)	• Slow controlled release devices – drug delivery (e.g. > 1 year)
Polyanhydrides • First synthesized in 1909	 sebacic acid (SA) hexadecandioic acid (HDA) Poly(SA-HDA anhydride)	• Orthopaedic reconstruction[5] • Drug delivery
Poly(β-hydroxy butyrate) (polyester) • Lemoigne (1920) discovered production of polyester by *Bacillus Megaterium* (bacteria)[13]	 Poly(β-hydroxybutyrate)	• Ocular drug delivery[14,15]
Poly(ortho esters)	 1,6-HD DETOSU t-CDM Poly(DETOSU- 1,6 HD-t-CDM ortho ester)	• Ocular drug delivery[16] • Periodontal antibiotic delivery and guided tissue regeneration[16] • Bone tissue regeneration[16]
Polyphosphazenes		• Insulin delivery[17] • New tissue engineering scaffolds (current research)
Polycarbonates		•

ADD polycarbonates? PPF?
Refs:
Biomat. 8, 311 (1987); Biomat 8,70 (1987); Biomat 8,289 (1987); J Contr Rel 2,167 (1985); Prog. Polym. Sci. 14, 679 (1989); J. Bioact. Compat. Polym. 6(1) 64 (1991); Polymer 34, 942(1993)

TABLE 2 Mechanical Properties of Some Degradable Polymers[a]

Polymer	Glass transition (°C)	Melting temperature (°C)	Tensile strength (MPa)	Tensile modulus (MPa)	Flexural modulus (MPa)	Elongation Yield (%)	Elongation Break (%)
Poly(glycolic acid) (MW: 50,000)	35	210	n/a	n/a	n/a	n/a	n/a
Poly(lactic acids)							
L-PLA (MW: 50,000)	54	170	28	1200	1400	3.7	6.0
L-PLA (MW: 100,000)	58	159	50	2700	3000	2.6	3.3
L-PLA (MW: 300,000)	59	178	48	3000	3250	1.8	2.0
D,L-PLA (MW: 20,000)	50	—	n/a	n/a	n/a	n/a	n/a
D,L-PLA (MW: 107,000)	51	—	29	1900	1950	4.0	6.0
D,L-PLA (MW: 550,000)	53	—	35	2400	2350	3.5	5.0
Poly(β-hydroxybutyrate) (MW: 422,000)	1	171	36	2500	2850	2.2	2.5
Poly(ε-caprolactone) (MW: 44,000)	−62	57	16	400	500	7.0	80
Polyanhydrides[b]							
Poly(SA-HDA anhydride) (MW: 142,000)	n/a	49	4	45	n/a	14	85
Poly(ortho esters)[c]							
DETOSU : t-CDM : 1,6-HD (MW: 99,700)	55	—	20	820	950	4.1	220
Polyiminocarbonates[d]							
Poly(BPA iminocarbonate) (MW: 105,000)	69	—	50	2150	2400	3.5	4.0
Poly(DTH iminocarbonate) (MW: 103,000)	55	—	40	1630	n/a	3.5	7.0

[a]Based on data published by Engelberg and Kohn (1991). n/a = not available, (—) = not applicable.
[b]A 1 : 1 copolymer of sebacic acid (SA) and hexadecanedioic acid (HDA) was selected as a specific example.
[c]A 100 : 35 : 65 copolymer of 3,9-bis(ethylidene 2,4,8,10-tetraoxaspiro[5,5] undecane) (DETOSU), *trans*-cyclohexane dimethanol (t-CDM) and 1,6-hexanediol (1,6-HD) was selected as a specific example.
[d]BPA: Bisphenol A; DTH: desaminotyrosyl-tyrosine hexyl ester. For detailed structures, see Fig. 1.

(Ratner, Biomaterials Science) *Semicrystalline materials highlighted

Physical chemistry of hydrolysis

Mechanisms of Dissolution

- two modes of erosion: surface and bulk

surface erosion – degradation from exterior only with little/no water penetration into bulk
bulk erosion – water penetrates entire structure and degrades entire device simultaneously

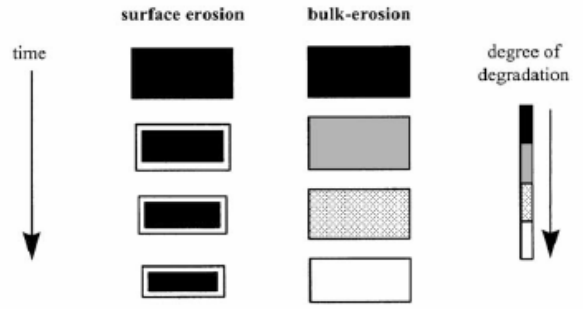
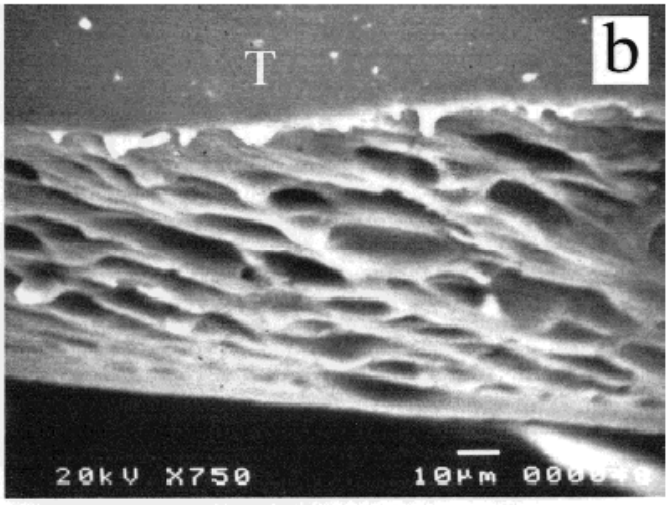


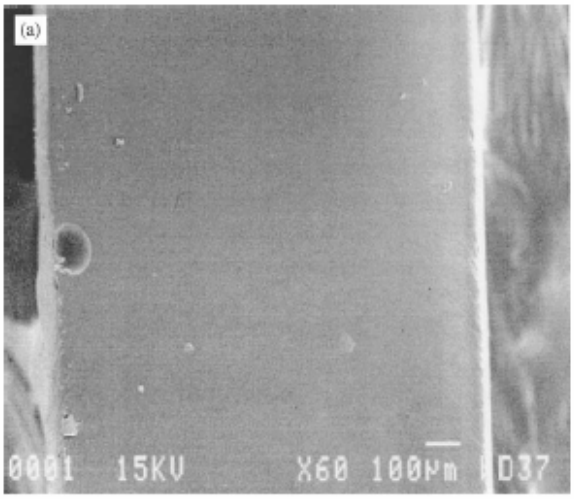
Fig. 1. Schematic illustration of the changes a polymer matrix undergoes during surface erosion and bulk erosion.

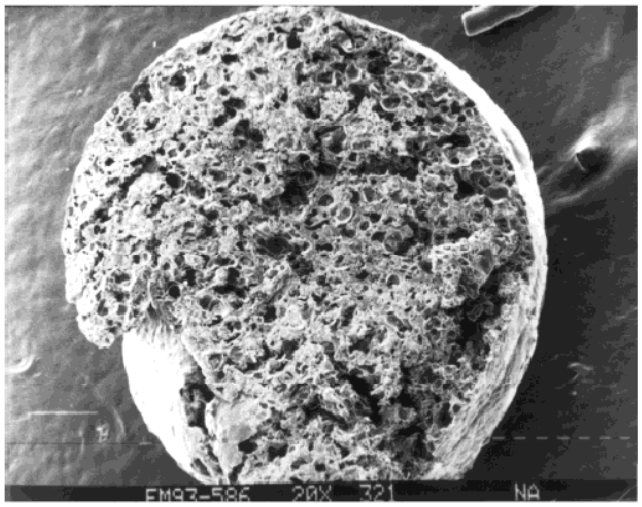
- Polymers hydrolyzing by mechanisms II or III can be either surface or bulk eroding.

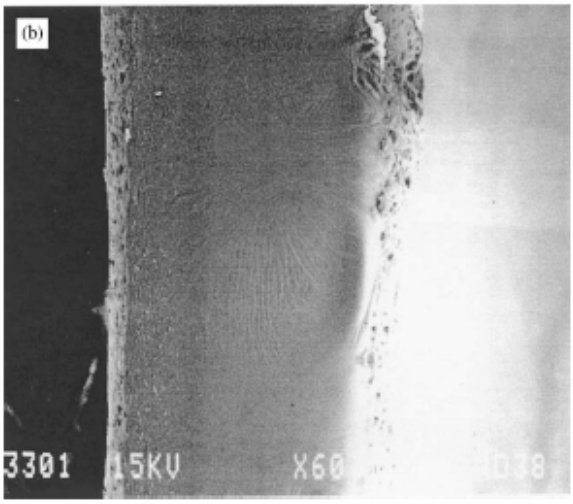
(SLIDE)

Bulk Erosion **Surface Erosion**









Scanning electron micrographs of PLA and PLGA polymer samples undergoing bulk or surface erosion by altering degradation conditions[18-20]

- typical weight loss profiles for these modes

(SLIDE)

Bulk (normal erosion at pH 7.4):

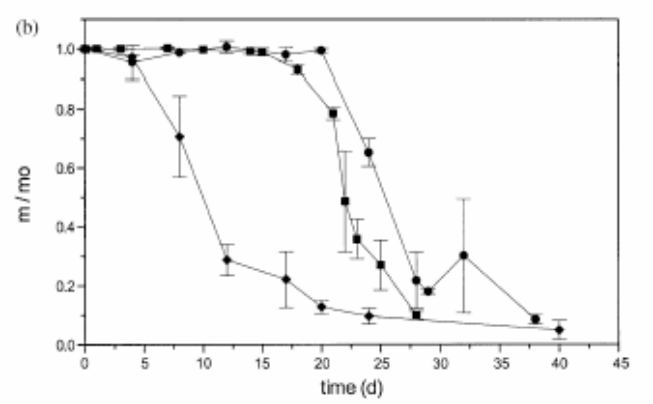


Fig. 4. Erosion profiles of poly(α-hydroxy esters) at pH 7.4: (a) $PLA_{50}11h$ (○) and PLA5017 (□), (b) $PLA_{25}GA_{50}8h$ (◆). $PLA_{25}GA_{50}14$ (●) and $PLA_{25}GA_{50}47h$ (■).

Surface (pH > 12):

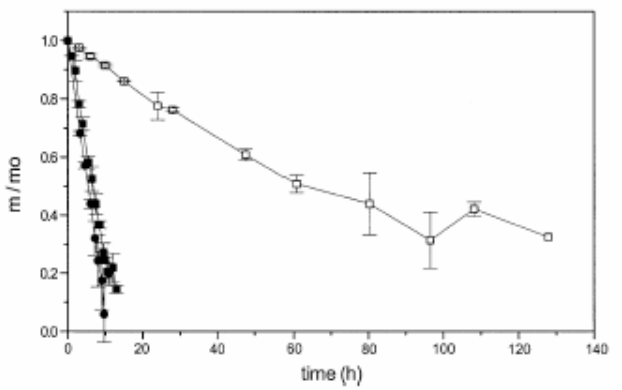


Fig. 9. Erosion of poly(α-hydroxy esters) at pH > 13: $PLA_{25}GA_{50}14$ (●) and $PLA_{50}17$ (□), $PLA_{25}GA_{50}47h$ (■).

SEM shown previously (Fig. 13) confirms transition to surface mode

- common polyesters composed of lactide and glycolide only soluble for oligomers Mn ≤ 1100 g/mole[21]

- schematic illustration

- networks show retarded breakdown compared to linear polymers: need to break more bonds to create free water-soluble oligomers

Molecular structure effects on hydrolytic breakdown

-hydrolysis requires water to access the bonds: so structure has a strong effect on hydrolysis rates

-factors influencing hydrolysis rate:

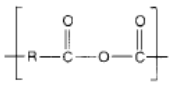
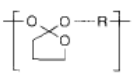
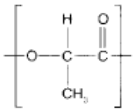
SUMMARY:

1. relative bond stability
2. hydrophobicity
3. steric effects
4. production of autocatalytic products
5. microstructure (phase separation)

1. relative bond stability

representative examples: bond half-lives at physiological pH/temperature:

Table 1 Classes of hydrolysable bonds with half-lives according to References 32 and 39

Polymer class	Half-life
 poly(anhydrides)	0.1 h
 poly(ortho esters)	4 h
 poly(esters)	3.3 yrs
 poly(amides)	83 000 yrs

- intrinsic stability of polyamide bond:
  - polypeptides and proteins are degradable due to action of enzymes
  - …whereas nylon isn't a biodegradable polymer

(SLIDE)

polyesters — reasonable hydrolytic stability

poly(ortho esters) — low hydrolytic stability

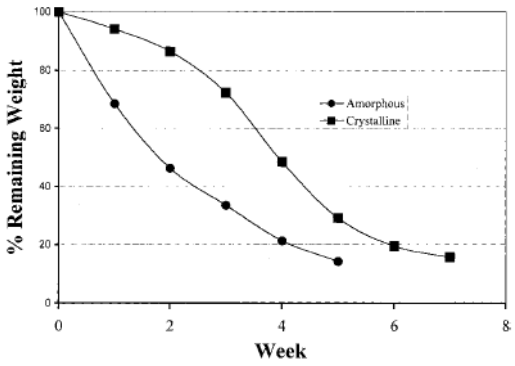


Figure 12. Weight loss profiles of crystalline and amorphous PGA-*co*-PLA (90/10) samples during in vitro degradation.

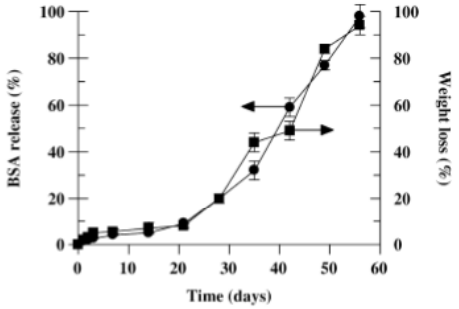


Fig. 12. Release of FITC-BSA (●) and weight loss (■) from a poly(ortho ester) IV prepared from DETOSU, 1,4-pentanediol and 1,6-hexanediol glycolide (100/95/5). Strands extruded at 70°C; 0.01 M phosphate-buffered saline, pH 7.4, 37°C. FITC-BSA loading 15 wt% (from Ref. [158]).

THIS DOESN'T MAKE THE POINT

2. Hydrophobicity
    a) Degradation rate decreases with increasing hydrophobicity

Polyesters: cleavage rate of PCL < PDLLA < PLGA

poly(anhydrides) of varying hydrophobicity[5]:

Table 2
Degradation kinetic constants and total degradation time for disks ($d = 2$ cm, $t = 2$ mm) as a function of the polymer network composition

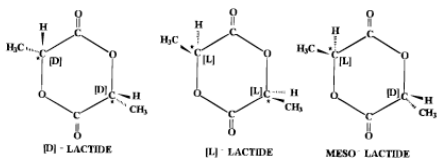
Polyanhydride composition	k (mm/h)	Degradation time (days)
Poly(MSA)	1.3×10^{-2}	3
Poly(MCPH)	8.4×10^{-5}	496
50/50 poly(MSA)/poly(CPP:CPH)	5.4×10^{-4}	78
75/25 poly(MSA)/poly(CPH)	1.9×10^{-3}	22
Copoly(MSA:MC) (75:25)	3.0×10^{-4}	138
Copoly(MSA:MStA) (75:25)	1.9×10^{-3}	22

effect of PLGA composition (varied hydrophobicity): Biomaterials 16, 1123 (1995)

b) as we will see later, hydrogels containing polyester segments degrade much more rapidly than their solid polymer counterparts (water intimately in contact with structure)

3. Steric effects
    - Local structure
        - Bulky substituents
            - PLA degrades more slowly than PGA due to bulky methyl group blocking water access SHOW SPACE-FILLING MODEL TO MAKE POINT?
    - Glass transition (Tg)
        - Rubbery polymers above Tg have more chain mobility; easier for water to penetrate the solid
    - Crystallinity
        - Stereoisomers:

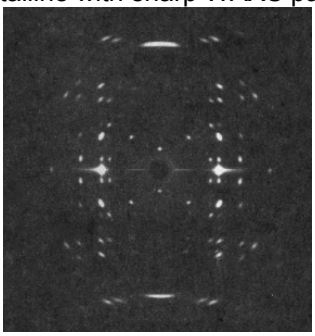
Lactide has 3 stereoisomers:



- Pure poly(D-lactide) or poly(L-lactide) are semicrystalline
- Copolymers of D- and L-monomer or meso-lactide are amorphous, but have similar Tg to isotactic polymers

- Fibers of PLLA can be highly crystalline with sharp WAXS patterns[22]:

(SLIDE)



crystal structure:

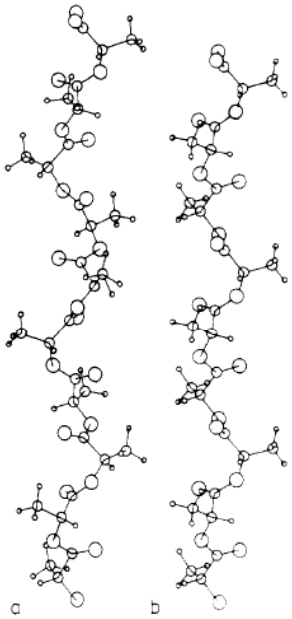


Figure 4. Projections along the helical axis of a −10/3 helical conformation (a) and a −3/1 helical conformation (b).

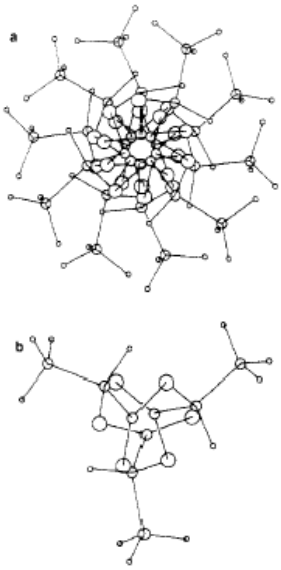
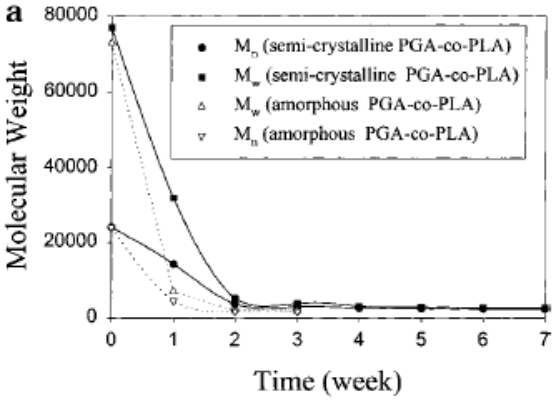


Figure 5. Projections perpendicular to the helical axis of a −10/3 helical conformation (a) and a −3/1 helical conformation (b).



NEED PDLLA VS. PLLA

amorphous regions degrade faster, causing total crystallinity remaining in solids to increase[23]: ***(SLIDE)***

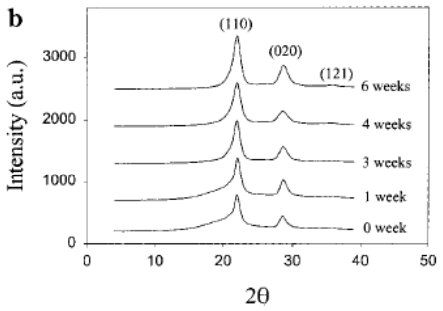


Figure 4. Selected WAXD profiles for the crystalline (a) PGA and (b) PGA-*co*-PLA samples during in vitro degradation.

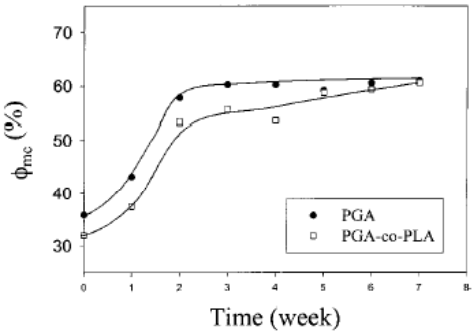


Figure 5. Changes of degree of crystallinity of crystalline PGA and PGA-*co*-PLA samples during in vitro degradation.

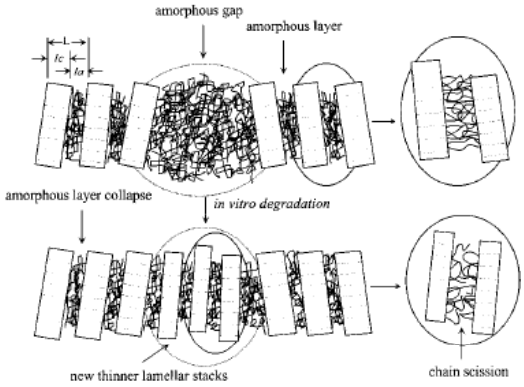
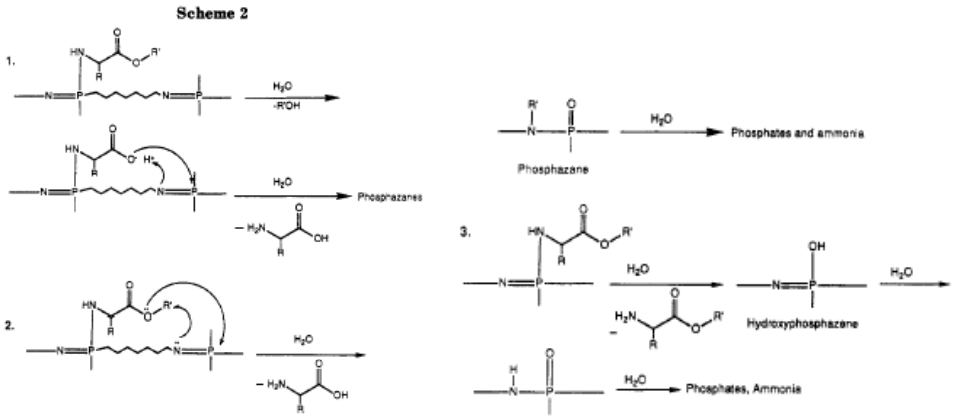


Figure 10. Schematic diagram of in vitro degradation mechanism in the dual lamellar stacks model of semicrystalline samples.

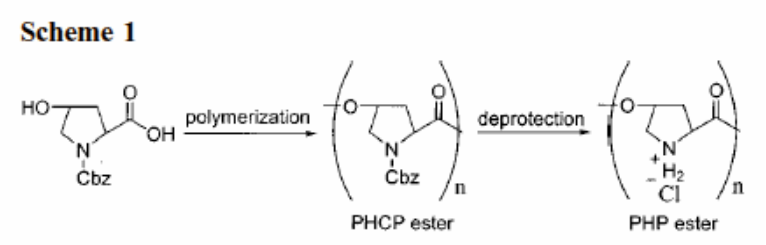
4. Production of autocatalytic products
    b) polyesters produce acid chain ends on breakdown and auto-catalyze acidic breakdown
        i. pH as low as 1.8 has been measured inside PLA structures immersed in pH 7.4 buffer
    c) polyanhydrides, producing 2 acid chain ends autocatalyze even more rapidly and also show dramatic pH drops in their environment
    d) self-destroying polymers

constituent of polymer chain attacks backbone:

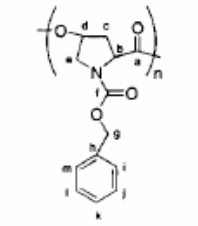
hydrolyzing side group attacks backbone: e.g. polyphosphazenes:



constitutive attack: e.g. Lim et al.[24,25]: primary amine side chains attack backbone)

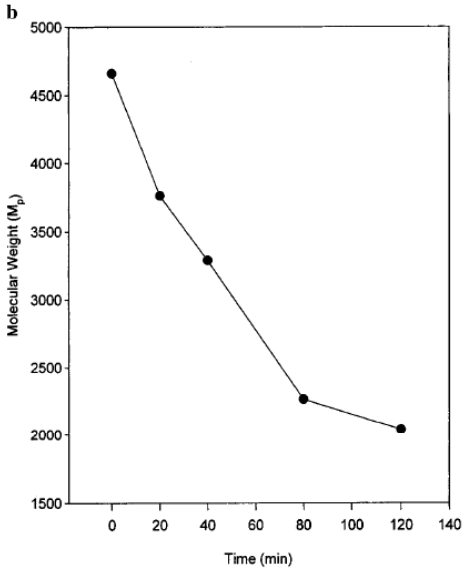


Cbz structure:



MECHANISM?
(SLIDE)

rapid degradation in water:



pH change as polymer breaks down:

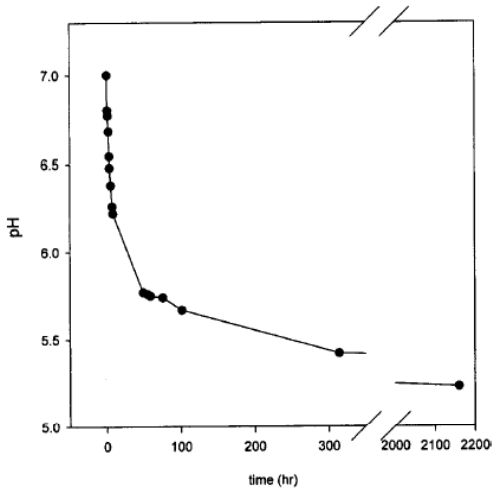
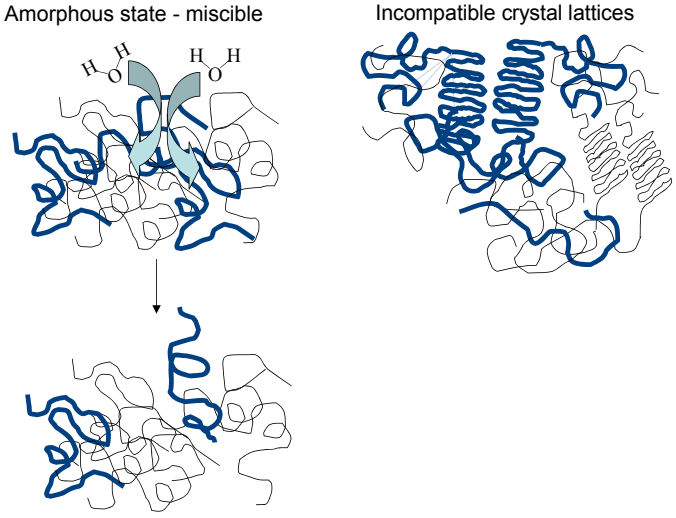


Figure 6. pH change profile during incubation of PHP ester. The pH change of PHP ester solution as described in the Experimental Section was monitored with time.

d) catalytic degradation products cannot be removed from the interior of the solid until a percolation threshold is reached

5. Phase separation in Composite materials and blends
    a. Formation of blends and phase separation has dramatic effects on mechanical, electrical, optical, magnetic properties of solids; we'll focus here on the effect on degradation
    b. Effect of blending with a hydrophilic polymer: case study of adding poly(ethylene glycol) to poly(L-lactide)[26,27]:
        i. PLLA and PEG both semicrystalline
        ii. Polymers are miscible in the amorphous phase, but crystallization forces phase separation:

(***SLIDE***)



If PEO amount is low enough to avoid much crystallization, water absorption is elevated in amorphous regions and degradation can be speeded up significantly:

(***SLIDE***)

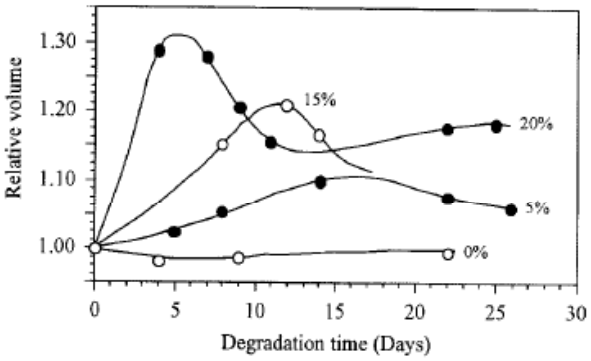


Figure 8 Change in volume during degradation of PLLA and blends of PLLA with PEO in water at 37°C

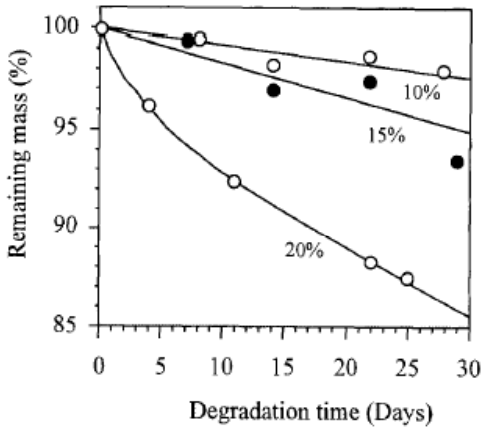


Figure 11 Mass loss of a number of PLLA/PEO blends during hydrolytic degradation. The initial PEO weight% is shown in the figure

peak in water sorption shifts left as blend becomes more hydrophilic and water uptake kinetics are speeded up (PLLA MW = 800K g/mol, PEO MW = 20K g/mol)

Addition of large amounts of PEG allows the hydrophilic component to crystallize as well:

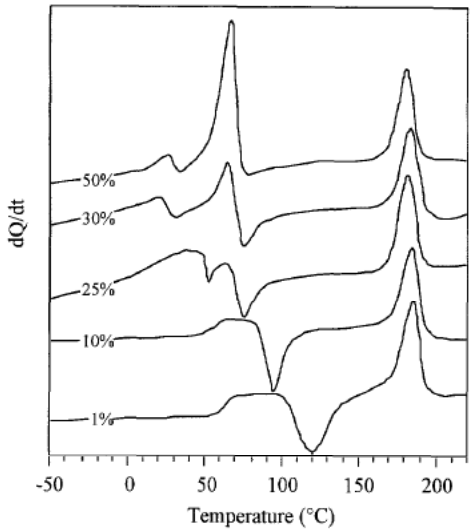
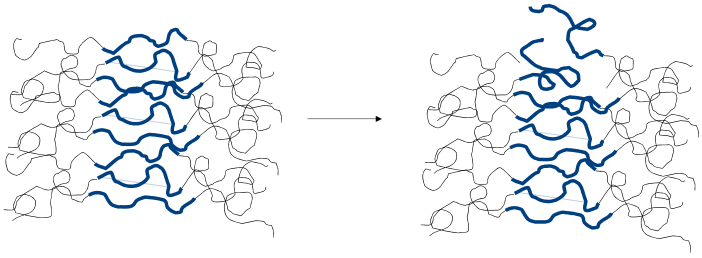


Figure 1 Thermograms of PLLA/PEO blends. The PEO concentration (weight%) is shown on the left of the figure. The curves are scaled to the PLLA melting peak

comparison of blend degradation with a triblock copolymer of PLLA-PEG-PLLA: PLLA (40K)-PEG (20K)-PLLA (40K) (***SLIDE)***

Constrained mass loss: triblock copolymers



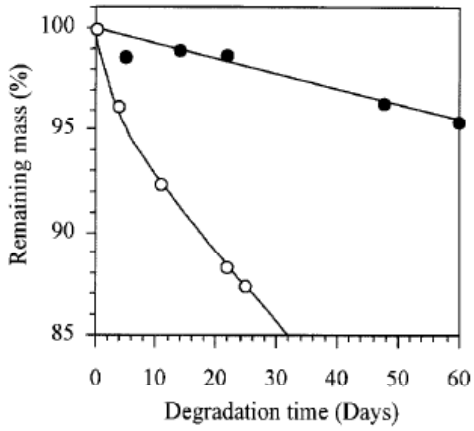


Figure 13 Mass loss during hydrolytic degradation of a compression moulded PLLA/PEO blend containing 20 weight% PEO (○) and a PLLA/PEO triblock-copolymer containing 20 weight% PEO (●)

Network polymers degrade more slowly: break down to soluble fragments requires multiple bond cleavages

controlling degradation behavior of solids for devices by choosing the right chemical structure:

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