The evolution of biomaterials

- Biodegradable Polymers
- Biofunctional materials

Commercial polymers

"Medical grade" polymers

Biomedical materials

Targeted and stimuli-responsive delivery systems

New design and fabrication techniques

Commercial process techniques

Improved knowledge of human body/materials interaction

Novel surface modification

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Design of biomaterials

• Biocompatible
• Processable
• Sterilizable
• Possibility to scale-up the production process
• Reasonable storage and shelf life
• Cost-effective production

• Biodegradable biomaterials

Biodegradable materials

bulk erosion

surface erosion

Time
Biodegradable polymers


Biodegradable polymers

Polymers

Biodegradable Polyesters

Poly(Ortho Esters)

Biodegradable Polymers Composed of Naturally Occurring α-Amino Acids

Biodegradable Polyurethanes and Poly(esther amide)s

Esters: condensation

\[ R\text{-COOH} + R'\text{-OH} \rightleftharpoons R\text{-COO-R'} + H_2O \]

This is simply the reverse of the acid-catalyzed hydrolysis of esters.
Polyesters

One method for driving the reaction toward completion is to remove the product water by azeotropic distillation using a Dean-Stark apparatus.

\[ R\text{-COOH} + R'\text{-OH} \rightleftharpoons R\text{-COO-R'} + H_2O \]

"Poly"condensation

"Poly"esters?

- di-acids + diols
- hydroxyacids + hydroxyacids
  - \( \alpha \)-hydroxyacids
  - \( \alpha, \beta \)-hydroxyacids
- Polyfunctional monomers
Traditional polyesters

- poly(glycolic acid) (PGA)
- poly(lactic acid) (PLA),
- copolymers poly(lactic acid-co-glycolic acid) (PLGA)
- polycaprolactones (PCL)
Polyesters: Poly(α-hydroxy acids) PLA

Synthesis of PLA

- 1854: Pelouze, polycondensation of lactic acid
- 1932: Carothers, lactide polymerization
- 1954: DuPont patent lactide polymerization
- 1970: PLA as biomedical material
- 1990: Cargill, Ring opening polymerization of L-LAC-10E

Polymers: polycondensation from lactic acid to PLA (glycolic acid to PGA)

L-lactic acid
D-lactic acid
DL-lactic acid

lactic acid = 2-hydroxypropanoic acid

glycolic acid = 2-hydroxyethanoic acid
Polyesters: polycondensation from lactic acid to PLA

\[
\text{L-lactic acid} + \text{D-lactic acid} \xrightarrow{\text{Polycondensation}} \text{atatic PDLLA}
\]
Polyesters: polycondensation from lactic acid to PLA

\[
\text{HO}_2\text{C-CH}_2\text{OH} + \text{HO}_2\text{C-CH}_2\text{OH} \xrightarrow{\text{Polycondensation}} \text{HO}_2\text{C-CH}_2\text{O-CH}_2\text{C-CH}_2\text{O-\ldots} + \text{H}_2\text{O}
\]

Equilibrium reaction: difficulties completely removing water can limit the maximum molecular weight attained due to hydrolysis of the ester bonds.
**Synthesis of PLA**


**Polyesters: ROP (ring opening polymerization) from lactide to PLA**

- **D-lactide**
- **meso-lactide**
- **L-lactide**

D- and L-lactides = two D- and L-lactic acids
meso-lactide = both D- and L-lactic acids

**Racemic lactide (rac-lactide)**
= equimolar mixture of D- and L-lactides
Polyesters: Poly(α-hydroxy acids) PLA

<table>
<thead>
<tr>
<th></th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-lactide</td>
<td>95–98</td>
</tr>
<tr>
<td>D-lactide</td>
<td>95–98</td>
</tr>
<tr>
<td>meso-lactide</td>
<td>53–54</td>
</tr>
<tr>
<td>rac-lactide</td>
<td>122–126</td>
</tr>
</tbody>
</table>

The crude lactide can be purified by melt crystallization or ordinary recrystallization from solution.

Polyesters: from lactide to PLA

Catalyzed by metal compounds involving Sn, Zn, Al and Sb ions, etc

Expected formation mechanism of lactide (back-biting mechanism)
Mechanisms for Ring Opening Polymerization (ROP)

Cationic mechanism (SN2)
Anionic mechanism (SN1)
Coordination-Insertion Mechanism (metal alkoxide and metal carboxylates as coordination-insertion initiators)

Polyesters: ROP from lactide to PLA

no water removal, no polycondensation
the precise mechanism of polymerisation depends greatly upon the initiator, monomer and polymerisation conditions
polymer molecules are formed by chain polymerisation mechanisms (sequential additions of monomer to the active centres)
Polyesters: ROP (ring opening polymerization) from lactide to PLA

1) Cationic Polymerization
   a) Protic Acid (HBr, HCl, triflic acid, etc)
   b) Lewis acid (ZnCl₂, AlCl₃, etc)
   c) Alkylating or Acylating agents (Et₃O⁺BF₄, etc)

2) Anionic Polymerization
   Proceed by nucleophilic reaction of the anion with the carbonyl
   and the subsequent acyl-oxygen cleavage, this produces an
   alkoxide end group which continuous propagate.

3) Coordination / Insertion Polymerization
   Use less reactive metal carboxylates, oxides, and alkoxides.
   Polymerization by tin, zinc, aluminum, and other heavy metal
   catalysts with thin (II) and zinc yielding the purest polymers.
Mechanism of ROP: Coordination-Insertion Initiators

Chemical structures of some coordination-insertion initiators used in the ROP of lactones and lactides (a) stannous octoate, (b) aluminium isopropoxide, (c) lanthanide isopropoxide (where the lanthanum atoms are represented by gray circles and the oxygen atoms by white circles; the black circle represents the bridging oxygen atom connecting all of the lanthanum atoms; alkyl groups are omitted for clarity).

Steroselectivity in the synthesis of PLAs
PLLA and PDLA are crystalline (Tm ~ 180°C). Their crystallinity and Tm usually decrease with decreasing optical purity (OP) of the lactate units.

Optically inactive poly(DL-lactide) (PDLLA), prepared from rac- and mesolactides, is an amorphous polymer.

Crystalline polymers can be obtained when the sequence of both D and L units are stereo-regularly controlled.
Polyesters: ROP (ring opening polymerization) from lactide to PLA

Polyesters: Poly(α-hydroxy acids)

Poly(α-hydroxy acids) (PGA, PLA, and their copolymers)
no functional groups available → copolymerize with monomers containing functional pendant groups (e.g. amino- and carboxyl- groups)

Examples:
- poly(L-lactide-co-RS-b-malic acid) with pendant carboxyl groups [He, B. et al., Polymer 2003]
- PLLA copolymers with succinic anhydride to obtain the corresponding carboxylic acid functions to attach amine-containing biological molecules [Noga, D.E., et al., Biomacromolecules, 2008]
- Copolymers of D,L-lactide to incorporate acryloyl groups [Chen, W., et al., Macromolecules, 2010]
- Copolymers poly(L-lactic acid-co-L-lysine) [Deng, C., et al, Biomacromolecules, 2006]
Polyesters: Poly(α-hydroxy acids)

A number of poly(alpha-hydroxy acids)-based block and graft copolymers have been designed and synthesized.

Examples:


Polyesters: ROP (ring opening polymerization) from ε-caprolactone to PCL

Co-polymerization with other lactones (e.g. γ-valerolactone)
**Polyesters: other**

![Polymer structure](image1)

**Biodegradable polyurethanes**

![Polyurethane structure](image2)

*RSC Adv., 2014, 4, 24736–24746*
Biodegradable polyurethanes

\[
R-N=\overset{\dddot{\circ}}{C}=O \quad \overset{\dddot{\circ}}{N} \quad \overset{\dddot{\circ}}{C}=O \quad R-N=\overset{\dddot{\circ}}{C}=O
\]
Biodegradable polyurethanes

\[
\text{R-N=C=O} \xrightarrow{\text{H-O-H}} \text{R-N-C-OH} \xrightarrow{\text{H+}} \text{R-NH}_2 + \text{CO}_2
\]
Biodegradable polyurethanes

\[
\text{diisocianato} + \text{diolo} \rightarrow \text{Biodegradable polyurethanes}
\]

Biodegradable polyurethanes

\[
\text{diisocianato} + \text{diammina} \rightarrow \text{Biodegradable polyurethanes}
\]
Biodegradable polyurethanes

\[
\begin{align*}
\text{diisocianato} & \quad + \quad \text{macrodiole} \\
\rightarrow & \\
\text{esterore (diole)}
\end{align*}
\]

Catalysts

\[
\begin{align*}
R-N=C=O & \quad + \quad R'-OH & \quad + \quad SnX_2 \\
\rightarrow & \\
R'-O-C-N-R & \quad + \quad SnX_2
\end{align*}
\]
Isocyanates

1,6-Diisocyanatohexane (HDI)

1,4-Diisocyanatobutane (BDI)

Isophorone diisocyanate (IPDI)

Dicyclohexylmethane diisocyanate (H12MDI)

Lysine methyl ester diisocyanate (LDI)

4,4’-Diphenylmethane diisocyanate (MDI)

Degradation of PUs

[S.A. Guelcher, Tissue Eng. Part B, 2008]
Degradable macrodiols

Poly(ethylene oxide) (PEO)

\[
\text{HO}-\text{CH}_2-\text{CH}_2-O-\text{H}
\]

Poly(propylene oxide) (PPO)

\[
\text{HO}-\text{CH}_2-\text{CH}_2-O-\text{H}
\]

Poly(ε-caprolactone) (PCL)

\[
\text{HO}\left[\left(\text{CH}_2\right)_5\text{C}\right]_m\text{O}\left[\left(\text{CH}_2\right)_5\text{C}\right]_m\text{OH}
\]

Poly(ε-lactide)

Poly(glycolide)

Polyester-based degradable polyurethane

The DegraPol® is a polyester-urethane and is made from two polyester diols linked through diisocynate unit. P(HB-co-CL) (poly(3-(R-hydroxybutirrate)-co-(ε-caprolactone))-diol) is the crystalline domain (hard segment), while the amorphous domain (Soft Segment) consist of poly(ε-caprolactone-co-glycolide)-diol.

Using different ratios of hard and soft segment can modulate the mechanical properties of the final product.
Degrapol®

Rapidly Degradable Block-Copolymers


Biodegradable materials for injectable systems

Open surgery  Minimally invasive surgery
Biodegradable materials for injectable systems

- **Soft materials**, e.g. hydrogels or preformes pastes
- **In vivo setting materials**
  - Materials able to undergo *in situ* polymerization
  - Smart materials (*thermoreponsive, pH responsive, environment responsive...*)
- **Particle systems** (micro- and nano-particles)

**Biodegradable materials for injectable systems**

- Solidification times
- Biocompatible reactions that undergo *in vivo*
- Rheology in the sol state
- Type of syringe/needle
- Good mechanical properties (*in situ*)
- Degradation or stability
- Easy to be prepared (to be prepared by medical staff!)

- Reasonable shelf life
- Sterilisable
- (Biocompatible)
Biodegradable materials for injectable systems

Injectability by physical methods
- thermosensitive
- pH sensitive
- stereocomplexed hydrogels
- peptide based (self assembled)
- micro and nanoparticle assembly

Injectability by chemical methods
- reaction of vinyl bearing macromers (redox- or thermally-initiated polymerization or photopolymerization)
- reactions through functional groups (Schiff-base formation, Michael-type additions, peptide ligation as well as “click”chemistry by cycloaddition reactions)
- enzymatically crosslinked (or natural products induced crosslinking)