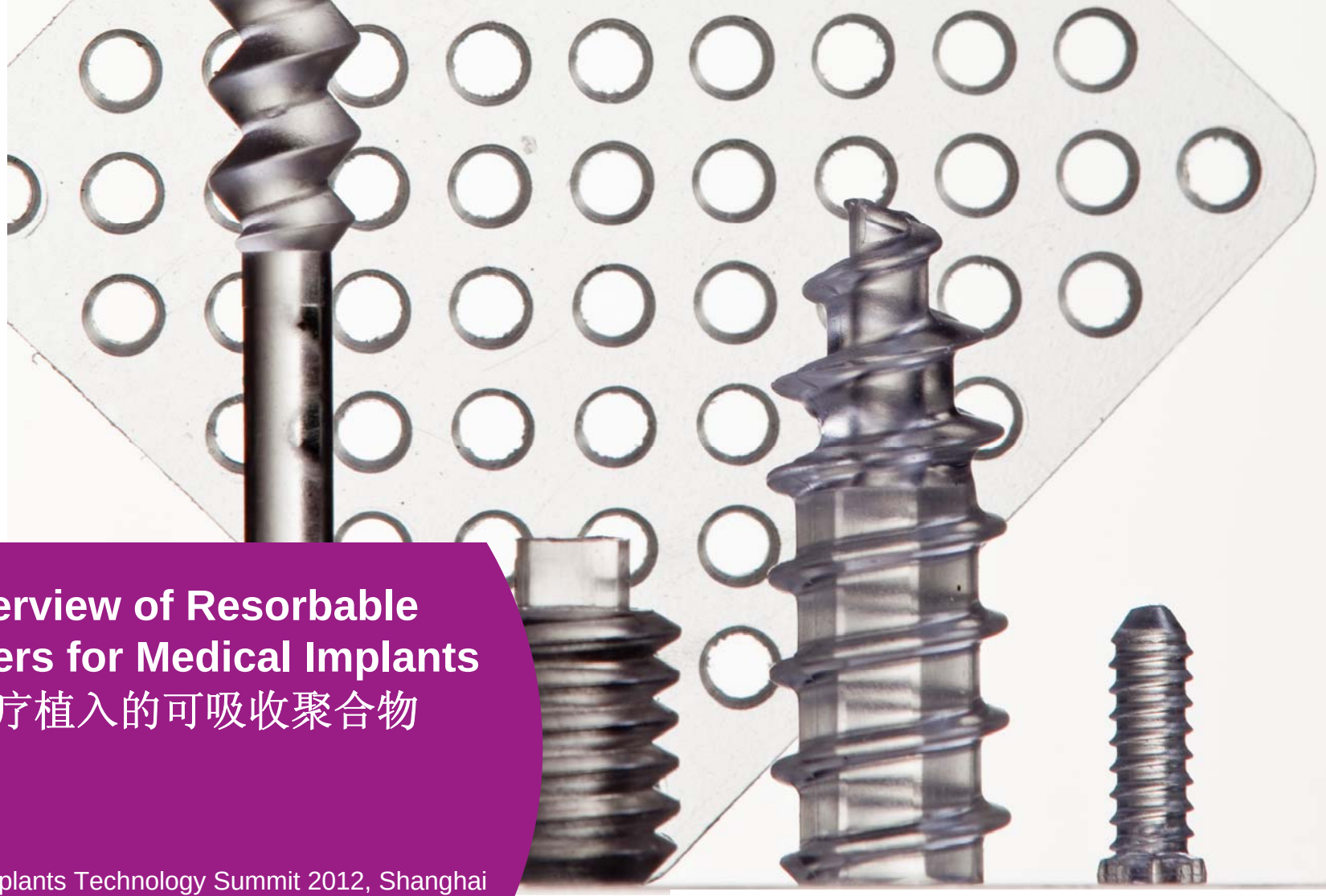


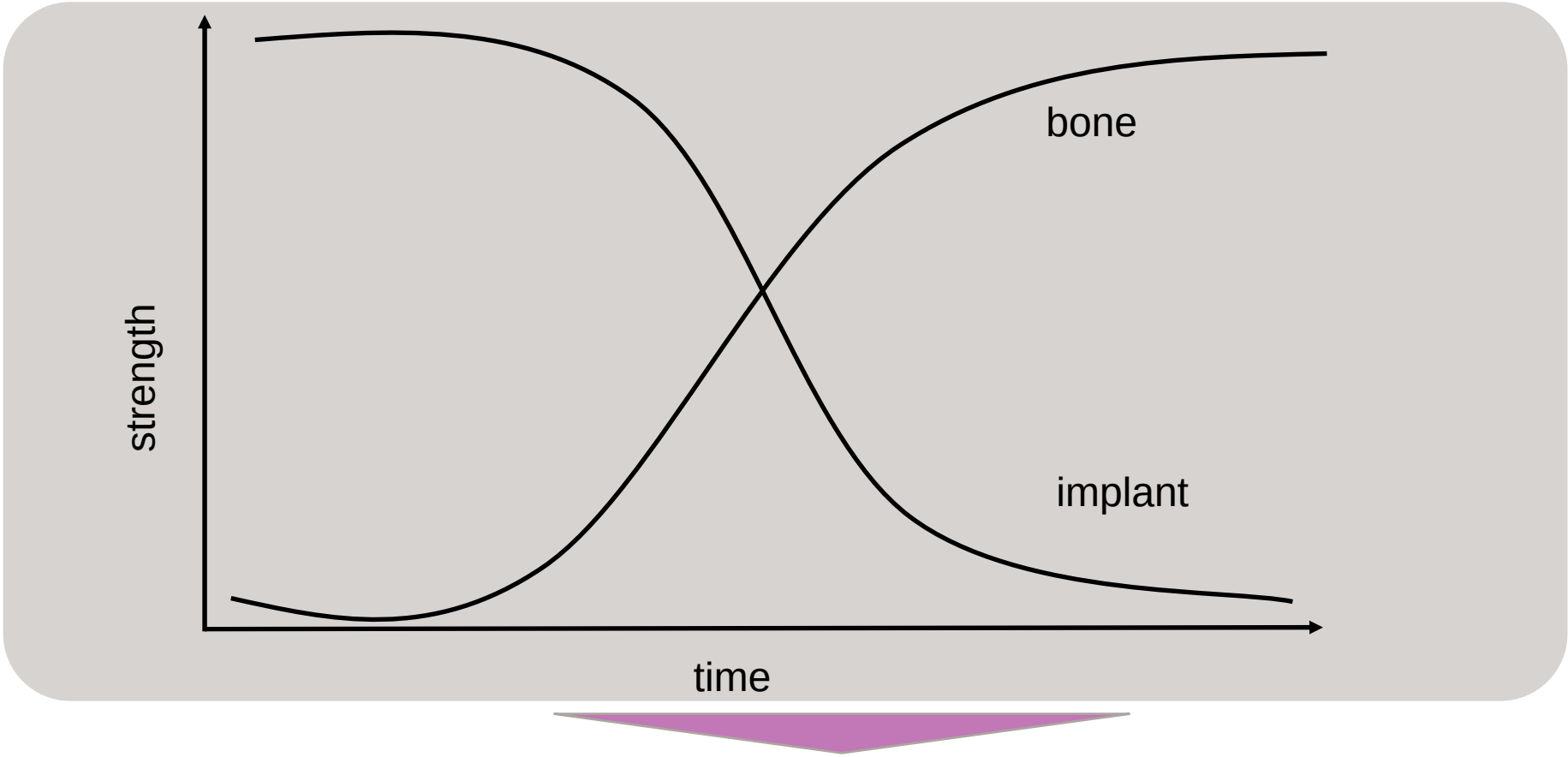
# An Overview of Resorbable Polymers for Medical Implants
# 用于医疗植入的可吸收聚合物

Medical Implants Technology Summit 2012, Shanghai

Dr. Howard Bowman

EVONIK INDUSTRIES

# Benefits of Biodegradable Medical Devices生物可降解医疗器械的优势




Implant removal is not required 无需将植入物取出

Data suggests transfer of mechanical load to bone improves healing (Orthopedic)数据支持从强度支撑到骨骼生长的治疗规律（骨科）

# Introduction 介绍

## Ideal Biodegradable Polymer理想的生物可降解聚合物

- Physical properties match application 物理性能适合应用
- No inflammatory or toxic response 无炎症或毒性反应
- Metabolized after fulfilling its purpose 当完成其使命后被代谢
- Easily processable into final product 简单工艺即可制备终产品
- Easily sterilized 容易灭菌
- Acceptable shelf life 可接受的保存期限

## Applications 应用

- Sutures >90% of market 缝线 >90% 的市场
- Orthopedic devices – anchors, pins, screws 骨骼装置- 铆钉，针，螺钉
- Drug delivery matrices – implants, microspheres, in-situ gels药物传递系统-植入剂，微球，在体凝胶
- Tissue engineering matrices (regenerative medicine)组织工程学（再生医学）
- Combination products – stents, stent coatings, drug eluting devices 复合产品-支架，包衣支架，药物洗脱支架

# Commonly Used Acronyms 常用聚合物列表

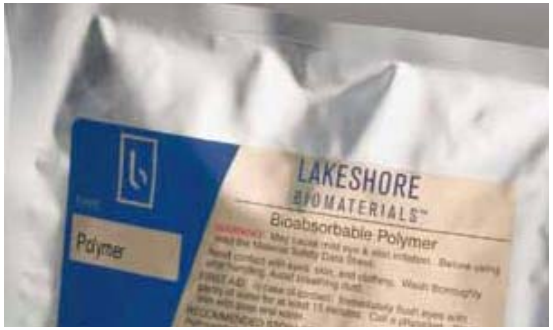
| | |
|---|---|
| **PLA** | **p**oly(**l**actic **a**cid)　聚乳酸 |
| **PLLA** | **p**oly(**L-l**actic **a**cid) 聚L-乳酸 |
| **PDLLA** | **p**oly(**DL-l**actic **a**cid) 聚DL-乳酸 |
| **PGA** | **p**oly(**g**lycolic **a**cid) 聚羟基乙酸 |
| **PGLA** | **p**oly(**g**lycolic-co-**l**actic **a**cid) 羟基乙酸乳酸共聚物 |
| **PDO** | **p**oly(**dio**xanone)聚对二氧环己酮 |
| **PDS** | **p**oly(**d**ioxanone) **s**uture聚对二氧环己酮 |
| **PCL** | **p**oly(**c**apro**l**actone)聚己内酯 |
| **TMC** | tri**m**ethylene **c**arbonate 三亚甲基碳酸酯 |

# Broad Product Range

## •RESOMER®

- **•RESOMER® L** Poly (L-lactide) 聚（L-丙交酯）
- **•RESOMER® R** Poly (DL-lactide)聚（DL-丙交酯）
- **•RESOMER® LR** Poly (L-lactide-co-DL-lactide) 聚（L-丙交酯-共-DL-乙交酯）
- **•RESOMER® LG** Poly(L-lactide-co-glycolide) 聚（L-丙交酯-共-乙交酯）
- **•RESOMER® RG** Poly (DL-lactide-co-glycolide) 聚（DL-丙交酯-共-乙交酯）
- **•RESOMER® LC** Poly (L-lactide-co-caprolactone) 聚（L-丙交酯-共-己内酯）
- **•RESOMER® X** Poly (dioxanone) 聚对二氧环己酮

## •Lakeshore Biomaterials™




- **•DLG** Poly (DL-lactide-co-glycolide) 聚（DL-丙交酯-共-乙交酯）
- **•DL** Poly (DL-lactide)聚（DL-丙交酯）
- **•LG** Poly (L-lactide-co-glycolide)聚（L-丙交酯-共-乙交酯）
- **•CL** Polycaprolactone 聚己内酯
- **•DLCL** Poly (DL-lactide-co-caprolactone)聚（DL-丙交酯-共-己内酯）
- **•LCL** Poly (L-lactide-co-caprolactone)聚（L-丙交酯-共-己内酯）
- **•G** Poly (glycolide) 聚（乙交酯）
- **•L** Poly (lactide)聚（丙交酯）
- **•PEG -PLG** PEG-Copolymers PEG-共聚物

# Polymer Synthesis 聚合物的合成

**RESOMER®** & **Lakeshore Biomaterials™**

## Monomer synthesis 单体合成

- Dimerize lactic acid, glycolic acid etc…将乳酸，羟基乙酸进行二聚
- Oligomer, Distillation寡聚物蒸馏
- Crystallization结晶

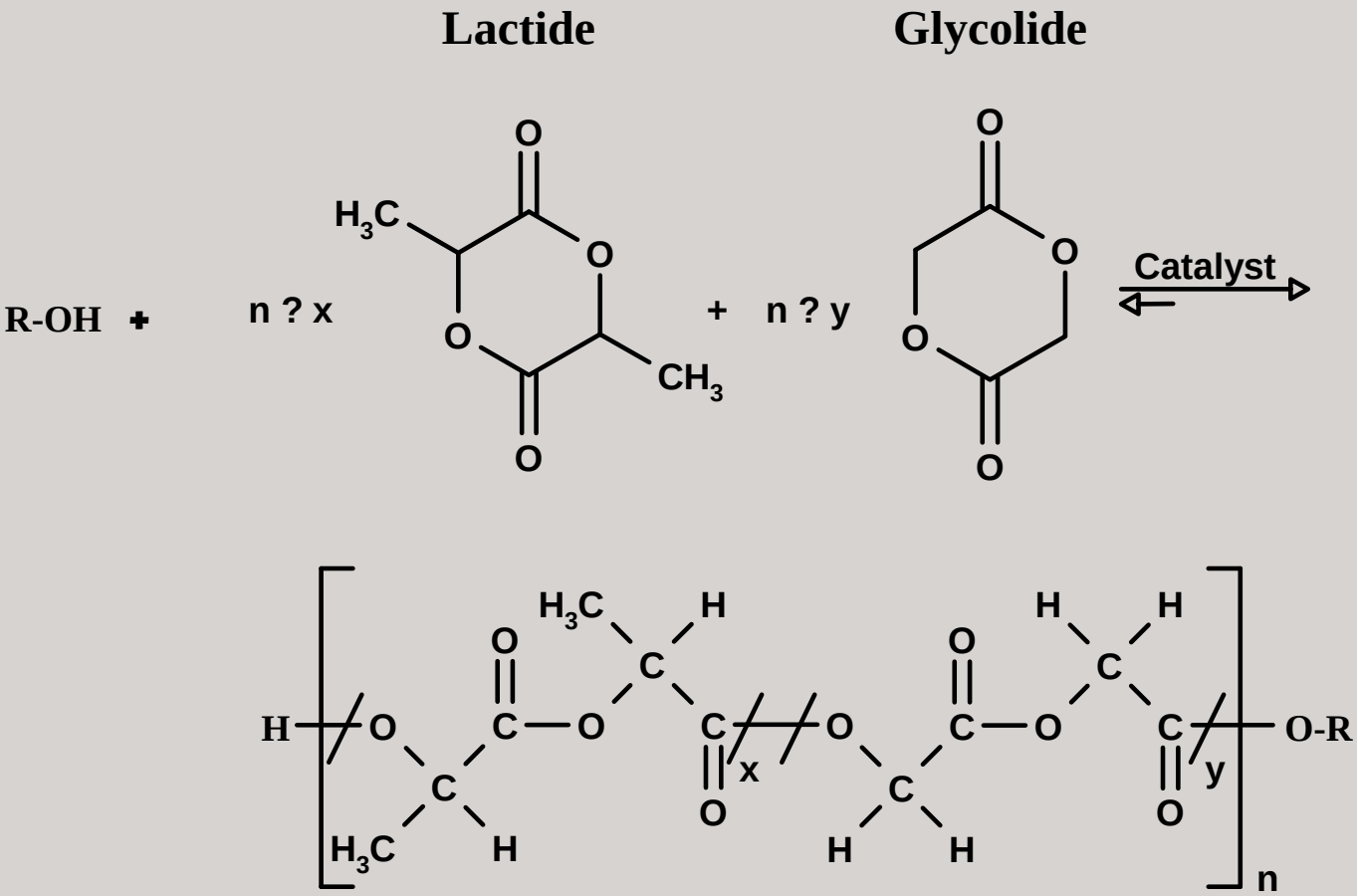
## Polymerization 加聚反应

- ROP of dimers 二聚体开环聚合
- Catalyst催化
- Heat 加热
- Initiator to control MW 加入引发剂控制MW

## Purfication 纯化

- **Semicrystalline**半结晶: SC $CO_2$, solvent precipitation 溶剂沉淀
- **Amorphous**无定形: Vacuum strip, solvent precipitation真空剥离，溶剂沉淀

# Polymer Synthesis: Ring-Opening Polymerization (ROP)聚合物合成：开环聚合（ROP）



# Flexible Chemistry 灵活的化学

## 输入…Input…

- Initiator 引发剂
- Composition 组成
- Chemical Constitution化学结构
- Heat & Reaction Time 加热&反应时间

## 效果…Effect…

- Mechanical Properties机械性能
- Degradation Kinetics降解动力学
- Monomer Sequence单体顺序
- Molecular Weight 分子量
- Water Uptake 水分的摄取
- Morphology 形态
- Solubility 溶解性

# Degradation and Resorption降解和重吸收

**Degradation降解**

…means decomposition to some other chemical structure. The term does not specify the conditions like temperature or chemical enviroment.指组成成分变为其它物质结构，这一定义并不限定条件，如温度或化学环境。

The term biodegradable polymers usually applies to polymers that degrade under physiological conditions to low molecular weight substances.

生物可降解聚合物通常指聚合物在生理条件下降解为低分子的物质。

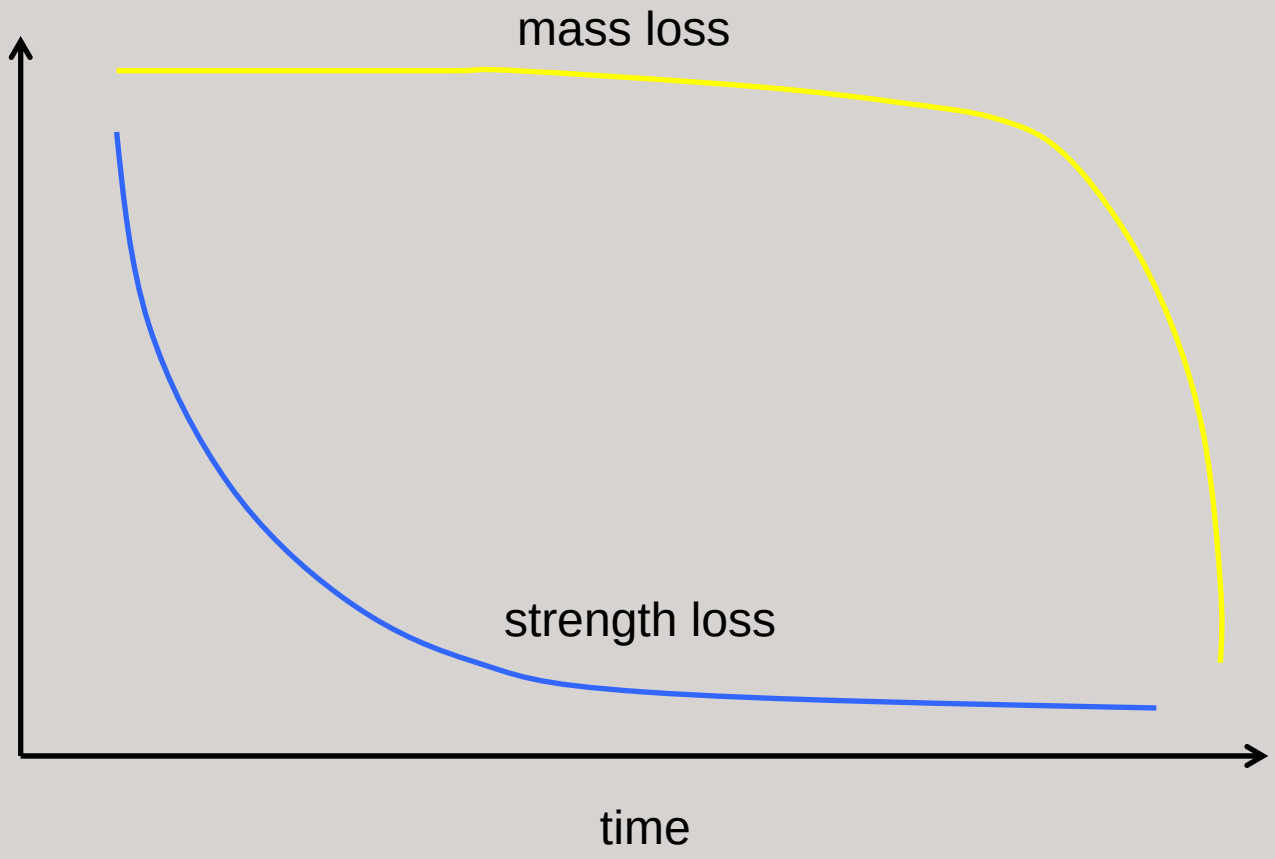
**Resorption重吸收**

…means uptake of any substance from tissue or body compartments into the blood plasma.指任何通过组织或身体器官吸收入血液的物质。

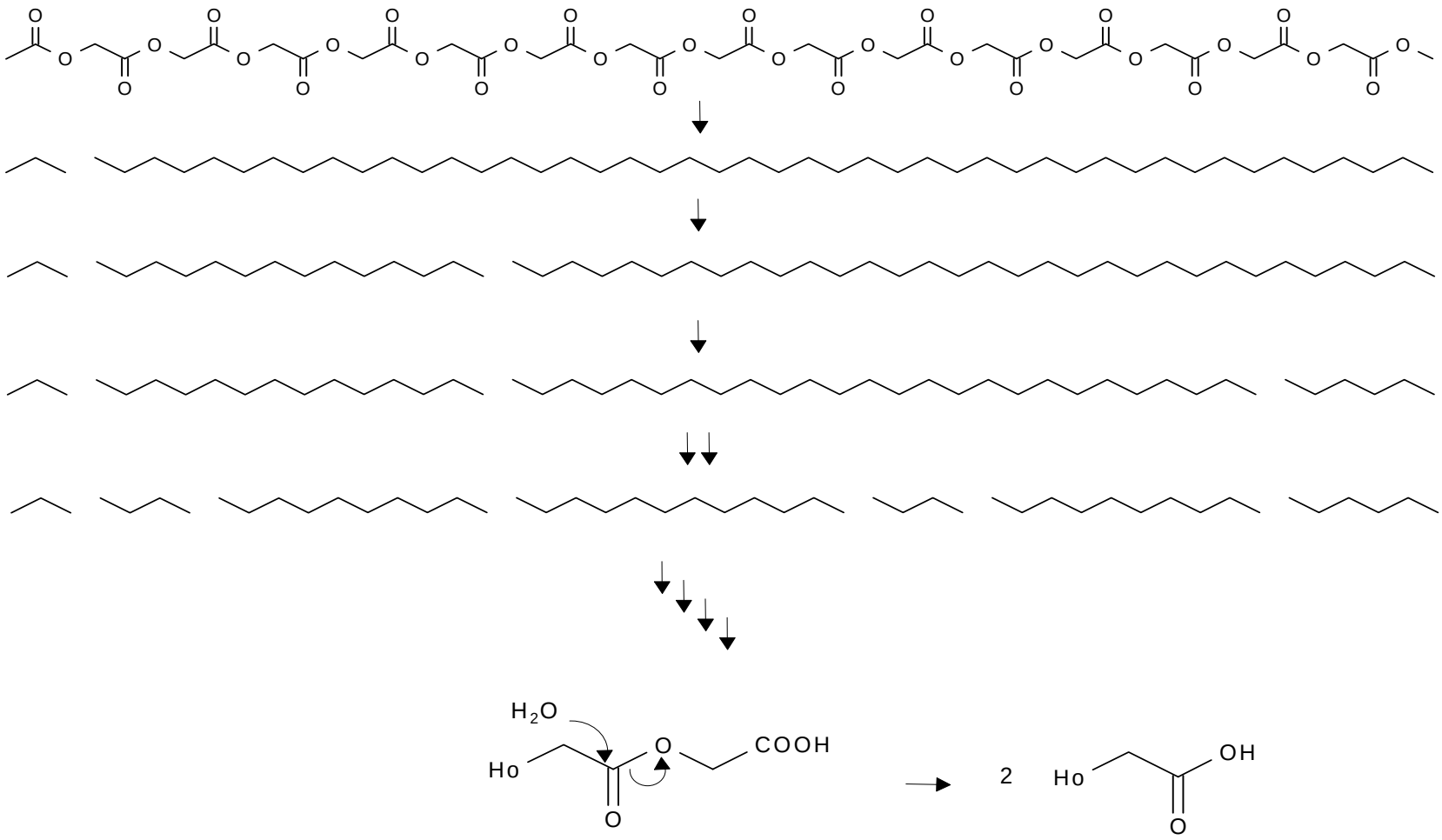
After implantation into the human body biodegradable or bioresorbable polymers degrade into low molecular weight substances that are then resorbed and metabolized.生物可降解或生物可吸收聚合物被植入人体后降解成小分子物质，这些物质被吸收和代谢。

# Bulk Erosion整体侵蚀

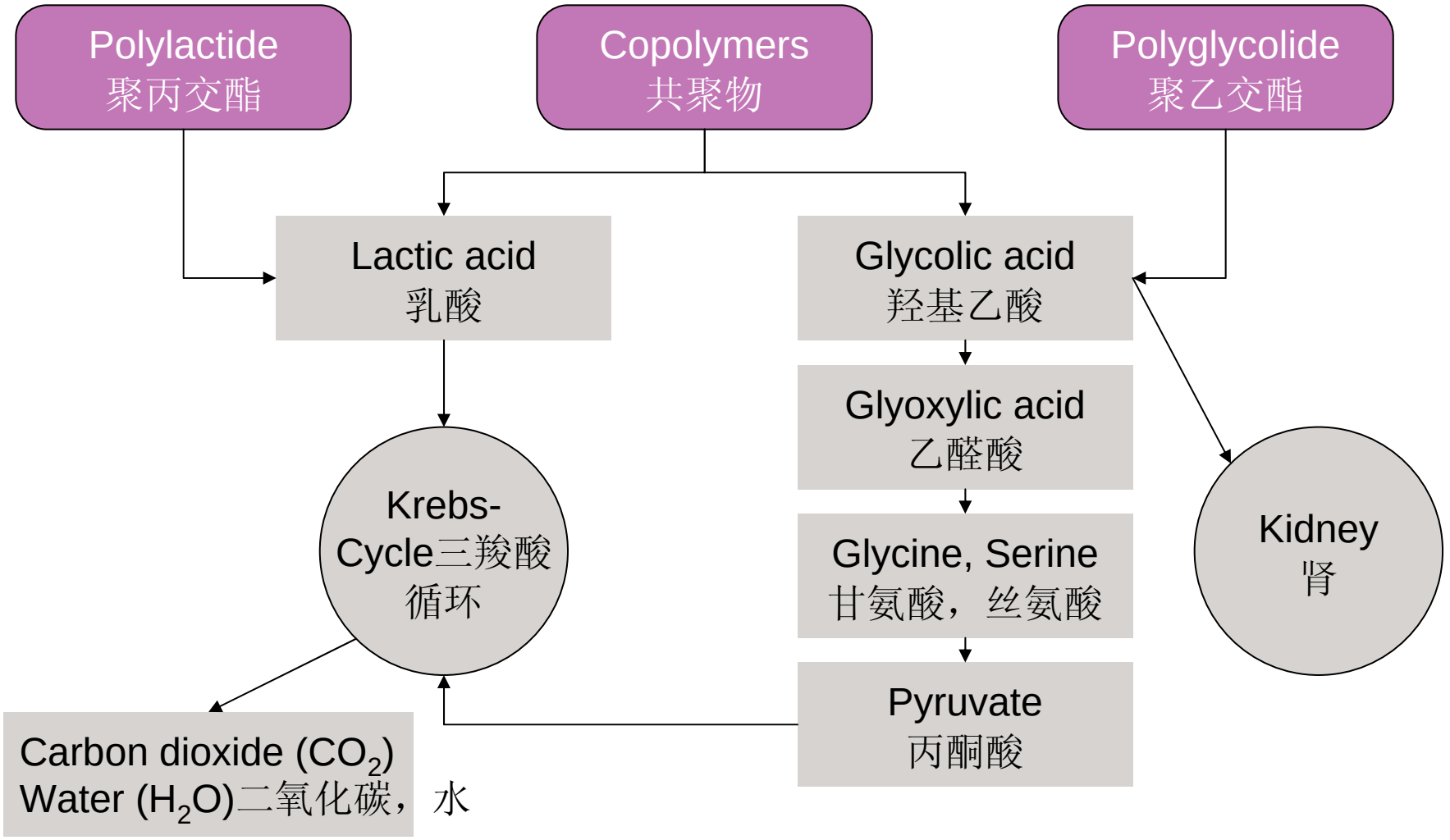
# Bulk Erosion整体侵蚀
# Mechanical Properties 机械特性



# Hydrolysis 水解

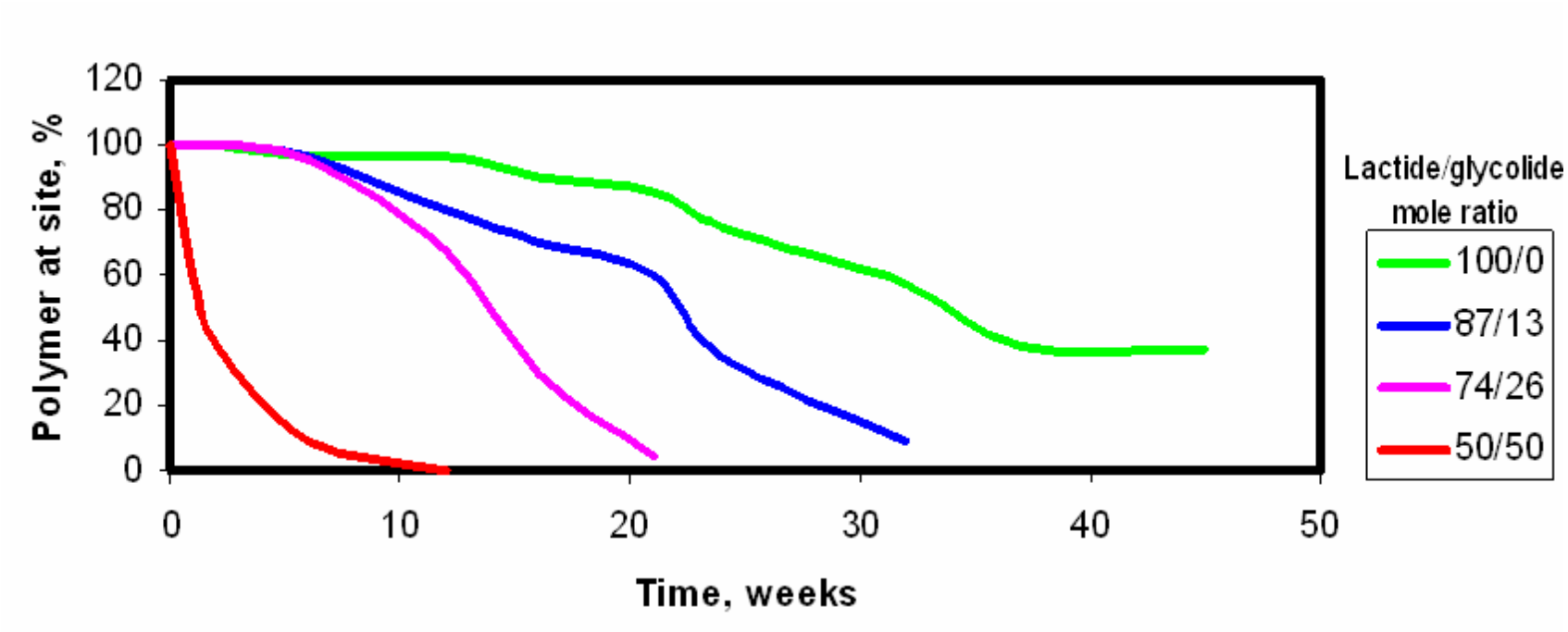


# Metabolism of Polyesters聚酯的代谢



# Degradation Times降解时间

Resorption of poly(DL-lactide-co-glycolide) microparticles in rats (polymer inherent viscosity of ~ 0.7 dL/g) 聚（DL-丙交酯-共-乙交酯）微粒在大鼠中的吸收（聚合物特性粘度~ 0.7 dL/g ）



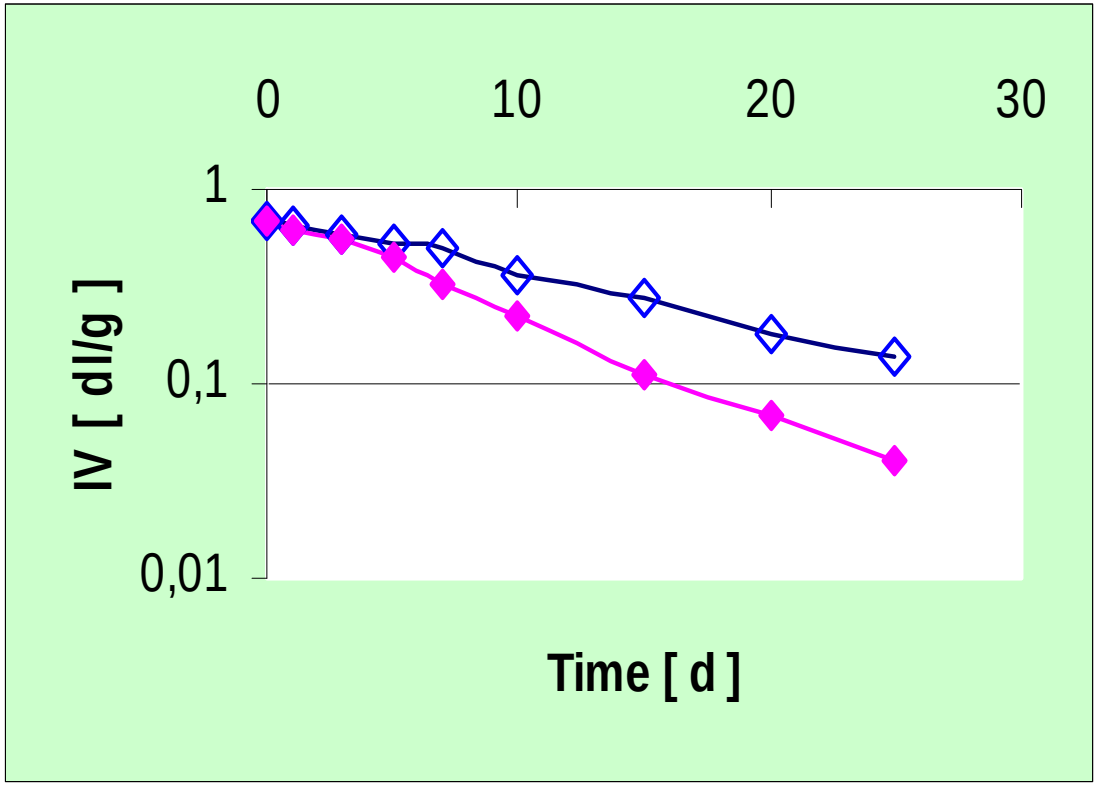
# Initiator 引发剂

| INITIATOR引发剂 | POLYMER END GROUPS聚合物末端 | EFFECTS影响 |
|---|---|---|
| **Monofunctional Alcohol (R-OH)**<br>单醇 | **Ester and Hydroxyl**酯和羟基 | **Hydrophobic**疏水 |
| **Diol (HO-R-OH)**<br>二元醇 | **Hydroxyl**羟基 | **Hydrophilic**亲水 |
| **Hydroxy Acid or Water**<br>羟基酸或水 | **Carboxylic Acid and Hydroxyl**羧酸和羟基 | **Increased water uptake, catalytic effect, and degradation rate**增加对水分的摄取，有催化效果，降解速度加快 |
| **Polyethylene glycol**聚乙二醇<br>**Methyl ether Polyethyene glycol**甲基醚聚乙二醇<br>**$HO-(-CH_2-CH_2-O-)-H$**<br>**$H_3CO-(-CH_2-CH_2-O-)-H$** | **Hydroxyl with PEG block in center (A-B-A)**两端羟基中间聚乙二醇<br>**Methyl Ether and Hydroxyl (A-B)**甲基醚和羟基 | **Slightly to greatly hydrophilic, increased water uptake, amphiphilic**轻微至很强的亲水性，增加对水的摄取，两亲性 |

# Effect of Initiator on Degradation Kinetics 引发剂对降解动力学的影响

*IN VITRO* Degradation of RESOMER RG 505 *vs*. RG 505 H at 37 ° C, pH 7.4

体外降解 RESOMER RG 505 *vs*. RG 505 H at 37 ° C, pH 7.4




**Ester End Group**

酯基末端

**RG 505**: $\tau_{1/2}$ = 10.6 d

**Acid End Group**

羧酸末端

**RG 505 H**: $\tau_{1/2}$ = 5.8 d

# Monomer Sequence单体的顺序

## Sequence in Copolymers在聚合物中的顺序

**L = L-lactide** **R = D,L-lactide** **G = glycolide**

| | |
|---|---|
| LLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLL | homo单聚 |
| GGGGGGGGGGGGGGGGGGGGGGGGGGGG | homo单聚 |
| LLLLLLLLLLLLLLLLGGGGGGGGGGGGGGGG | block封端 |
| LLLLLGLLGLLLLLGLLLGLLLLLGGLLLLLGGLLL | random随机 |

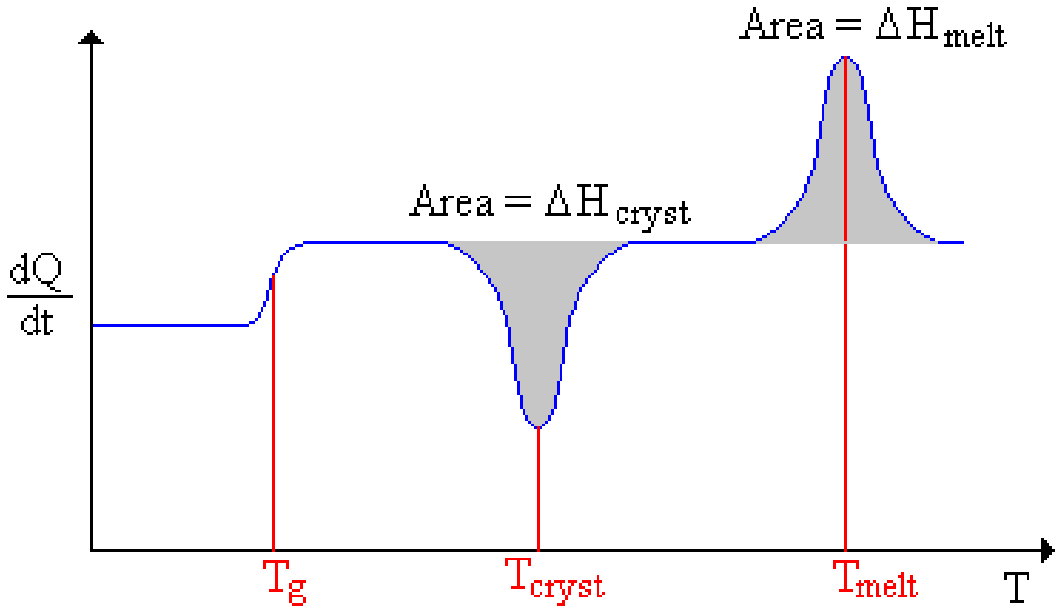
**Semi-Crystalline**
半结晶聚合物

| | |
|---|---|
| RGRRGRGGRRGRRGRGGRRRGGRGGGRRRG | random随机 |
| RRRRRRRRRRRRRRRRRRRRRRRRRRRRRRRR | homo均聚 |

**Amorphous**
无定形

The monomer sequence of a copolymer impacts physical properties and performance!共聚物中单体的顺序影响了聚合物的物理性质和性能

# Thermal Transitions 热转变



# Polymer Morphology 聚合物形态

In the solid state, **semicrystalline** polymers posses two phases固体状态，半结晶聚合物有两种形态

- Crystalline 结晶
- Amorphous 无定形

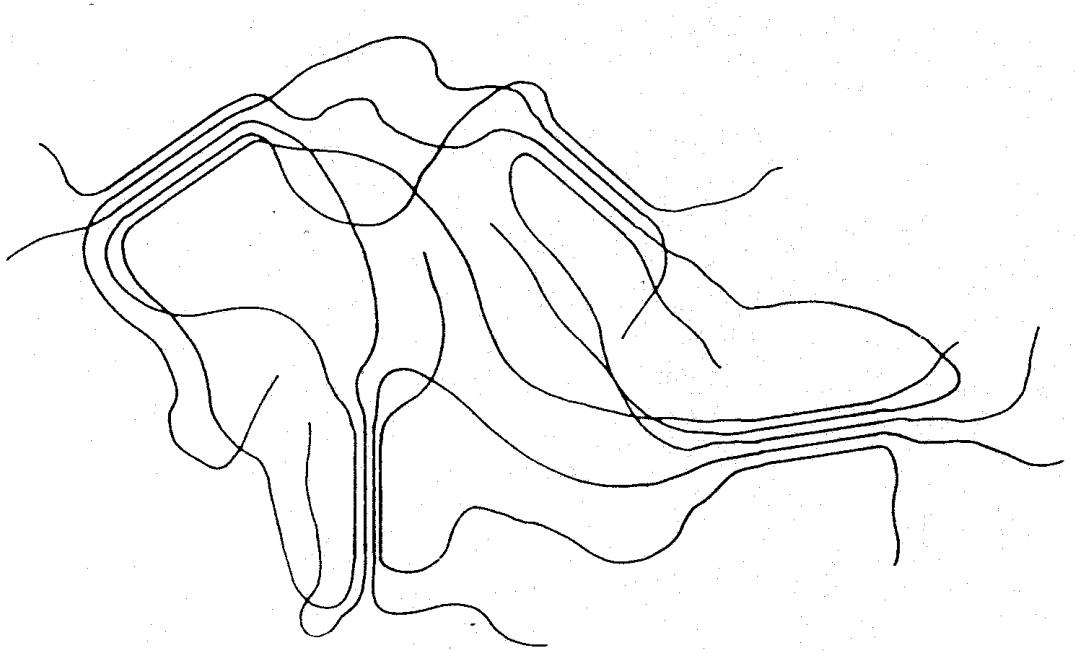
Subsequently, semicrystalline polymers have two different transition points at different temperatures: glass transition ($\mathbf{T_g}$) and melting point ($\mathbf{T_m}$).因此，半结晶聚合物在两种不同温度下有相变点：玻璃态转变温度（Tg）和熔点（Tm）

e. g. poly(L-lactide)如聚（L-丙交酯）：

$T_g$ = ~ 60 ° C

$T_m$ = 185 ° C

# Semicrystalline Polymers
# 半结晶聚合物



Amorphous and crystalline phases in semicrystalline polymers (schematic)

半结晶聚合物中的无定形和结晶区域(示意图）

# Tg and Tm

| Polymer | Tg | Tm |
|---|---|---|
| RESOMER L 206 S | 60 - 65 °C | 180 - 185 °C |
| RESOMER L 207 S | 60 - 65 °C | 180 - 185 °C |
| RESOMER L 209 S | 60 - 65 °C | 180 - 185 °C |
| RESOMER L 210 | 60 - 65 °C | 180 - 185 °C |
| RESOMER L 210 S | 60 - 65 °C | 180 - 185 °C |
| RESOMER LR 704 S | 56 - 62 °C | amorphous |
| RESOMER LR 706 S | 56 - 62 °C | amorphous |
| RESOMER LR 708 | 56 - 62 °C | amorphous |
| RESOMER LC 703 S | 32 - 42 °C | amorphous |
| RESOMER LG 824 S | 54 - 60 °C | amorphous |
| RESOMER LG 857 S | 57 - 63 °C | amorphous |
| RESOMER RG 509 S | 46 - 52 °C | amorphous |

# Tg and Tm

| Polymer | Tg | Tm |
|---|---|---|
| RESOMER RG 502 / H | 42 - 46 °C | amorphous |
| RESOMER RG 503 / H | 44 - 48 °C | amorphous |
| RESOMER RG 504 / H | 46 - 50 °C | amorphous |
| RESOMER R 202 S | 38 - 42 °C | amorphous |
| RESOMER R 202 H | 46 - 50 °C | amorphous |
| RESOMER R 203 S | 46 - 50 °C | amorphous |
| RESOMER R 203 H | 48 - 52 °C | amorphous |
| RESOMER RG 752 S | 44 - 50 °C | amorphous |
| RESOMER RG 753 S | 44 - 50 °C | amorphous |
| RESOMER RG 755 S | 48 - 54 °C | amorphous |
| RESOMER RG 756 S | 49 - 55 °C | amorphous |

# Degradation Times Approximate!大致的降解时间

| Polymer<br>聚合物 | Degradation Time<br>降解时间 |
|---|---|
| Poly(L-lactide) 聚（L-丙交酯） | |
| Resomer® L | |
| Lakeshore Biomaterials™ 100 L | > 3 y |
| Poly(L-lactide-co-DL-lactide)聚（L-丙交酯-共-DL丙交酯） | |
| Resomer® LR | 2.5 y |
| Poly(DL-lactide-co-glycolide)聚（DL-丙交酯-共-乙交酯） | |
| Resomer® RG | |
| Lakeshore Biomaterials™ DLG | 3 m – 1 yr |

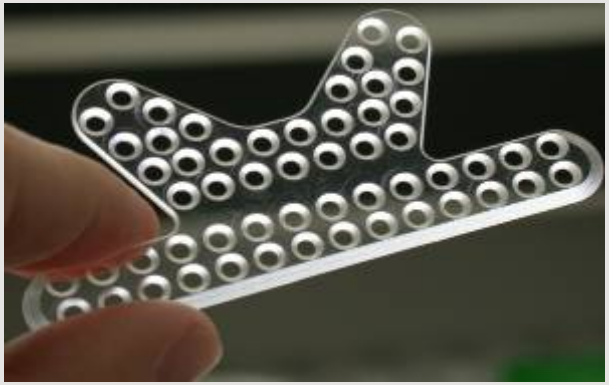
# Examples for Medical Devices医疗器械应用实例

| Manufacturer | Product Name | Material | MW kD (IV) | Sterilized | Absorption time (months) |
|---|---|---|---|---|---|
| Arthrex | Soft Tissue Fastner | PLA | | | |
| Bionx | Smart Pins | SR PGA | 10 | ETO | 12 |
| DePuy | Tissue Fixation Screw | PLLA | 520-600 | Gamma | 36-60 |
| JNJ | Orthosorb Pin | PDO | | ETO | 6 |
| Arthrex | Bio-interference Screw | PLLA | (IV 3.2) | ETO | |
| Linvatec | BioScrew | PLLA | | ETO | 36-60 |
| Smith&Nephew | Bioresorbable Interface Screw | PLA | | | |
| Bionx | Bankart Tack | SR PLLA | 45-65 | Gamma | 36-60 |
| Bionx | Smart Anchor | SR PDLL | 35-50 | Gamma | 30 |
| Innovasive Devices | BioROC EZ 2.8 mm | PLLA | | ETO | No wt loss after 18 mo. |
| Mitek | Panalok | PLLA | 100-125 | ETO | 24-48 |
| Smith&Nephew | Absorbable Suture Anchor | PLLA | | | |
| Surgical Dynamics | SD Sorb Suture Anchor | 82:18 PLG | 100 | ETO | 12-15 |
| Zimmer | Bio-Statak | PLLA | 200-300 | Gamma | 36-60 |
| Biomet | LactoSorb | 82:18 PLG | 40-100 | ETO | 9 - 15 |
| Bionx | Meniscus Arrow | SR PLLA | 45-65 | Gamma | 18-30 |



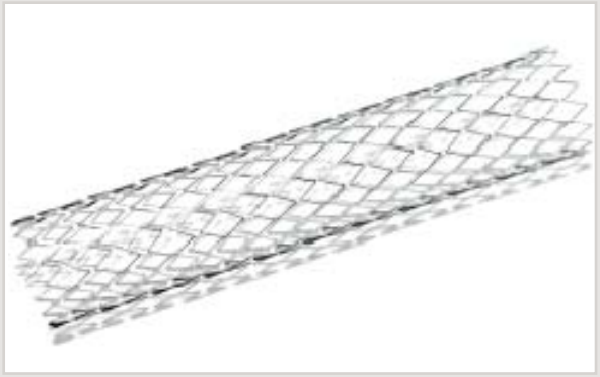
Source: Barber Orthopedic Special Edition 4(3), 1998

# Examples Medical Devices
# 医疗器械应用实例



CMF plate CMF板

Staple 夹

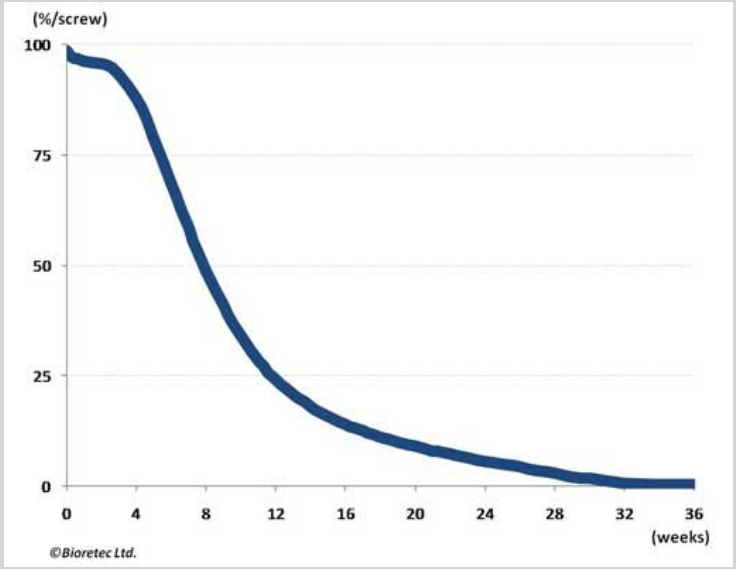


Coronary stent 冠状支架

Interference screw 界面螺钉

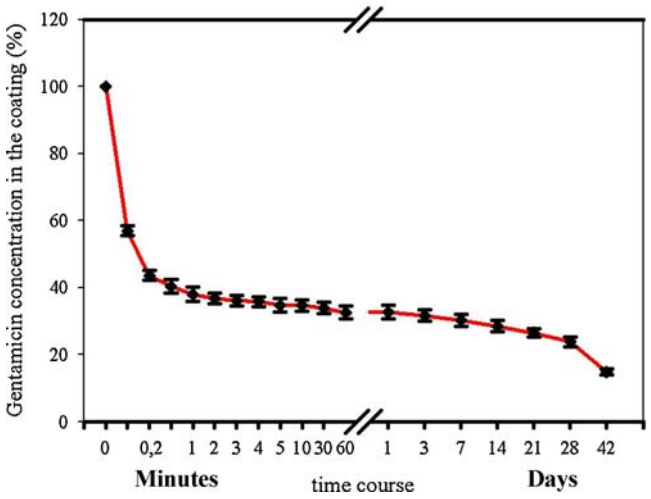
# Drug Eluting Fixation Device
# 载药固定器械 Bioretec

*CiproScrew™*

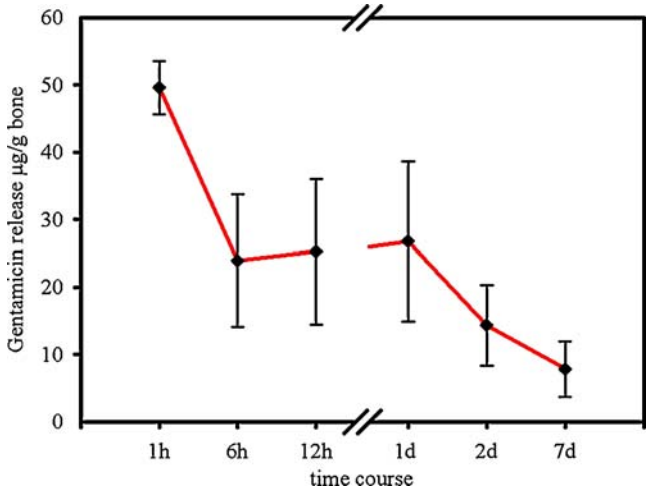



Release profile of ciprofloxacin from the *CiproScrew™* implant in vitro.
环丙沙星从CiproScrew植入装置中体外释放曲线

# Antibacterial Coatings
# Prophylaxis for Implant-Related Infections
# 抗生素包衣预防植入后相关反应




**Gentamicin release in vitro over a period of 42 days.**
庆大霉素体外释放超过**42**天

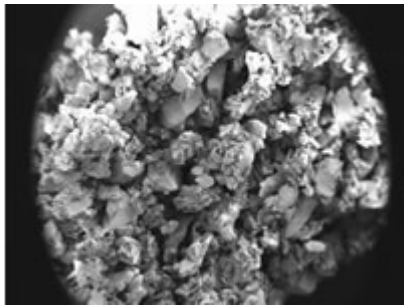


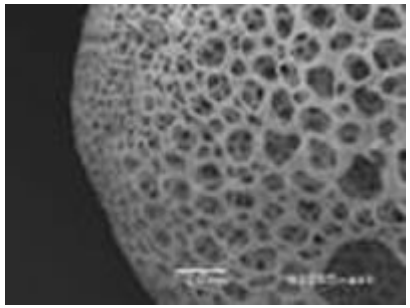

**Bone concentration of gentamicin in vivo over the observation period of 7 days.**
体内在骨中检测到庆大霉素持续**7**天

Antibiotic-coated tibial nail marketed by ***Depuy-Synthes*** impedes bacteria from adhering to the implant surface and producing biofilms. The polyester coating releases high doses of antibiotics higher than in systemic application.
由***Depuy-Synthes***生产上市的抗生素包裹胫骨钉阻止了细菌在植入剂表面和产生的生物包膜处生长。采用聚酯包裹后可以释放比系统给药更高浓度的抗生素。

Vester *et al.*, Injury, *Int. J. Care Injured* **41** (2010) 1053–1059

# Regenerative Orthopedics
# RegenTec 再生骨科





Injectable polymer scaffold可注射聚合物矩阵

- Space-filling material 中空材料
- Support natural bone repair processes 支持自然的骨修复过程
- Deliver patient's own bone progenitor cells 传递患者自身的成骨细胞
- Controlled release of orthobiologicals
- 骨生物物质控释
- Stem cell therapies
- 干细胞治疗

# Processing工艺

Injection Molding注塑成型

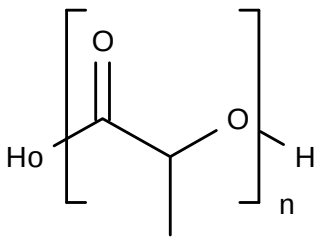
Compression Molding挤压成型

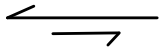
Melt Extrusion 热熔挤出

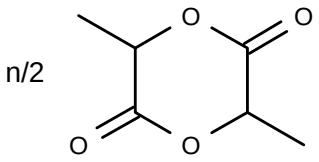
Each process transforms polymer resin in the form of pellets or granules to a finished part by applying heat and mechanical force.
每种工艺均可以通过热或机械力将聚合物由球丸状或颗粒状塑型成最终的形态

Polyesters are designed to degrade thus processing must be controlled to limit loss of molecular weight!
由于聚酯材料在设计时就是为了能够降解的，因此在工艺中必须将分子量的损耗限定在最低。

# Influence of Residual Monomers残留单体的影响





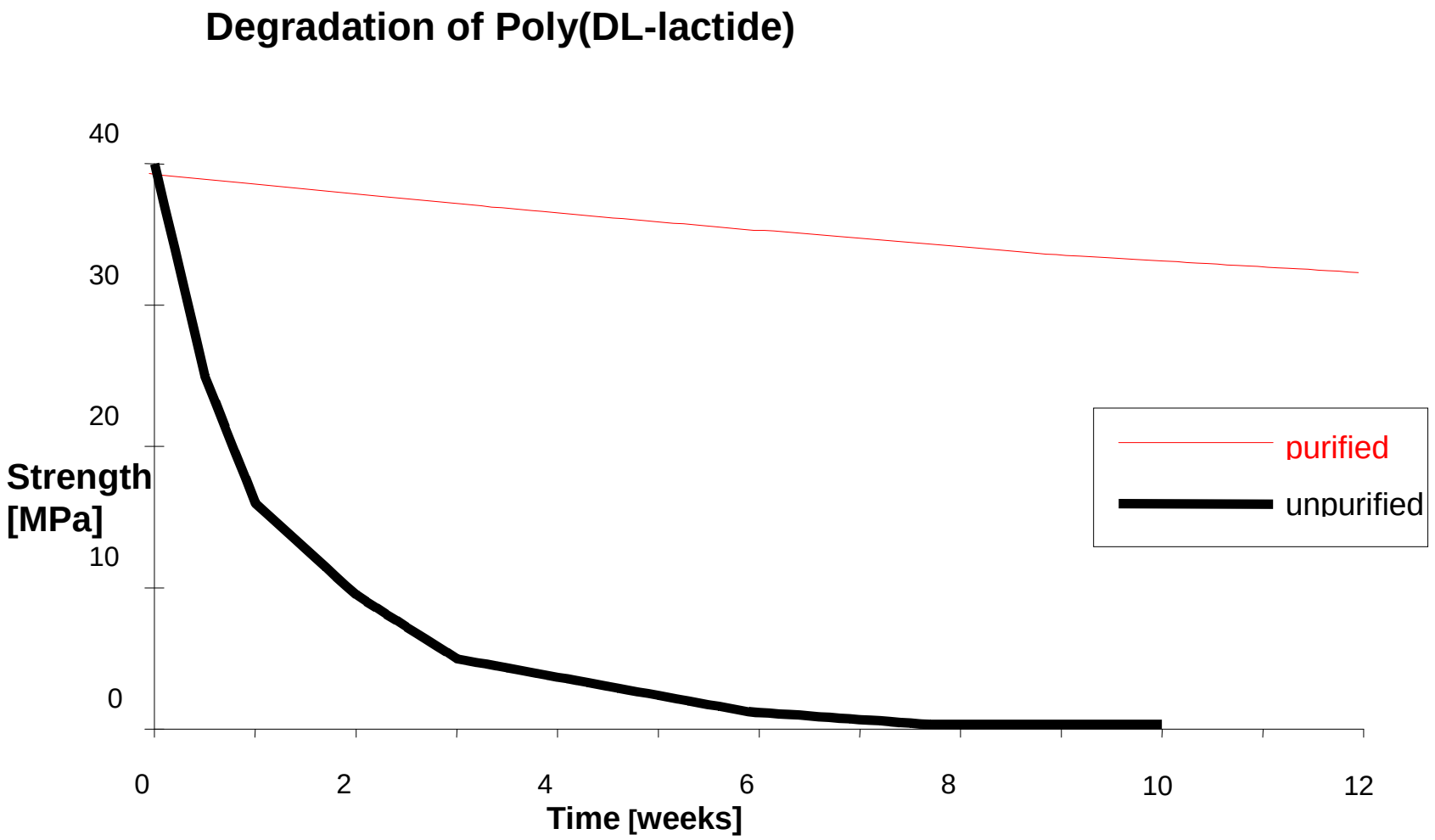

equilibrium monomer concentration: ~ 1 - 5 %

平衡单体浓度：**1-5%**

**Impact of impurities can be loss of molecular weight during processing and accelerated loss of mechanical strength**

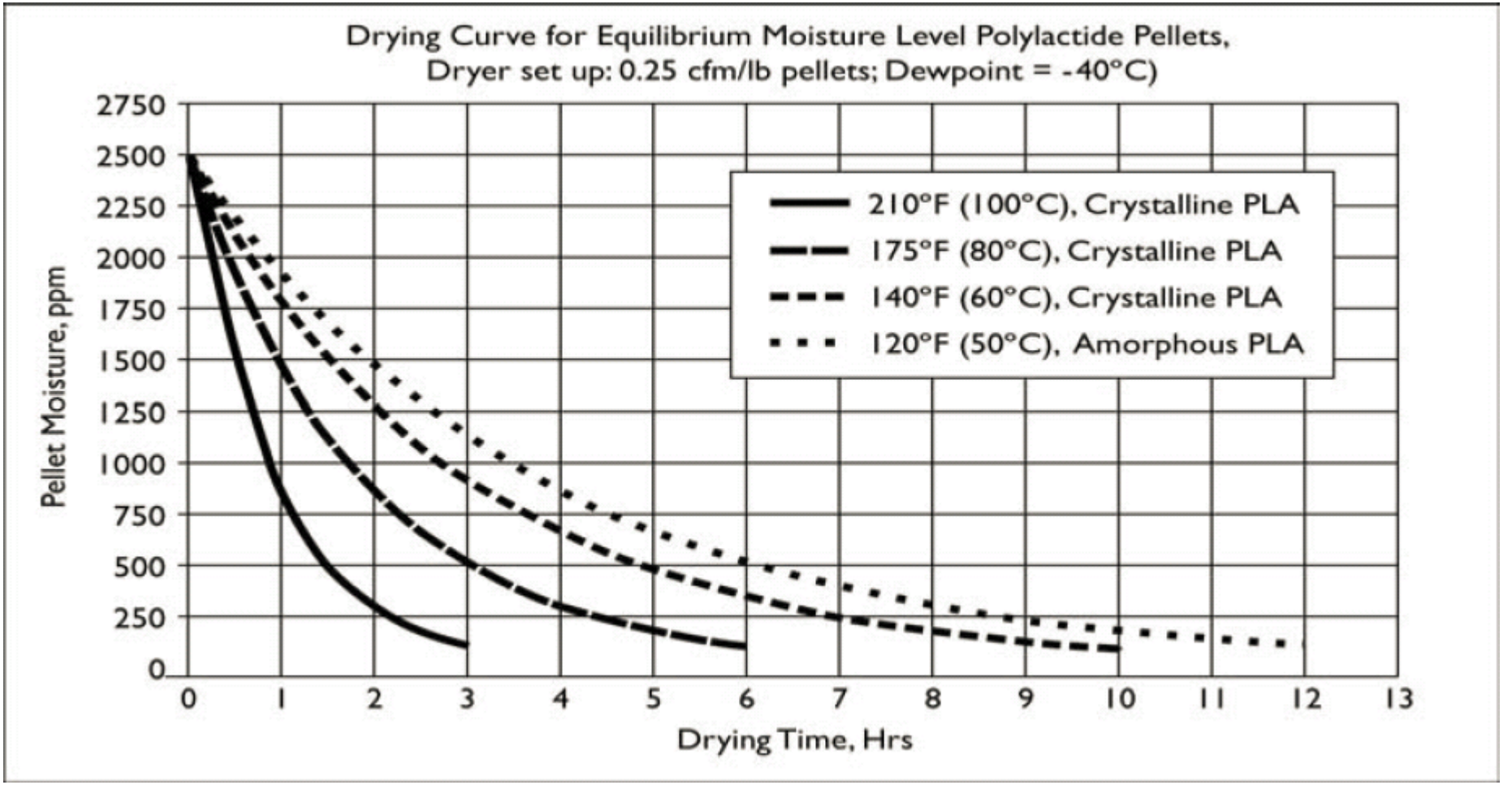
杂质可能导致工艺过程中分子量的损失，以及机械强度的加速下降

# Influence of Residual Monomers
# 残留单体的影响




Source: Fambri et al., 12th European Conference on Biomaterials, Porto, 1995

# Processing 工艺过程



# Sterilization灭菌

**γ-irradiation** has the disadvantage of lowering the molecular weight of the part due to the high energy content. But it is the standard method in the medical device industry and it is cost effective.

Y-射线的缺点是分子量的降低，部分是由于其极高的能量，但是这是在医疗器械领域中标准的方法，并且经济。

**E-beam** is a new method and up to now not often used. It seems to be more favorable due to its lower energy. The loss of molecular weight is reported to be smaller compared to γ-irradiation.

E-beam是一种新的方法，并没有被普遍使用，这种方法由于其能量较低可能更加适用。研究表明聚合物分子量的降低要小于Y射线

**Gas sterilization** with ethylene oxide is much gentler for the part, but degassing may require two to three weeks. Ethylene oxide is very toxic and can plasticize polyesters.

环氧乙烯气体灭菌是一种温和的方式，但是需要2-3周的时间将气体抽走。环氧乙烯是一种剧毒气体，而且有塑化聚酯的作用

# Effect of Sterilization on IV灭菌效果

| | Resin | Molded | Post γ-Sterilization |
|---|---|---|---|
| LR 706 | 3.6 | 3.0 | 1.5 |
| LT 706 | 1.4 | 1.4 | 1.1 |
| LG 857 | 5.9 | 3.0 | 1.5 |

# Summary总结

**Resorbable polyesters have a long history of use and are very well understood in terms of safety and toxicity**

可吸收聚酯具有很长的应用历史，其安全性和毒性已经被充分的研究

**The performance is determined by chemical composition, molecular weight, monomer sequence, and end groups.**

聚合物的性能由化学组成，分子量，结构单元顺利和末端基团决定的

**Well understood structure/property relationships makes this family of biomaterials useful for a variety of applications including load bearing devices, drug delivery matrices, and tissue engineering scaffolds**

对结构/性能关系的充分认识使这类生物材料被应用于广泛的领域包括载药器械，药物传递矩阵，和组织工程学基质。

**Drug release profiles and rate of degradation can be adjusted to fit many different applications**

药物释放曲线和降解速度可调使其适用用多种用途。

**Thermal processing allows the production of devices as well as carriers for active ingredients**

热塑工艺可用于制备器械和载药。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