Biodegradable Polyesteramide (PEA) Materials – An Elegant Solution to Acidic Microclimate Challenge

CRS 2022 Annual Meeting

Dr. George Mihov
12 July 2022

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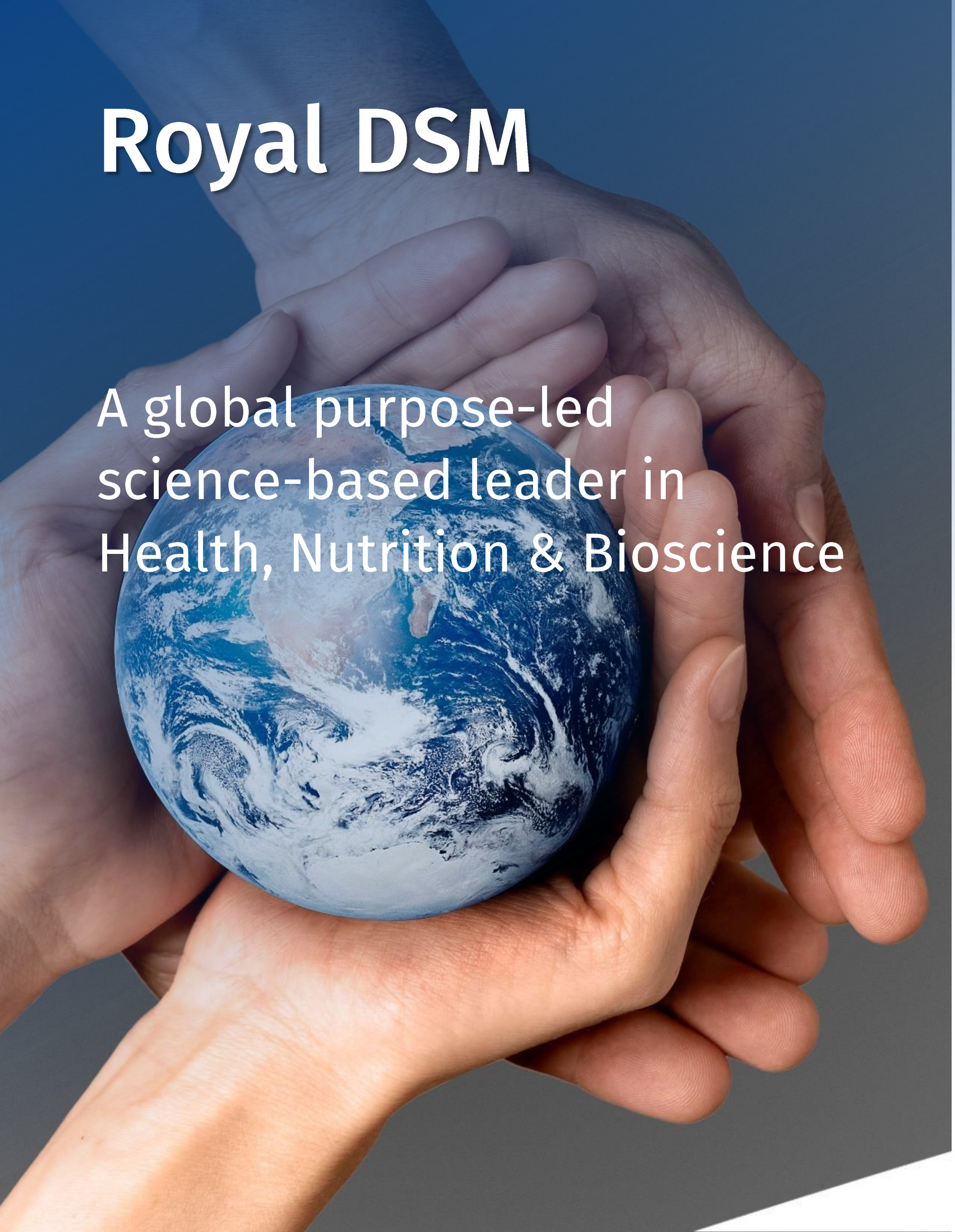
Royal DSM

A global purpose-led science-based leader in Health, Nutrition & Bioscience



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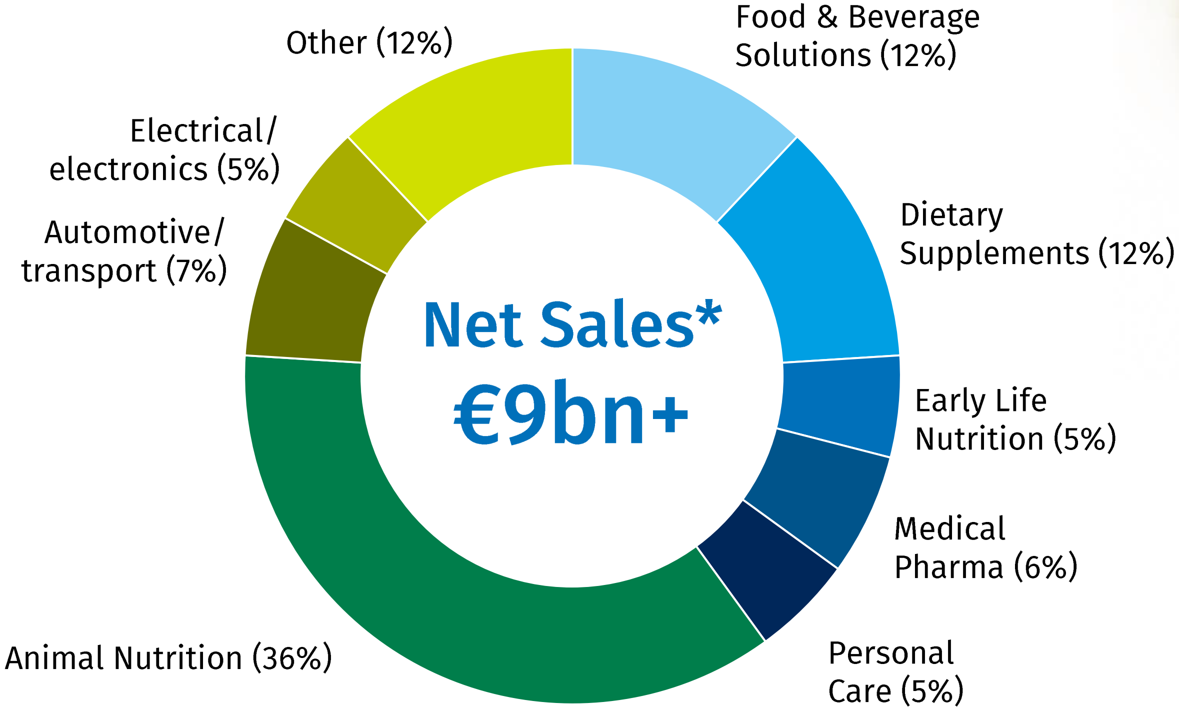

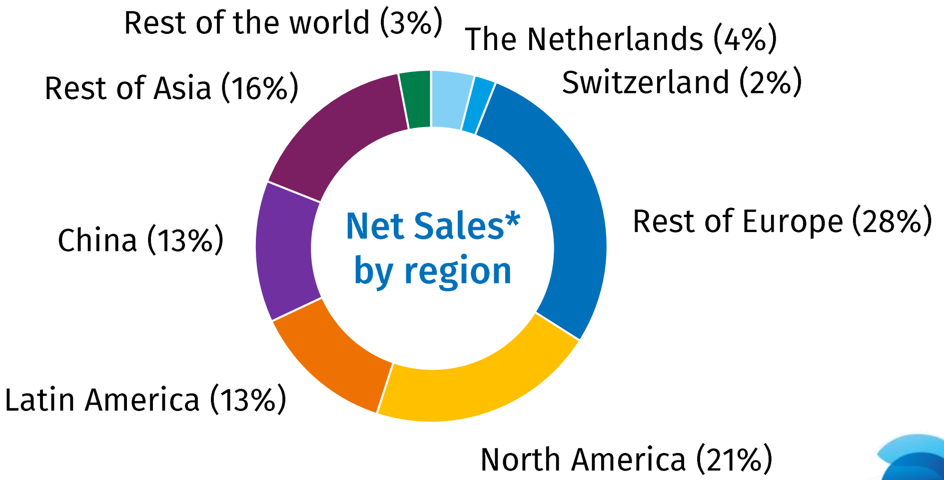

* Based on continuing operations, full year 2021

Three Business Groups with clear end-market orientation

Animal Nutrition & Health

Radically more sustainable animal farming

€3.4bn*

Health, Nutrition & Care

Keeping the world's growing population healthy

€2.5bn*

Food & Beverage

Healthy diets for all through nutritious, delicious and sustainable solutions

€1.3bn*

* Based on 2021 Net Sales

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Taking Biomaterials Further

Transformative biomedical solutions advancing healthcare innovation

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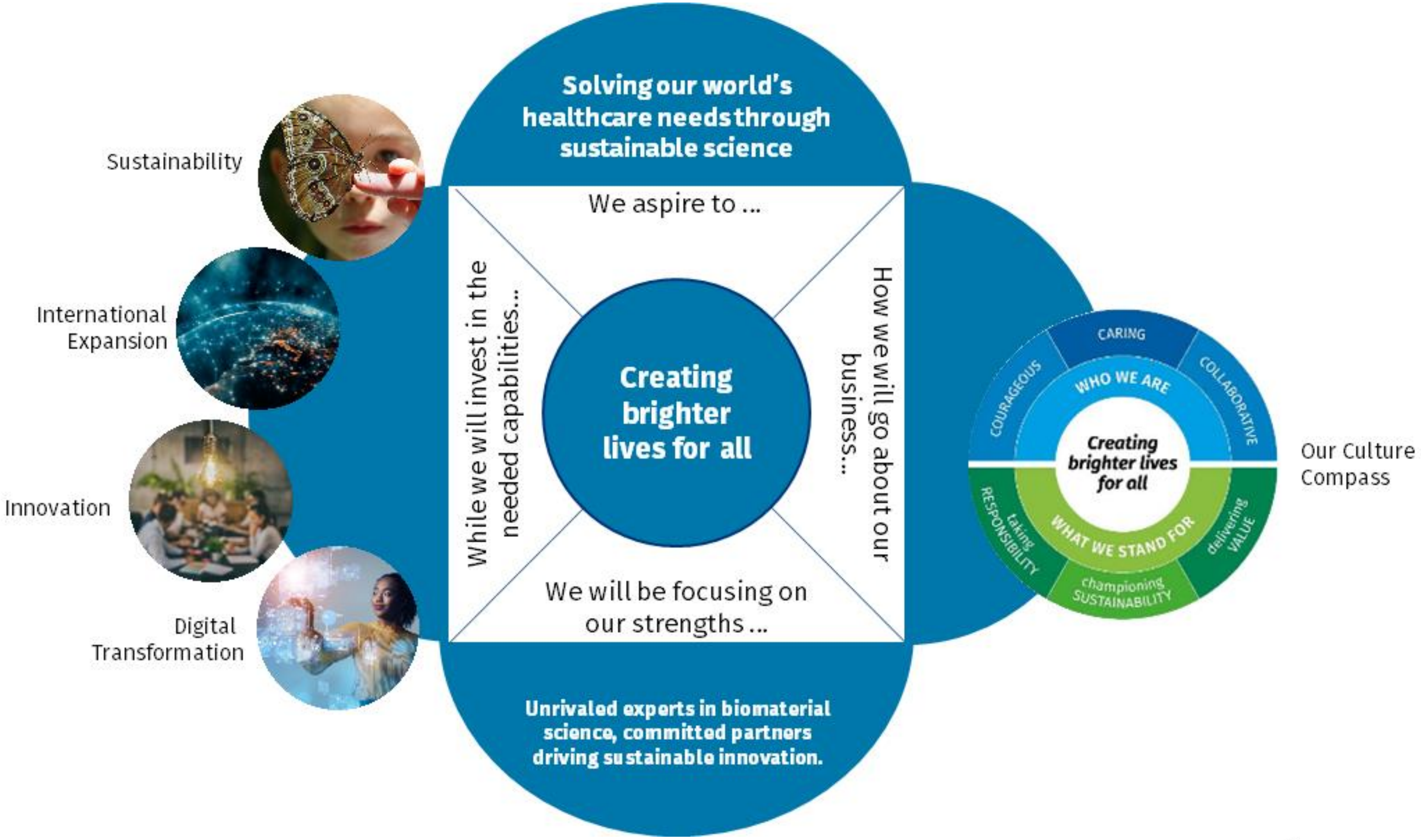
Our strategic priorities

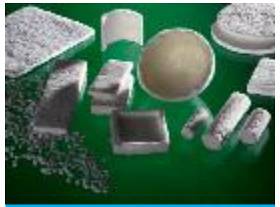


Our extensive biomaterials portfolio

Optimized to meet your needs

Bioceramics

Osteoconductive, osteostimulative and osteoinductive ceramic materials with tunable shapes, porosities, and chemistries



Collagen

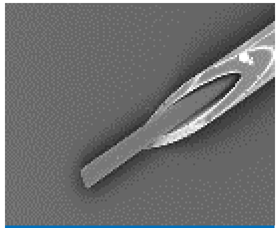
Soluble, fibrillar, and fibrous bovine collagen with a long clinical history, available as a material, component, or device

Polyethylenes

Dyneema Purity® fibers are the strongest and most reliable medical-grade UHMWPE fibers in the world

Cell Concentration

Produce a concentrated solution of cells from blood or bone marrow from the fastest, smallest, and lightest device on the market



Drug Delivery Solutions

Enabling product innovation in sustained drug delivery with the development of customized solutions with tunable properties

Polyurethanes

Implant-grade thermoplastic and thermoset polyurethanes with long clinical history that can be customized for your application

Coatings

Lubricious, hydrophilic ComfortCoat® coatings applied using an industry-leading process with ready-to-use coating reagents, for continence care and vascular intervention applications

Extracellular Matrices

Animal-derived scaffolds with unique handling produced using OPTRIX™ process to preserve the natural matrix and selectively remove antigens

Polymer Processing

Ability to engineer and manufacture products from bioabsorbable polymers, bioinert polymers, and bioceramic composites

Our global therapeutic areas

Orthopedics

- Joint preservation
- Joint reconstruction
- Replacement
- Spine
- Sports medicine
- Trauma

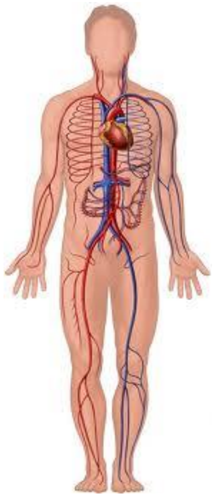
Cardiovascular

- Cardiac Assist
- Cardiac Rhythm Management
- Electrophysiology
- Interventional Cardiology
- Neurostimulation
- Neurovascular
- Peripheral Vascular
- Structural Heart
- Vascular Access
- Vascular Closure

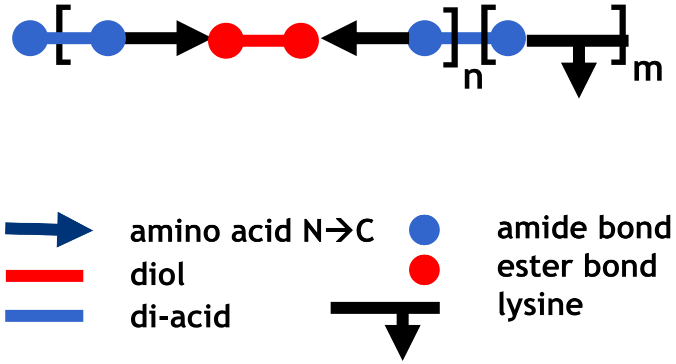
Drug Delivery Solutions

- Ophthalmic
- Oncology
- Pain Management
- Metabolic Disease
- Women's Health
- Viral Management
- Cardiovascular

Drug Delivery Platform

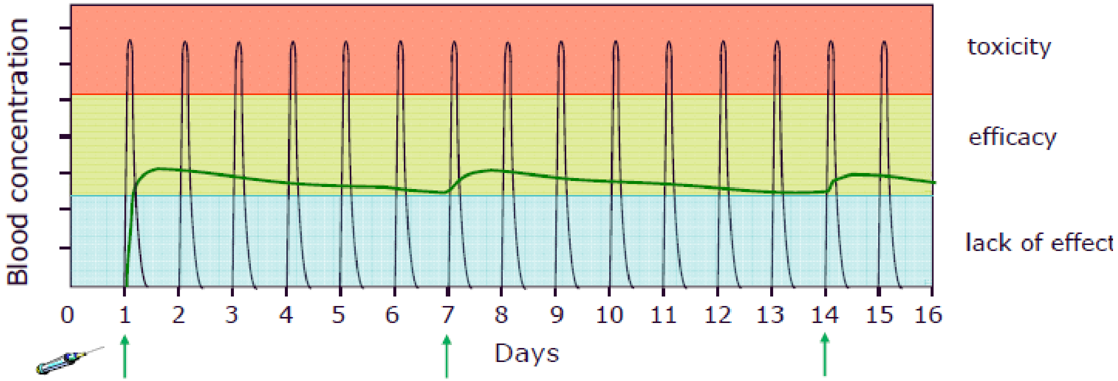


- Novel proprietary biodegradable material platform.
- Experience in extended release solutions for Ophthalmology, Cardiovascular, Pain Management and Musculo-skeletal therapies.
- Dedicated formulation development Team in support of our partners
- Currently the first product is commercially available as biodegradable drug eluting coating on CV stent.



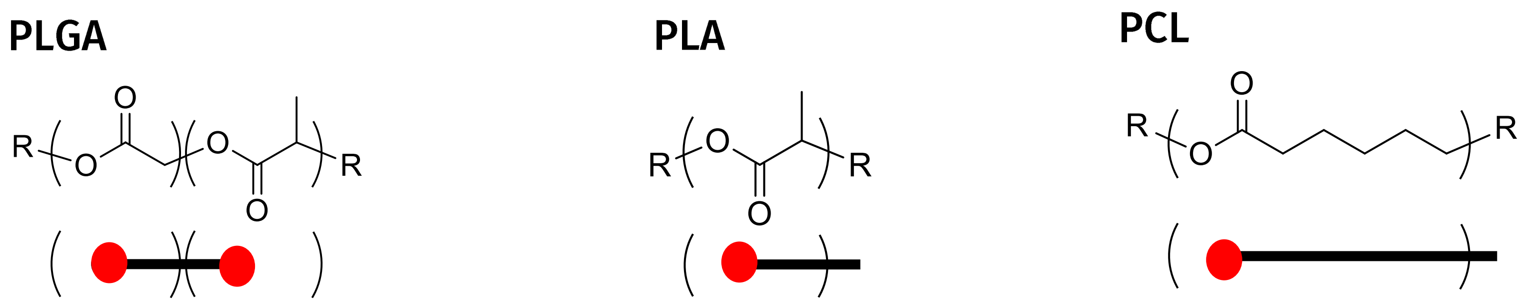
Poly(ester amide) polymer platform

DD competence

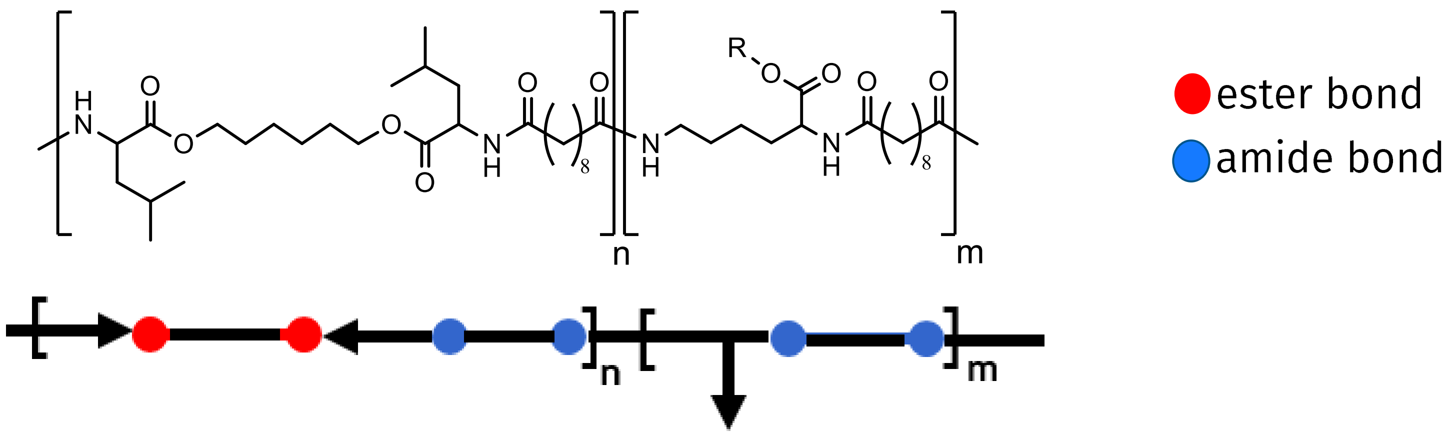


Despite not being an active component, the DD system plays a key role in drug safety and drug efficacy

Traditional Polyesters vs. DSM Biomedical's PEA Platform



Polyesteramides (PEA)



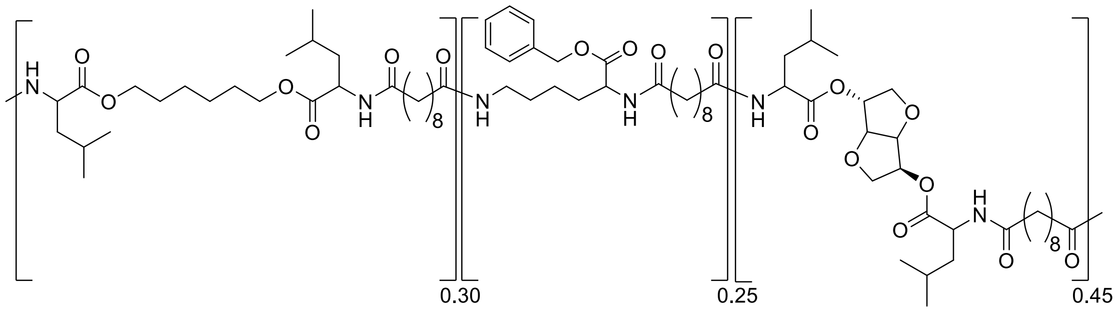
Success in CV Therapy

Svelte® DES technology delivers outstanding clinical results

- Natural building blocks
- Unique degradation mechanism
- Highly biocompatible
- Long-term shelf-life stability
- Optimal adhesion to metal
- Demonstrated coating integrity

- Low late loss, including in diabetes
- Lowest rates ever reported in a US pivotal study through 1 year:
  - ➢ Reintervention at stent site (TLR, 1.5%)
  - ➢ Stent thrombosis (0.38%)
  - ➢ Cardiac death (0.25%)

Commercial in CV applications: PEA III drug eluting stent coating

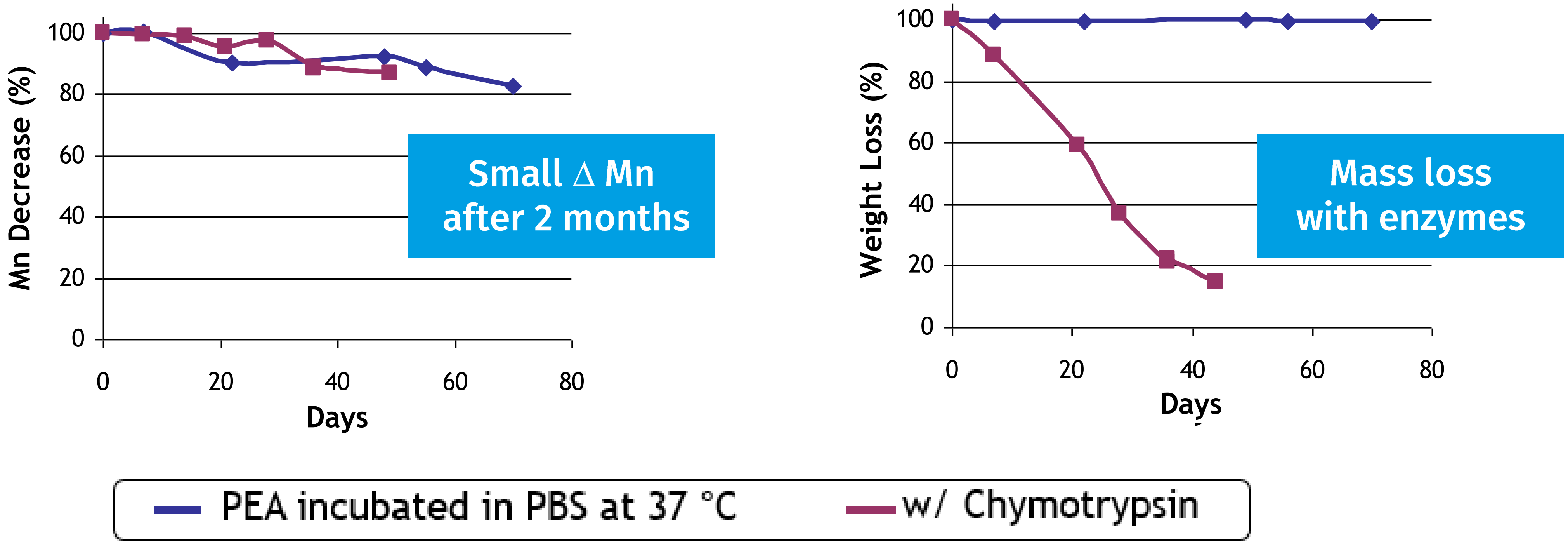


Svelte® Medical Systems OPTIMIZE Study

Source: http://www.sveltemedical.com/outcomes/des-clinical-trials/

Polyesteramides Unique Degradation

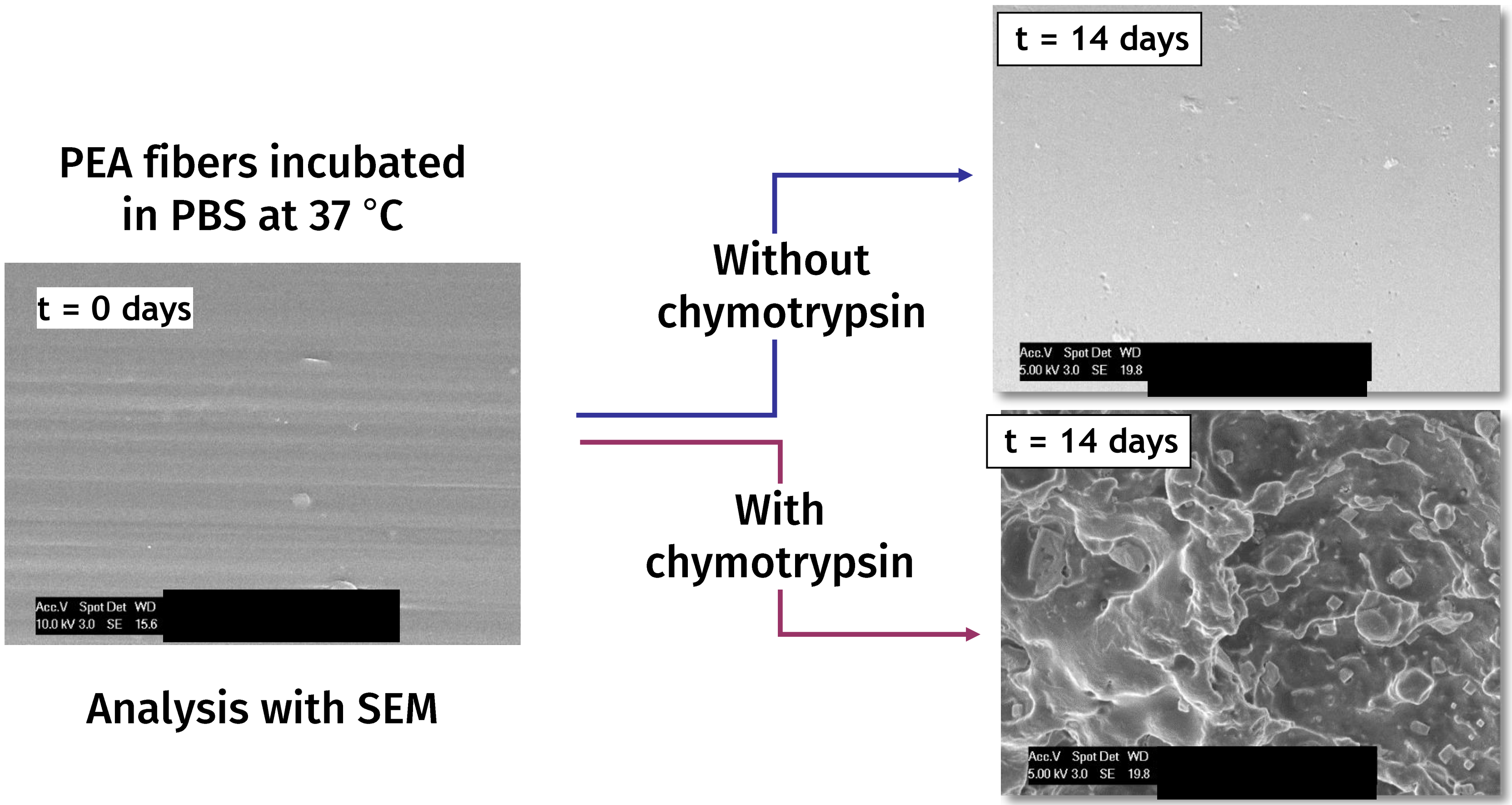
Hydrolytic vs. Enzymatic



Biodegradable material of unique hydrolytic stability degrading by enzyme-mediated surface erosion mechanism

Polyesteramides Unique Degradation

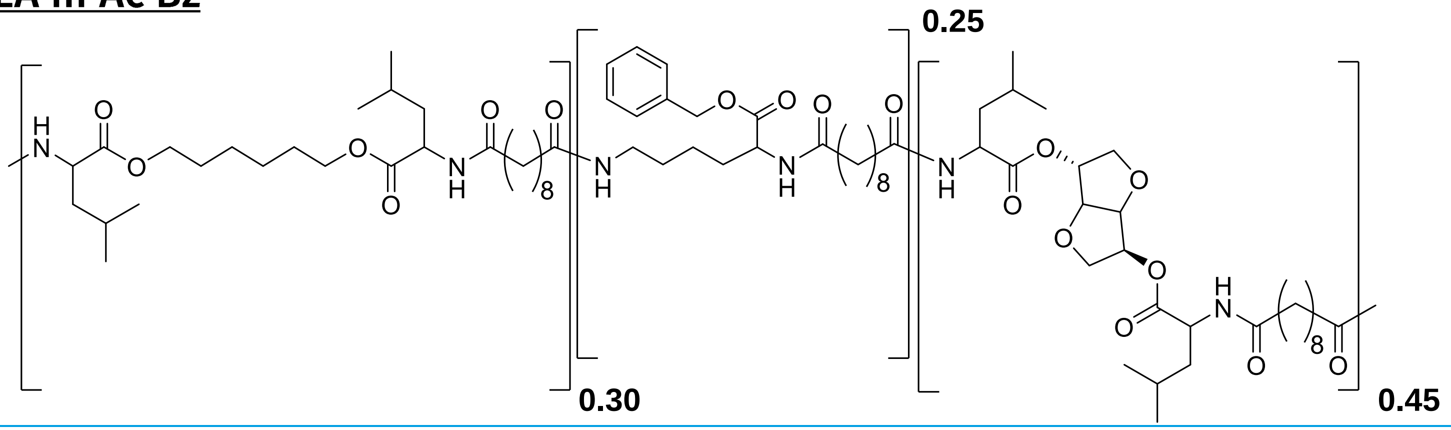
Surface Erosion Demonstrated



Inspired by the Challenges of Ophthalmic Drug Delivery

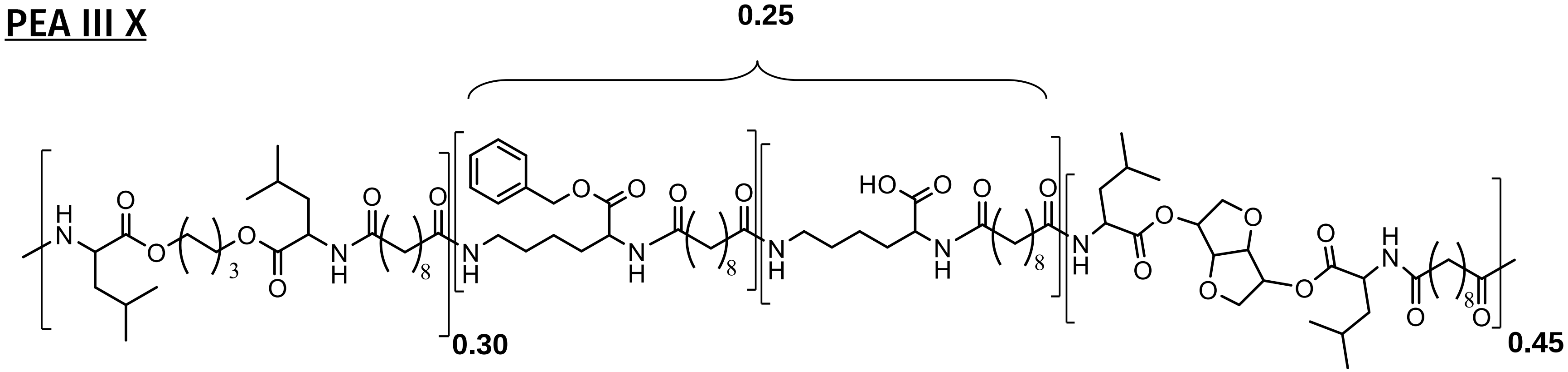
Structural Control on Degradation Mechanism

PEA III Ac Bz



Enzymatically degradable

PEA III X

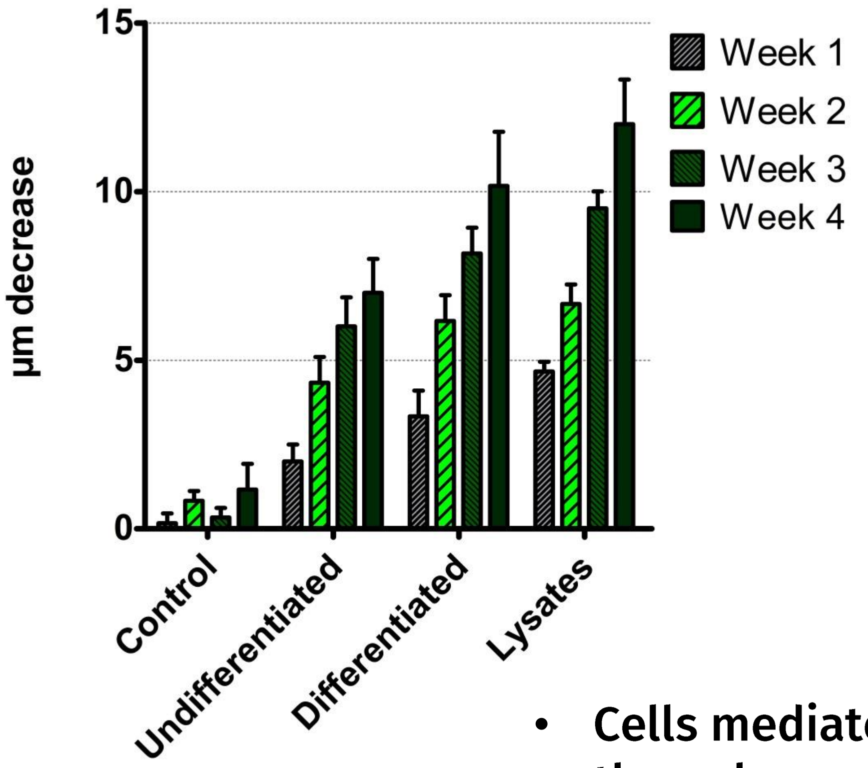


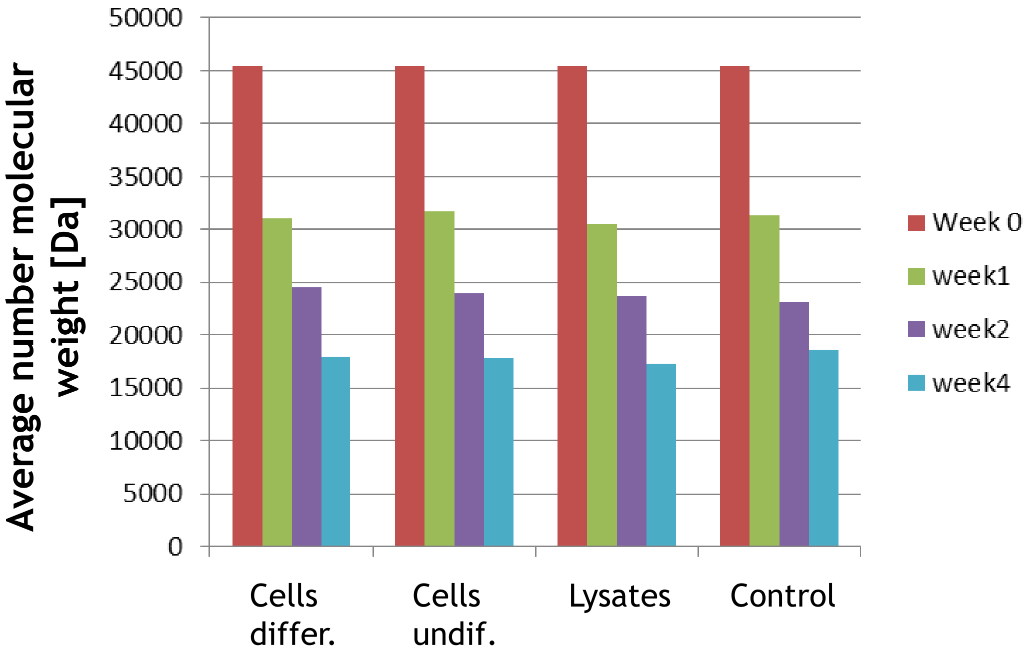
Hydrolytically degradable

Enzymatic and hydrolytic degradation of PEA polymers

Neutrophiles-mediated Degradation (Thickness and Mn change)

PEX III X50 (n=3)

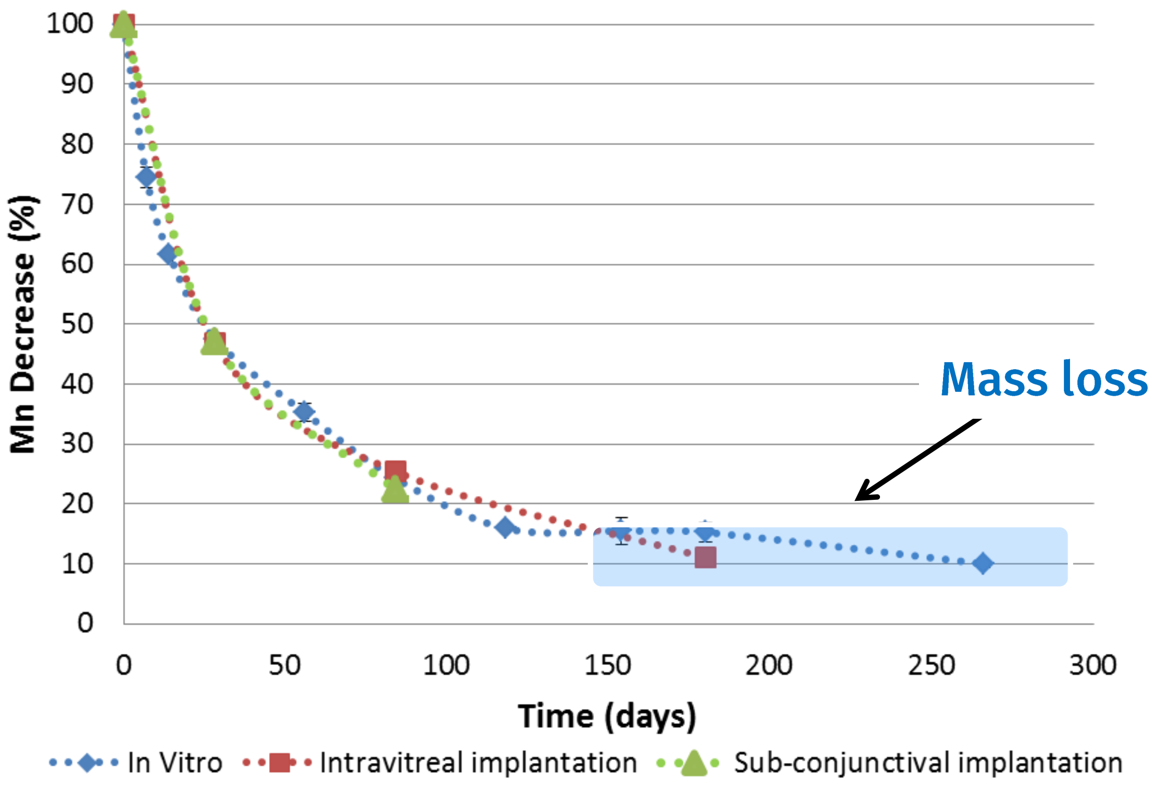




- **Cells mediated degradation occurs at the polymer surface**
- **Water hydrolysis dominates in the polymer bulk**

Polyesteramides *In-Vivo* Degradation

Ocular Degradation of PEA-X in a Rabbit Model

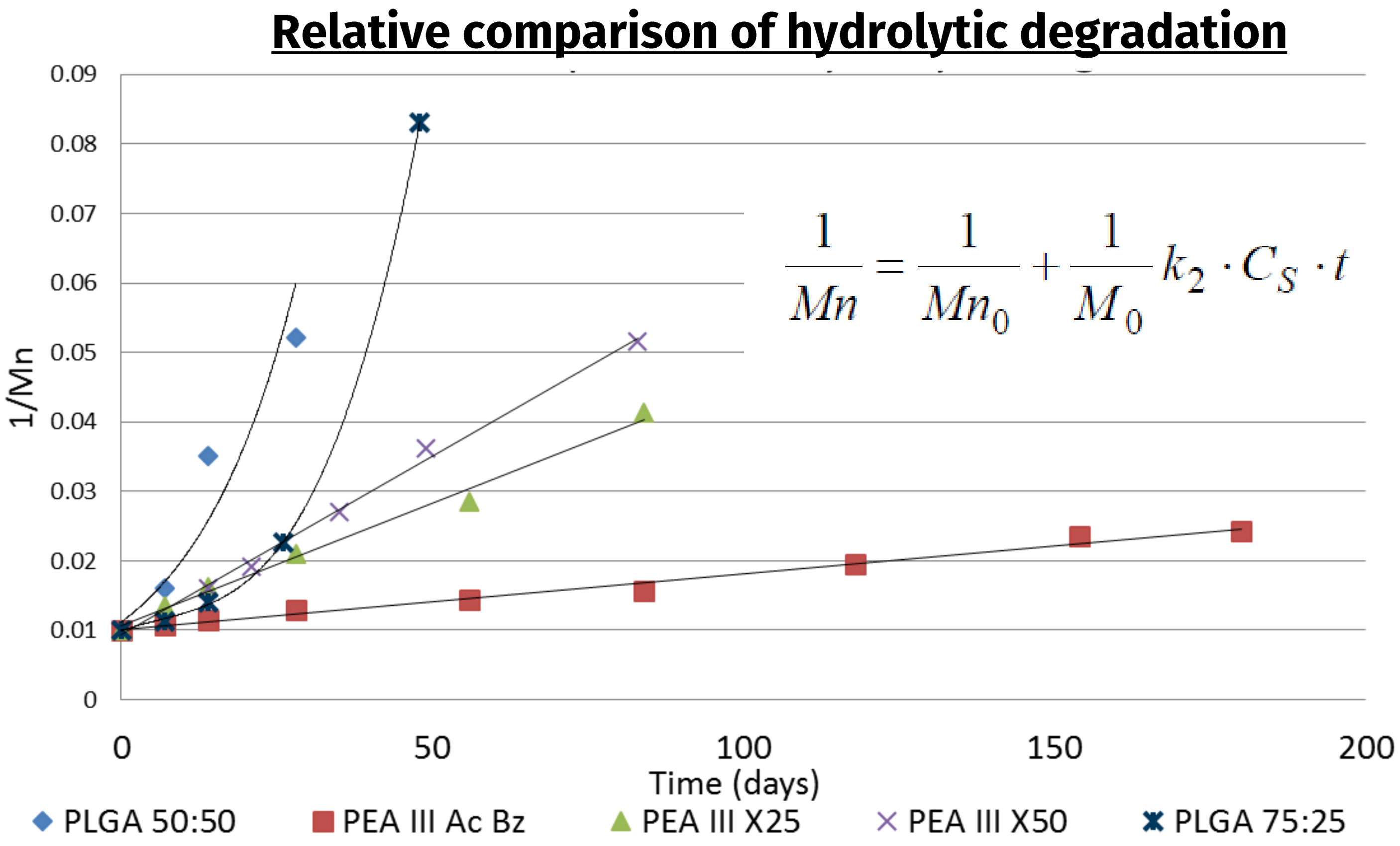


Slow hydrolytic PEA-X degradation

Good correlation to in vitro results up to 180 days

Fiber diameter ≈ 200µm
Fiber contains a fluorescent dye

Degradation Kinetics of PEAs

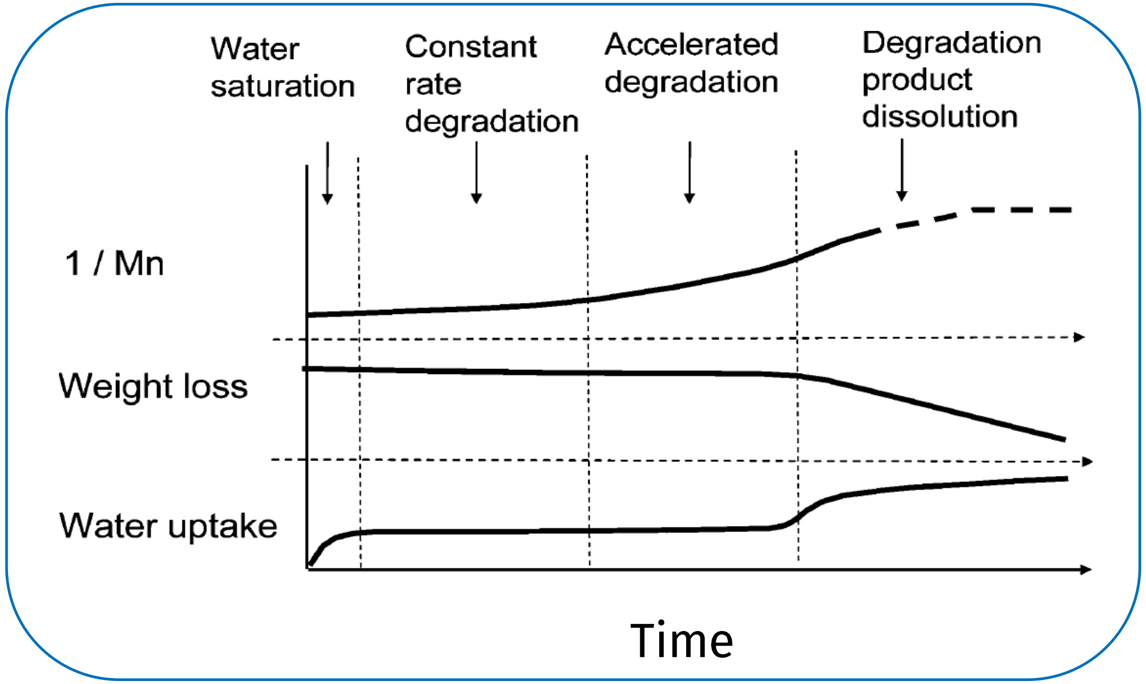


$$\frac{1}{Mn} = \frac{1}{Mn_0} + \frac{1}{M_0} k_2 \cdot C_S \cdot t$$

Surprising behavior of PEAs compared to PLGA

Lyu, S. Untereker, D. Degradability of Polymers for Implantable Biomedical Devices *Int. J. Mol. Sci.* 2009, *10*, 4033-4065

Degradation Kinetics of Polyesters



Second order (non-catalytic):

$$\frac{1}{Mn} = \frac{1}{Mn_0} + \frac{1}{M_0} k_2 \cdot C_S \cdot t$$

- C_s=water conc
- C_b=reactive bond concentration

Third order (auto-catalytic):

$$\log(Mn) = \log(Mn_0) - k_3 \cdot C_B \cdot C_S \cdot t$$

- Mn=number avg molecular weight
- M_0=molecular weight repeating unit
- t=time

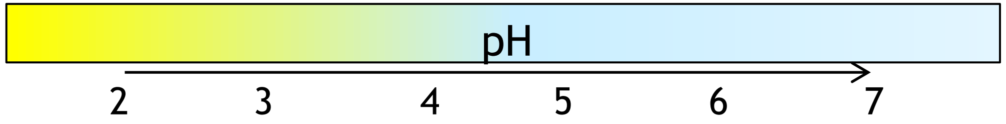
 SuPing Kinetics and Time−Temperature Equivalence of Polymer Degradation *Biomacromolecules*, **2007**, *8* (7), pp 2301-2310

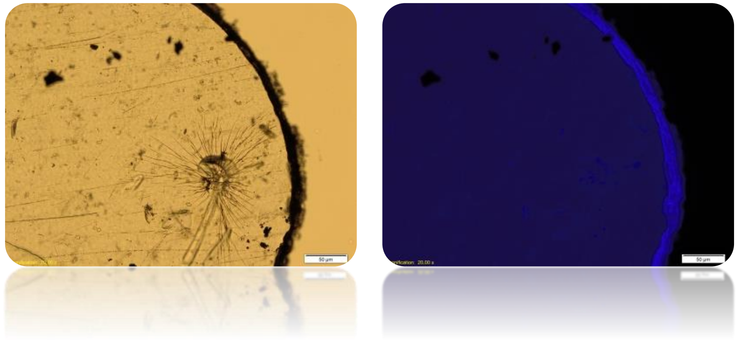
Acidic micro-environment upon PLGA degradation

Case study

Aim:

- To compare the pH inside polymers upon hydrolytic degradation – PEA vs PLGA





Approach:

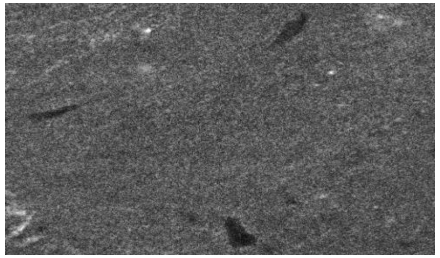
- pH sensitive fluorescent dye
- Melt pressed polymer disks
- Dual photon microscopy

Schwendeman, S., Ding, A., *Acidic Microclimate pH Distribution in PLGA Microspheres Monitored by Confocal Laser Scanning Microscopy*. Pharmaceutical Research, Vol. 25, No. 9, September 2008

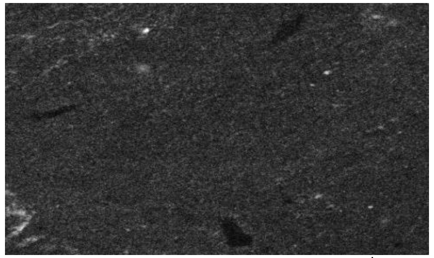
pH Mapping

- Quantification based on image analysis of emission intensity per wavelengths
- Fluorescence lifetime imaging (FLIM)

Emission 450nm

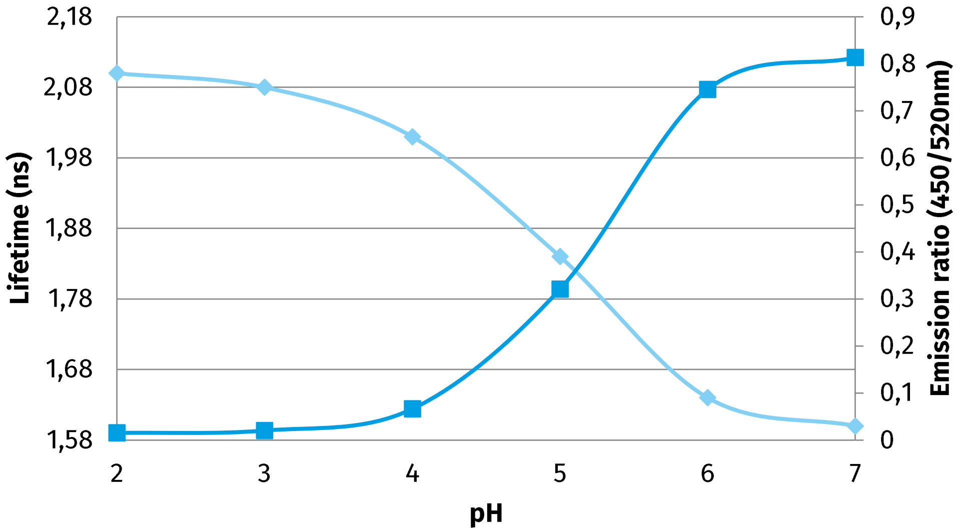


Emission 520nm



$$emission\ ratio = \frac{emission\ 450nm}{emission\ 520nm}$$

Fluorescence as function of pH



Initial pH of the evaluated polymers

Material	Initial pH (ratio)	Initial pH (lifetime)
PEA III Ac Bz	>7	>7
PEA III X25	5-6	~5
Polymer III X50	5-6	~4
PLGA	>7	>7

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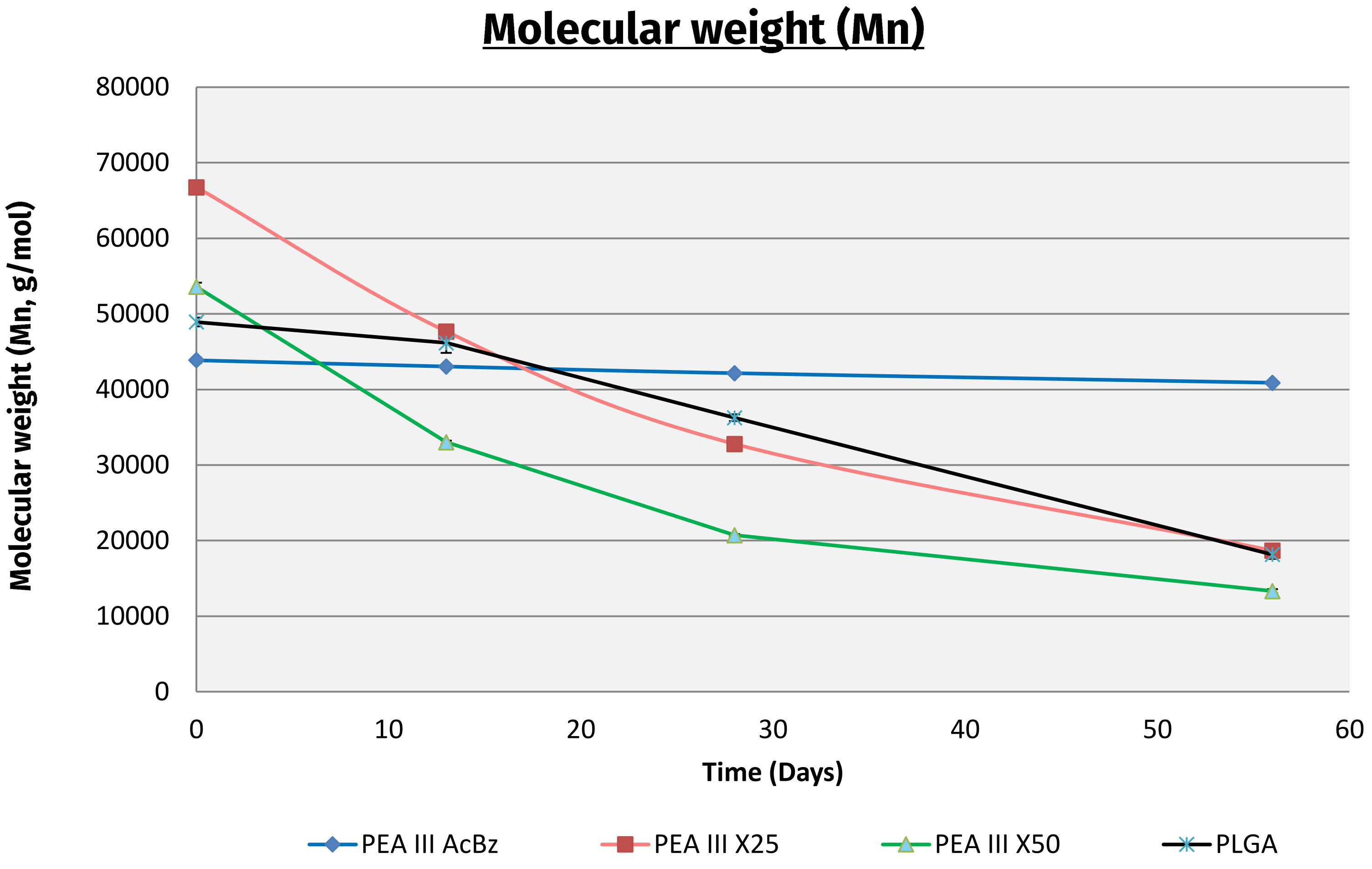
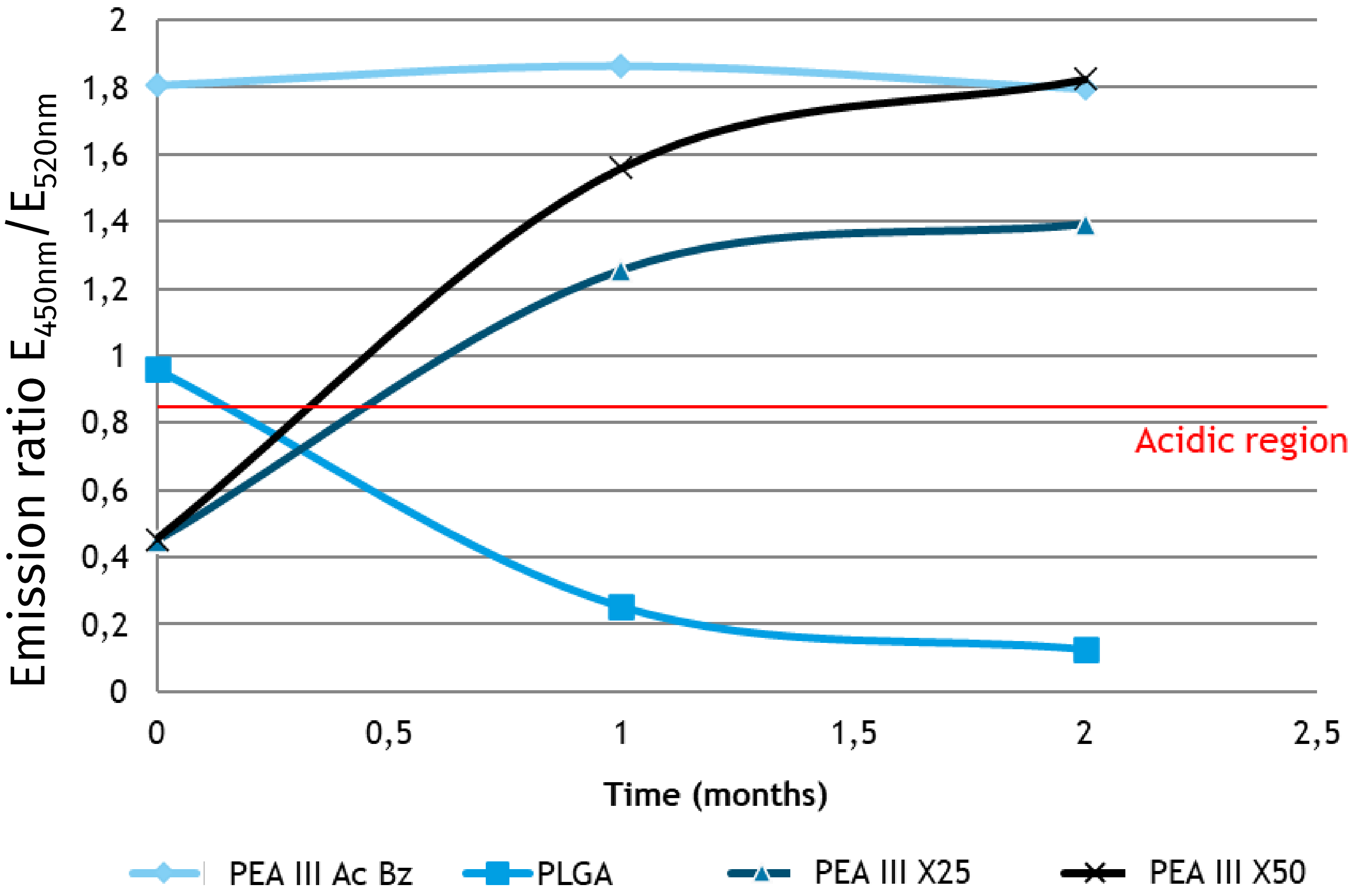
Molecular Weight



- PEA III Ac Bz ‘constant’ molecular weight hydrolytically most stable.
- PEA III X and PLGA gradually decrease in molecular weight.

pH Mapping



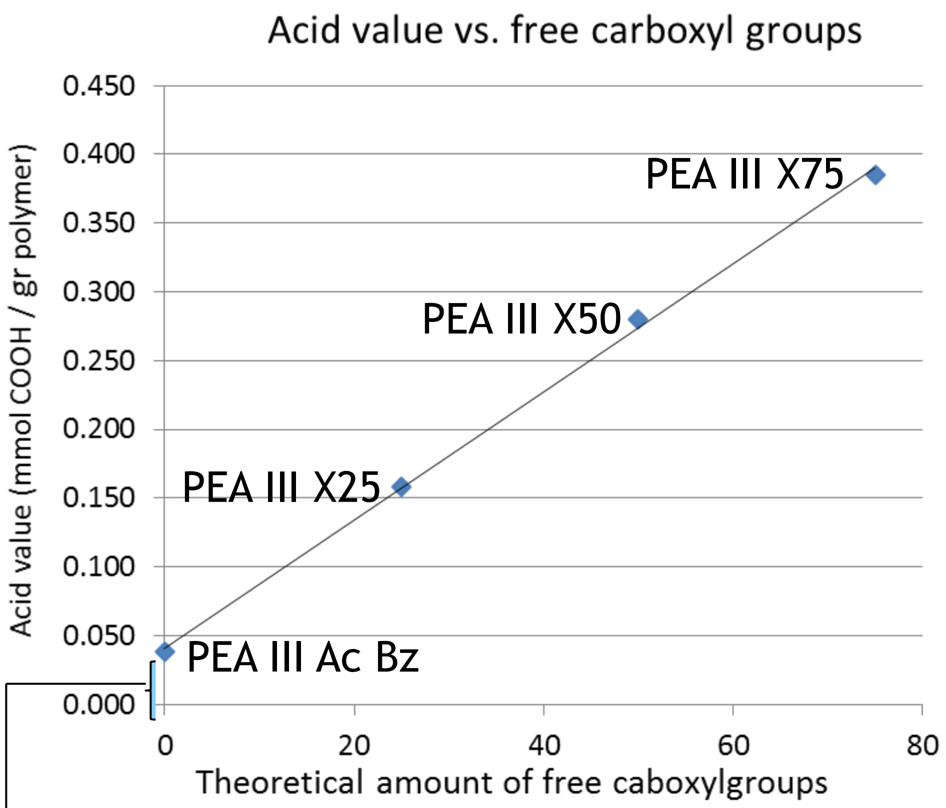
- PLGA shows a drop in pH
- PEA III Ac Bz has a constant pH
- PEA III 25 and 50X go up in pH

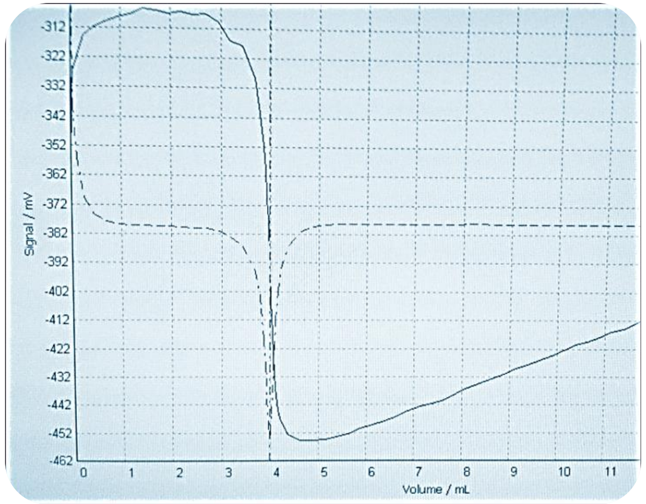
Insights About the Degradation Mechanism

Potentiometric titration

Acid Value (mmol COOH / gr POLYMER)

±140 mg PEA III X50 titration with 0.01 mol/l KOH in methanol.



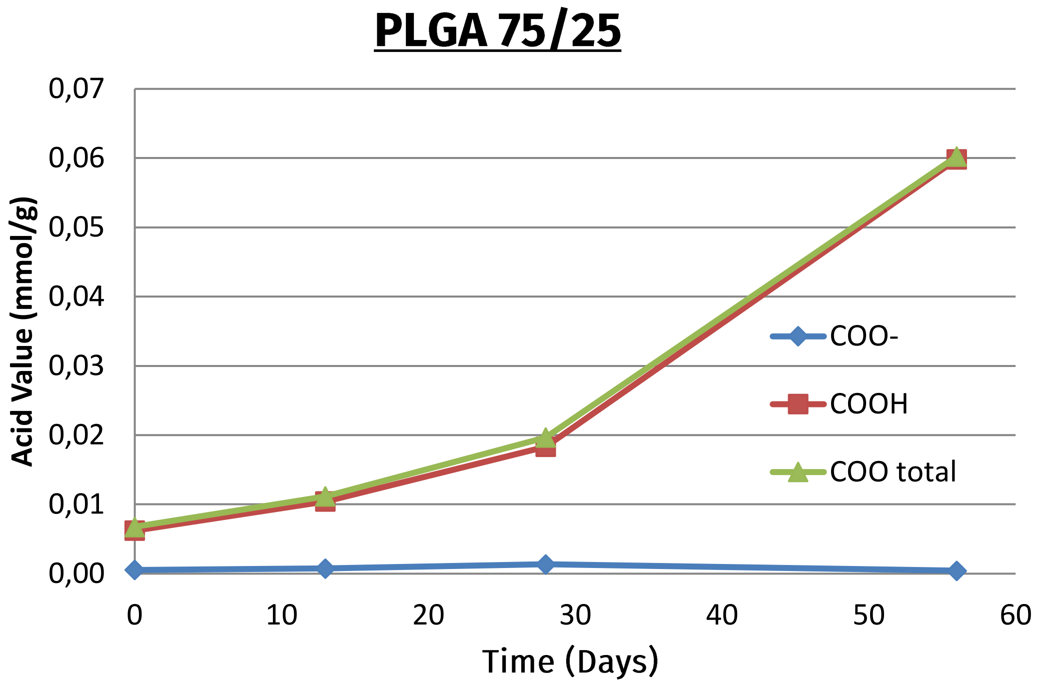


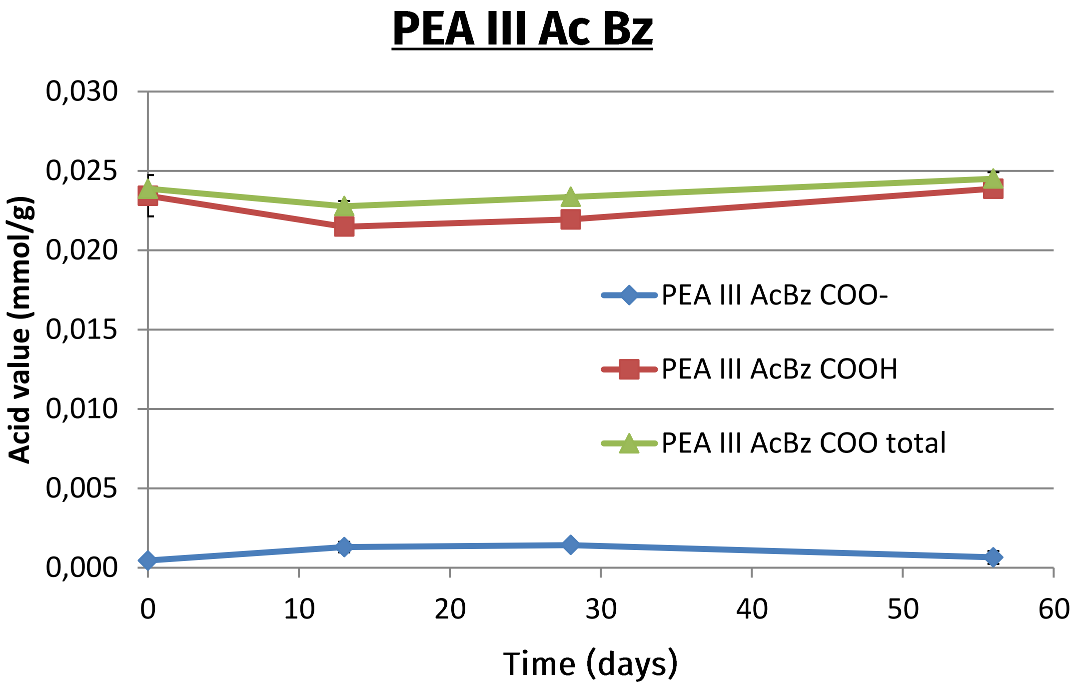
Polymer dissolved in DMSO
0.280 mmol/gr acid
stdev. 0.004 (2%)

Acid groups in PEA III Ac Bz (0.038mmol/g)

→ *About 1 carboxyl group per polymer chain*

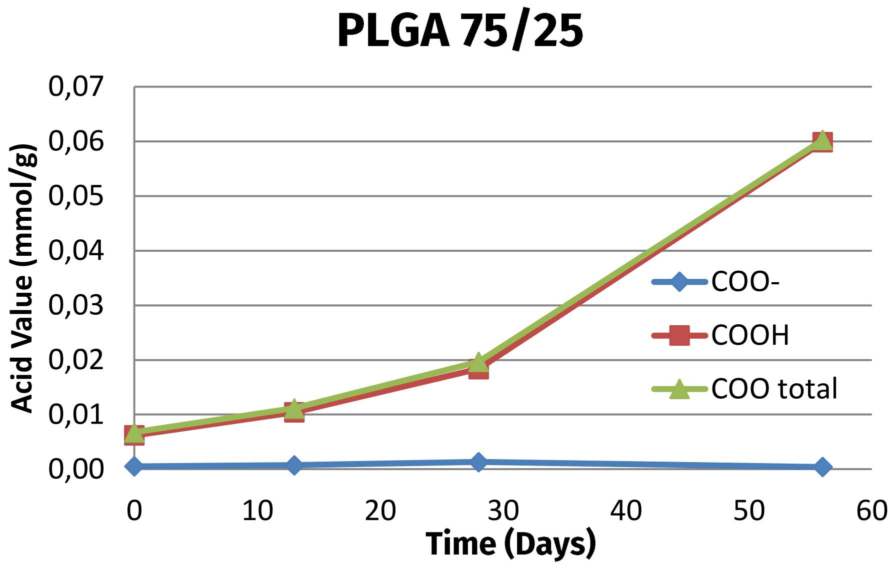
Acid Values

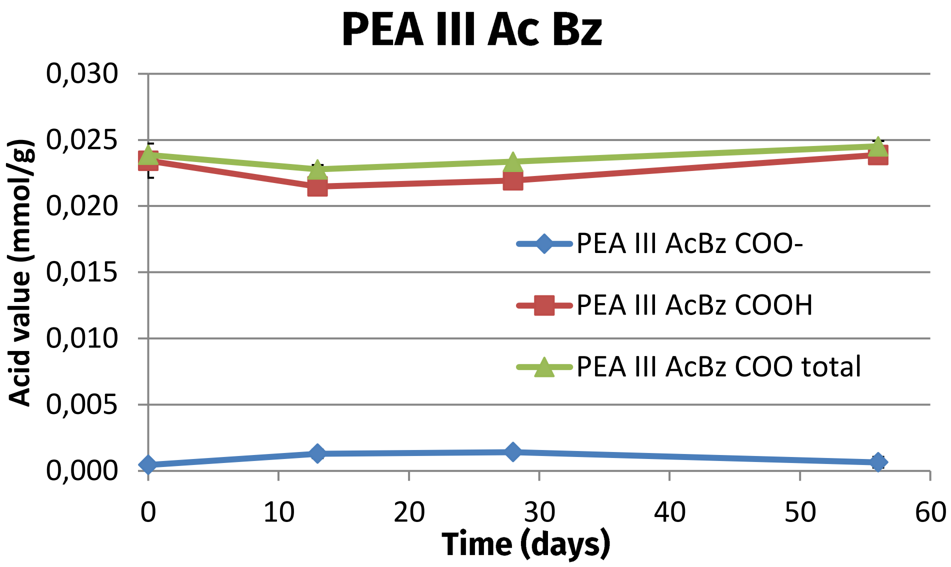


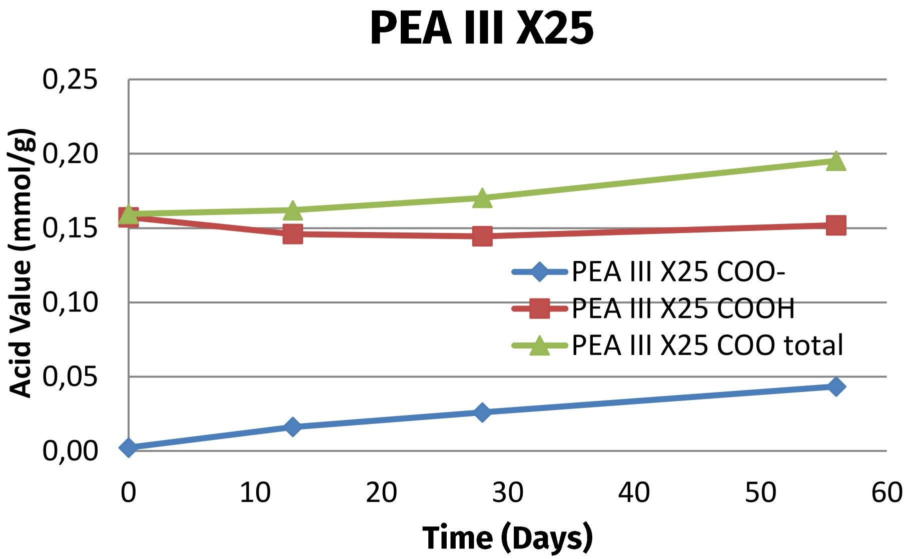


- Samples measured in triplicate.
- PEA III Ac Bz 'constant' acid value.
- PLGA 75/25 gradual increase of acid value.

Acid Values



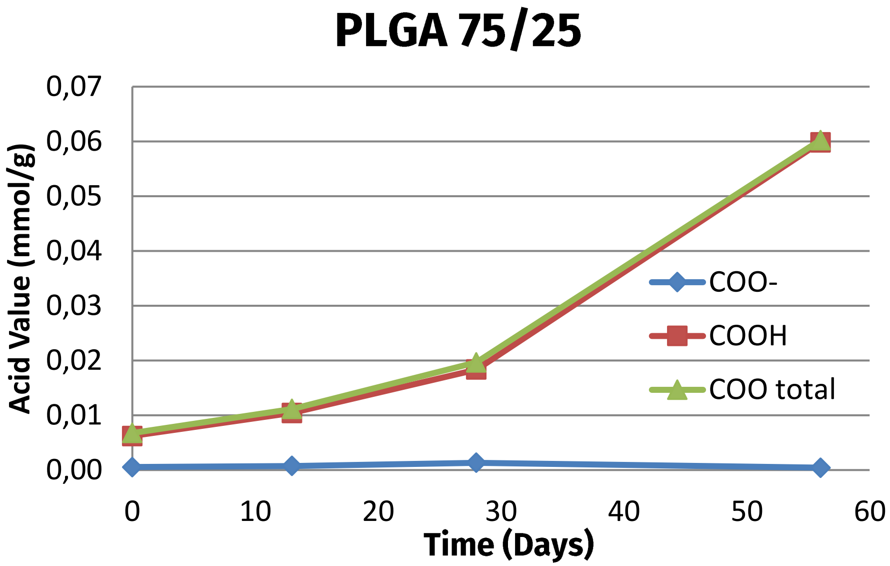


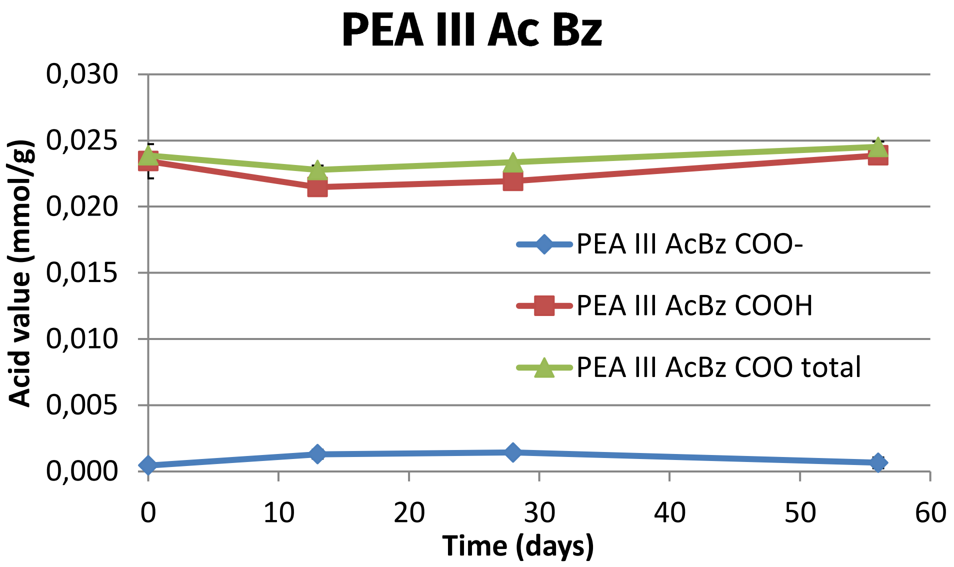


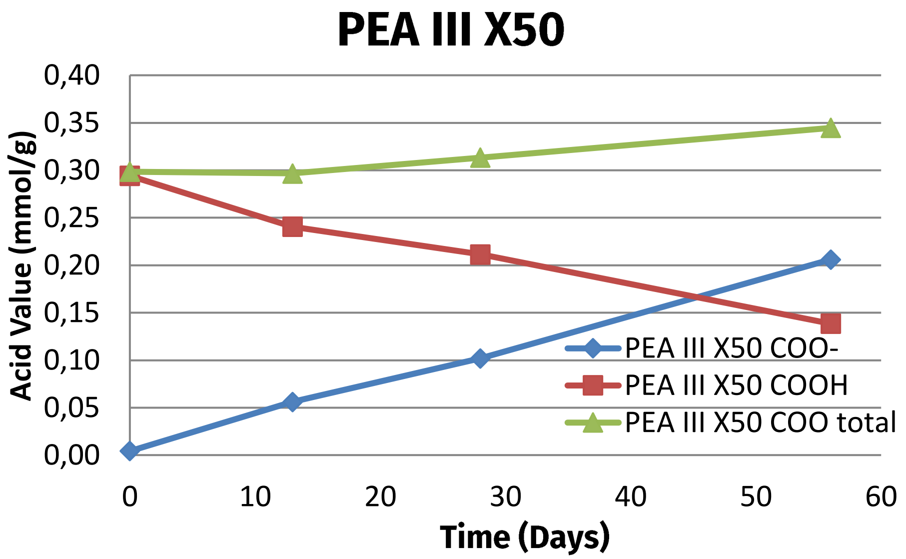
$$\mathrm{pH} = \mathrm{pK_a} + {}^{10}\log\frac{[\mathrm{A}^-]}{[\mathrm{HA}]}$$

Buffering effect observed

Acid Values







- Buffering effect observed
- Buffering effect is larger with increasing X content (water uptake)

Advantages of the Unique PEA Degradation

- Structural control on the degradation mechanism
- Absence of Acidic Microclimate formed during bio-degradation
- Zero-order, predictable degradation kinetics
- Good tolerability and biocompatibility
- A solution for acid-sensitive ester-reactive APIs
- Formulation of biologic-moieties

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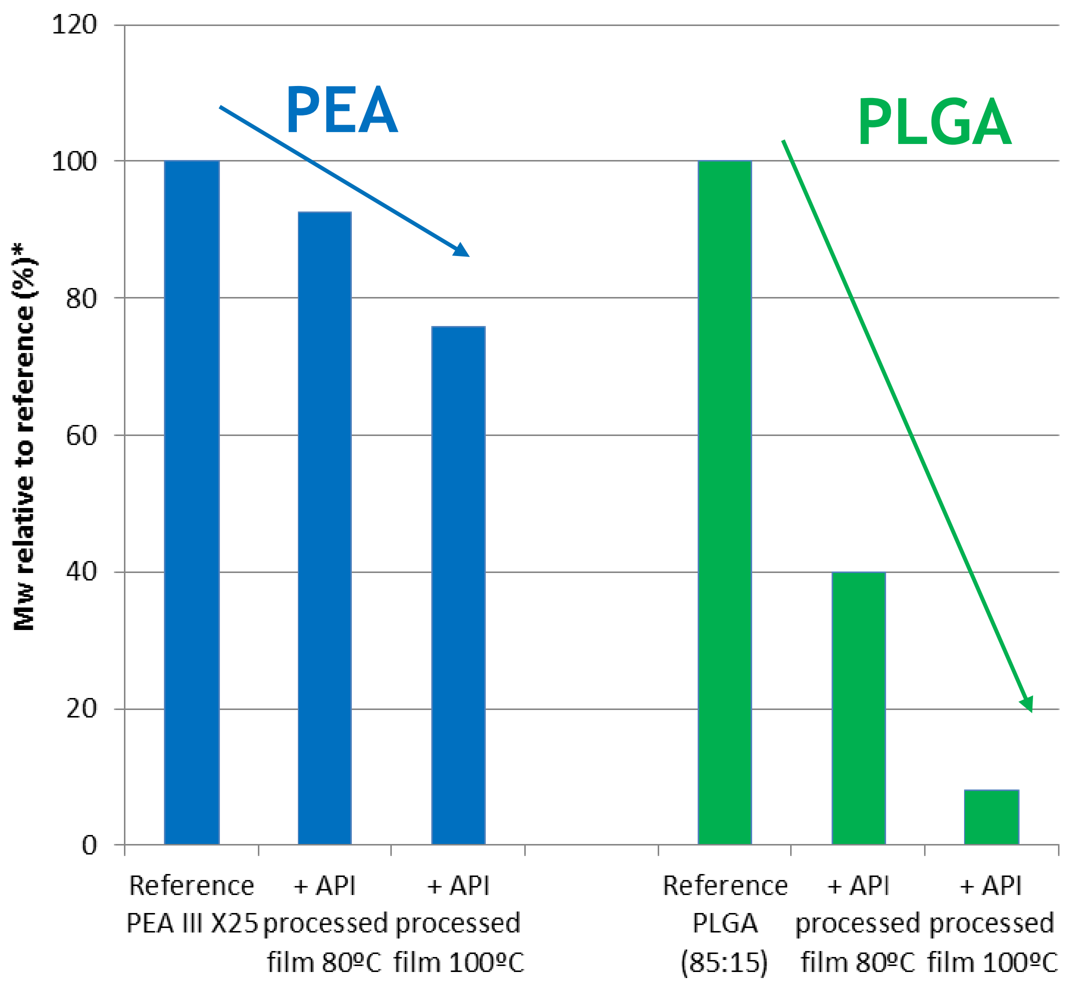
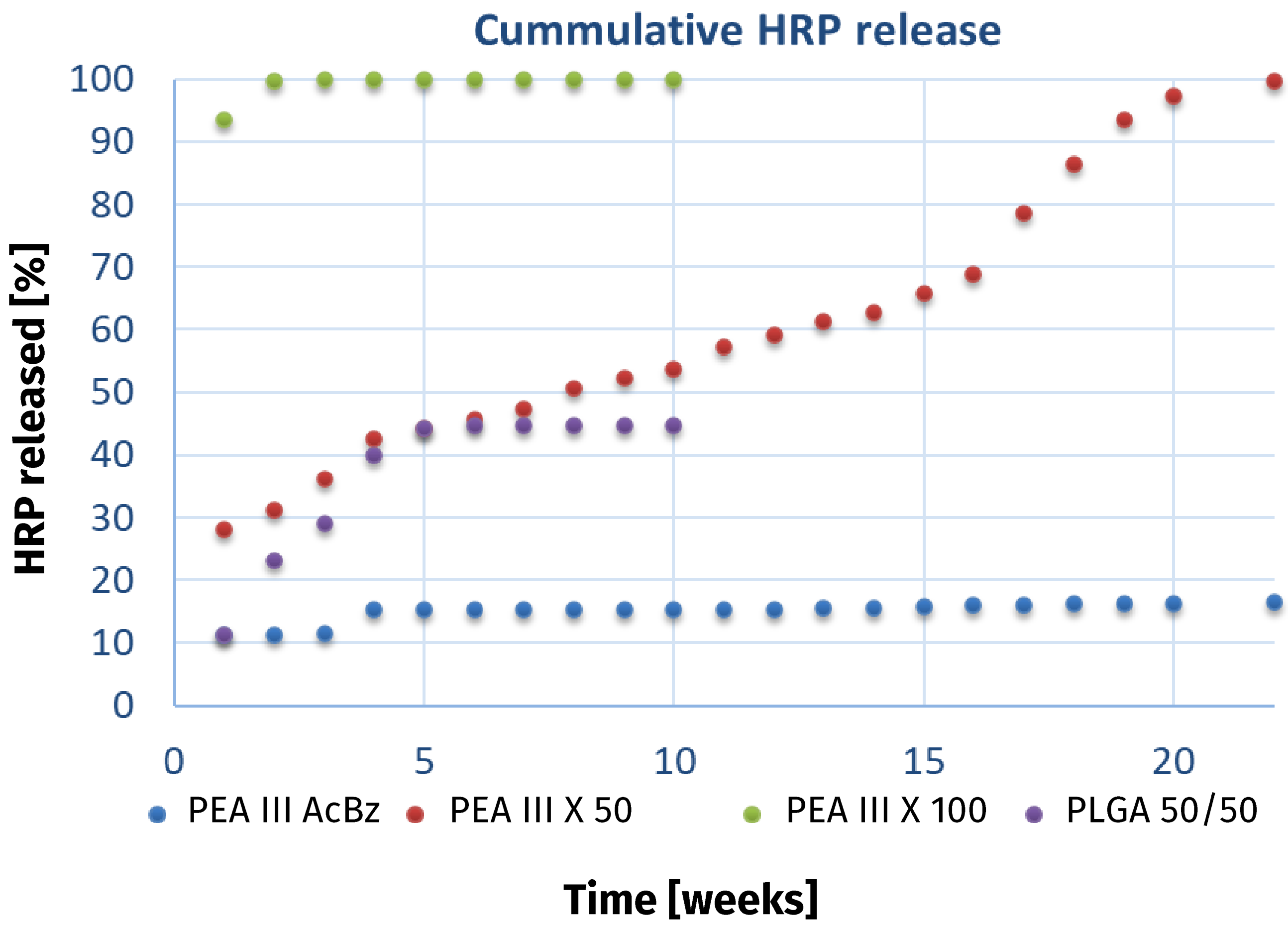
Delivery of challenging molecules

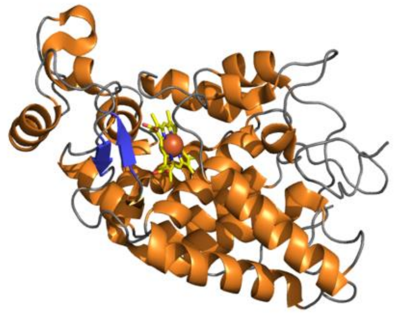


Example of formulation and processing with a nucleophilic API

- The polyester shows rapid degradation during the hot-melt processing
- PEA polymer retains its properties in a much more robust way

Formulation and release of acid-sensitive molecules

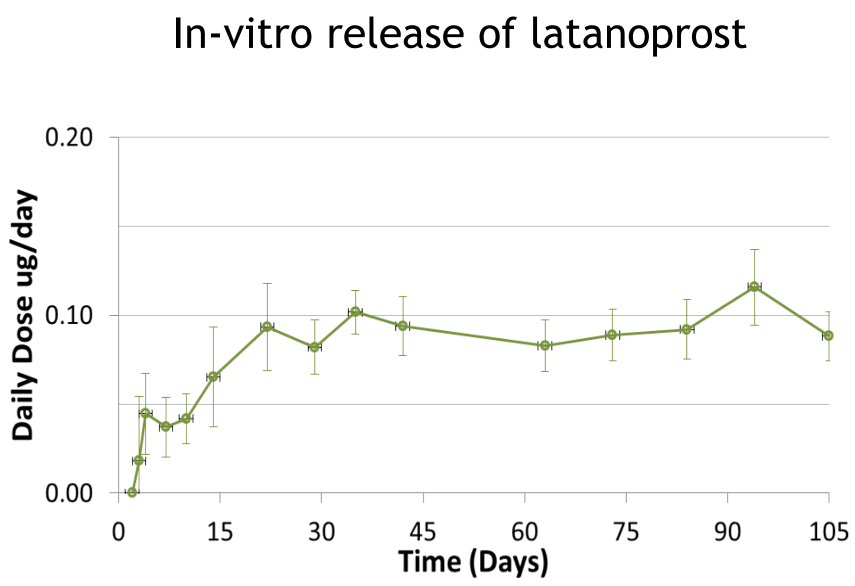




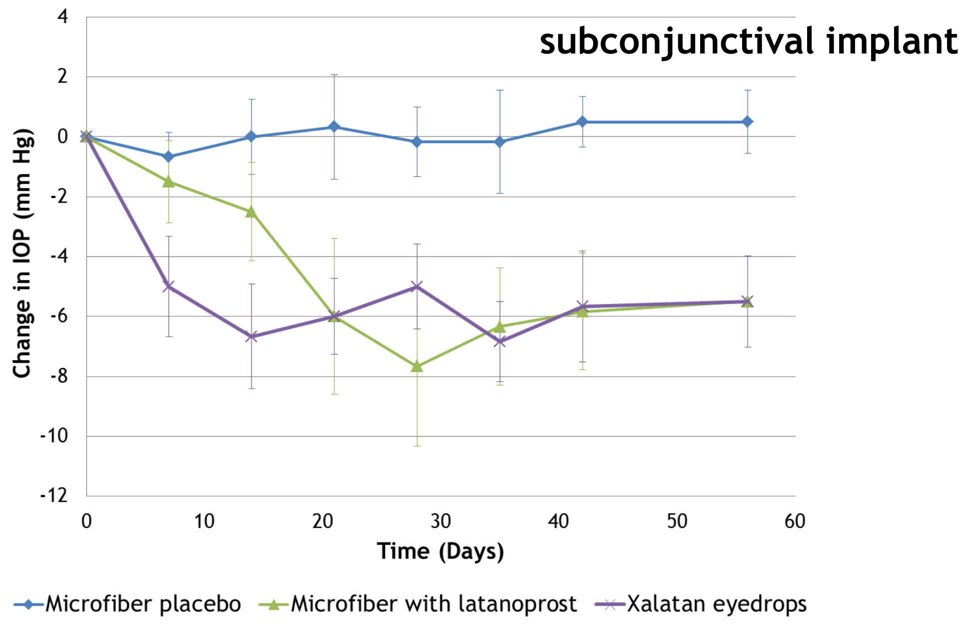
- Horseradish Peroxidase (HRP) was selected as a model molecule
- HRP was formulated with variety of biopolymers into specimens
- Release was followed by both protein quantification and activity
- The experiment confirmed the good protein/PEA compatibility even at advance stage of polymer degradation

Fit for ophthalmology validated in-vivo

In-vitro Results

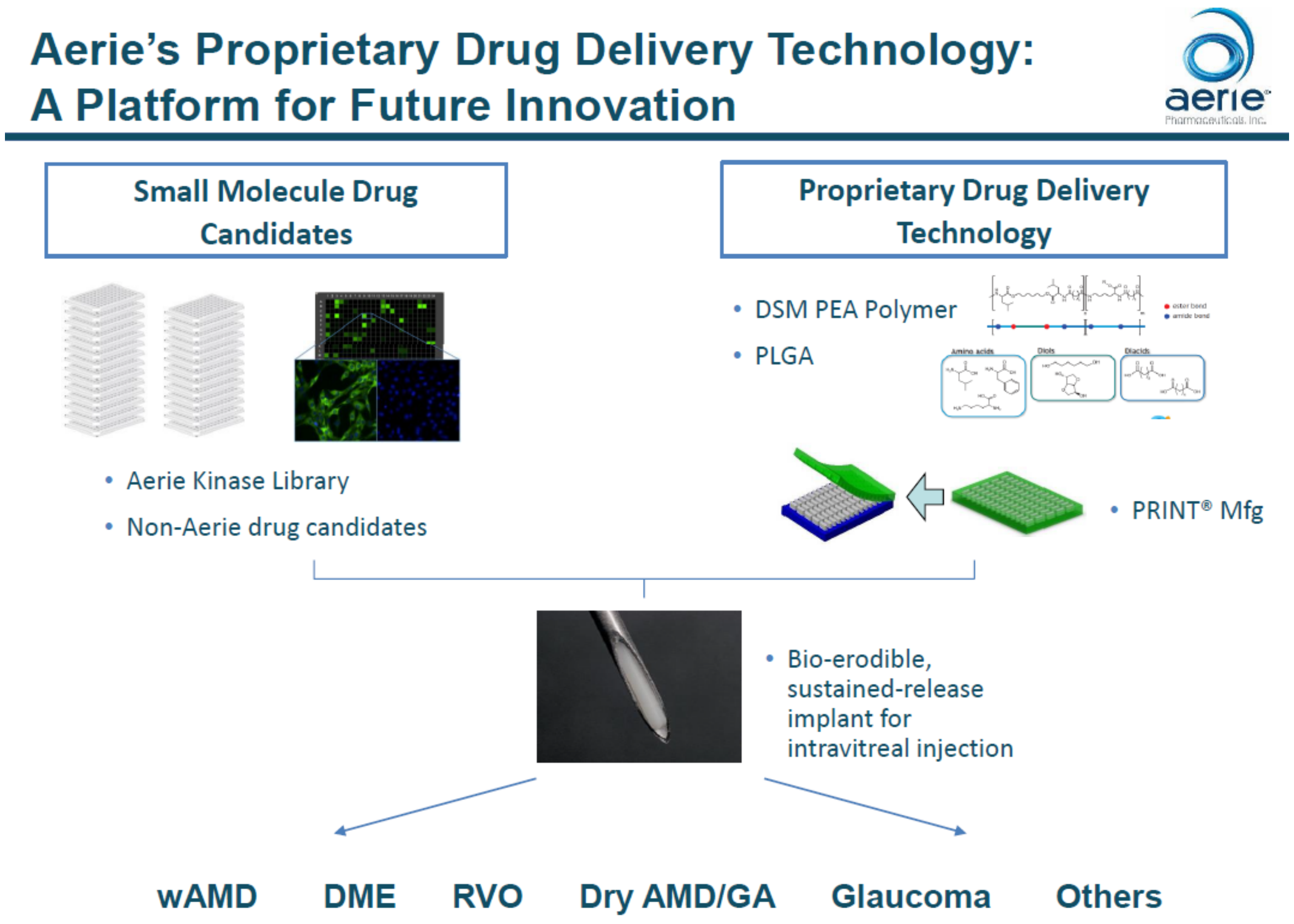


In-vivo Results



- *In vitro* release for months
- Reduced intra ocular tension *In vivo* in normotensive dog model
- Similar IOP reduction to Xalatan® droplets
- Implants are very well tolerated upon subconjunctival implantation

Accelerating Partner's Innovative Technology

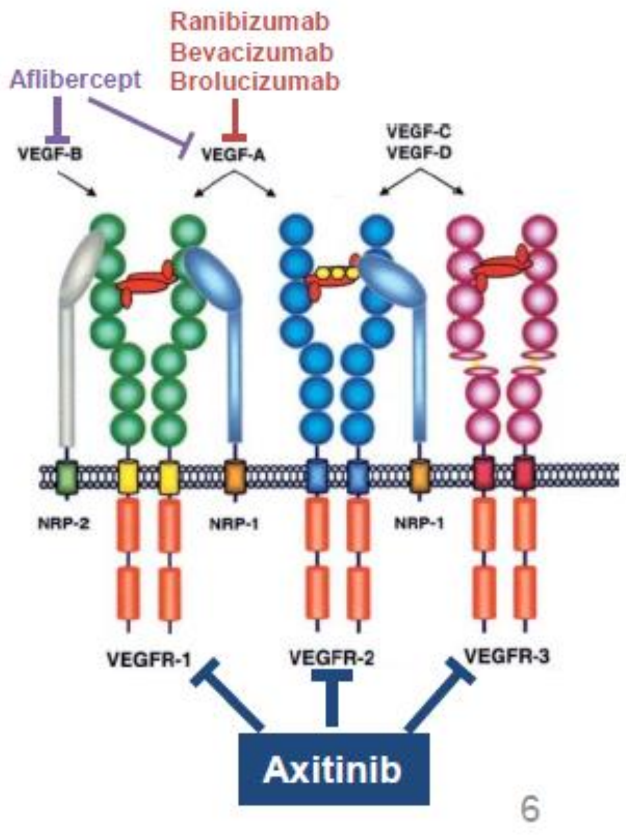


- Collaborating since 2016
- First concept proven in-vivo 2017
- Reinforcing the PRINT® technology towards novel ophthalmic therapies for the benefit of the patients and clinicians

Aerie Pharma, Corporate presentation for Investors

https://investors.aeriepharma.com/static-files/d342e410-4699-49fc-9663-a82649ac7360

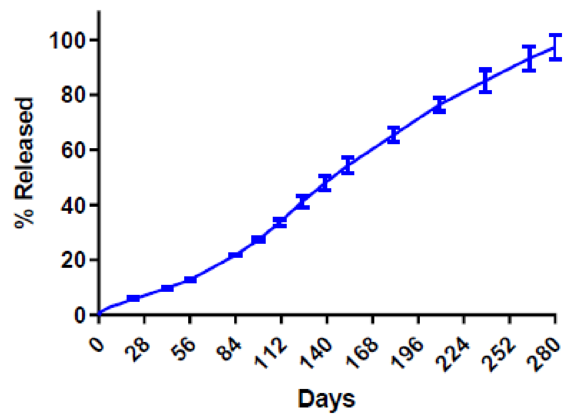
Polymer excipients maintain the elution rate for 12 months



AR-14034 Implant offers multiple potential advantages vs. current and future products.

Efficacy: potential for greater efficacy through broad inhibition of all VEGF receptor signaling.

Drug release rate from the implant in rabbits predicts up to 12-months duration (once a year injection) in clinic.



In vitro: In vivo Comparison

Time	Percent drug released	
	In vitro	In rabbits
Day 14/16	10%	6-9%
Day 29/31	17%	14%
Month 5	60%	50-60%

Aerie Pharma, Corporate presentation for Investors
https://investors.aeriepharma.com/static-files/d342e410-4699-49fc-9663-a82649ac7360

Conclusions

- Novel biodegradable polymer addressing challenges in Drug Delivery
- Structural control on the degradation mechanism
- Absence of Acidic Microclimate formed during bio-degradation
- Zero-order, predictable degradation kinetics and well tolerated in-vivo
- A solution for challenging to formulate therapeutics
- Providing solution for delivery of acid sensitive biopharmaceuticals without co-encapsulation with pH controlling excipients.

Questions About How DSM Biomedical Can Elevate Your Next Sustained Delivery Project?

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DSM's Scientific Poster will be featured Wednesday July 13th from 7:00 PM – 9:00 PM and on Thursday July 14th from 5:00 PM – 6:00 PM.

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Info.Biomedical@DSM.com

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Let DSM Biomedical take you further

Every second, a patient receives a medical device containing a DSM Biomedical material.

Millions of patients benefitting worldwide.

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