Real-time assessment of in-situ forming implants in vitro and in vivo using CT imaging

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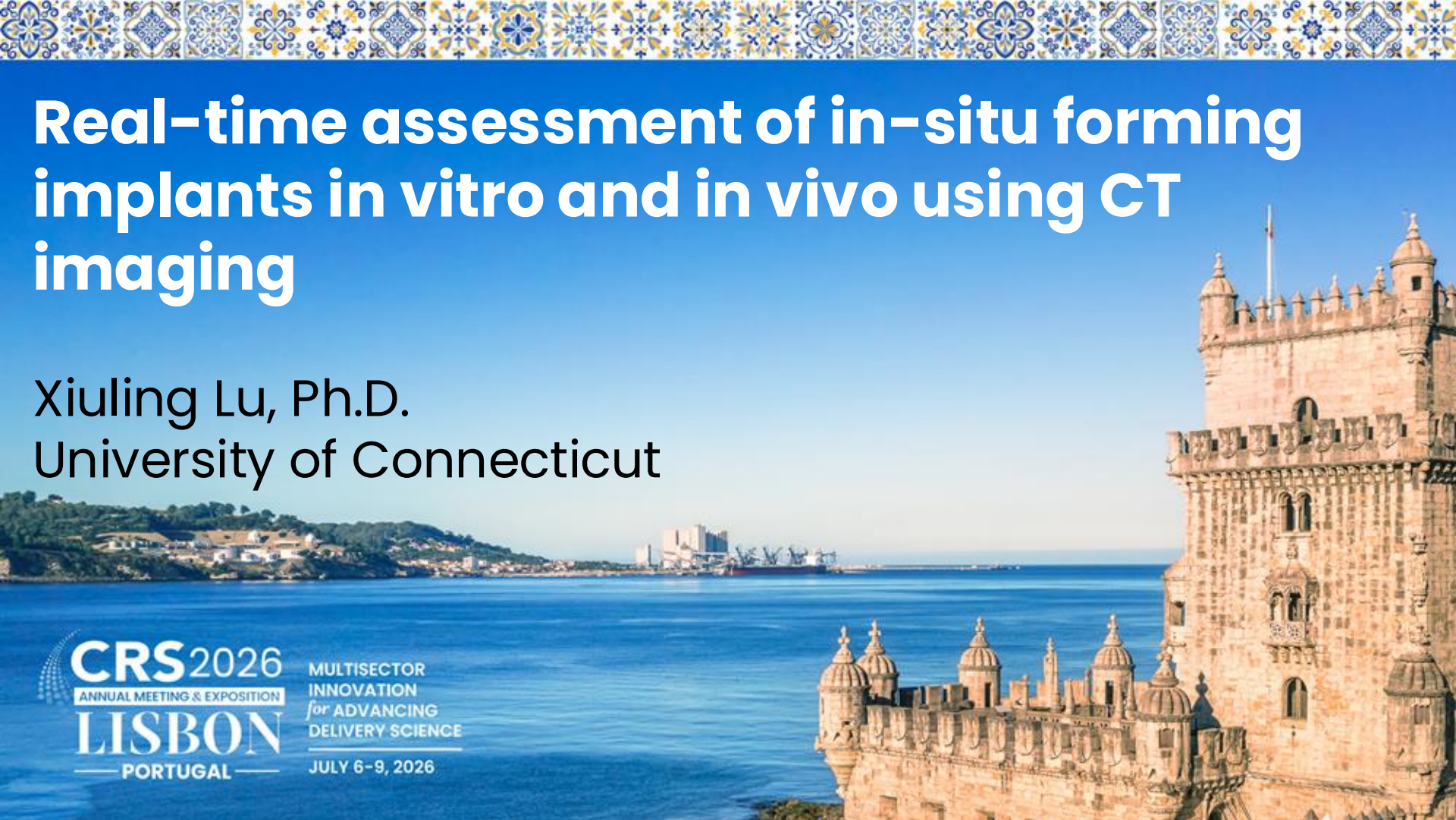
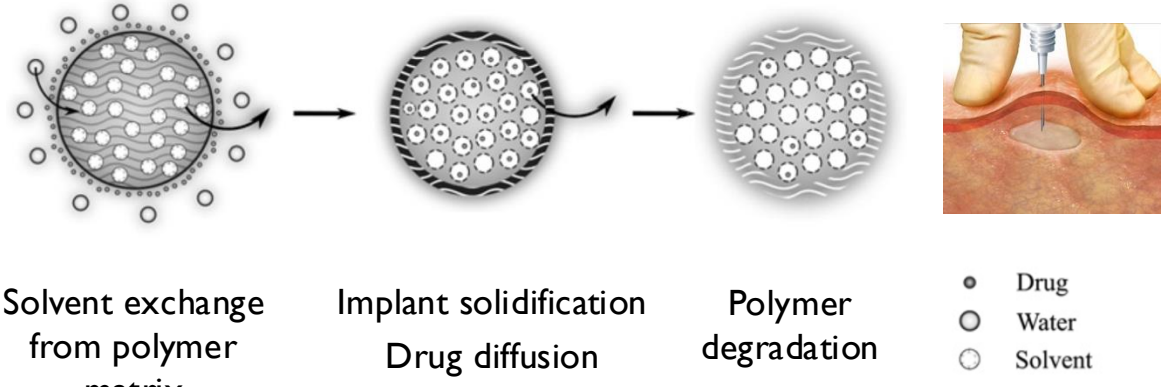


Background:

– *Current understanding of in situ forming implants*

Mechanism of implant formation and drug release:

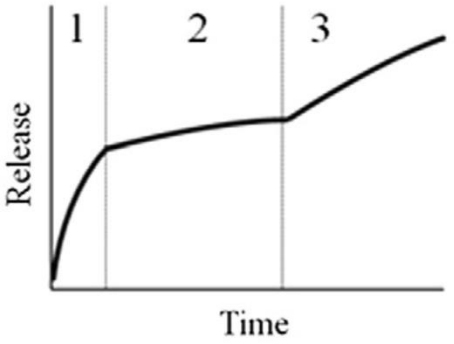


Solvent exchange from polymer matrix

Implant solidification
Drug diffusion

Polymer degradation

Typical release profile:



Juvekar, S.; Kathpalia, H. Solvent removal precipitation based in situ forming implant for controlled drug delivery in periodontitis. J Control Release 2017, 251, 75-81. DOI: 10.1016/j.jconrel.2017.02.022.
Parent, M; et. PLGA in situ implants formed by phase inversion: critical physicochemical parameters to modulate drug release. J Control Release 2013, 172 (1), 292-304.

Background:

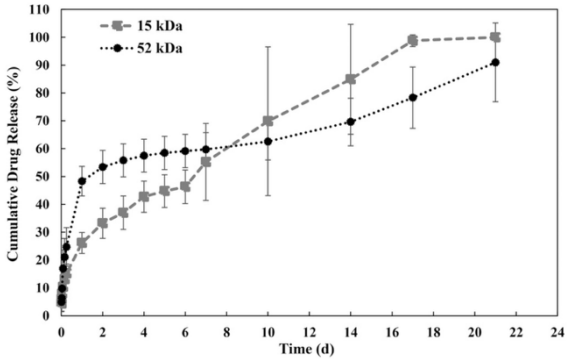
– *Commercial products*

Product	Approval year	Duration	Polymer	Solvent	API	Indication
Atridox	1988	7 days	PLA	NMP	Doxycycline	Chronic periodontitis
Eligard	2002	1-6 months	PLGA	NMP	Leuprolide acetate	Prostate cancer
Sublocade	2017	1 month	PLGA	NMP	Buprenorphine	Opioid use disorder
Perseris	2018	1 month	PLGA	NMP	Risperidone	Schizophrenia
Fensolvi	2020	6 months	PLGA	NMP	Leuprolide acetate	Central precocious puberty (Children)
Camcevi	2021	6 months	PLA	NMP	Leuprolide acetate	Prostate cancer
Uzedy	2023	1-2 months	MPEG-PLA PLA-PEG-PLA	DMSO	Risperidone	Schizophrenia

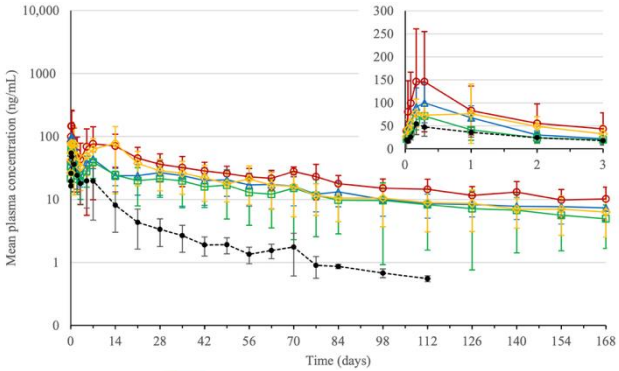
Background:

– *Current performance tests & characterization methods*

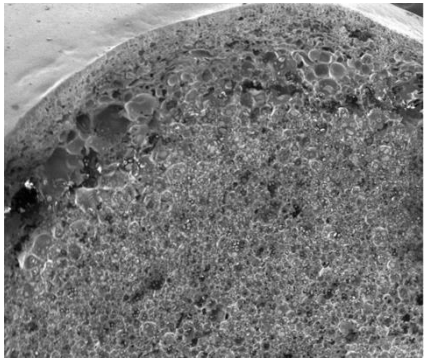
In vitro release test



Pharmacokinetic study



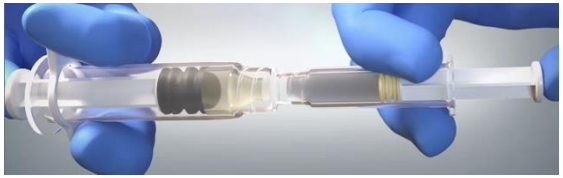
Scanning electron microscopy



Hopkins, K. A.; Vike, N.; Li, X.; Kennedy, J.; Simmons, E.; Rispoli, J.; Solorio, L., Noninvasive characterization of in situ forming implant diffusivity using diffusion-weighted MRI. J Control Release 2019, 309, 289-301.
https://microbenotes.com/scanning-electron-microscope-sem/
Van Hemelryck, S. et. In Vitro Evaluation of Poly(lactide-co-glycolide) In Situ Forming Gels for Bedaquiline Fumarate Salt and Pharmacokinetics Following Subcutaneous Injection in Rats. Pharmaceutics 2021, 13 (8).

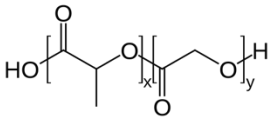
Overview

Eligard®

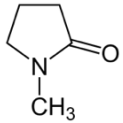


Atrigel®

Iohexol
Leuprolide acetate
(LA)



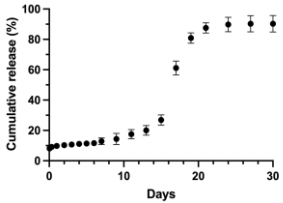
PLGA
(poly(lactic-co-glycolic acid))
50:50, 25.8 kDa



NMP
(N-Methylpyrrolidone)

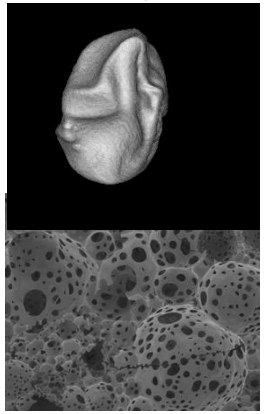
in vitro

In vitro release study



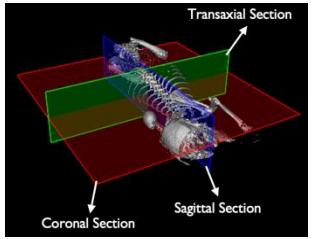
CT imaging

SEM



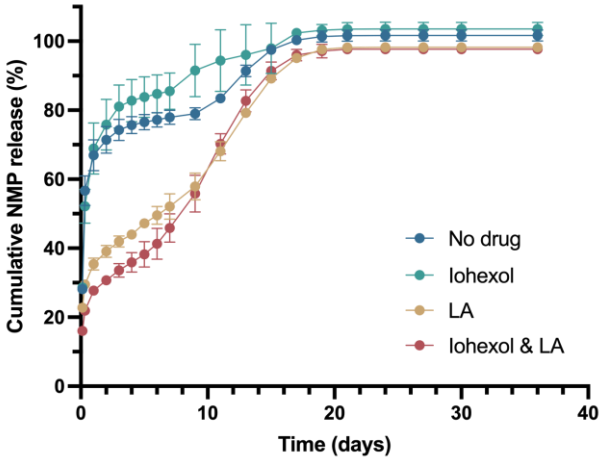
in vivo

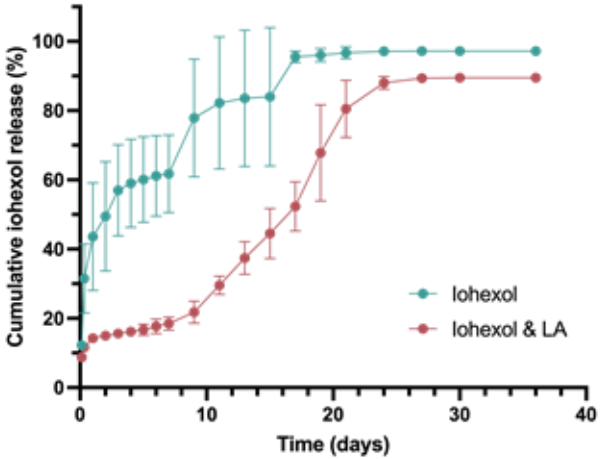
CT imaging

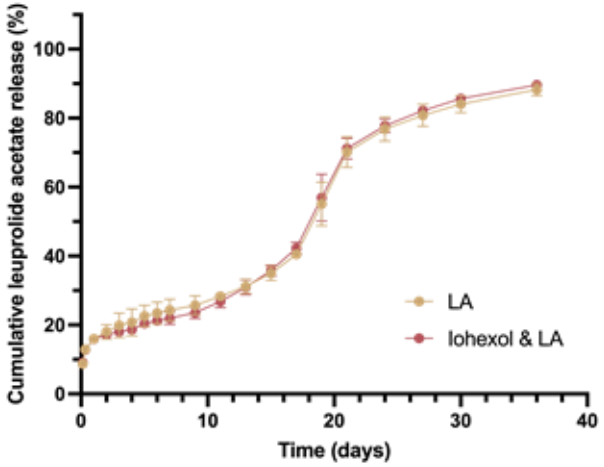


Assessing depot formation and degradation of ISFI using CT imaging

– *In vitro release test*





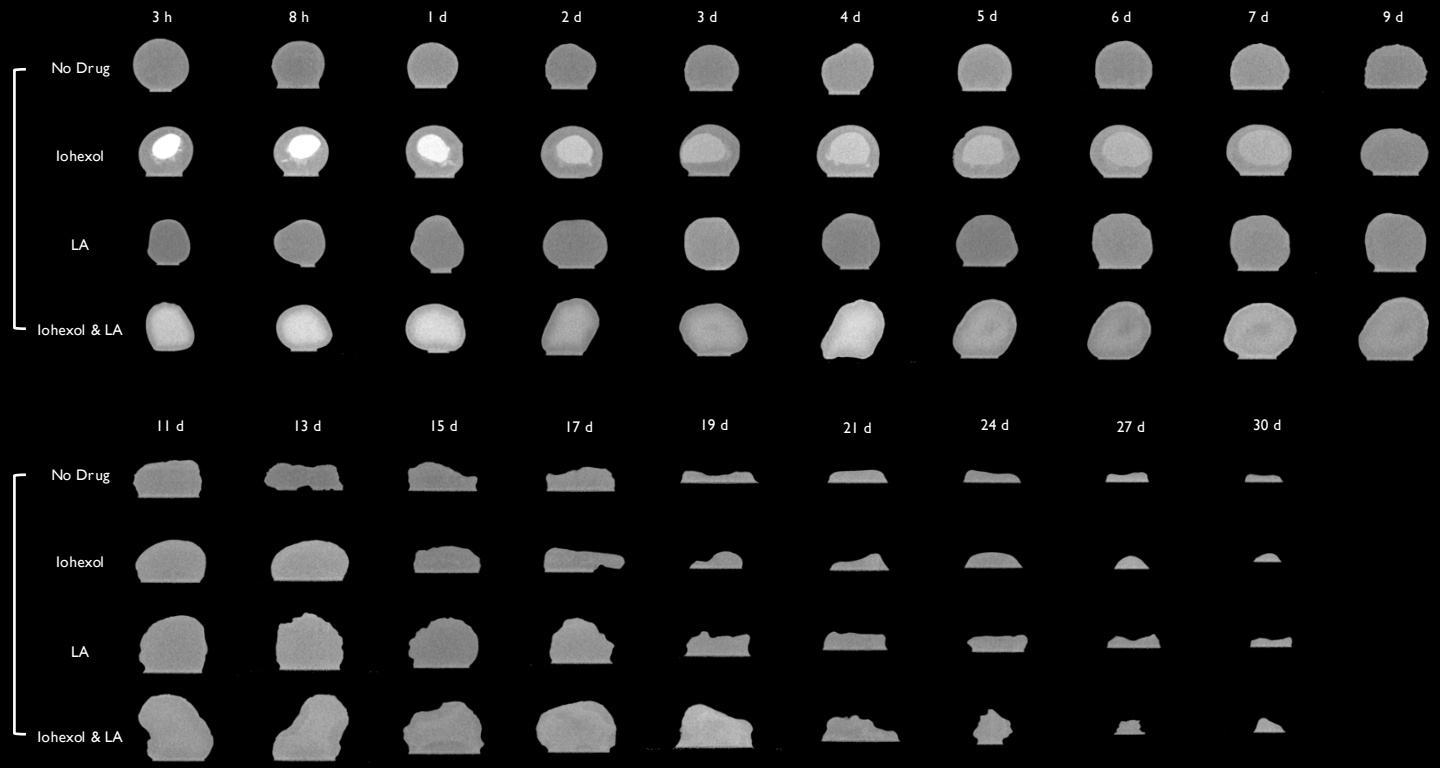


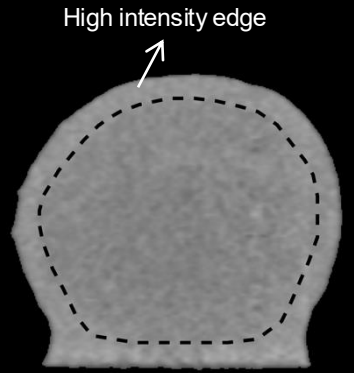
- Classic drug release profiles from *in situ* forming implants with three phases.
- Addition of LA inhibited the burst release of NMP and iohexol.
- Iohexol didn't change the release profile of LA.

Lin X, et al. Implant dynamics, inner structure, and their impact on drug release of in situ forming implants uncovered through CT imaging. J Control Release. 2024 Nov;375:802-811.

Assessing depot formation and degradation of ISFI using CT imaging

– *CT images of in vitro formed implants*





Morphology:

Spheroid-like

Thin edge:

Brighter signal → Dense

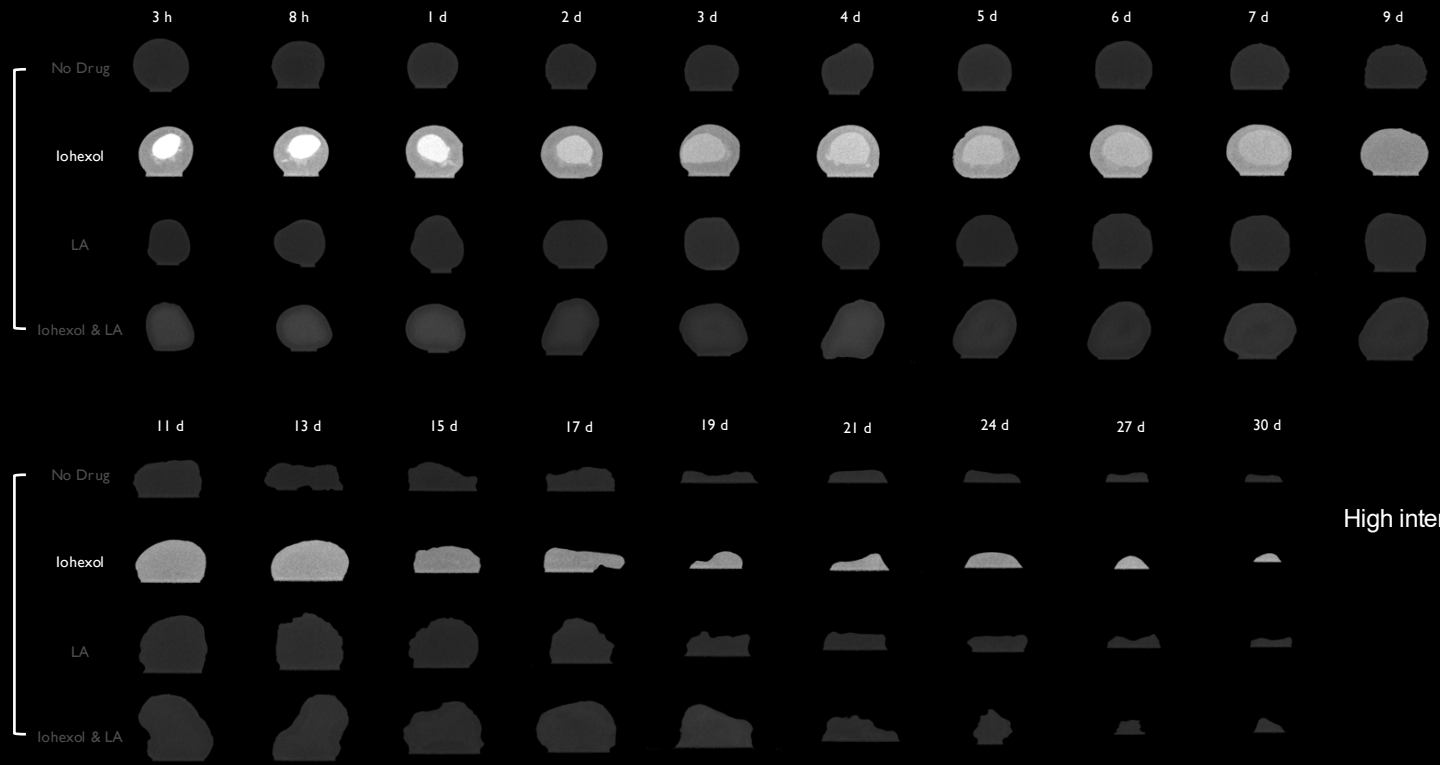
Until 9-11d

Texture surface:

Starting around 9d

Assessing depot formation and degradation of ISFI using CT imaging

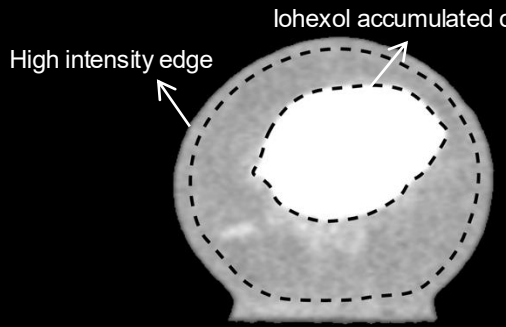
– *CT images of in vitro formed implants*



Iohexol distribution showed core-shell structure until 7d with signal decrease.

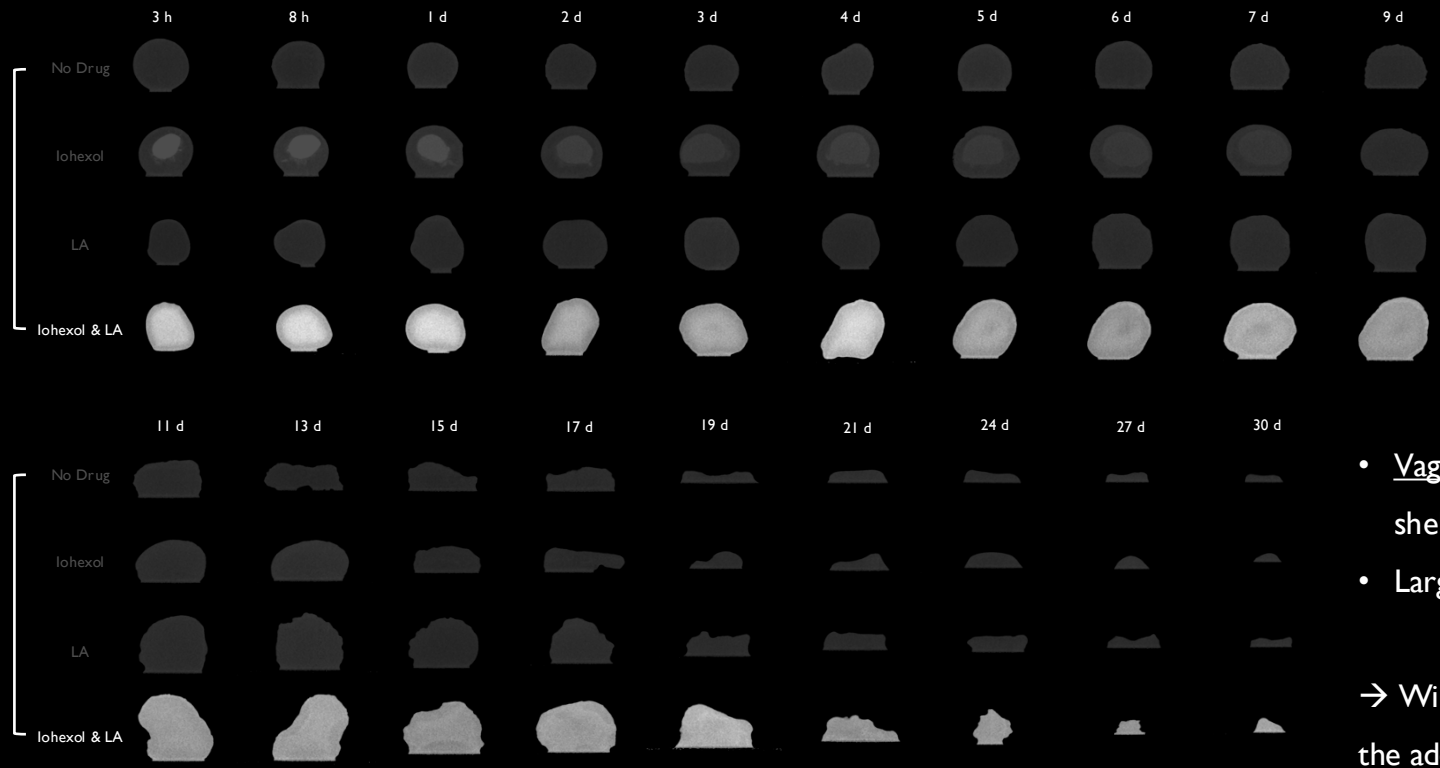
Scattered core before 2d.

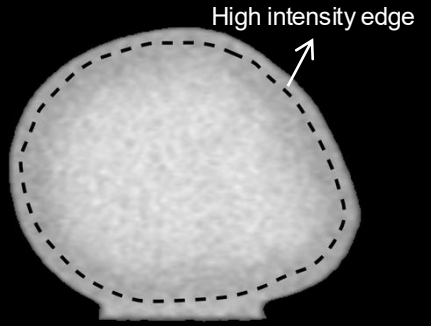
→ Iohexol was trapped inside the implant by the high intensity shell



Assessing depot formation and degradation of ISFI using CT imaging

– *CT images of in vitro formed implants*



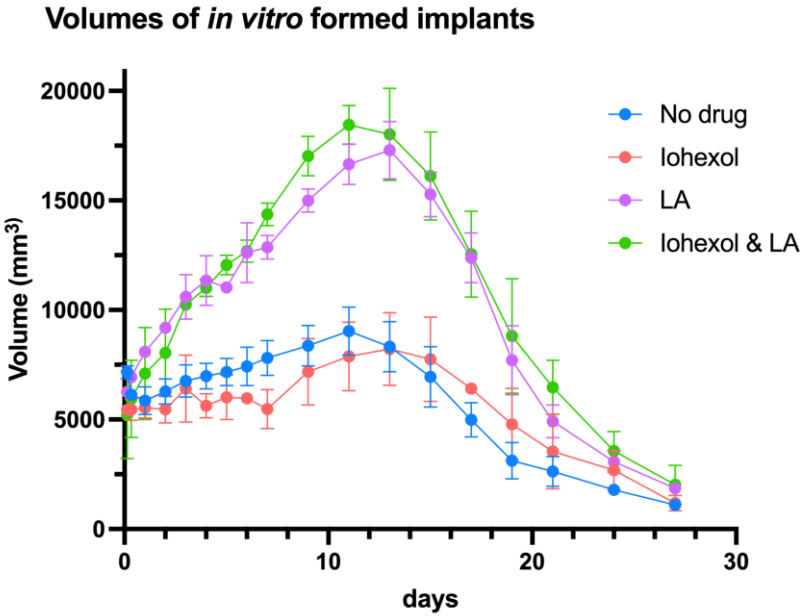


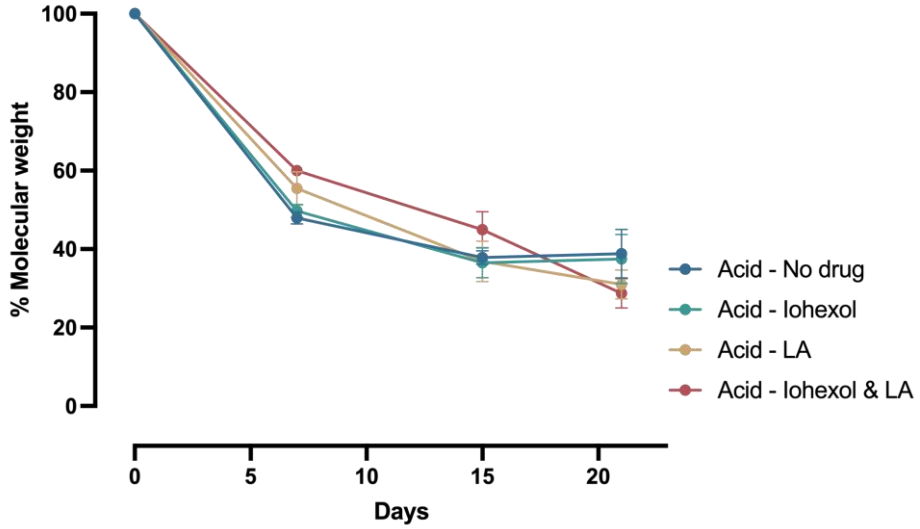
- Vague boundary between the core-shell structure.
- Larger radius of the core.

→ Wilder deposition of iohexol with the addition of LA

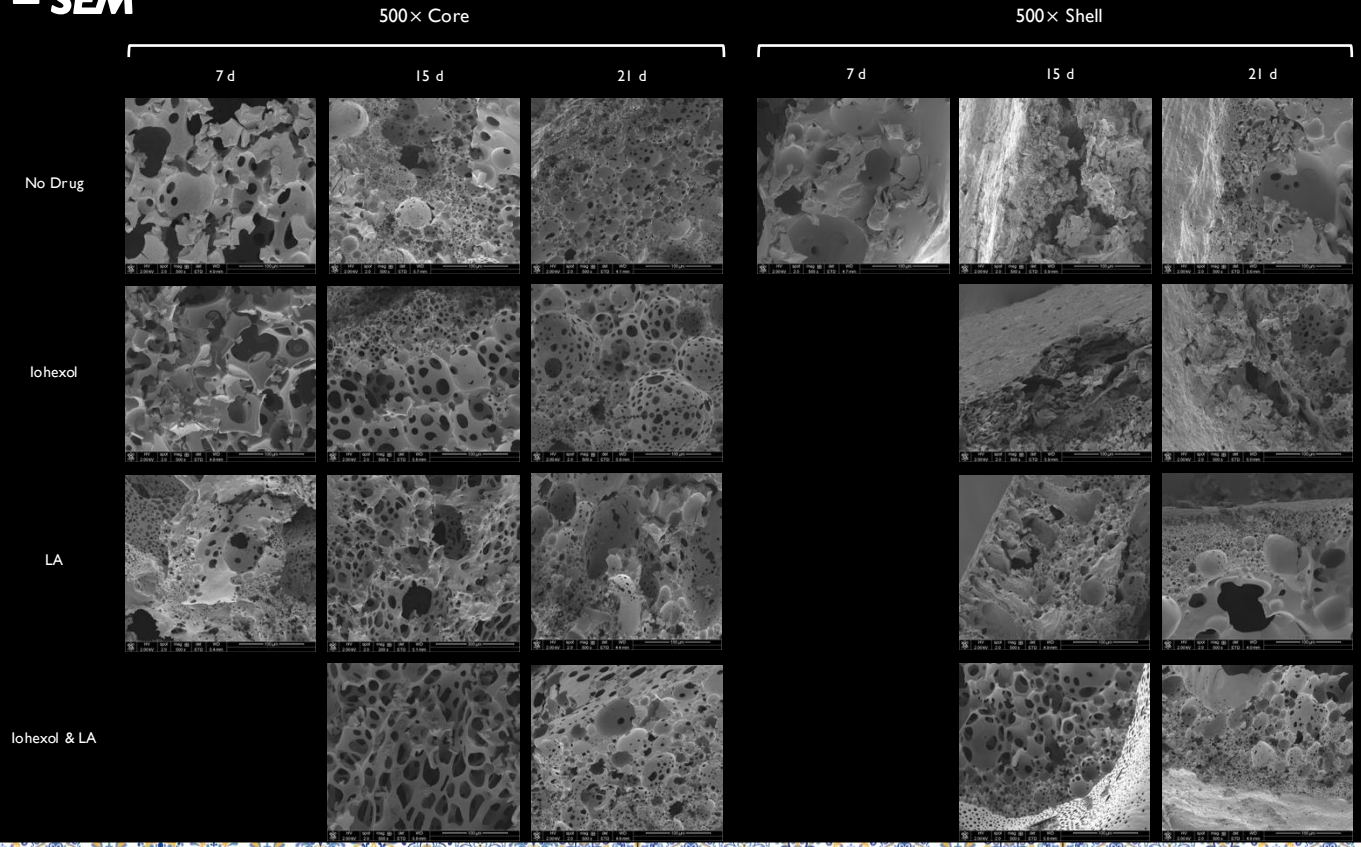
In vitro formed implants

– *Volume, weigh, PLGA degradation*





In vitro formed implants – *SEM*



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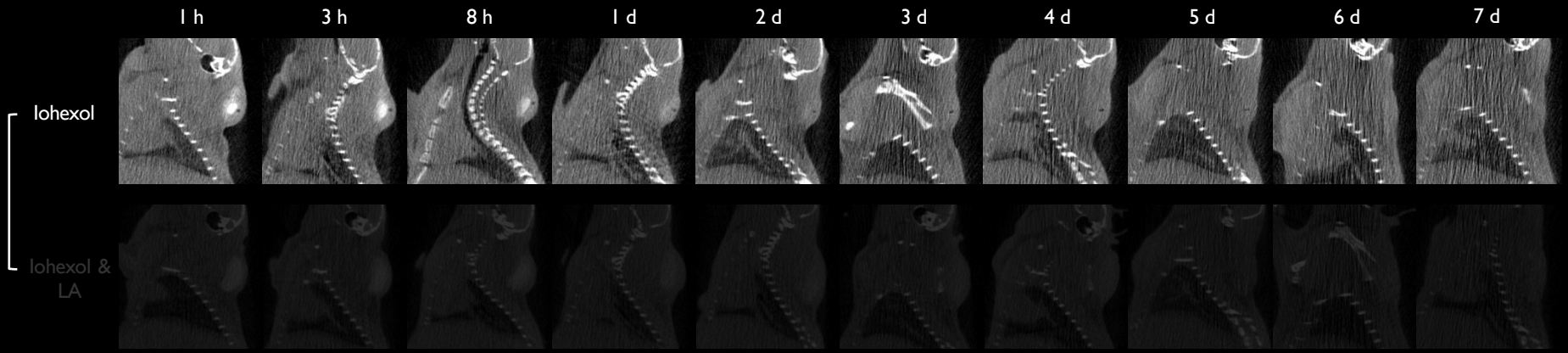
Assessing depot formation and degradation of ISFI using CT imaging

– *CT images of in vivo formed implants*



Morphology:

Spheroid-like

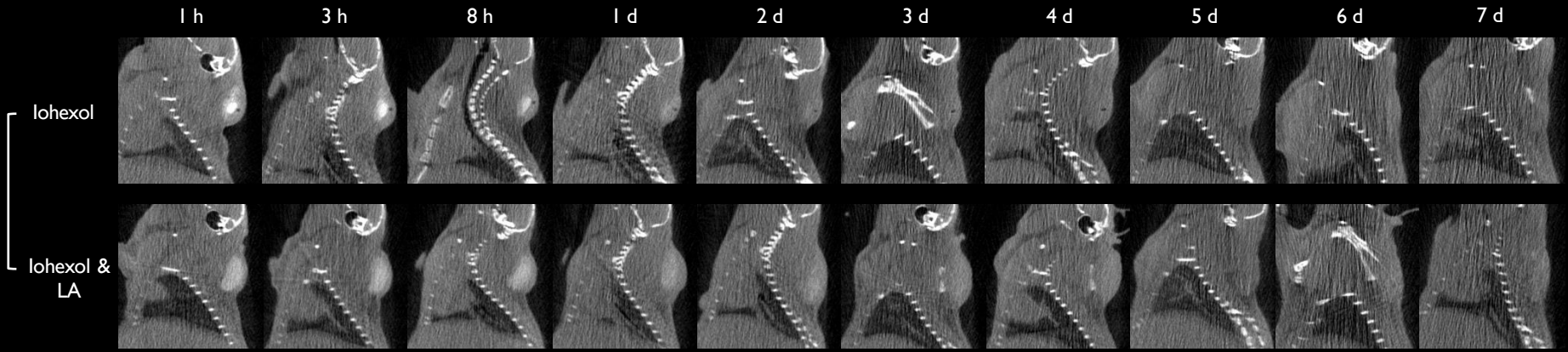
Inner structure:

Core-shell structure of the Iohexol distribution in first 2 days

Scattered Iohexol signal in first 3 hours

Assessing depot formation and degradation of ISFI using CT imaging

– CT images of in vivo formed implants



Morphology:

Spheroid-like

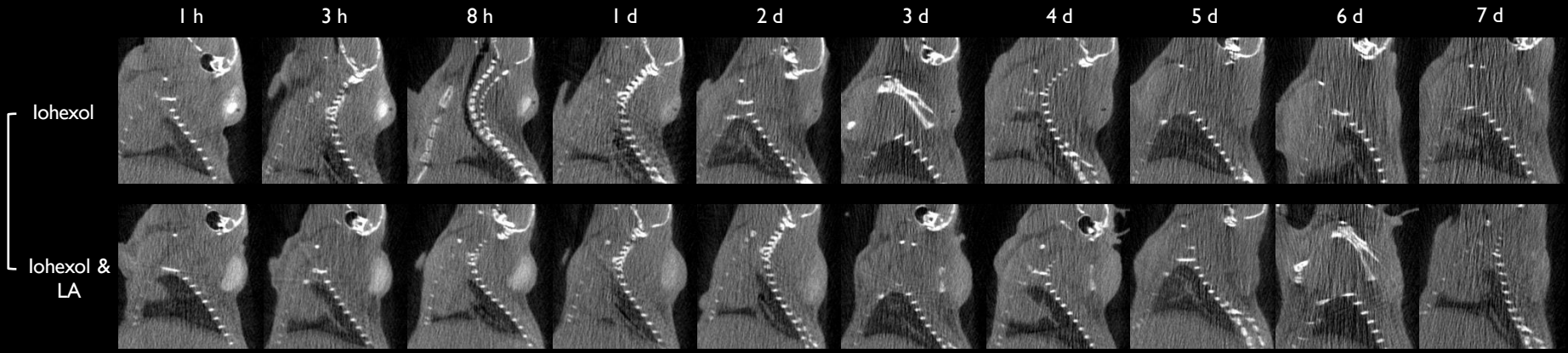
Inner structure:

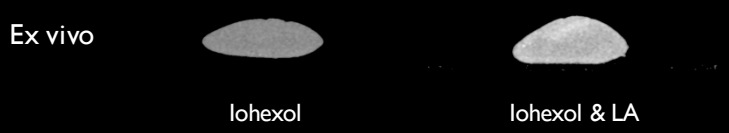
Larger iohexol accumulated core

Vague boundary between the core shell structure in first 2 days

Assessing depot formation and degradation of ISFI using CT imaging

– *CT images of in vivo formed implants*





Comparison with *in vitro* formed implants:

Common:

Similar morphology and inner structure

Difference:

Faster process

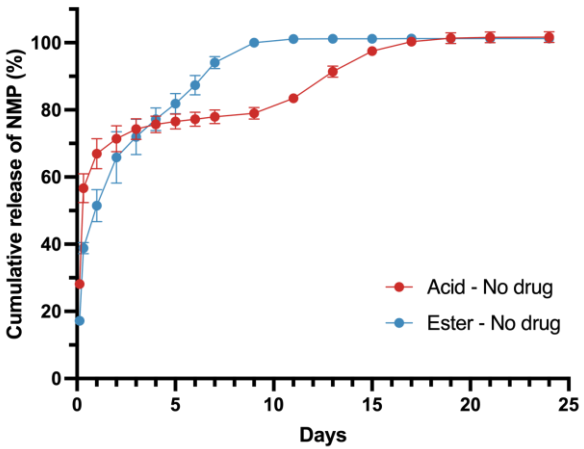
Less size expansion (less fluid and tissue pressure)

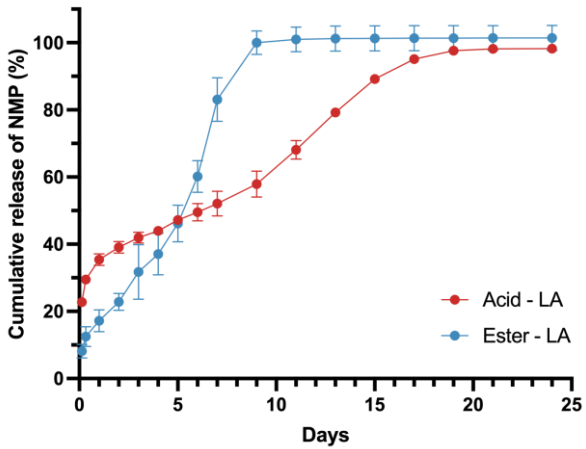
Summary I

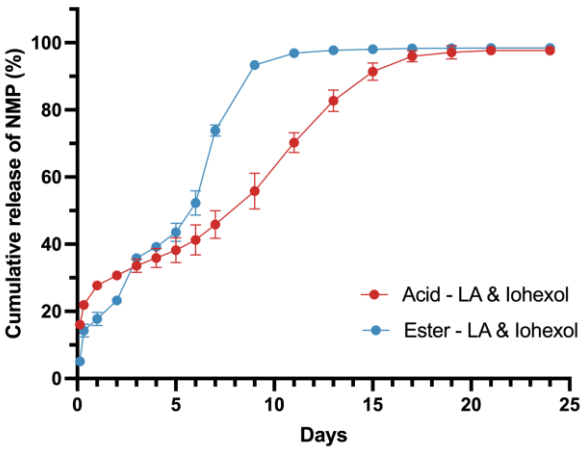
- Inner structure and drug deposition of in situ forming implant formed by both in vitro and in vivo are unveiled by CT imaging.
- CT images show the core-shell structure of the polymer matrix, which is also confirmed by SEM.
- Instead of homogeneous distribution, hydrophilic drug, iohexol, accumulates in the core of the implant and diffuses out.
- Addition of hydrophobic drug, leuprolide acetate, inhibits the burst release of the solvent and iohexol. Moreover, leuprolide acetate promotes and size expansion and PLGA degradation.
- In vivo formed implants have similar inner structure of the implant to in vitro formed implants, but process of the evolution is faster when implants are formed in vivo.

Impact of PLGA endcaps on the implant formation and degradation

– *NMP in vitro release*





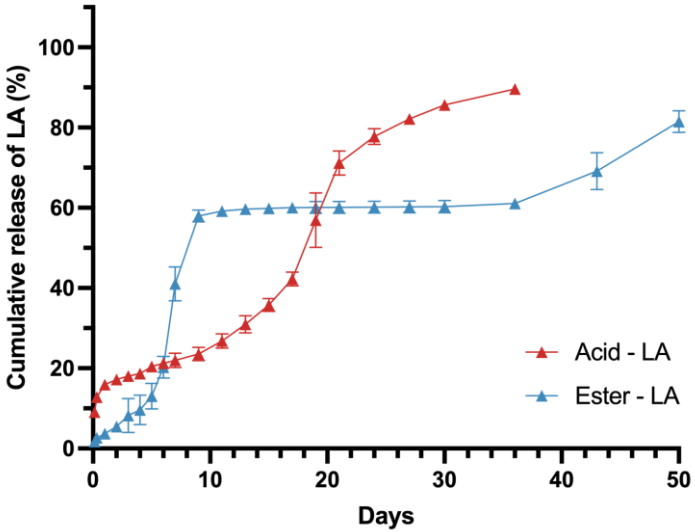


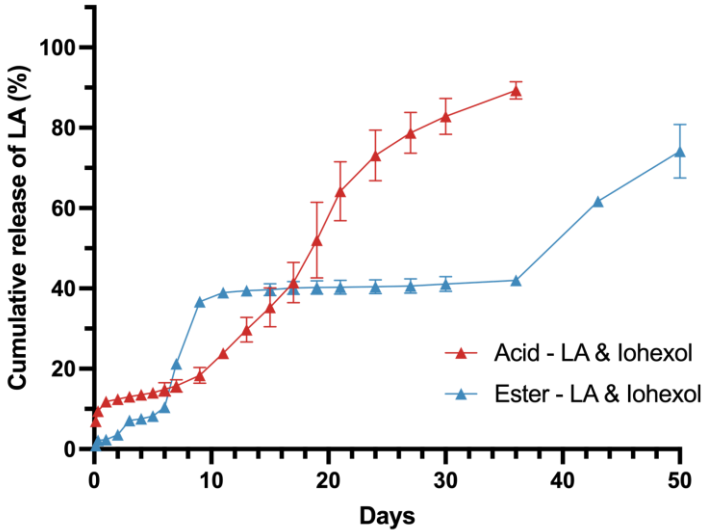
- Classic drug release profile from *in situ* forming implants with three phases.
- Group with acid-ending PLGA showed higher extent of burst release, but later starting point of second fast release period.
- NMP release of implants formed by ester-ending PLGA reached the plateau earlier.

Lin X. et al. Computed Tomography Imaging and Characteristics of In Situ Forming Implants with Different PLGA Endcaps Chemical & Biomedical Imaging, 2026. DOI: 10.1021/cbmi.6c00001

Impact of PLGA endcaps on the implant formation and degradation

– *LA in vitro release*

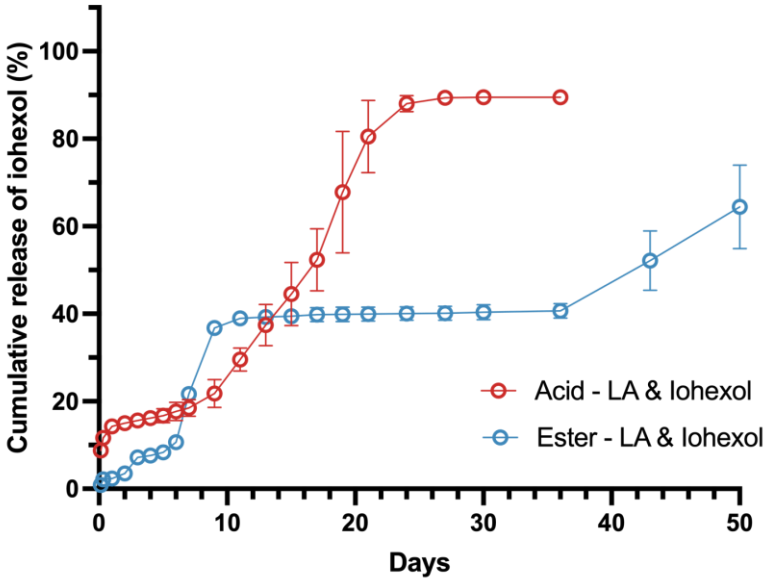




- LA release from implants with acid-ending PLGA showed drug release profile with three phases.
- For the group of PLGA with ester endcap: limited burst release → no drug release from 9-36 days → second fast-release period after 36 days.
- Group of acid-ending PLGA reached 100% release earlier.

Impact of PLGA endcaps on the implant formation and degradation

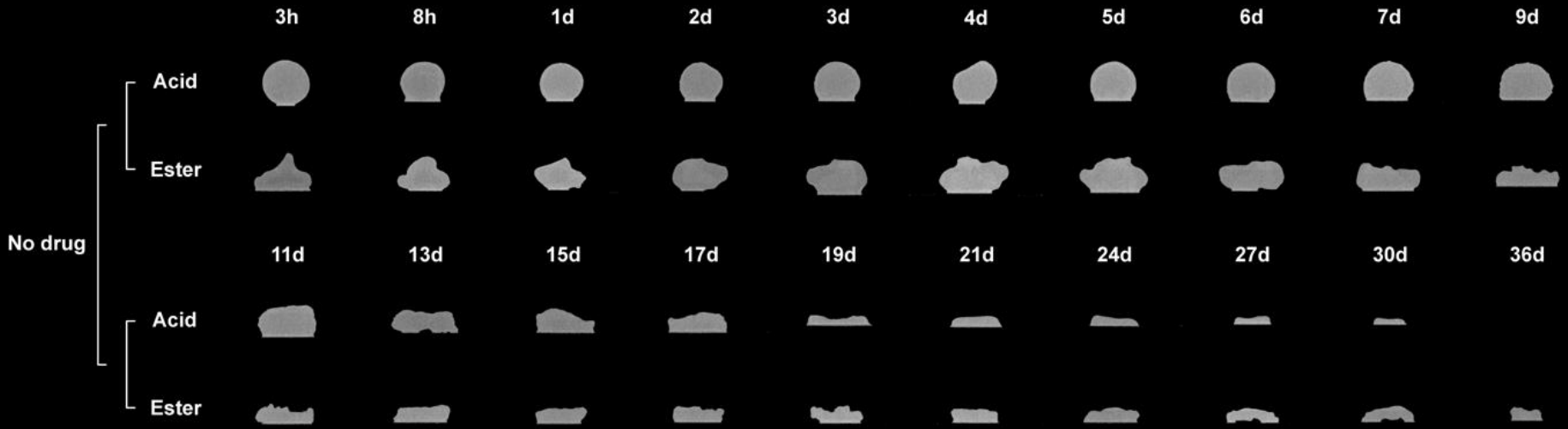
– Iohexol in vitro release



- Similar release profile to leuprolide acetate.

Impact of PLGA endcaps on the implant formation and degradation

– *CT images of in vitro formed implants*



Morphology:

Acid-ending PLGA: spheroid-like

Ester-ending PLGA: irregular shape

High-intensity edge:

Only observed in acid-ending PLGA

→ Reached the NMP release plateau earlier from ester-ending PLGA

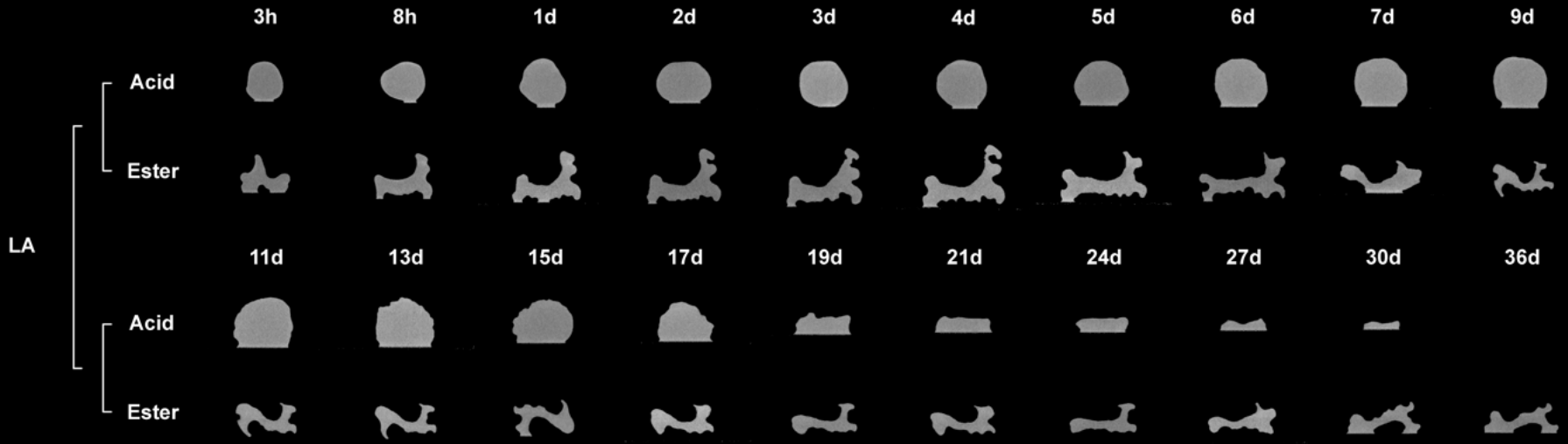
Inner structure:

Acid-ending PLGA: Homogeneous

Ester-ending PLGA: Heterogeneous polymer matrix in first 5 days

Impact of PLGA endcaps on the implant formation and degradation

– *CT images of in vitro formed implants*



Morphology:

Acid-ending PLGA: spheroid-like

Ester-ending PLGA: irregular shape

Thin edge:

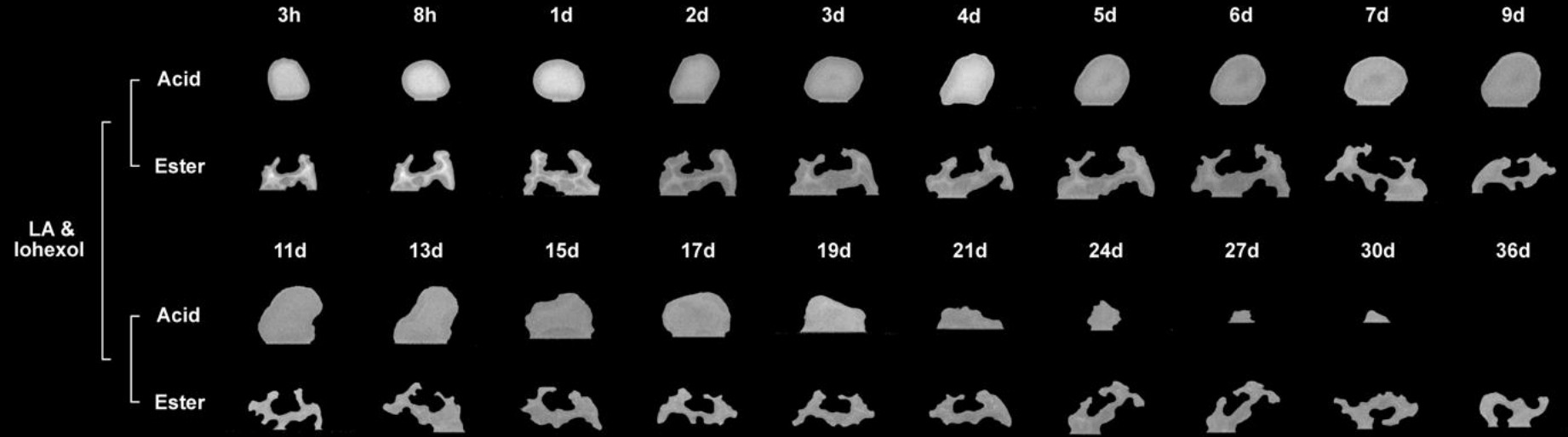
Acid-ending PLGA: Until 11d

Inner structure:

Homogeneous

Impact of PLGA endcaps on the implant formation and degradation

– CT images of in vitro formed implants



Morphology:

Acid-ending PLGA: spheroid-like

Ester-ending PLGA: irregular shape

Thin edge:

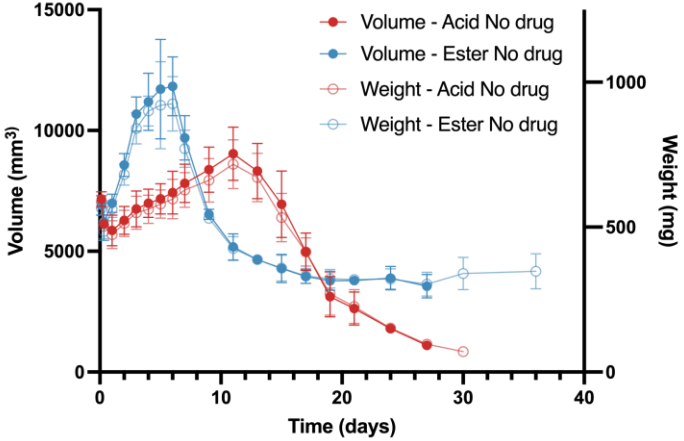
Acid-ending PLGA: Until 11d

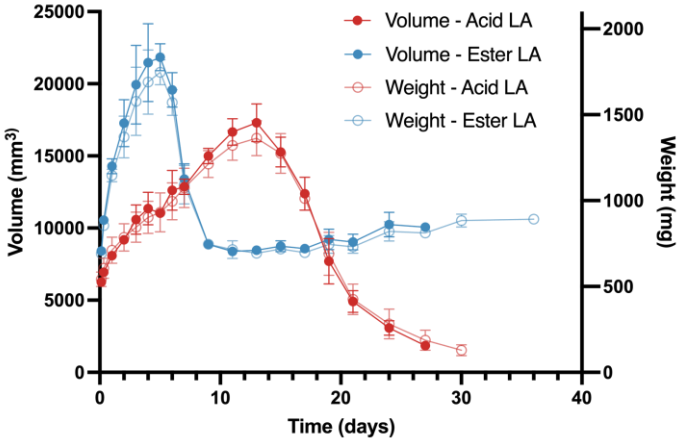
Inner structure:

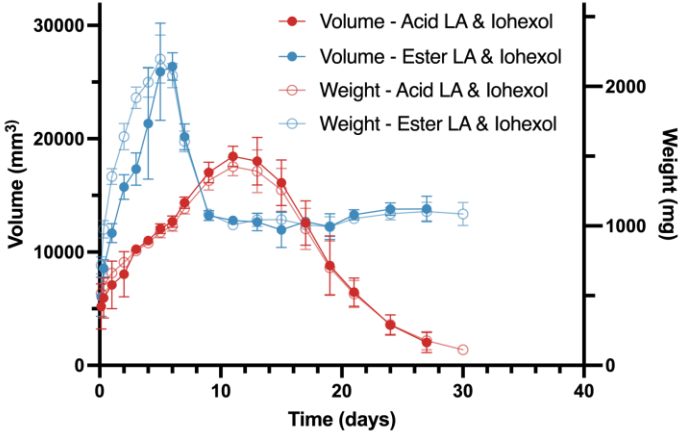
Iohexol accumulated in the center

Impact of PLGA endcaps on the implant formation and degradation

—*Volume and weight*

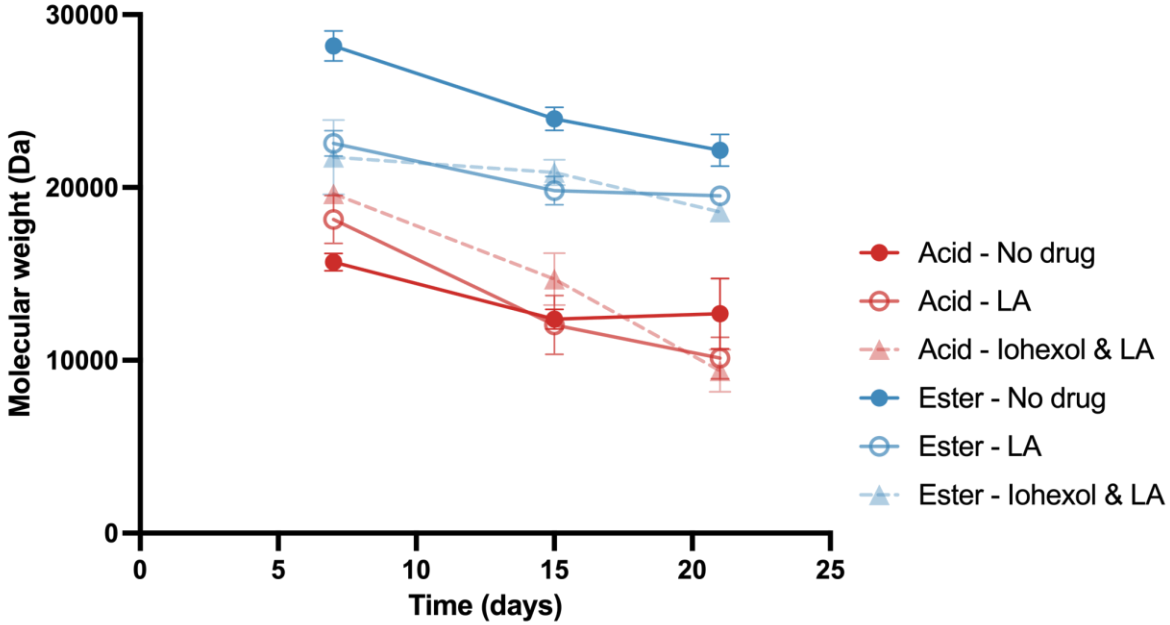






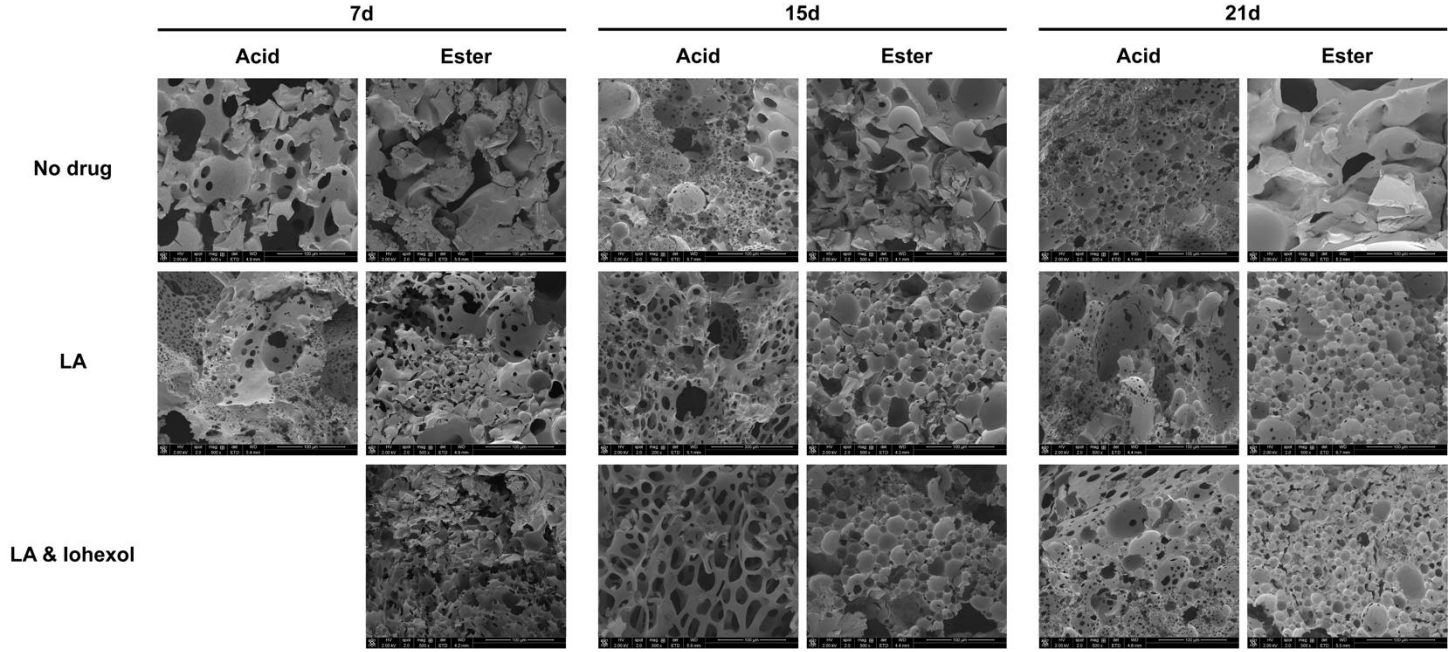
- Weight and volume showed the similar trend.
- Group with acid-ending PLGA reached the peak later than the group with ester-ending PLGA.
- Volumes and weights of implants formed by ester-ending PLGA remained stable after 11 days, corresponding to the stable period of LA release and slow polymer degradation.
- Volume and weight decrease appeared in the group of No Drug.

Impact of PLGA endcaps on the implant formation and degradation – *GPC*



- Less extent of degradation of PLGA in formulations with ester-ending PLGA.

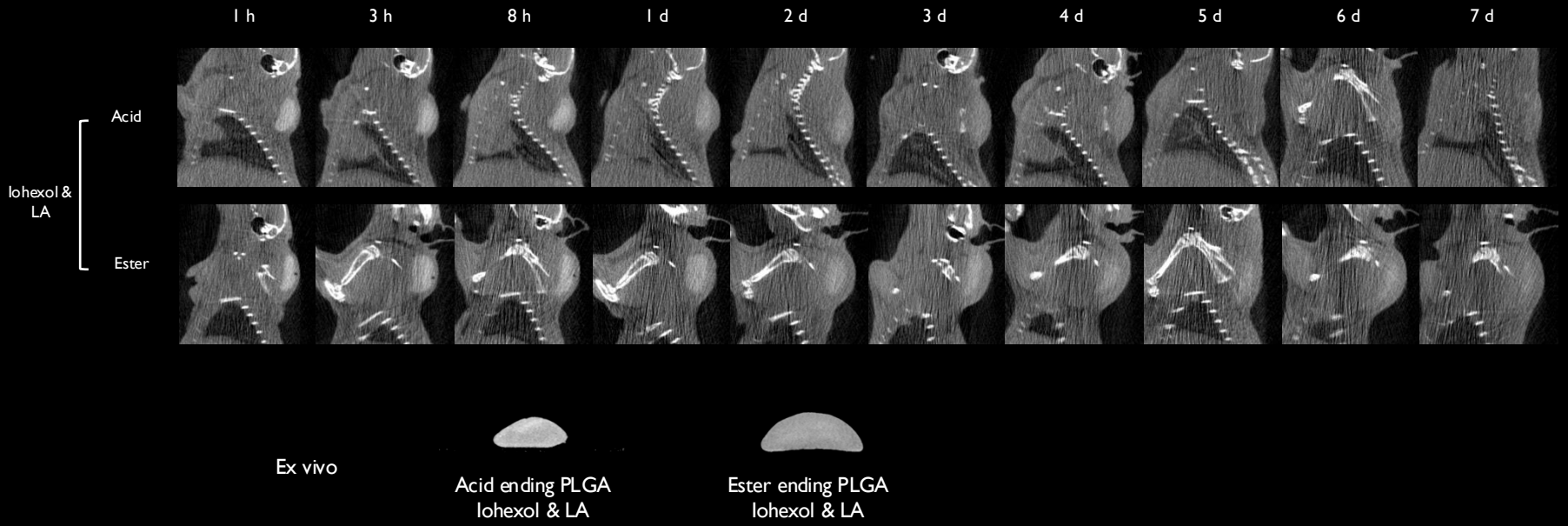
Impact of PLGA endcaps on the implant formation and degradation – *SEM*



- Acid-ending PLGA: Porous microstructure with uniform distribution, high degree of interconnectivity
- Ester-ending PLGA: Porosity varies depending on leuprolide acetate

Impact of PLGA endcaps on the implant formation and degradation

– *In vivo formed implants*



Spheroid-like morphology

Size expansion of *in vivo* formed implant with ester-ending PLGA.

Summary II

Impact of PLGA endcaps on the implant formation and degradation

- Ester-ending PLGA inhibits the burst release of drugs and solvent. However, the lack of high-intensity edge promotes the solvent diffusion and reaches the plateau earlier.
- Both solvent release kinetics and hydrophobicity of the drug influence the drug release profile.
- Polymer matrix swelling with ester-ending PLGA induces the irregular shape of the *in vitro* formed implants.
- *In vivo* formed implants showed similar trend of size expansion. However, because of tissue and skin pressure, implants with both endcaps of the PLGAs showed spheroid-like morphology.

Acknowledgement

Collaborators

Michael Jay, Ph.D. (UNC)
Hong Yuan, Ph.D. (UNC)
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