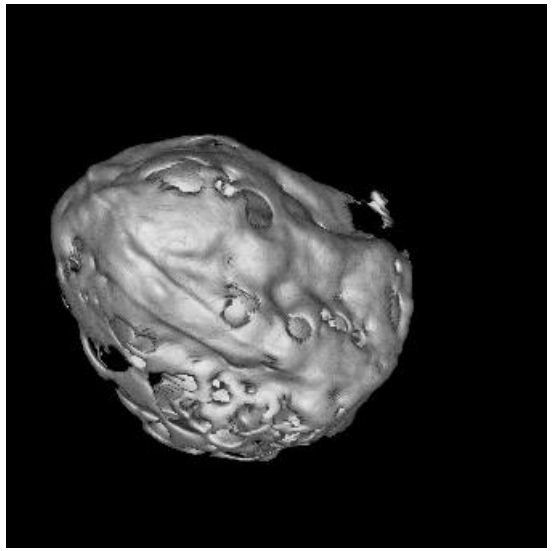

Imaging *In Situ* Forming Implants for Advanced Characterization

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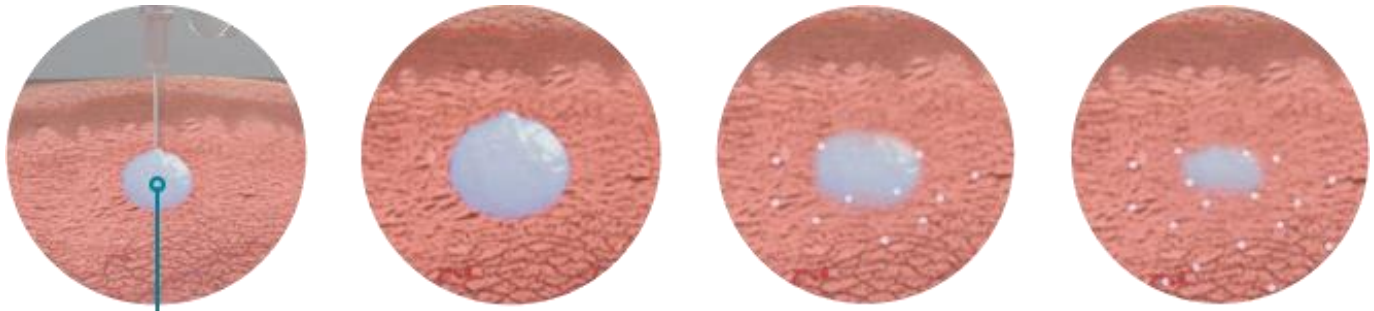
Background



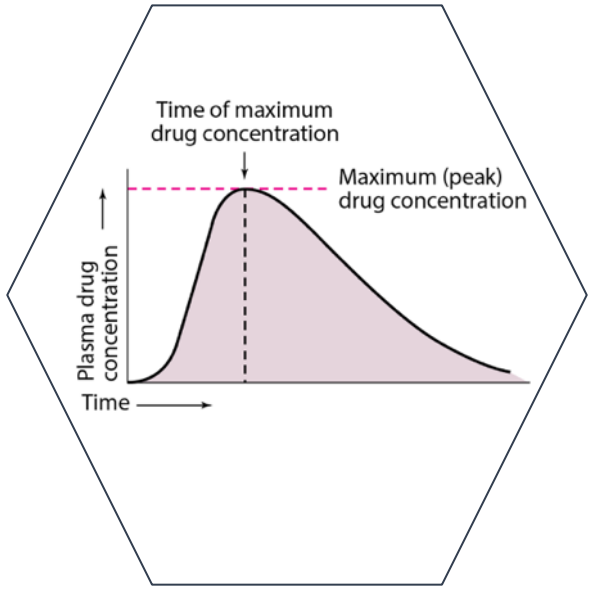
ELIGARD® injects as a liquid into subcutaneous tissue and remains in-situ as it slowly biodegrades over the intended dosing interval

Sustained release **Improved patient compliance** **Compatibility** **Simple manufacture process**

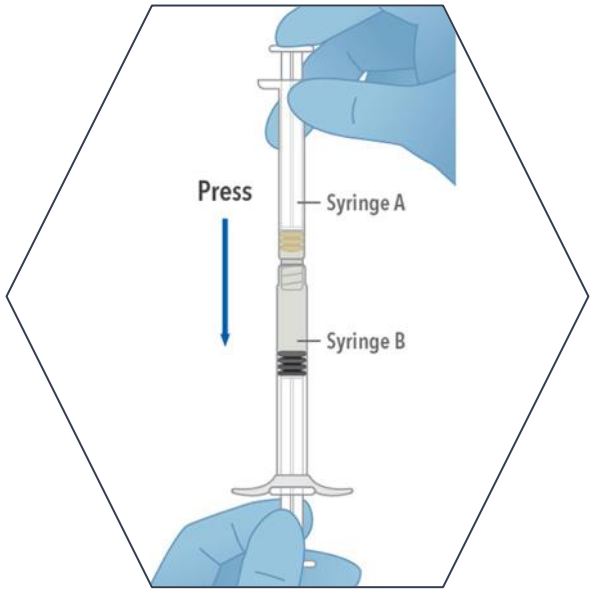
http://eligard.com/about-eligard/how-eligard-works/

Challenges

No standard *in vitro* drug release method



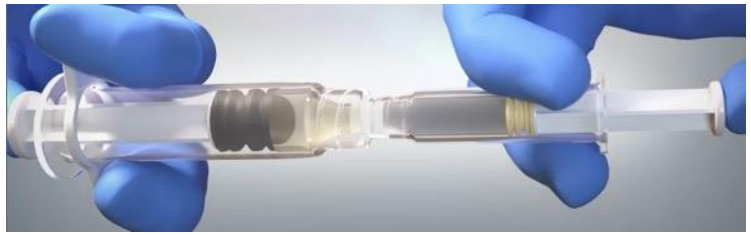
Variation in pharmacokinetics study



Lack of complete understanding of what parameters would affect the implant formation and the drug release

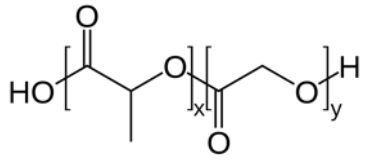
Overview

Eligard ®

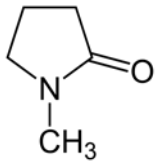


Atrigel ®

Iohexol
Leuprolide
acetate (LA)

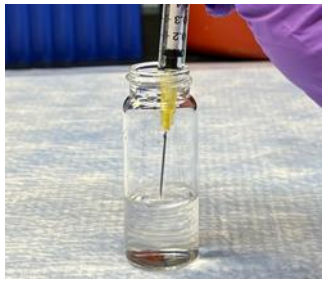


PLGA
(poly(lactic-co-glycolic acid))
50:50, 25.8 kDa

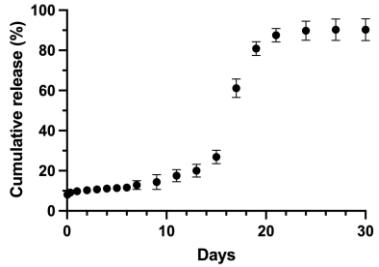


NMP
(N-Methylpyrrolidone)

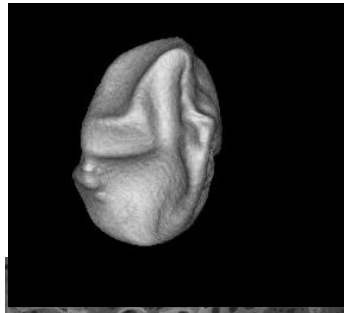
in vitro



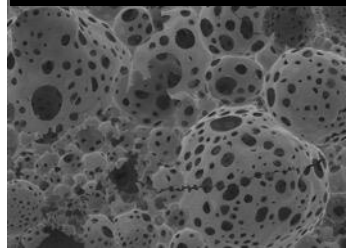
In vitro release study



CT imaging

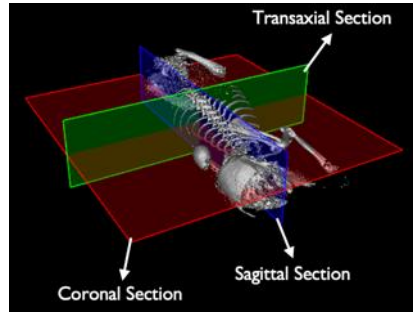


SEM

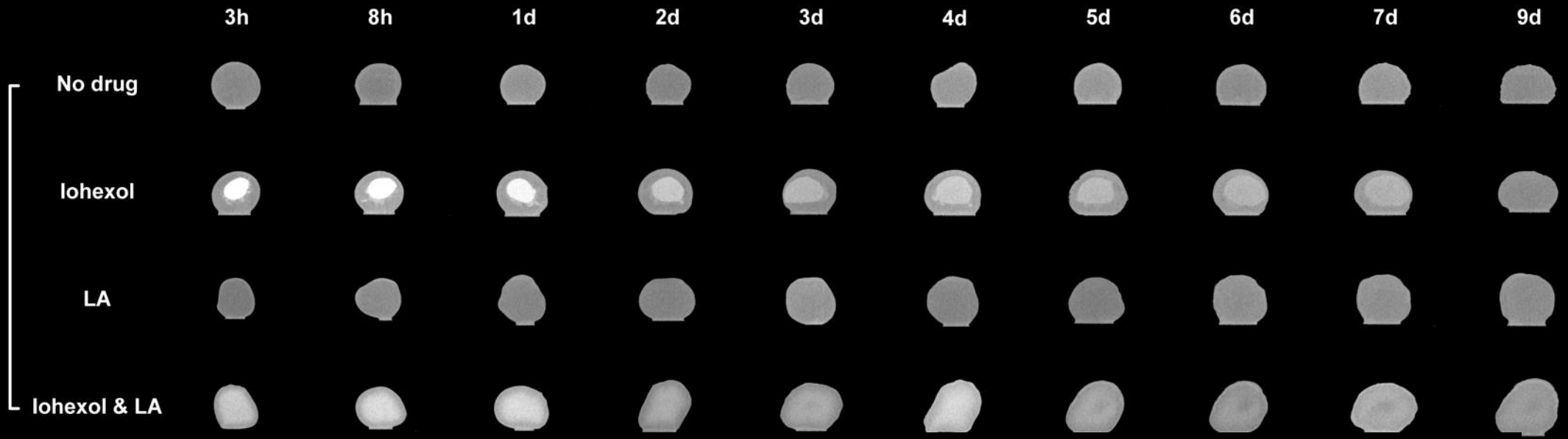


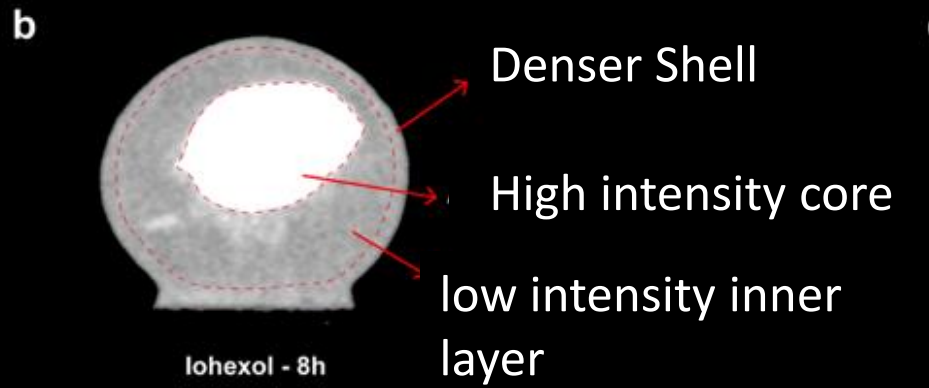
in vivo

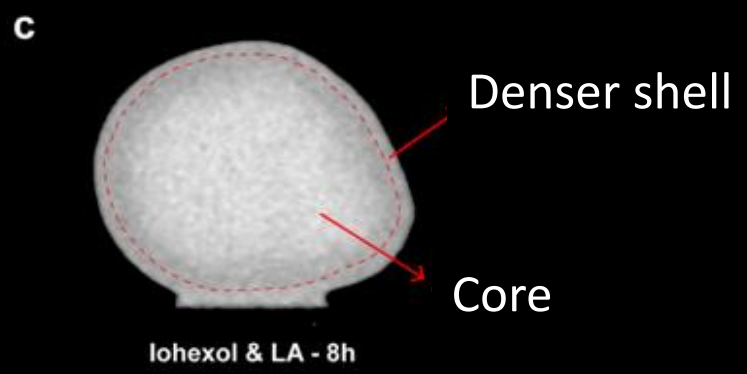
CT imaging



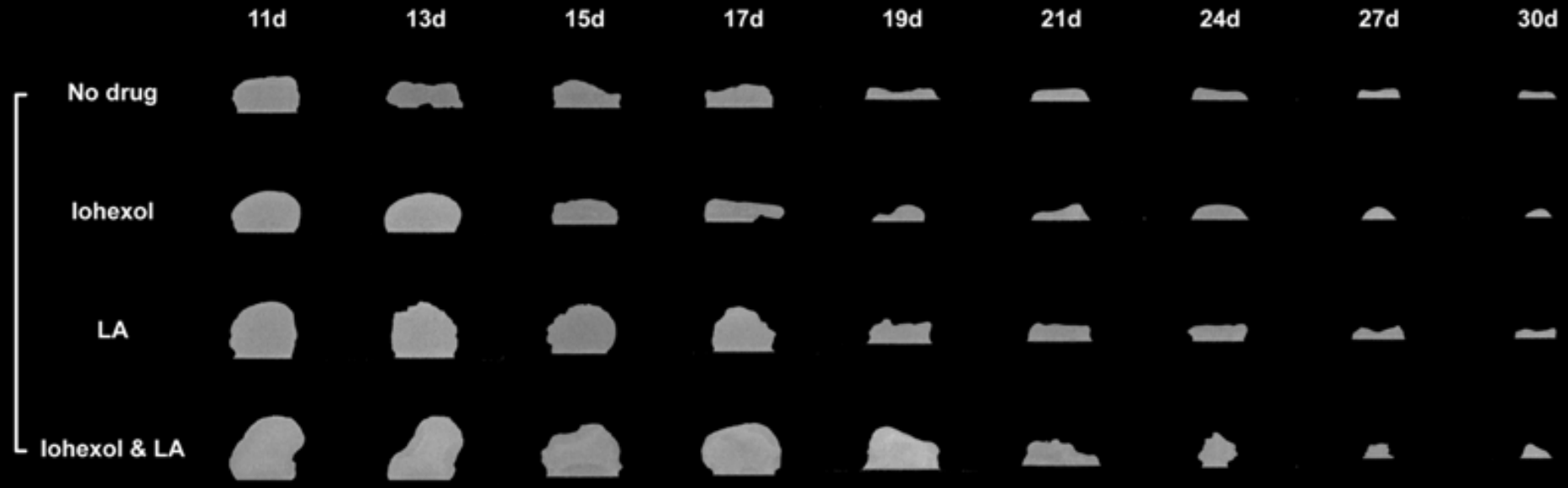
In vitro formed implants
– *CT imaging*







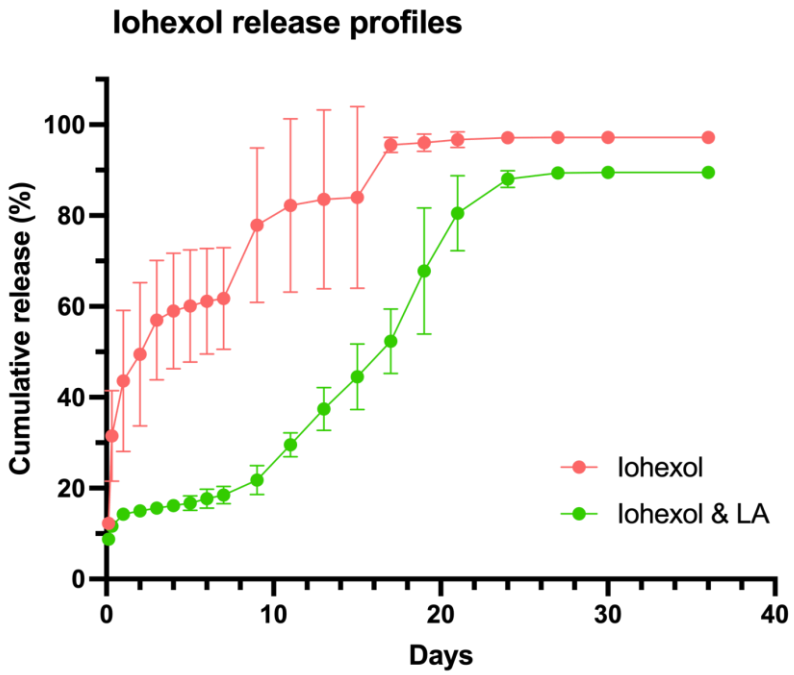
In vitro formed implants
– *CT imaging*

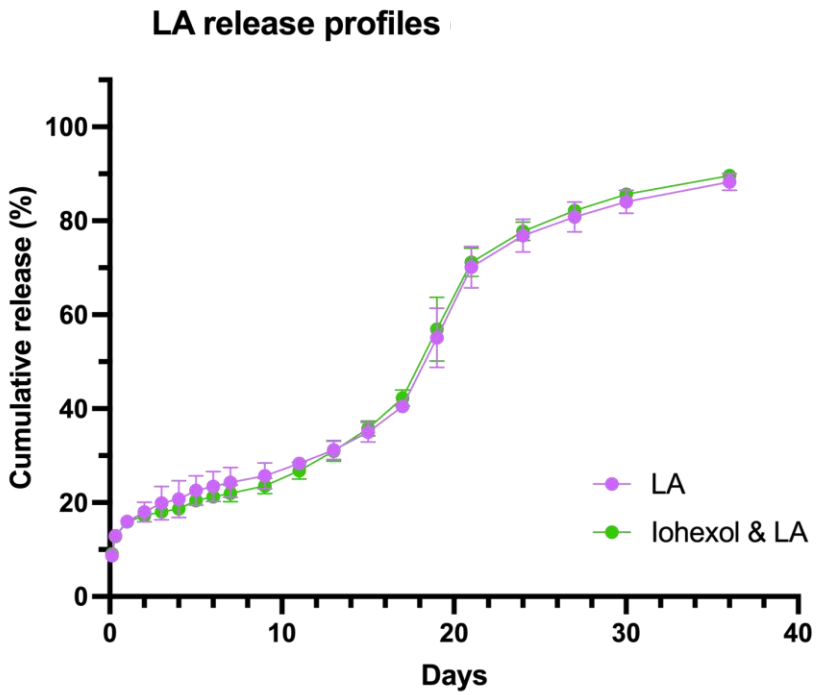


- **Morphology:** Spherical, size decrease
- **Thin shell:** Until 9-11d
- **Texture surface:** Starting on 7-11d

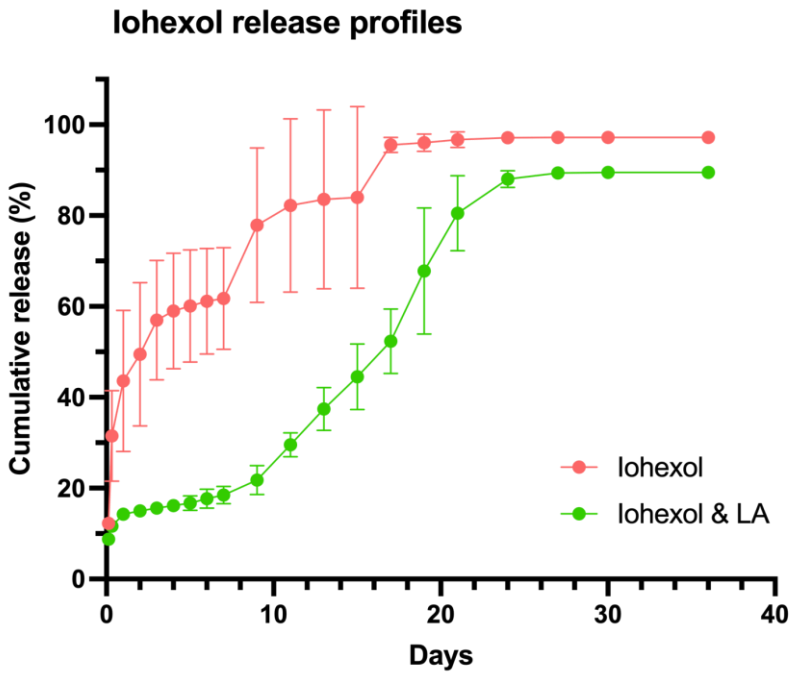
- **Inner structure:**
  Core shell structure of Iohexol distribution (Iohexol)
  Vague boundary between the core-shell structure (Iohexol&LA)

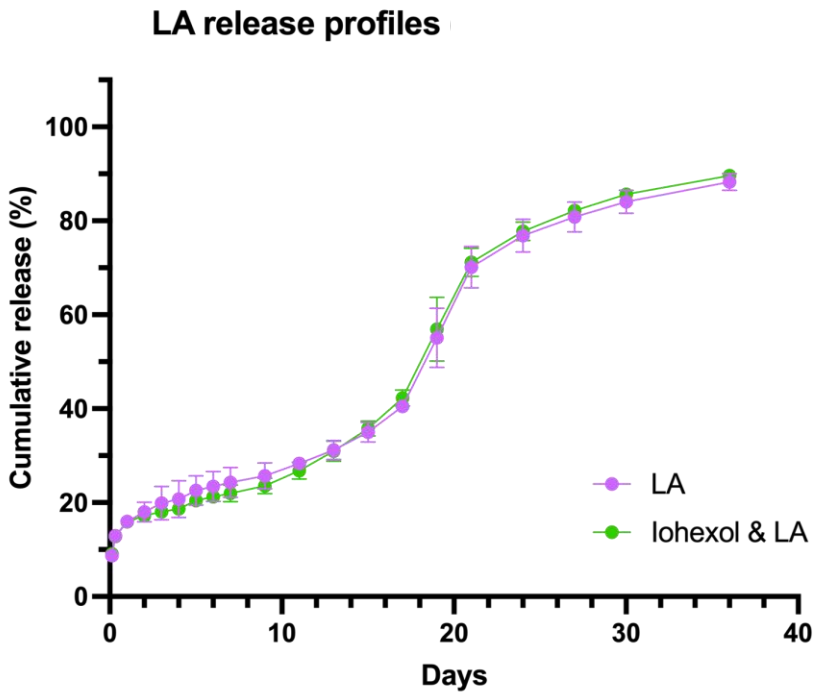
In vitro formed implants
– *In vitro* release profiles

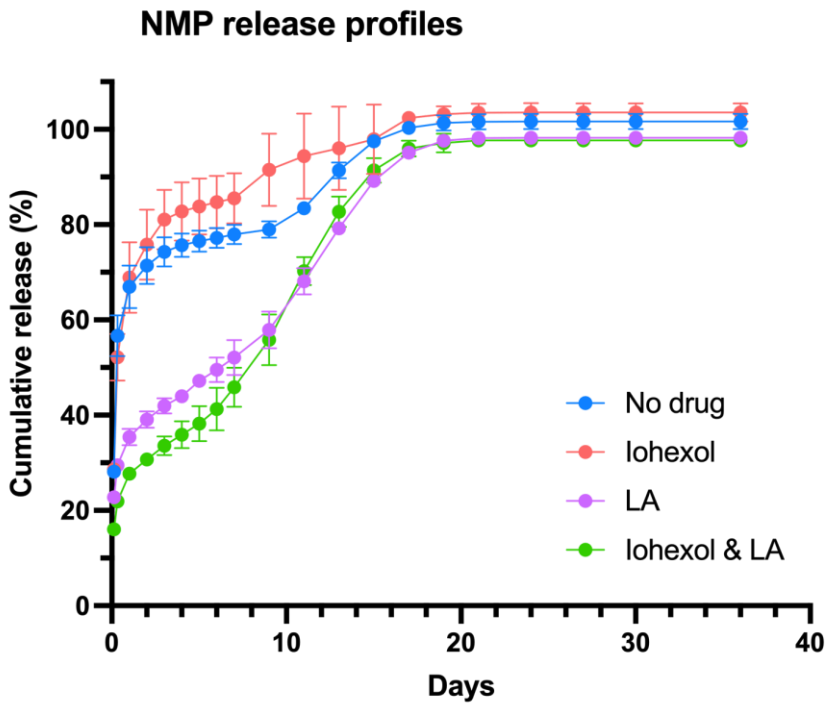




In vitro formed implants
– *In vitro* release profiles

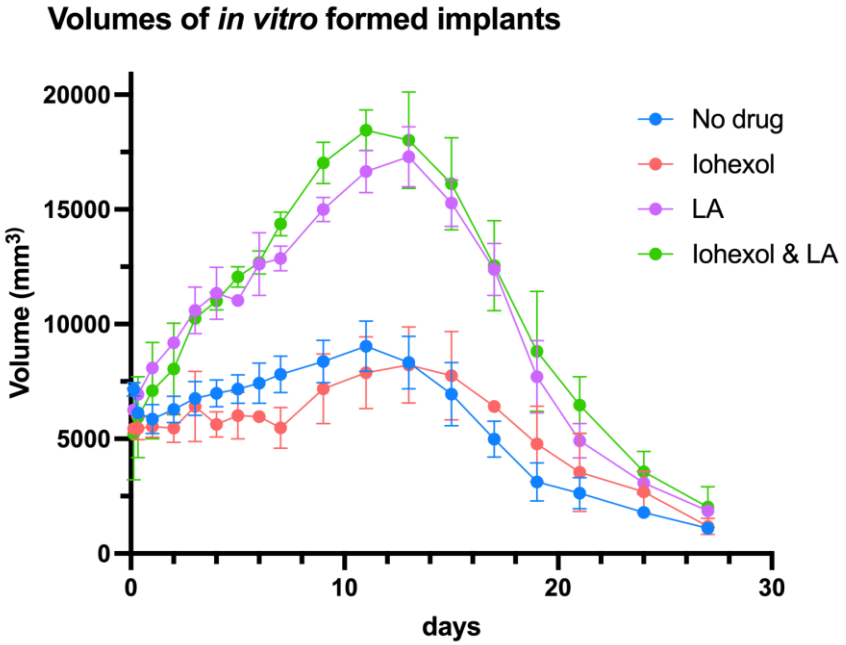


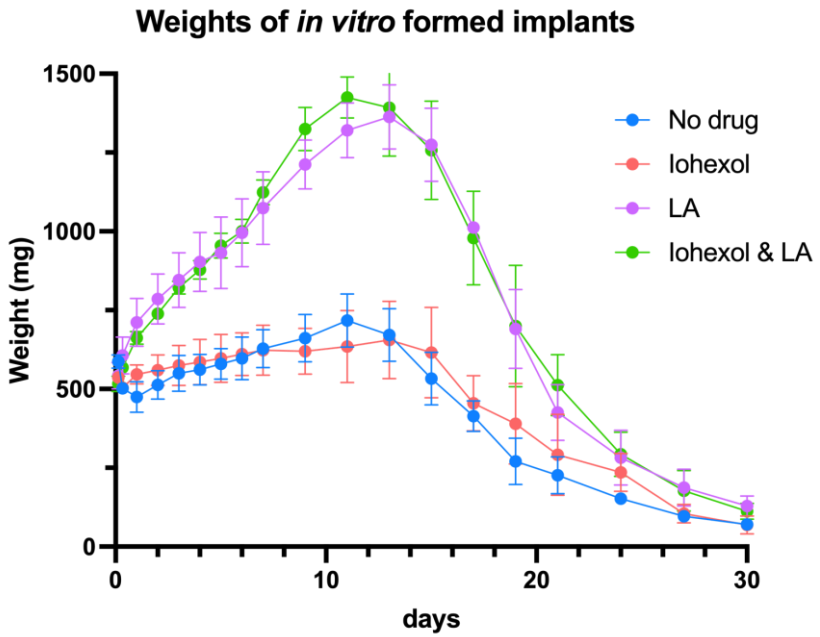


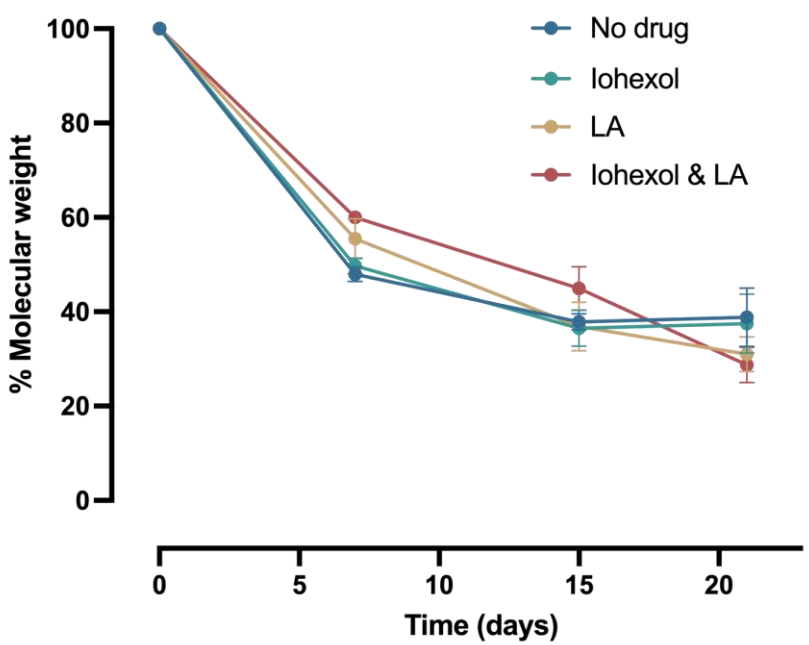


- Iohexol release is consistent with solvent NMP release
- Leuprolide acetate affects NMP release, and thus changed iohexol release when mixing with leuprolide acetate

In vitro formed implants
– *Volume, weigh, PLGA degradation*

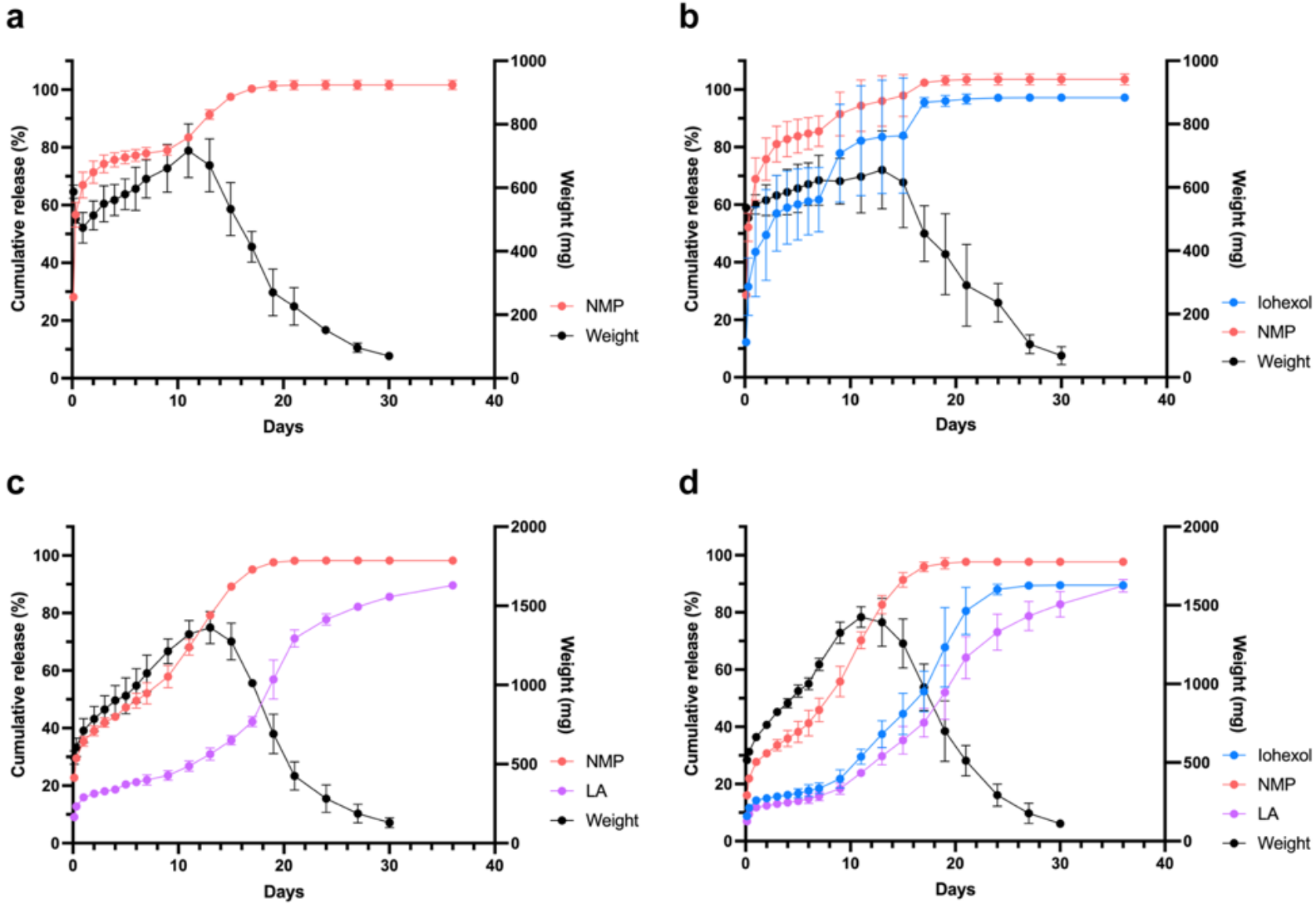






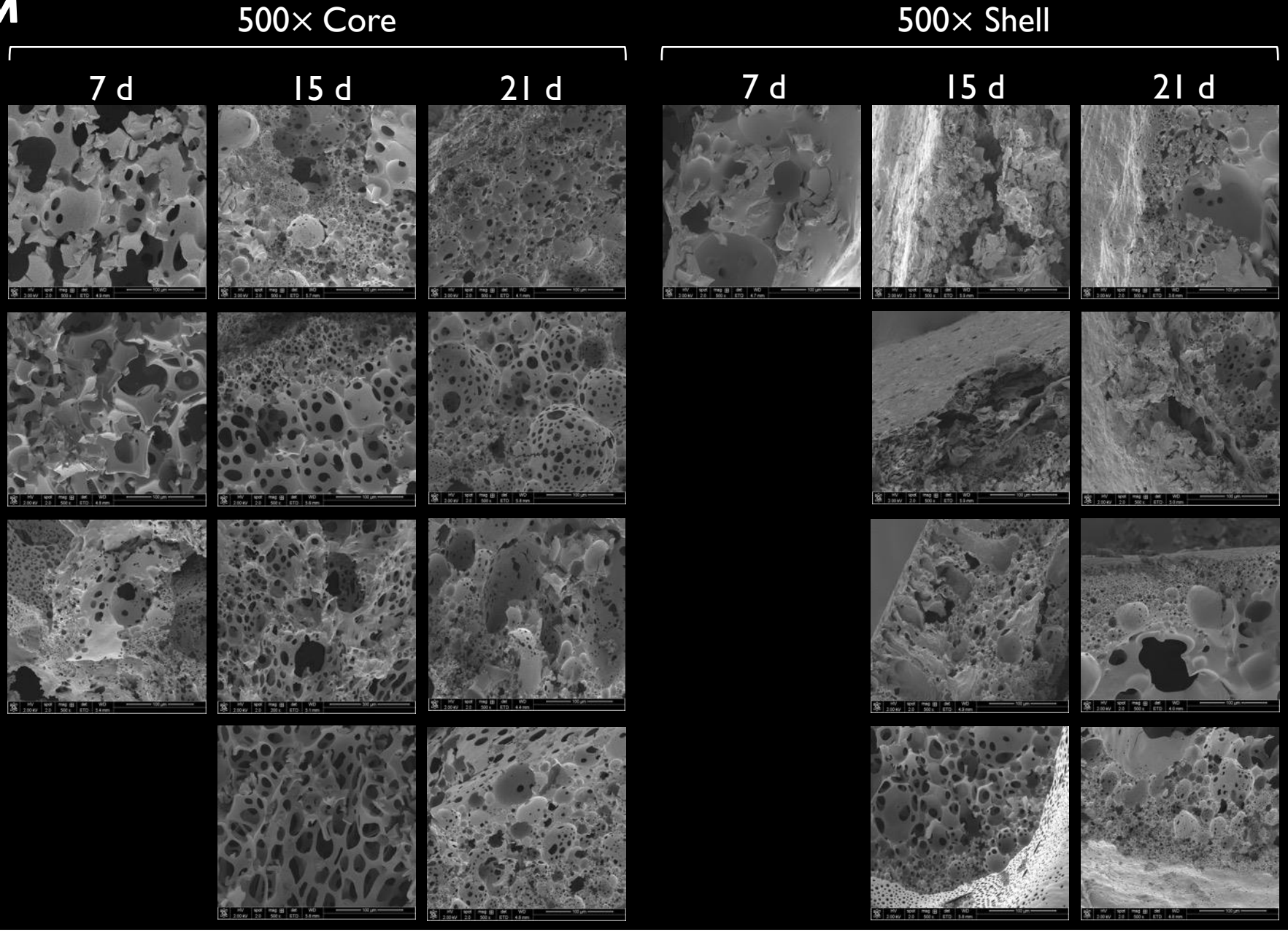
- Volume and weight changes are consistent.
- Addition of leuprolide acetate promoted the weight increase of the implants.
- Weight decrease at early time points was observed in a few formulations with higher extent of NMP burst release.

In Vitro Release and Weights

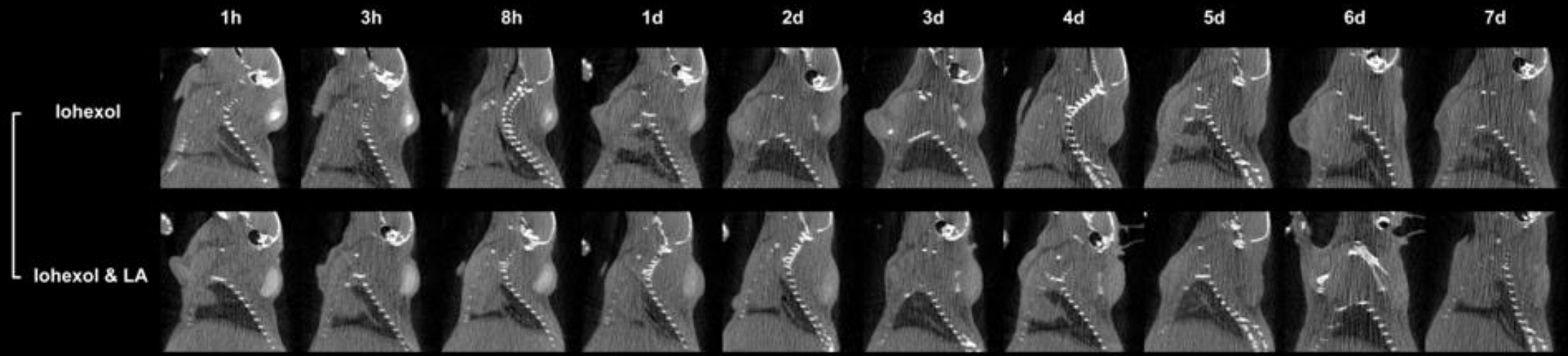


***In vitro* release profiles combined with the weights of the implants.** (a), No drug. (b), Iohexol. (c), Leuprolide acetate. (d), Leuprolide acetate and iohexol. All error bars are equivalent (s.d. positive and negative values) and represent standard deviation with $n = 3$.

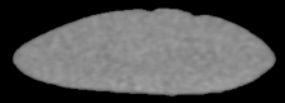
In vitro formed implants – *SEM*



In vivo formed implants – CT imaging



PLGA
Iohexol



PLGA
Iohexol & LA

Comparison with *in vitro* formed implants:

Similarity:

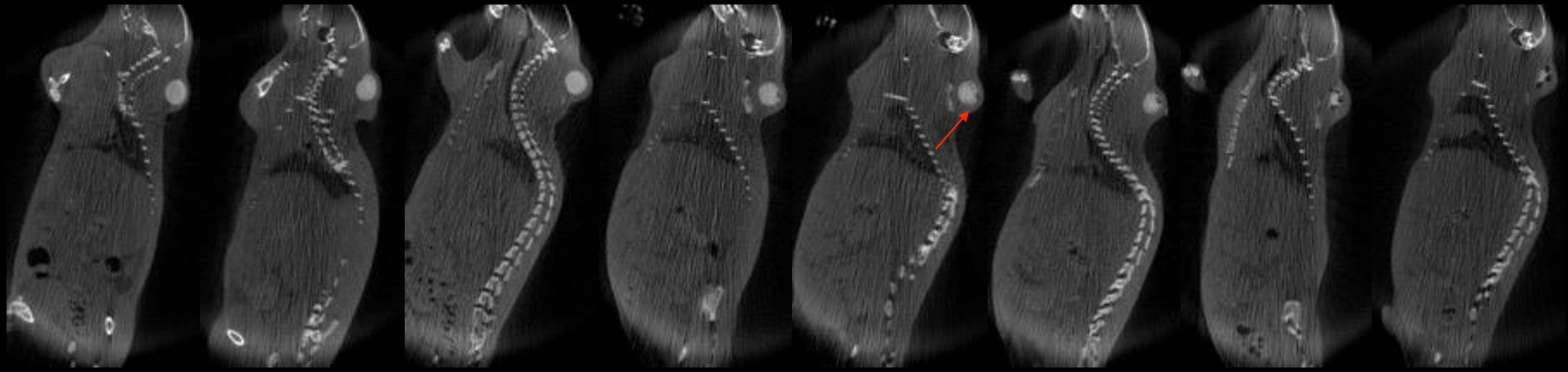
- Core-shell structure of the iohexol deposition and scattered iohexol
- Size expansion

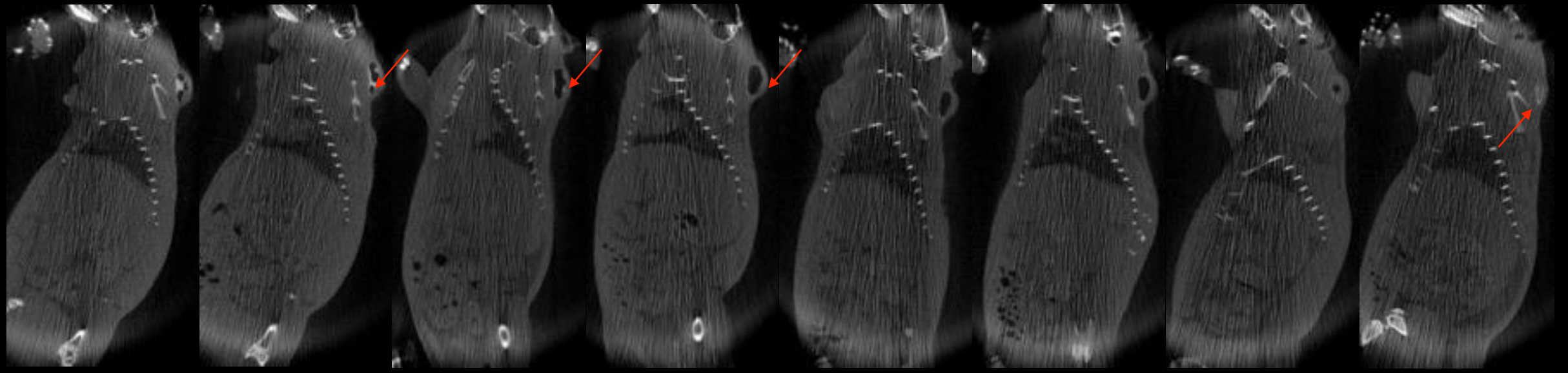
Difference:

- Process of the evolution is faster when implants are formed *in vivo*.

Implant Using PLGA from a Different Vendor

Coronal Sections





Summary

- 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.
- Implants made from different vendors of PLGA showed different *in vivo* implant morphology and inner structure changes.

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Collaborators

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