Assessing In Situ Forming Implant Formulations Using In Vivo Imaging

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PURPOSE

In situ forming implants (ISFI) have attracted increasing attention due to their sustained release property and good compatibility with a variety of molecules, including small molecules, peptides, and antibodies. The implant formation process can significantly affect the morphology of the implants and drug release profiles. However, there are limited approaches to investigate the implant formation process in real time.

We developed a non-invasive imaging approach in order to obtain improved understanding of *in vitro* and *in vivo* implant formation and degradation. The impact of drugs in the formulations on the morphologies of the ISFIs was also explored.

METHODS

An X-ray computed tomography (CT) contrast agent, iohexol, was used for imaging to observe implant formation. To prepare the injectable formulation, poly(lactic-co-glycolic acid) (PLGA) copolymer (50:50, acid endcap, 25 kDa) was dissolved in N-methyl-2-pyrrolidone (NMP) and then iohexol and leuprolide acetate (LA) were added to the PLGA gel.

- For *in vitro* formed ISFIs, 250 µL of the formulation was injected into sample vials with 10 mL PBS (pH 7.4) and maintained in a bath shaker at 37°C. *In vitro* release test was conducted by replenishing medium at each time point. The volumes and weights of the implants were measured at each time point. *In vitro* formed ISFIs for scanning electron microscope (SEM) imaging and molecular weight measurement by gel permeation chromatography (GPC) were also subjected to the same conditions described above.
- For *in vivo* formed implants, the same volume of the formulation was administered subcutaneously to rats (n=5). CT images were obtained using the IVIS Spectrum CT system (PerkinElmer, USA).

RESULTS

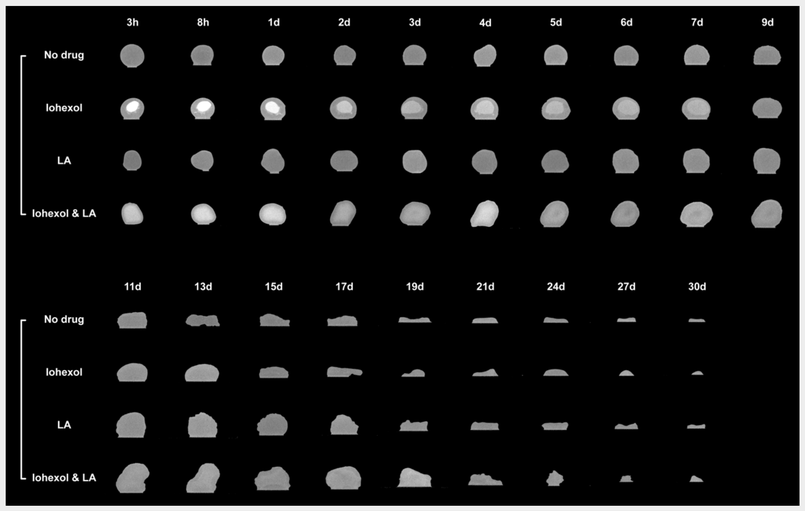

Figure 1. IVIS spectrum CT images of *in vitro* formed ISFIs with different drug compositions.

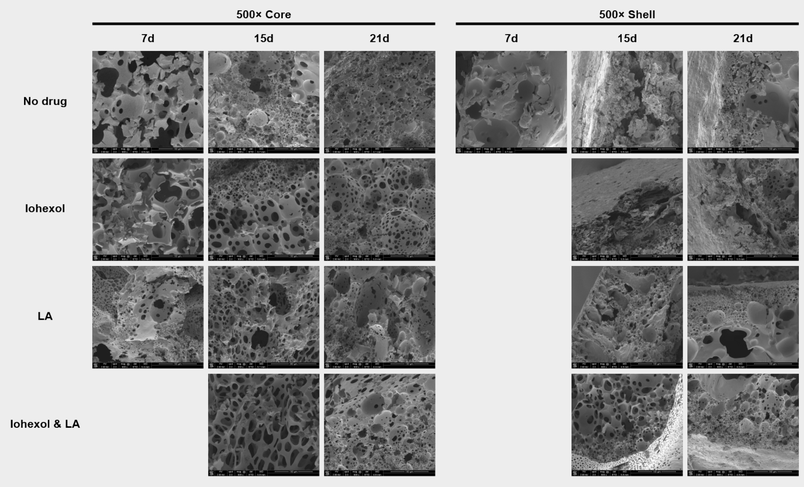

Figure 2. SEM images of *in vitro* formed ISFIs.

CT images of *in vitro* formed implants: *(Figure 1)*

- Formation of thin shell under the surface of the implants until 9-11 days.
- A core-shell structure of the iohexol distribution with clear boundary and scattered iohexol signal from the core were observed for the formulation with only iohexol.

SEM images of *in vitro* formed implants: *(Figure 2)*

- Comparing with the core structures, the shell layer of the implant showed higher density and lower porosity from day 7 to 21, based on SEM images. Inner structure changes occurred faster when implants were formed *in vivo*.

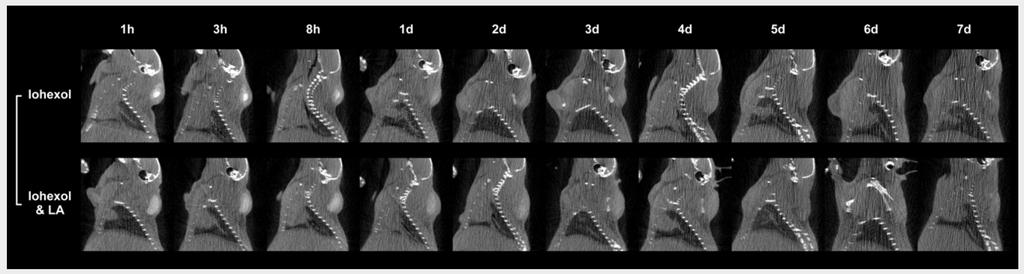

Figure 3. IVIS spectrum CT images of *in vivo* formed ISFIs with different drug compositions.

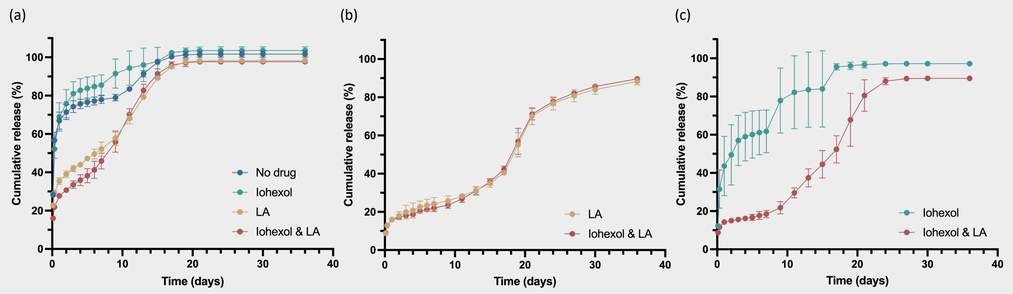

Figure 4. Mean and standard deviation of *in vitro* release profiles of ISFIs (n=3). (a) *in vitro* release profile of NMP, (b) *in vitro* release profile of Iohexol, (c) *in vitro* release profile of leuprolide acetate

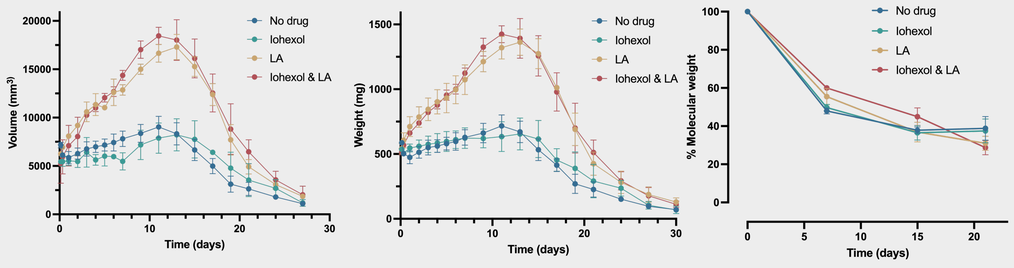

Figure 5. Volumes and weights of *in vitro* formed ISFIs and molecular weight of PLGA.

CT images of *in vivo* formed implants: *(Figure 3)*

- Implants formed *in vivo* showed similar morphologies and inner structures to *in vitro* formed implants.

***In vitro* release profiles:** *(Figure 4)*

- Addition of leuprolide acetate inhibited the burst release of NMP and iohexol.
- Leuprolide acetate showed prolongated release profile.

Volumes and weights of *in vitro* formed implants: *(Figure 5)*

- Formulations with high extent of burst release showed volume and weight decreases at the beginning. Moreover, formulation with leuprolide acetate showed higher extent of weight and volume increase, indicating the more water uptake.
- Volumes and weights increased in a consistent manner and reached the peak at 11 days.

CONCLUSIONS

- Inner structure and drug distribution inside the ISFIs are unveiled by CT imaging.
- Addition of hydrophobic drug in the formulation inhibits the solvent exchange and promote the size expansion and weight increase.
- Changes in the implant's inner structure happen faster in vivo than in vitro

FUNDING

The authors would like to acknowledge the U.S. Food and Drug Administration for financial support of this research (contract number: 75F40120C00136).

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.