W1030-02-08

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. However, there are limited approaches to investigate the implant formation process in real time. We developed a non-invasive imaging approach to obtain an improved understanding of implant formation and degradation. The impact of the addition of drugs on the morphologies of the ISFIs was also explored.

OBJECTIVE(S)

- To observe the morphology and inner structure of *in vitro* and *in vivo* formed implants in real time
- To understand how the addition of drugs impacts on implant formation and drug release profile of each other.

METHOD(S)

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. 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 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).

RESULT(S)

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

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

SEM images of *in vitro* formed implants: *(Figure 5)*

- The shell layer of the implant showed higher density and lower porosity from day 7 to 21.

CT images of *in vivo* formed implants: *(Figure 2)*

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

***In vitro* release profiles:** *(Figure 3)*

- 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 4)*

- 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 more water uptake occurs.
- Volumes and weights increased in a consistent manner and plateaued at 11 days of study.

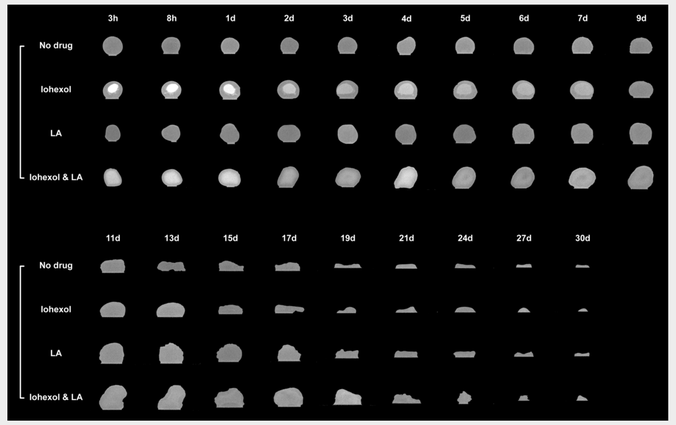

Figure 1. IVIS Spectrum CT images of *in vitro* formed ISFIs with different drug compositions.

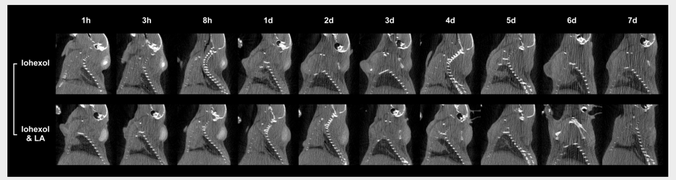

Figure 2. IVIS Spectrum CT images of *in vivo* formed ISFIs with different drug compositions.

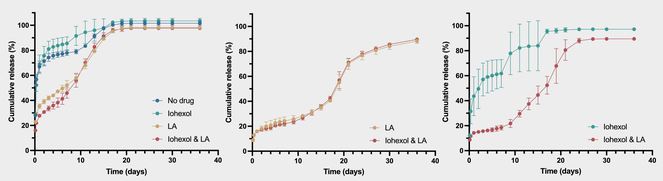

Figure 3. Mean and standard deviation of *in vitro* release profiles of ISFIs (n=3). (a) *in vitro* release profile of NMP, (b) *in vitro* release profile of Iohexol, (c) *in vitro* release profile of leuprolide acetate

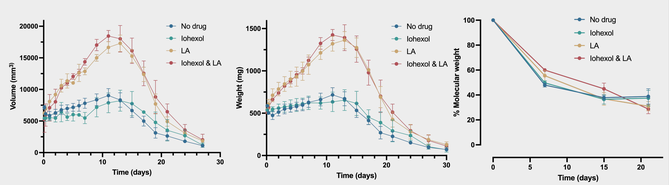

Figure 4. Volumes and weights of *in vitro* formed ISFIs and molecular weight of PLGA.

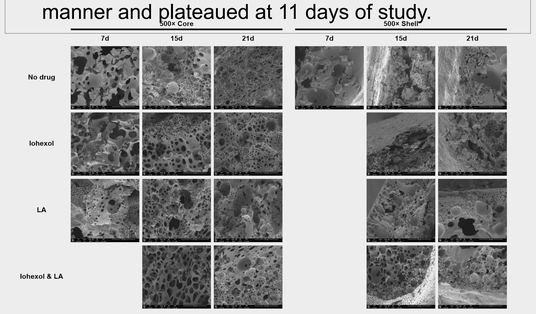

Figure 5. SEM images of *in vitro* formed ISFIs.

CONCLUSION(S)

From *in vitro* formed implants:

- Inner structure and drug distribution inside the ISFIs are unveiled by CT imaging.
- Addition of hydrophobic drug, leuprolide acetate, in the formulation inhibits the solvent exchange process and leads to slower drug release.
- Volume expansion and weight increase are observed for formulations with leuprolide acetate.
- Degradation rates of PLGA are faster for formulations with leuprolide acetate during the polymer degradation-driven release period.

From *in vivo* formed implants:

- Both *in vitro* and *in vivo* formed implants share the same process of implant formation.
- 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).