Pilot Investigation of Sustained Leuprolide Delivery Through a Novel Implantable Personalized Molecular Drug Delivery System with 3 nm Nanochannels

**Introduction**

- The gastrointestinal tract presents many obstacles preventing successful delivery of an active pharmaceutical ingredient (API) including gastric pH changes, highly reactive enzymes and biological defense systems.

- In order to overcome these, peptide/polymer therapies often require frequent injections creating patient compliance issues.

- Pulmonary protein therapy researchers have developed suitable drug formulations. However, these formulations have a number of issues including but not limited to difficulty in manufacturing/formulation stability problems, clearance by macrophages and other cells, and formulation rejection from the respiratory tract making intratracheal delivery difficult.

- Therefore an implantable drug delivery device capable of prolonging therapy, while reducing maintenance to highly desirable.

- Deliverables of an implantable drug delivery device include:
  - Reduction in the frequency of drug administration over duration of treatment
  - Increase in therapeutic agent circulating concentration
  - Easier of intravesical chemotherapy
  - Safe with strong mechanical strength

- Nanoscale systems have developed a novel drug delivery device for intravesical treatment.

- The prototype device was an enameled titanium capsule. (Figure A) containing a nanochannel delivery system (NCDs) (Figure B) into and internal Niobium stent to be inserted suburethrally.

- Release of the API is controlled by diffusion through the 3 nm slit in independent of zone solution concentration.

- Validation of the 3 nm slit allows for alteration of the release rate such that desired rate is achieved for a given API.

**Materials and Methods**

- **Leuprolide Acetate**: Prolivex Laboratories, San Diego, CA
- **Benzalkonium Chloride (BNK)**: Aesar Organics, New Jersey, NJ
- **Silver Sulfate (SS)**: Sigma-Aldrich, St Louis, MO
- **Niemann-Pick C1 Like 1 Cationic Liposome (NPC1)**: Invitrogen, CA
- **Protogen Implantable Drug Delivery Systems (Nanoliberal Systems, Austin, TX)

**In Vitro Dissolution**

- **LA solution (40 mg/mL)**: prepared in saline solution (0.9%) with 0.01% BNK as a preservative
- **CG solution (40 mg/mL)**: prepared in saline solution (0.9%) with 0.01% BNK as a preservative
- 1 ml of solution filled into each assembled capsule
- Assembly placed in pH5 buffer solution approximating a small volume vessels. Each vessel contained 100 mL, 24/24 mL of 37% and 17% assembled capsule

- Total amount of LA to 52.0 mg to ensure homogeneous dissolution media during sampling
- Samples (1 mL) were drawn at each time point, analyzed for leuprolide by HPLC. RA was analyzed with pre-column derivatization using FITRAM (Fast Urban, FL)
- HPLC equipped with 4.6 mm i.d., 25 cm long column packed with 5 μm silica (Nanotech, CA) with 0.6 mL/minute flow rate detected at 230 nm.

**In Vitro Study**

- All animal work was performed at the Texas A&M Institute for Preclinical Studies, under approval from the Institutional Animal Care and Use Committee.

- Under sterile conditions, 3 mice devises were filled with LA solution and implanted into nude mice (6 per group).

- Blood samples collected at predetermined time points.

- Leuprolide and testosterone serum levels quantified by LC/MS/MS.

**Results**

- Sustained release was achieved in vitro, average release rate 2.7 ng/mL.

- Plasma testosterone concentration was maintained at a high level. (Figure C)

**Hypothesis**

The novel implantable DDS incorporates time nanochannels and will provide sustained release of leuprolide acetate over a prolonged period of time. This will provide long term therapeutic effect in locally treating bladder cancer.

**Conclusions**

- The assembled DDS provided the release of leuprolide acetate through 3 nm nanochannels for a prolonged period of time.
- The device provided a long-term therapeutic effect in vivo, with no interference by releasing plasma testosterone levels.
- Nanoscale systems have developed a biocompatible device delivered through it's nanochannels.
- Use of the DDS in vivo studies in reduction in the frequency of drug administration over duration of treatment.
- Device is readily retrievable for therapy termination.
- The minimal construction provides strong mechanical strength increasing safety post implantation.

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**References**