In Vitro - In Vivo Evaluation of a Biodegradable Implant Containing TAF for HIV PrEP

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Abstract 420

Overview

Despite great successes, current pre-exposure prophylaxis (PrEP) approaches remain plagued with suboptimal adherence. Alternative long-acting injectables are non-removable and exhibit first-order kinetics with extended sub-optimal dosing and resistance risks. We developed a user-independent mechanism of arthrotidal (ARV) delivery that uses a biodegradable, retrievable, subcutaneous implant we call the thin-film polymer device (TFPD). The TFPD design controls ARV release kinetics by drug solubility, film properties and device geometry. Here, we assessed release of Tenofovir (TFV) Alafenamide Fumarate (TAF) from TFPDs containing polycaprolactone (PCL) films. We aimed to establish a correlation between in vitro studies and in vivo experiments in the rabbit model to inform device design for dose targeting, to ultimately achieve sustained, zero-order release kinetics of TAF.

Materials and Methods

- **Tenofovir Alafenamide Fumarate (TAF)** – nucleotide reverse transcriptase inhibitor (NRTI) (Figure 2).
- Dosing Target Range: ≤ 2.8 mg/day (equivalent to 8 mg oral dose) or as low as 0.14 mg/day.
- This molecule was chosen due to its potency and chemical properties (i.e., water solubility). With limited implant volume, a lower dose translates to a longer possible release period.

**Fabrication of films and TFPD prototypes**

- Films were fabricated via a solvent cast process from solutions of 80:20 DDE (Sigma Aldrich) in toluene to produce 250 µm film thicknesses.
- Prototypes were fabricated by forming films into an open-ended hollow rod and loaded with a CMC surfactant (1% w/v) in a 2:1 weight ratio. A heat sealer was used to form continuous seams. Dose was adjusted by scaling the surface area of the devices for each dosing group.

In Vitro Release of TAF from the TFPD

- TFPDs were evaluated in female New Zealand White rabbits at 3 dosage levels (mg/day) and vehicle control (PEO20, n=6) over a 1-month period.
- Under aseptic surgical conditions, the implants were subcutaneously inserted in the dorsal-scapular region and blood samples were collected at 1, 3, 7, 10, 14, 21, 30, 38, and 45 days.
- Blood was collected in EDTA (K3) tubes for TFV levels in this dosage group were sustained over the same period, at a concentration of approximately 20 ng/mL.

In Vivo Evaluation

- Release of TAF from prototype implants in vivo was evaluated in phosphate buffered saline (PBS) pH 7.4 in a shaking incubator at 37°C and 120 rpm. Appropriate volumes (30 mL) and exchange rates (1-3 mL) were maintained to ensure sink conditions. Concentrations of TAF in buffer were quantified via ultraviolet (UV) spectrophotometry.

In Vivo Evaluation in Rabbits

- TFPDs were evaluated in female New Zealand White rabbits at 3 dosage levels (mg/day) and vehicle control (PEO20, n=6) over a 1 month period.
- Under aseptic surgical conditions, the implants were subcutaneously inserted in the dorsal-scapular region and blood samples were collected at 1, 3, 7, 10, 14, 21, 30, 38, and 45 days.
- Implants were retrieved and target tissue samples (vagina, cervix, rectum) taken on day 30 for half of the animals in each group. The remaining animals were euthanized on day 45.

**Drug concentrations were determined via liquid chromatographic-tandem mass spectrometric analysis. Here we report plasma TFV and TAF concentrations (ng/mL) and PBMC TFV diphosphate (TFV-DP) concentrations (mmol/10^6 cells).**

Figure 3. Cumulative in vivo release of TAF from devices measured by UV-Vis absorbance in PBS over 30 days (left). Cumulative release as a percentage of the total release from devices over 30 days (right). The in vivo devices released approximately 50% faster than intended. The actual in vivo release was quantified over the linear release period, determined as having an R² value > 0.95. These actual values were used for determining the in vitro/in vivo correlation, and are reflected in Table 1.

**Evaluation of TFPD Implants In Vivo**

- In vitro/in vivo correlation of TAF release in PBS to plasma concentrations of TAF (left) and TFV (right) after approximately 14 days.

- From the average data over the linear release period determined by in vitro release, a correlation was determined between in vitro TAF release and in vivo plasma TFV and TAF sustained concentrations. TAF concentrations for the lowest dosage group were insufficient at day 14 to determine a correlation. The correlation appears to be roughly linear with an R² value of 0.981 for plasma TFV concentration.

**Ongoing Development and Next Steps**

- TFV, TAF and TFV-DP concentrations in target tissues (vagina, cervix, rectum) collected in this study have been analyzed and will be presented at a later time.
- A single dose, 45 day study in rabbits (n=6) which aims to demonstrate non-convolution plasma levels of TAF for the duration, sustained PBMC TFV-DP levels for the duration and the TFPD implants are well tolerated is currently underway.

**References**


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