A Long-Acting Biodegradable Subcutaneous Implant for Tenofovir Alafenamide Fumarate HIV PrEP

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Introduction
Recent breakthroughs for HIV prevention show that therapeutic anti-retrovirals (ARVs) are effective for pre-exposure prophylaxis (PrEP). While only one product (oral Truvada) holds FDA approval, researchers are currently evaluating other ARVs and delivery systems for PrEP. Daily regimens or on-demand products are burdensome to users, and adequate protection from PrEP hinges on correct and consistent product use[2,3]. Here, we describe the early development of a biodegradable subcutaneous implant to deliver Tenofovir Alafenamide Fumarate (TAF) for HIV PrEP. The technology utilizes a biodegradable polycaprolactone (PCL) thin-film membrane to control release from a reservoir. The ARV release kinetics and PCL biodegradation are independently controlled, allowing for device retrieval during use, if needed.

Thin-Film Polymer Device

Device Fabrication: Devices were fabricated with solvent cast PCL films with a hollow rod with an open end using a wire-heated sealing apparatus. TAF was loaded into the reservoir with or without formulation excipients.

In Vitro Studies: Devices were sealed and incubated in PBS, pH 7.4 at 37°C and TAF concentration in media was measured over time. Sink conditions were maintained throughout. Relationships between release rate and device parameters were evaluated using devices with 10-30µm thick membranes and 50-320 mm² surface areas.

In Vitro release studies indicate that TAF release is linear and tunable with device geometry (surface area) and membrane thickness.

Experimental Methods

In Vitro Prototype Devices

Goal: Evaluate TAF release rates by tuning surface area or membrane thickness.

• Device volume determines loading capacity.
• Estimated loading capacity with 2:1 TAF:PEG300 formulation is 190 mg (2.5mm x 40mm rod-shaped device).
• Results: Release profile is linear until device nears depletion. Linear regression determines average release rate for each prototype group (mg/day).

In Vitro TAF Release From Thin Film PCL Devices

In Vitro TAF Stability in Device Reservoir

In Vitro studies In Parallel with PK Study

Goal: Evaluate in vitro TAF release rates, concurrent with PK studies in rats.

Approach: TAF (2:1, TAF: PEG300) release rates controlled via surface area of device over 14 days.

TFPD TAF Release Profiles - In Vitro Controls

In Vitro release studies indicate that TAF release is linear and tunable with device geometry (surface area) and membrane thickness.

Future Directions

Conduct in vivo PK and PD evaluations of subq inserted TAF – TFPD

• Preliminary Observations from Exploratory 14-day Rat PK Study (n=4, per study group):
  • TFPD was well tolerated in rats, without substantial irritation from devices. Groups 1 and 2 devices retained full integrity upon retrieval at day 14, with remaining TAF still present in the reservoir, as designed (see images).
  • Analyses of TFV concentrations in plasma and target tissues are ongoing.
  • Future studies in rabbits are planned to evaluate TAF plasma concentration and TFV-DP in PBMCs and target tissues.
  • Additional PK studies can help determine effective release rate for TAF PrEP

Conclusions

• PCL thin-film polymer device (TFPD) was developed for linear release of TAF over 3 months.
• TAF displays membrane-controlled release when formulated with PEG300 and appears stable in the device at 37°C, for at least 89 days in vitro.
• Release rate of TAF can be tuned in estimated target ranges by changing device geometry (surface area) and membrane thickness.
• In Vitro prototype devices demonstrate linear release profiles and tunable release rates.
• Ambient shipping and γ-sterilization do not impact TFPD performance nor TAF and polymer properties

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