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

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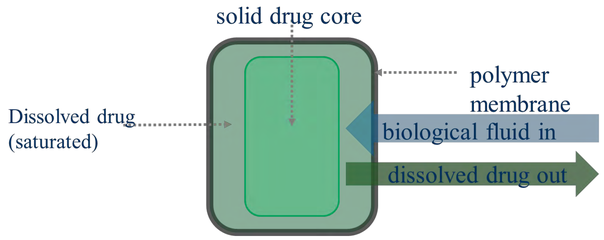
Introduction

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 regimen or on-demand products are burdensome to users, and adequate protection from PrEP hinges on correct and consistent product use[1,2,3]. 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



Full-scale TAF-TFPD prototype devices
4 cm long x 2-2.5mm diameter

Insertion devices for contraceptive implants*
[Jadelle, Implanon, Nexplanon]

**Contraceptive implants are rods 2-2.5mm diameter and up to 4cm long*

Experimental Methods

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

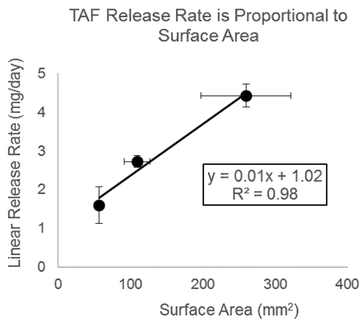
***In Vitro* Release Studies**: Devices were sealed and incubated in PBS, pH7.4 at 37˚C and TAF concentration in media was measured over time. Sink conditions were maintained throughout. Relationships between release rate and device parameters were evaluated using devices with 10-30µm thick membranes and 50-320 mm^2 surface areas.

ARV Stability: TAF chemical stability in the TFPD reservoir was evaluated by RP-HPLC. All data presented is the average of three replicate devices with error bars representing 1 standard deviation.

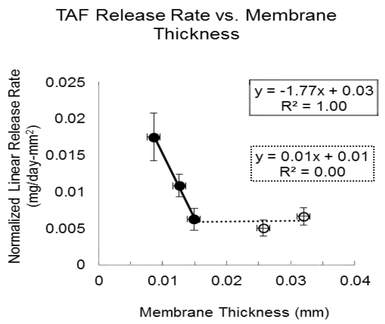
Tuning TAF Release Using Device Design

Goal: Evaluate TAF release kinetics from devices with different surface areas and PCL membrane thickness.

Conditions: All data here includes TAF formulated as a PEG_{300} slurry, which increases the rate of dissolution and solubility of TAF in the device reservoir to achieve membrane controlled release in potential target ranges (< 3 mg/day).



TAF Release From TFPD (PEG300 Formulation) 8.5µm PCL nonporous membrane

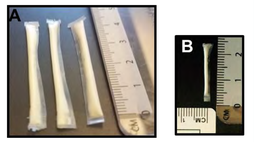


TAF Release From TFPD (PEG300 Formulation) 294 mm^2 (+/- 36) Surface Area

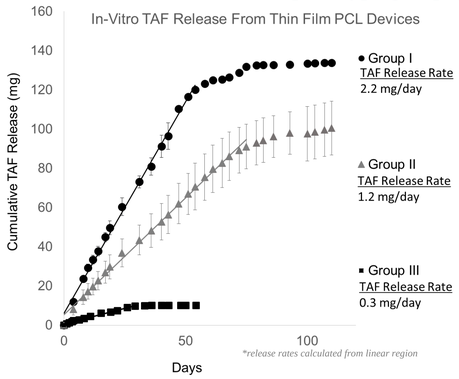
In Vitro Prototype Devices

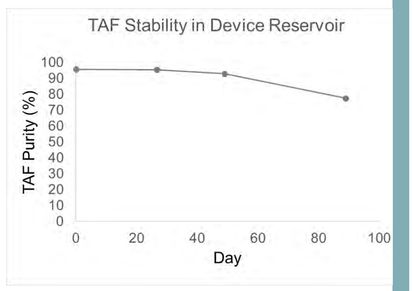
Goal: Evaluate TAF release rates by tuning surface area or membrane thickness.

- Device volume determines loading capacity.
  - Estimated loading capacity with 2:1 TAF:PEG_{300} 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).



Images of Prototype Devices





Group	Target Device Dimensions (Rod, DXL)	Membrane Area (mm^2)	Membrane Thickness (µm)	TAF Load (mg)	Predicted Device Duration (days)	Target Release Rate (mg/day)
I	2.5 x 40 mm	254 +/- 39	13 +/- 1	128 +/- 33	51	2.5
II	2.5 x 40 mm	238 +/- 3	32 +/- 1	115 +/- 10	82	1.4
III	0.6 x 20 mm	40 +/- 0.5	31 +/- 1	13 +/- 6	33	0.4

Target values are calculated based on compilation of data correlating membrane surface area and thickness to release rates.

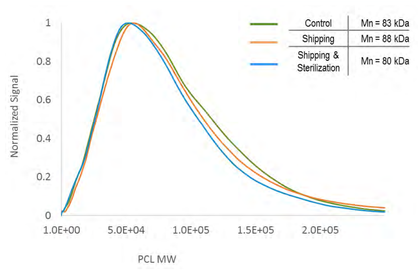
Ambient Shipping & Terminal γ-Sterilization

Results: Neither transcontinental (USA) ambient shipping during summer months nor γ-sterilization negatively impact device performance (release rates), polymer molecular weight, nor API stability. Minor increases in mass for loaded and unloaded TFPDs suggest a moisture uptake of 9-15 uL which could be mitigated in the future using standard packaging techniques.

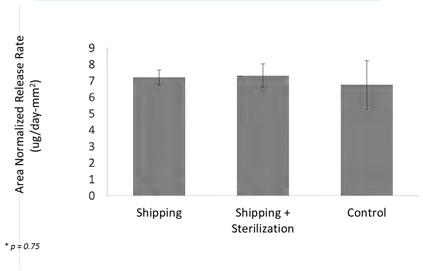
Shipping & Sterilization Study Results

	Surface Area (mm^2) (n=4)		Membrane Thickness (µm) (n=4)		Change in Mass (mg) (n=4)		Purity (n=1) (starting purity, 96%)
Formulation	Average	SD	Average	Condition	Average	SD	% TAF
TAF	115	6	10	Shipping	10	2	97
TAF	129	11	10	Shipping + Sterilization	11	4	96
TAF/PEG300 (1:1 w/w)	125	6	10	Shipping	9	0	93
TAF/PEG300 (1:1 w/w)	118	5	10	Shipping + Sterilization	12	0	95
Empty	205	40	10	Shipping + Sterilization	15	2	
Empty	121	15	20	Shipping + Sterilization	9	1	

Shipping & Sterilization Study
PCL Molecular Weight Distribution

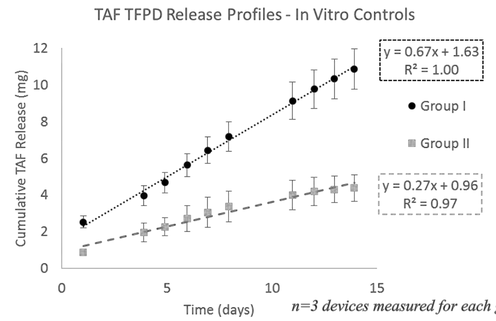


Shipping & Sterilization Study
Area Normalized Release Rate



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: PEG_{300}) release rates controlled via surface area of device over 14 days.



n=3 devices measured for each group

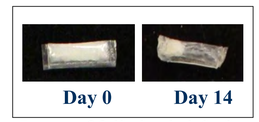


Image of fully loaded device before implantation (day 0) and partially depleted device after *in vivo* use (day 14)

Group	Device Dimensions (Rod, DXL)	Membrane Area (mm^2)	Membrane Thickness (µm)	TAF Load (mg)	Target Release Rate (mg/day)	Actual *in vitro* Release Rate (mg/day)
I	2 x 20mm	91 +/- 7	15 +/- 3	18	1.11	0.7
II	2 x 8mm	36 +/- 8	15 +/- 3	6	0.45	0.3

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 I and II 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 PEG_{300}, and appears stable in the device at 37ºC, 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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References

1. Baeten, J. , et al. (2013) Curr HIV/AIDS Rep. Published online: Mar. 14 2013 ; 2. Ambia, J. et al. (2013) Int. STD Research & Reviews, 1(1):12-29. 3. Van der Straten, A. et al. (2014) PLoS One 9(2)e89118-. 4. Ruane, P., et.al. (2013) J Acquir Immune Defic Syndr 63(4):449-455 ; 5. Babusis, D., et. Al. (2013) Mol Pharm 10(2):459-466