

Abstract

Antiretroviral drugs such of tenofovir alafenamide (TAF) and emtricitabine (FTC), are effective pre-exposure prophylaxis (PrEP) for HIV prevention. To address the issue of poor patient adherence, we developed a novel transcutaneously refillable nanochannel system (nDS) for the delivery of TAF and FTC. We hypothesized that the nDS implant could deliver sustained doses of HIV PrEP drugs, TAF and FTC, in non-human primates. We microfabricated silicon nanochannel membranes in compliance with FDA requirement for implantable devices. In this study, nDS was tailored for the controlled delivery of TAF and FTC and designed for transcutaneous refilling to extend treatment duration. PK studies were performed in three rhesus macaques with nDS subcutaneously inserted in the dorsum. The nDS implants demonstrated sustained release of both TAF and FTC for over 83 days, with transcutaneous refilling procedure performed on Day 70. PK data showed that nDS achieved sustained preventative levels of TFVdp above 70 fmol/10⁶ PBMCs over 83 days. FTCtp levels of approximately 1.5 pmol/10⁶ PBMCs were sustained for 28 days followed by a gradual decrease due to drug depletion in the implant reservoir. Transcutaneous refilling proved successful with FTCtp levels restored to above 1.5 pmol/10⁶ PBMCs. The nDS implants were well tolerated. Our results demonstrate the feasibility of the nDS approach as a solution to poor patient adherence to HIV PrEP.

nDS Platform

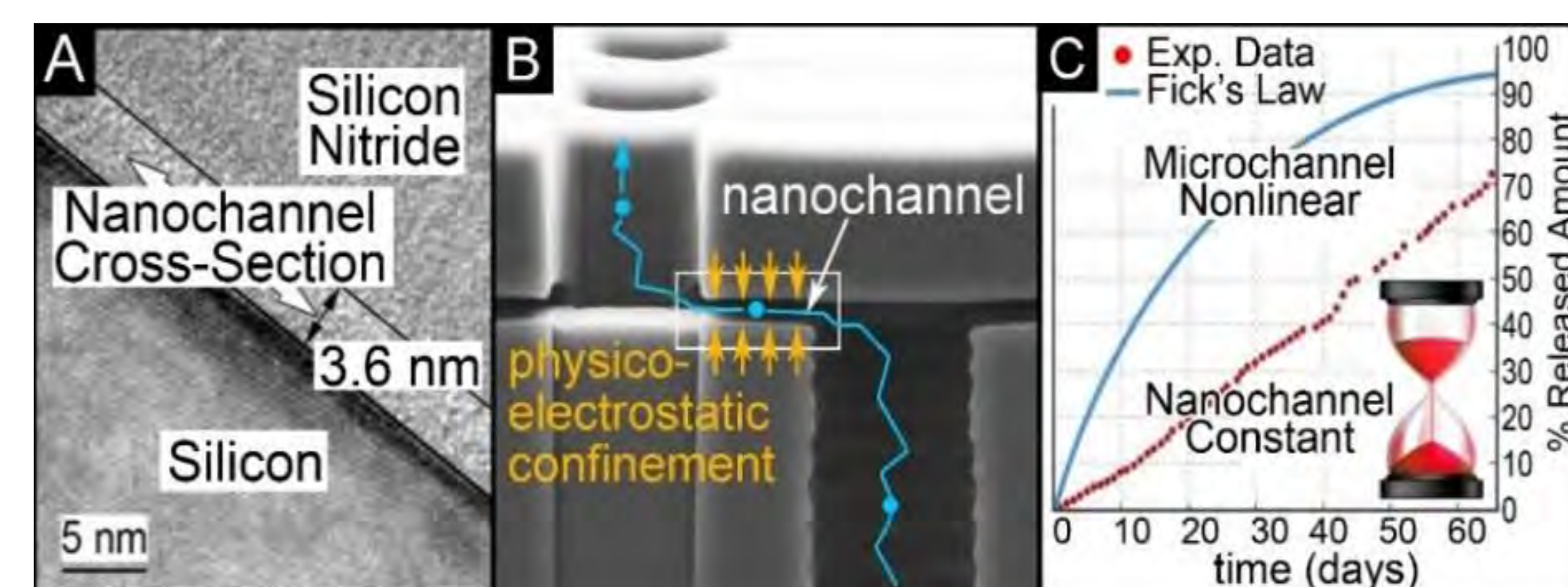


Figure 1. The nDS achieves zero-order drug delivery through physico-electrostatic confinement of the nanochannels, which limits diffusive transport from a drug reservoir.

nDS implants for HIV PrEP

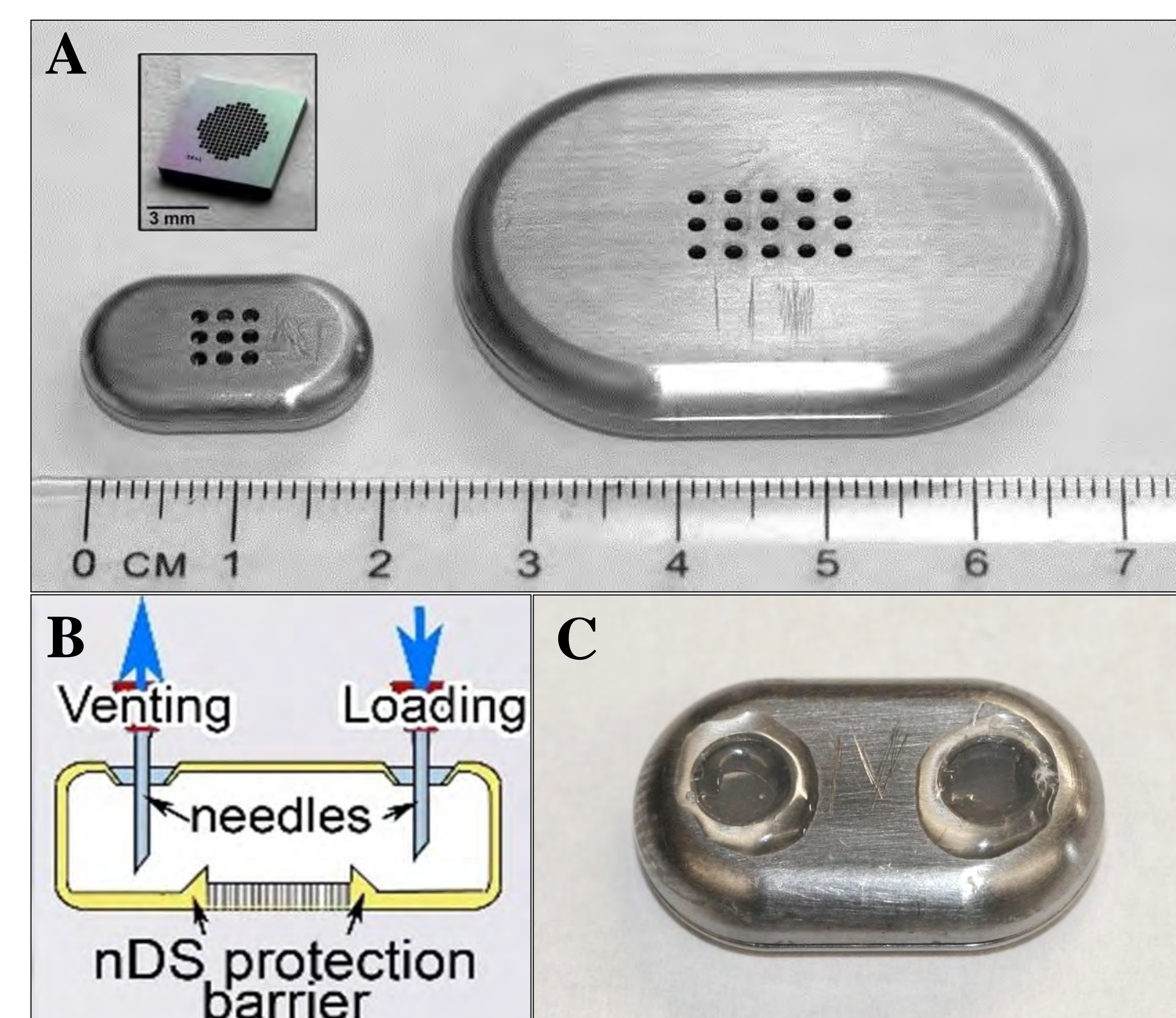


Figure 2. (A) nDS implant in medical grade titanium for TAF (left) and FTC (right) with nanochannel membrane (inset). (B) Depiction of loading and venting ports on nDS. (C) Loading ports with resealable silicon plug on nDS.

In Vitro Release Analysis

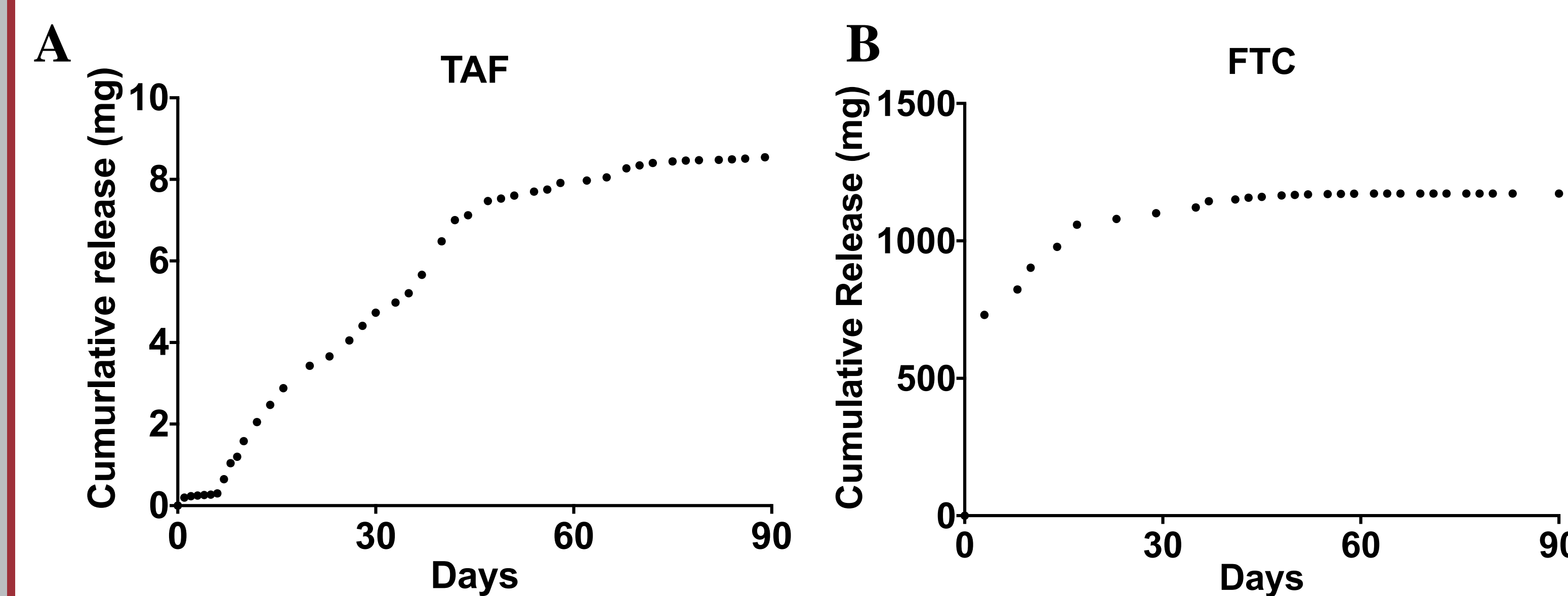


Figure 3. *In vitro* release analysis of nDS implants with (A) TAF (20 nm nanochannel membranes), and (B) FTC (250 nm) over 90 days. nDS implants were filled with powder drug and incubated in sink solution of 1X HBSS + 0.05% HEPES at 37°C. Sampling was performed every 2-3 days and sink solution fully replenished. TAF and FTC levels were quantified using HPLC.

In Vivo study of nDS-TAF and nDS-FTC efficacy in rhesus macaques

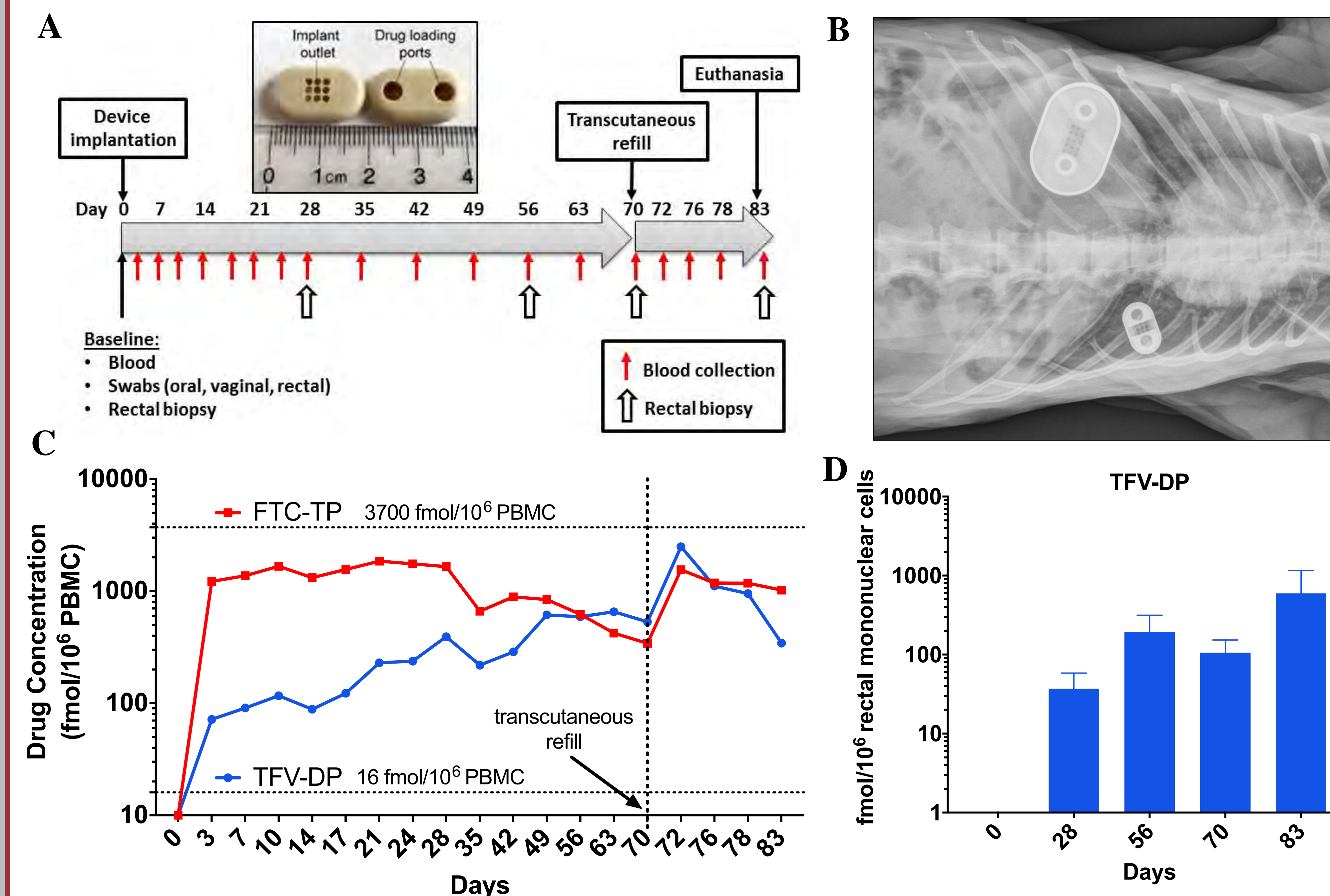


Figure 4. (A) Timeline for rhesus macaque study (n = 3). (B) Radiograph of powder drug-filled nDS subcutaneously implanted in the dorsum of animals. (C) Active metabolite levels TFV-DP and FTC-TP in PBMCs. (D) TFV-DP levels in rectal mononuclear cells. (E) Ex vivo test of transcutaneous refilling procedure. 50 µg/mL FTC was injected through loading port with excess collected through venting port. (F) Transcutaneous refilling procedure on rhesus macaque on Day 70.

Tissue and nDS membrane analysis

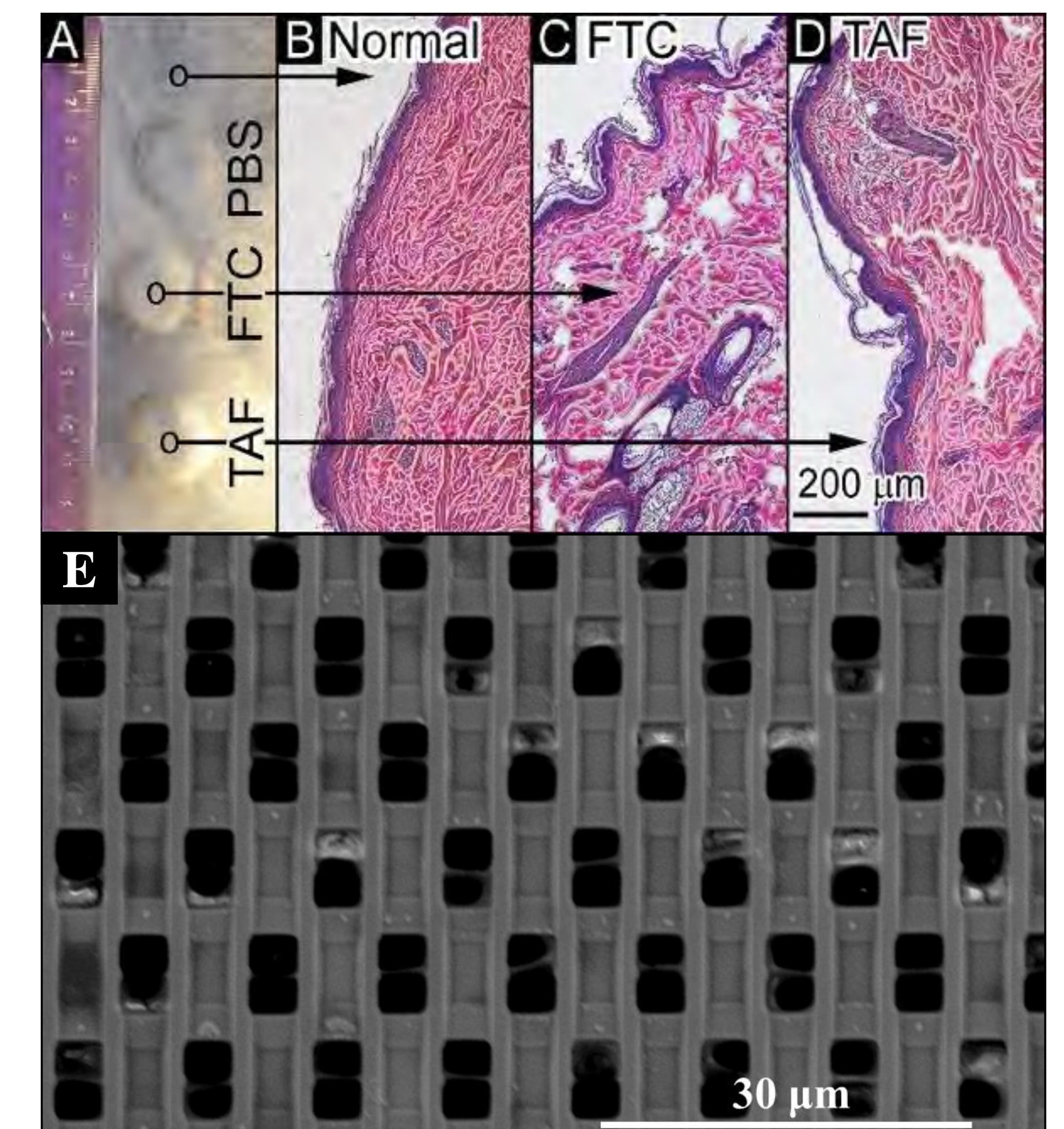


Figure 5. (A) nDS implants from pilot study in a rhesus macaque. H&E histology of (B) normal skin, (C) skin adjacent to nDS-FTC and (D) nDS-TAF. (E) Scanning electron microscopy (SEM) image of nanochannel membrane retrieved from rhesus macaque in pilot study after 60 days of implantation.

Conclusions

- Nanochannel membrane-controlled drug release achieved sustained delivery of TAF and FTC for ~3 months.
- Successful transcutaneous refilling of drug reservoir was achieved in rhesus macaques.
- Compatible with HIV PrEP, target preventative TFV-DP levels were exceeded in PBMCs.
- FTC-TP did not reach preventative concentrations, so a study to increase release rate and drug concentration is currently being developed.
- Future studies with SHIV challenge (supported by NIH and Gilead) will be performed to examine the potential of nDS as a breakthrough delivery system to address poor patient compliance to HIV PrEP.

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