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An intravaginal ring for the sustained delivery of tenofovir disoproxil fumarate

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ABSTRACT

Recent clinical trials have demonstrated that pre-exposure prophylaxis (PrEP) may prevent HIV infection in a significant number of HIV-1 negative individuals in venerable populations; however, trial efficacy has been highly variable, with notable successes and failures. Poor adherence to PrEP regimens has been implicated as a primary factor in determining efficacy of these trials. With the exception of CAPRISA 004 where use of a pericoital tenofovir gel led to a 39% reduction in HIV infection, all successful PrEP regimens to date have used the fumarate salt of the tenofovir disoproxil ester prodrug of tenofovir (TDF) alone or in combination with emtricitabine (FTC). A sustained-release, intravaginal ring (IVR) formulation of TDF holds promise for improving adherence and, thus, increasing the effectiveness of PrEP. Here, a novel IVR delivering TDF with sustained zero-order release characteristics that may be controlled over nearly two orders of magnitude is described. Pod-IVRs containing 1–10 pods delivering TDF at 0.01–10 mg d^{-1} were fabricated and their release characteristics evaluated *in vitro*. The pod-IVRs stabilized TDF against hydrolytic degradation both in storage and during *in vitro* release experiments. Successful translation of the TDF pod-IVR from laboratory evaluation to large-scale clinical trials requires the ability to manufacture the devices at low cost and in high quantity. Methods for manufacturing and scale-up were developed and applied to pilot-scale production of TDF pod-IVRs that maintained the IVR's release characteristics while significantly decreasing the variability in release rate observed between pod-IVRs. This pod-IVR enables for the first time the dose-ranging clinical studies that are required to optimize topical TDF PrEP in terms of efficacy and safety.

1. Introduction

The global human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic is now in its fourth decade, with over 6300 new HIV infections occurring daily (Hecht et al., 2010; Shattock et al., 2011; UNAIDS, 2013). In the absence of an effective vaccine, pre-exposure prophylaxis (PrEP) is a promising strategy for preventing HIV transmission. Tenofovir disoproxil fumarate (TDF) is a prodrug of the nucleoside analog reverse transcriptase inhibitor (NRTI) tenofovir (TFV), developed to improve bioavailability following oral dosing. Four recent clinical trials have demonstrated that PrEP regimens based on TDF or TFV, alone or in combination with the NRTI emtricitabine (FTC), can be effective in preventing of HIV infection in a significant proportion of individuals. The relative risk reduction, however, varied from 39 to 75% among studies (Baeten et al., 2012; Grant et al., 2010; Karim et al., 2010; Thigpen et al., 2012). In contrast, trials where women used a once daily vaginal TFV gel or daily oral TDF or TDF-FTC pill, PrEP did not show efficacy in preventing HIV acquisition (MTN, 2013; Van Damme et al., 2012). Currently, all HIV PrEP regimens with demonstrated clinical efficacy include TFV or TDF, and daily oral TDF in combination with FTC was approved in 2012 by the U.S. Food and Drug Administration to reduce the risk of HIV infection in uninfected individuals who are at high risk for HIV infection.

A critical factor driving success or failure in these clinical trials was adherence to frequent dosing: study participants who followed the prescribed antiretroviral (ARV) dosing regimens were significantly protected from HIV infection compared to those who did not (Amico et al., 2013). These results underscore the need for successful non-vaccine prevention methods against HIV infection that not only exhibit high pharmacologic efficacy, but also encourage higher compliance. It is well established across

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different delivery methods that adherence to therapy is inversely related to dosing period (Bhanji et al., 2004; Haycox, 2005; Kruse et al., 1991; Kutilek et al., 2003; Quraishi and David, 2000; Sershen and West, 2002; Small and Dubois, 2007; Yeaw et al., 2009), suggesting that sustained-release delivery methods can improve the poor adherence observed in many of the previous trials. Topical delivery of ARV drugs using intravaginal rings (IVRs) has the potential to provide the sustained mucosal levels required for protection against HIV infection (Malcolm et al., 2010), and IVR methods are believed to improve adherence compared to coitally dependent and daily dosing methods (Montgomery et al., 2012).

We demonstrated in an *in vivo* sheep model that IVRs delivering the prodrug TDF topically to the vagina resulted in significantly higher drug levels (86× higher) in vaginal tissues than IVRs delivering an equivalent vaginal fluid concentration of TFV, suggesting that local delivery of TDF to the vagina will more effectively prevent HIV infection (Moss et al., 2012). Subsequently, Smith et al. (2013) reported an IVR releasing 0.4–4 mg d^{-1} TDF that provided complete protection of pigtail macaques against multiple simian-HIV (SHIV) challenges in a low-dose model. Although these studies demonstrate proof of concept that IVRs delivering TDF may be an effective approach for preventing sexual vaginal HIV infection, multiple technologies will likely be required to advance candidate products through the development pipeline. Successful IVR platforms must meet a number of important characteristics, including: consistent daily release at a target rate, the ability to control and modify the release rate simply and precisely, and the capability to be rapidly transitioned to scalable production in preparation for large-scale clinical trials. Here we describe the *in vitro* characterization and pilot-scale manufacturing of an IVR platform that meets these important criteria.

2. Material and methods

2.1. Material

Tenofovir disoproxil fumarate (TDF) was kindly provided by Gilead Sciences, Inc. (Foster City, CA). Liquid silicone resin (LSR, MED-4940 and MED-4840) and silicone adhesive (MED3-4213) was obtained from Nusil, Inc. (Carpenteria, CA). Polyvinyl alcohol, USP (PVA, viscosity = 23.6 mPa s, 85–89% hydrolyzed) was obtained from Spectrum Chemical (Gardena, CA). D,L-Polylactic acid (PLA, Resomer R 202 S) was obtained from Evonik Industries AG (Darmstadt, Germany). All other chemicals were NF grade or equivalent and used as received.

2.2. Manufacture of silicone pod-intravaginal rings

Intravaginal rings of the pod-IVR design containing TDF were prepared using methods previously reported in detail (Baum et al., 2012). Briefly, cylindrical cores (3.2 mm diam.) of 20–40 mg TDF admixed with 0.5% magnesium stearate were formed using compaction with a pellet press (Globe Pharma MTCM-I, North Brunswick, NJ). The compressed TDF cores were coated with either PVA or PLA. Polymers were applied by drop coating from a 5% (w/v) aqueous PVA solution or 5% (w/v) PLA in 2:1 dichloromethane: ethyl acetate (v/v). A 6 μL aliquot of polymer solution was applied to one flat side of the core and allowed to dry. The core was inverted and a second 6 μL aliquot applied. After drying for ~4 h, a second layer was applied using the same technique. As described previously (Baum et al., 2012), the polymer-coated TDF pods were embedded in silicone rings or ring segments fabricated by injection molding from LSR, with one to three delivery channels per pod (channel diameter 0.75–2.0 mm) formed by mechanical punching.

2.3. Pod-IVR production scale-up

For TDF core manufacture on commercial tableting equipment, a formulation consisting of 69.3% (w/w) TDF, 23.7% microcrystalline cellulose (Ceolus KG-1000, Asahi Kasei Pharma Corp., Tokyo, Japan), 3.0% cellulose ether (Methocel E5 Premium LV, Dow Chemical, Midland, MI), and 4.0% sodium stearyl fumarate (Pruv, JRS Pharma, Patterson, NY) was used. The TDF, Ceolus KG-1000, and Methocel were wet-granulated in a 4 L high shear granulator bowl using 40 g water per 100 g solids. The granulate was dried in a fluid bed dryer with inlet air at 50 °C and the dried granulate milled in a Model 197 Quadro Comil (Quadro Engineering, Waterloo, ON, Canada) using a 0.055 in. round-hole screen and #1601 impeller. The milled granulate was blended with the sodium stearyl fumarate lubricant in a V-shell blender and compressed into solid cores (3.2 mm diam. × 4 mm ht.) using a FlexiTab single-station press (Robert Bosch GmbH Packaging Technology, Waiblingen, Germany) with custom 12-tip tooling. Cores were coated with PVA in a fluid-bed spray coating system (MFL.01 Micro Fluid Bed, Freund-Vector, Marion IA) from a 2% (w/v) solution of PVA in 1:3 (v/v) isopropanol:deionized water solution with fluidizing air at 25 L min^{-1} and 100 °C. The PVA solution was applied at 0.5 mL PVA solution per 1 g cores using a 0.5 s spray cycle with a 2:3 on:off ratio. Silicone IVR scaffolds were manufactured by Specialty Silicone Fabricators (Paso Robles, CA) using a custom, production quality four-cavity mold. IVR scaffolds were of identical dimensions those described previously (56 mm O.D., 40 mm I.D., 8.0 mm cross-sectional diameter) (Baum et al., 2012) and contained four empty pod cavities (3.1 mm diameter, 6.5 mm depth) with delivery channels formed during the molding process (1.0 mm diameter, 1.2 mm length). Pod-IVRs using these production-quality pods and IVR scaffolds were assembled using an identical method (Baum et al., 2012) to that used for the ring segments described above.

2.4. In vitro *studies*

Studies to measure *in vitro* release of TDF into a simplified vaginal fluid simulant (VFS) were carried out on IVRs containing between one and ten PLA-coated or PVA-coated TDF pods. The VFS was adapted from Owen and Katz (1999) and consisted of 25 mM acetate buffer (pH 4.2) with NaCl added to yield a 200 mOs solution. For *in vitro* release studies, the IVRs were placed in glass jars containing 100 mL VFS at 25 ± 2 °C with shaking at 60 rpm on an orbital shaker. For *in vitro* release from the ten-pod IVR (~10 mg d^{-1}), 700 mL deionized water was used as the release medium. Aliquots of the release medium were removed at specified time intervals and were replaced with an equal volume of fresh dissolution media, with compensation for dilution in the concentration determinations. The concentration of TDF in the aliquots was measured using UV absorption spectroscopy (λ_{max} = 260 nm,) with a UV-2401PC dual-beam spectrophotometer (Shimadzu, Columbia, MD). Complete media changes were carried out as needed to maintain sink conditions.

2.5. Hydrolytic stability of TDF in pod-IVRs

Drug pods were extracted from IVRs by cutting away excess silicone between pods to isolate a single pod, taking care not to cut into the pod itself, excising the pod from the silicone, and placing the pod and surrounding silicone in a vial containing 10 mL methanol. The vial was sonicated 5 min and placed on an orbital shaker for 1 h. A 25 μL aliquot of this solution was diluted to 1 mL with deionized water containing 0.1% formic acid. The concentration of TDF [bis(POC)TFV], TFV isoproxil [mono(POC)TFV], and TFV in the diluted solution was determined using an Agilent 1100 Series HPLC with diode-array (DAD) and single-quadrupole mass-