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Short Communication

Osmotic pump tablets for delivery of antiretrovirals to the vaginal mucosa

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ABSTRACT

Vaginal pre-exposure prophylaxis has focused heavily on gel formulations. Low adherence linked with frequent dosing and short therapeutic duration has emerged as the major reason for inconsistent efficacy outcomes with gels in clinical trials. Osmotic pumps can achieve versatile drug release profiles however, have not been explored for vaginal delivery. In this report, we describe an osmotic pump tablet (OPT) that can deliver antiretrovirals for several days. We also describe configuring the OPT for pH sensitive delivery where the drug delivery system consistently delivers an antiretroviral at vaginal pH and then gives a burst release triggered by a coitally associated pH increase. We have investigated the vaginal OPT for multiple day delivery of a potent antiretroviral, IQP-0528 in a sheep model. To effectively register spatial drug distribution we also engineered a tool to precisely collect multiple vaginal fluid samples. In a 10-day duration post single application, high micromolar mucosal levels were obtained with peak concentration more than 6 logs higher than the EC_{50} of IQP-0528. Overall, our results show successful implementation of the osmotic pump technology for vaginal antiretroviral delivery.

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The pre-exposure prophylaxis (PrEP) drug delivery system (DDS) portfolio is dominated by short-acting coitally associated gel formulations and long-acting intravaginal rings. Currently the field lacks antiretroviral (ARV) delivery systems that can be used 'on-demand' and with durations between that of gels and intravaginal rings. While 'on demand' vaginal tablets can be an alternative with higher user acceptance compared to gels (Minkin et al., 2013; Rioux et al., 2000), they have been less explored as HIV prevention technology platforms. Vaginal tablets can be manufactured easily using standard tabletting equipment, are suitable for formulation of water-sensitive drugs and can have long term stability without cold-chain storage requirements (Adams and Kashuba, 2012). However, a common problem among conventional vaginal tablets and gels is the short duration of pharmacokinetics (PK) for most drugs (an exception is Class I drugs (Amidon et al., 1995) with high intracellular half-lives); therefore, they require repeated dosing to ensure consistently protective drug levels. Frequent administration and the potentially associated low adherence ultimately may impact the performance of topical PrEP agents in clinical trials (Marrazzo et al., 2013). Therefore, we investigated the use of a medium-duration elementary osmotic pump tablet (OPT) that can actively and in a controlled manner deliver topical AVR for one to multiple days after a single intravaginal application. This, to our knowledge, is the first reported work on the use of an osmotic pump for topical vaginal drug delivery.

The underlying mechanism behind osmotic pump technology has not changed despite the large amount of work on the design and application in oral and implantable drug delivery (Theeuwes, 1975). Drug release rate from these systems is typically a function of rate of water entry into the device due to an osmotic pressure gradient between the device core and the environment (Theeuwes and Yum, 1976). The osmotic pressure difference can be controlled by the nature and concentration of the osmotic agent, the water vapor transmission rate (P) of the semipermeable membrane (SPM) and geometry of the drug delivery orifices (Fig. 1a). The interplay between these properties aids in achieving controlled zero order drug release for timed durations. Unless inserted as implants, osmotic pumps are currently utilized for 24-h controlled oral delivery (Herrlich et al., 2012; Malaterre et al., 2009). We are uncertain why there are no reports on osmotic tablets for vaginal delivery but perhaps researchers assumed there was limited fluid to drive the drug release. Therefore, to achieve multiple day drug delivery, we modified the OPT to ensure retention in the vaginal tract for extended durations by designing an OPT, coated with a bioadhesive polymer (Grabovac et al., 2005), that delivers a viscous gel. The gel, we hypothesized, might aid in retaining the formulation in the vaginal canal and may improve drug distribution in the vaginal tract. Our approach utilized a semi-solid gel forming

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polymer, hydroxypropyl cellulose (HPC) as the osmoattractant core instead of NaCl or polyethylene glycol. The high molecular weight of this gel-forming polymer is unlikely to cause osmotic stresses to mucosal tissues unlike other systems that have high salt concentrations. Water is driven into the HPC core resulting in polymer swelling and extrusion of a vaginal gel through the orifice and delivery of drug in the vaginal canal (Fig. 1a).

In this report we describe the fabrication of a multi-day intravaginal OPT for delivery of IQP-0528, a pyrimidinedione, with potent nanomolar non-nucleoside reverse transcriptase and entry inhibition activity (Buckheit et al., 2008; Johnson et al., 2012), and its evaluation in the sheep vaginal model. Vaginal fluid samples were collected using a multiswab device to determine spatial drug distribution by placing several circular sponges at precise positions along a penis shaped rod. This allowed us to map the drug distribution in the vaginal tract as a function of time and distance. In addition, the ability of IQP-0528 present in vaginal swabs to inhibit HIV-1 infection was evaluated in vitro.

Vaginal tablets with 10 wt.% IQP-0528 in HPC matrix were fabricated using a standard pellet press, spray-coated with SPM forming polymers, cellulose acetate phthalate (CAP) (Daugherity and Nause, 2009b) or cellulose acetate (CA) (Daugherity and Nause, 2009a) and a drug delivery orifice was manually drilled (S. Fig. 1). CAP, an enteric coating polymer is insoluble at the approximate vaginal pH 4, but is soluble at seminal pH of 6–8 (Daugherity and Nause, 2009b), a feature we utilized for engineering a semen-triggered burst drug release system. Samples were tested for in vitro drug elution under simulated vaginal conditions. Next, two uncoated tablets ($N = 3$) or CA-OPT ($N = 5$) were administered in adult female sheep using a custom-designed applicator (Supplementary methods). To study vaginal drug distribution, we engineered a multiswab device (S. Fig. 2) to allow us to collect spatially registered vaginal fluid samples at varying time-points up to 10 days. Vaginal swabs were tested for drug levels and antiviral activity (Supplementary methods).

To study the advantage of an OPT over conventional tablet formulations, we maintained an identical core composition (S. Fig. 1; 8.4 ± 0.6 wt.%, $N = 10$). As expected, uncoated tablets exhibited faster swelling with almost complete drug dissolution (91.8 ± 4.1% ($N = 5$) in 48 h; S. Fig. 3a). In contrast, OPTs showed multi-day IQP-0528 release in vitro. Slow drug release was noted early on with 0.9 ± 0.06 mg (10.7 ± 0.7%) and 0.4 ± 0.09 mg (4.6 ± 1%) drug released on day 1 from CA- and CAP-OPTs respectively. A total of 29.5 ± 8.4% ($N = 4$) and 47.1 ± 3.3% ($N = 6$) [$P = 0.0015$] of the drug load was delivered by day 10 from CA- and CAP-OPTs, respectively. (Fig. 1c and d) The variation in the amount of drug released was significantly different and can be attributed to the difference in the water vapor transmission rate (P) of the two membranes. Since membrane thickness and area, and orifice area were constant for both the OPTs, the membrane permeability will control water uptake by the core and resulting drug release ($P_{CAP} = 0.52$ g m^{-2}/24 h or 0.002 mg cm^{-2}h^{-1} and $P_{CA} = 5$ mg cm^{-2}h^{-1} (Crawford and Esmerian, 1971; Sprockel et al., 1990). Although the data indicated that release could have continued for more than 10 days we believe that short to medium duration delivery systems that last on the order of 2–5 days will be of the most utility in the HIV prevention field.

Semen can cause a large pH change in the vaginal canal that can be used to design semen triggered release of drugs (Clark et al., 2011; Gupta et al., 2007; Zhang et al., 2013). To test the suitability of the CAP-OPT as a semen-triggered DDS we changed the release media from acetate buffer pH 4.2 (simulated vaginal conditions) to seminal fluid simulant pH 7.6 on day 10. Dissolution of the CAP coating occurred within minutes of the pH change, exposing a gel core followed by 49% of the drug load being delivered in the next 2.5 days amounting to 97% total drug release (Fig. 1d). To visualize the working of the CAP-OPT, we formulated a yellow dye-loaded HPC core with a rhodamine B-CAP coating (Fig. 1b). A bright yellow gel labeled with the dye was seen to extrude out of the drug delivery orifice under osmotic forces when the system

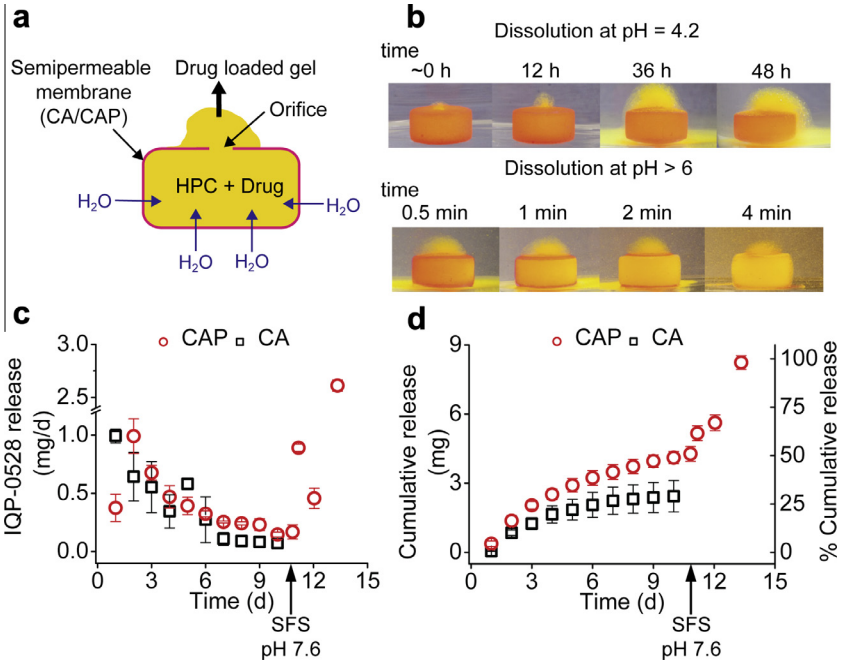

Fig. 1. In vitro IQP-0528 release from OPT. (a) Diagram showing working of an OPT. Water is driven through the semipermeable membrane (CA/CAP) into the core (HPC + Drug) due to osmotic pressure difference, causing polymer swelling and extrusion of a drug loaded gel though the orifice. (b) Photograph showing a dye loaded CAP-OPT in release media at pH 4.2 (upper panel) and >6 (lower panel). Extrusion of a dye-loaded gel can be seen within the first hour. Upon increase in pH > 6, the CAP coating was instantaneously seen to dissolve leaving a gelled core. (c) Daily and (d) cumulative release of IQP-0528 from CAP- and CA-OPT in 25 mM acetate buffer pH 4.2 (simulated vaginal conditions) followed by mimicking pH increase by changing release media to seminal fluid simulant (SFS) pH 7.6 ($N = 3$; Mean ± SD).

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