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Review

Electrospun fibers for vaginal anti-HIV drug delivery

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ABSTRACT

Diversity of microbicide delivery systems is essential for future success in the prevention and treatment of HIV in order to account for the varied populations of women all over the world that may benefit from use of these products. Recently, a novel dosage form for intravaginal drug delivery has been developed using drug-eluting fibers fabricated by electrospinning. There is a strong rationale to support the idea that drug-eluting fibers can be designed to realize multiple design constraints in a single product for topical HIV prevention: fibers are able to deliver a wide range of agents, incorporate multiple agents via composites, and facilitate controlled release over relevant time frames for pericoital and sustained (coitally-independent) use. It is also technologically feasible to scale-up production of fiber-based microbicides. Electrospun fibers may allow for prioritization of physical attributes that affect user perceptions without compromising biological efficacy. Challenges with using fibers as a microbicide include issues related to vehicle deployment, spreading and retention in the vaginal vault. In addition, studies will need to address the interaction of the fibers with the mucosal environment, including unknown safety and toxicity. Sustained release fiber microbicides capable of delivering multiple antiretroviral drugs while simultaneously exhibiting tunable degradation or dissolution of the fibers is also a challenge. However, electrospun fibers are a promising new platform for vaginal delivery of anti-HIV agents and future research will inform their place in the field. This article is based on a presentation at the "Product Development Workshop 2013: HIV and Multipurpose Prevention Technologies", held in Arlington, Virginia on February 20–21, 2013. It forms part of a special supplement to *Antiviral Research*.

Contents

1. Introduction . . . S9
2. Electrospun fibers for drug delivery . . . S10
   2.1. Breadth of API delivery using electrospun fibers . . . S11
   2.2. Rapid and sustained release from drug-eluting fibers . . . S12
   2.3. Challenges in electrospun fibers for vaginal delivery . . . S13
3. Scale-up of electrospun fibers . . . S13
   3.1. Materials and capital investments . . . S13
   3.2. Manufacturing capability . . . S13
   3.3. Scale-up equipment . . . S14
4. Conclusion . . . S14
   References . . . S15

1. Introduction

Topical microbicides are a critical component of the prevention portfolio to combat sexual transmission of HIV. One of the priorities in the field is to confront the low levels of user adherence that have been documented in clinical trials of microbicides. The early termination of VOICE due to low user adherence compromised evaluation of efficacy (Marrazzo et al., 2013). Vaginal drug delivery systems (DDS) play a principle role in bridging biological efficacy and behavioral adherence, which collectively determine the overall impact of a topical microbicide product. It is unlikely that a single DDS technology will solve the prevention needs for all women,

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particularly for adolescent women in low-resource settings where the crises of women's reproductive health is complicated by issues of poverty, malnutrition, poor education, and gender inequality. For this reason, the portfolio of available microbicide DDS needs to be numerous and diverse.

The advancement and development of any single microbicide DDS must prioritize the capacity of the DDS to design for physical attributes that impact user perceptions without compromising the design for biological efficacy. The ultimate decision to use a microbicide product is influenced by a complex combination of product attributes (sensory perceptions, dosing frequency, coital association), user demographics (age, race, culture), and perceived risks for HIV as well as perceived benefits from product use. These user perceptions are the first barrier to designing effective microbicide products, but are often the last consideration in product development. In addition to being acceptable to users, the product must deliver bioactive compounds, possibly in combination, over a relevant period of time (both coitally dependent and independent), be affordable, and have the ability to be manufactured on a production scale. Future development of products will likely incorporate design iterations informed by user perception as well as biological efficacy.

A number of microbicide products are in various stages of the development pipeline, but the lead technologies include gels, films, tablets and intravaginal rings (IVRs) (Abdool Karim et al., 2010; Akil et al., 2011; Garg et al., 2010; Malcolm et al., 2010). There are a number of advantages and disadvantages associated with the leading DDS. Vaginal gels are relevant for pericoital or daily use but have limited ability to deliver physicochemically diverse agents, are not amenable to sustained protection and are messy and may leak out of the vaginal cavity after application. Tablets are easily formulated and manufactured but may leave a grainy residue in the vaginal cavity after dissolution (Garg et al., 2003). IVRs are currently the only sustained release dosage method and have enhanced product stability as a solid dosage form, but are relatively complicated and expensive to fabricate (Malcolm et al., 2010). Vaginal films are also relevant for pericoital use, have demonstrated capability for delivering physicochemically diverse agents, and exhibit enhanced product stability compared to semi-solid dosage forms such as gels. However, vaginal microbicide films have reported loadings of <~1%, and their low overall mass may preclude delivery of sufficient doses of certain APIs (Akil et al., 2011; Mahalingam et al., 2011; Sassi et al., 2011). In addition, the bulk physical properties of films must be controlled to avoid sharp edges and corners that could induce abrasion upon application and use. It is also not clear if current films will be amenable for sustained drug delivery and coitally independent applications.

Recently, a novel dosage form for intravaginal drug delivery has been developed using drug-eluting fibers fabricated by electrospinning, a technique that applies electrostatic forces to form polymeric fibers. Electrospinning is an elegant and facile method for formulating a solid-dosage form microbicide product. The process of electrospinning fibers is well-established (Schiffman and Schauer, 2008), efficient and relatively inexpensive and, since most synthetic and many biological polymers can be electrospun, there is a wide array of possible formulations envisioned for diverse antiretroviral (ARV) drugs. A number of physicochemically diverse drugs have already been encapsulated into electrospun fibers (Taepaiboon et al., 2006), typically with high loading and encapsulation efficiency (Agarwal et al., 2008). Fiber-based "fabrics" are typically soft and non-abrasive, highly flexible, lack sharp corners and can realize a number of geometries (sheets, tubes, coatings). In addition, there is no leakage or mess expected with delivery of fibers into the vaginal cavity. Therefore, there is a strong rationale to support that drug-eluting fibers can be designed to realize multiple design constraints in a single product for topical HIV prevention.

2. Electrospun fibers for drug delivery

Two recent publications investigated electrospun fibers as a platform for vaginal delivery as a topical microbicide for HIV prevention (Ball et al., 2012; Huang et al., 2012). Huang et al. encapsulated the reverse transcriptase inhibitors etravirine or tenofovir disproxil fumarate (Viread) into fibers based on cellulose acetate phthalate (CAP) (Huang et al., 2012). CAP has documented anti-HIV activity, which is thought to be mediated by interactions of the polymer with HIV glycoproteins. In addition, CAP undergoes a solution-to-gel phase transition in response to pH due to the phthalate function group of CAP (pKa of ~5.5). In the low pH environment of the vagina (pH of ~4–5) CAP is a semi-solid, but dissolves upon a semen-induced increase in pH. Thus, CAP fibers were designed to dissolve and release antiretrovirals within seconds to minutes after exposure to semen (Fig. 1). CAP fibers were found to be safe *in vitro* at concentrations of up to 1.8 mg/mL, with minimal toxicity in both TZM-bl cells and vaginal epithelial cells. Exposure to only 0.05 mg/mL of CAP fibers resulted in 50% HIV neutralization and complete neutralization was achieved upon incorporation of 17.8% (wt. drug/wt. polymer) TDF, for a final concentration of TDF of ~0.1 μg/mL.

Ball et al. fabricated nanofiber meshes from a polymer blend of poly-L-lactic acid (PLLA) and polyethylene oxide (PEO) with an assortment of antiretroviral and contraceptive agents for the dual prevention of HIV transmission and unintended pregnancy (Fig. 2) (Ball et al., 2012). Fibers were loaded with maraviroc (MVC), an inhibitor of CCR5-mediated HIV fusion, or 3′-azido-3′deoxythymidine (AZT). Both ARV drug-fibers were found to be non-toxic to TZM-bl cells and macaque ectocervical explants. ARV drug-loaded fibers also had comparable HIV inhibition to the free drugs and maintained IC50 levels at concentrations of 0.90 nM for MVC and 120 nM for AZT. Both MVC and AZT were found to exhibit burst-release from the fibers, but sustained release on the timescale of weeks was achieved by incorporation of

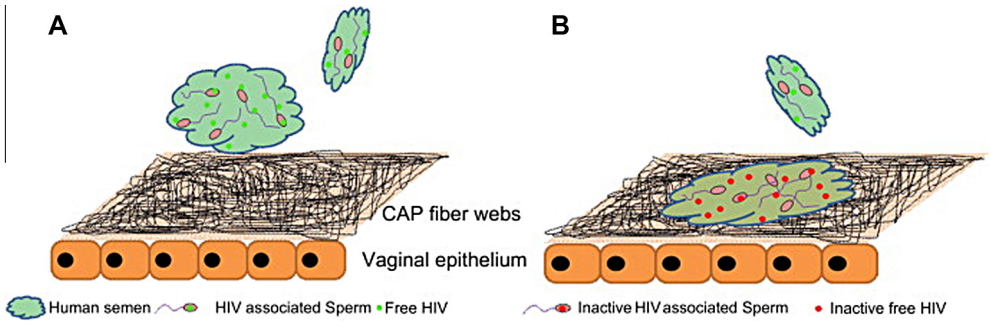

Fig. 1. Schematic by Huang et al. depicting a layer of vaginal epithelial cells covered by a web of electrospun fibers containing antiretroviral drug before (left) and after (right) contacting human semen contaminated with HIV. Used with permission from Elsevier (Huang et al., 2012).