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Nanoparticle-releasing nanofiber composites for enhanced *in vivo* vaginal retention

Emily A. Krogstad [a], Renuka Ramanathan [a], Christina Nhan [a], John C. Kraft [b], Anna K. Blakney [a], Shijie Cao [a], Rodney J.Y. Ho [a, b], Kim A. Woodrow [a, *]

[a] Department of Bioengineering, University of Washington, Seattle, WA 98195, United States
[b] Department of Pharmaceutics, University of Washington, Seattle, WA 98195, United States

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ABSTRACT

Current approaches for topical vaginal administration of nanoparticles result in poor retention and extensive leakage. To overcome these challenges, we developed a nanoparticle-releasing nanofiber delivery platform and evaluated its ability to improve nanoparticle retention in a murine model. We individually tailored two components of this drug delivery system for optimal interaction with mucus, designing (1) mucoadhesive fibers for better retention in the vaginal tract, and (2) PEGylated nanoparticles that diffuse quickly through mucus. We hypothesized that this novel dual-functioning (mucoadhesive/mucus−penetrating) composite material would provide enhanced retention of nanoparticles in the vaginal mucosa. Equivalent doses of fluorescent nanoparticles were vaginally administered to mice in either water (aqueous suspension) or fiber composites, and fluorescent content was quantified in cervicovaginal mucus and vaginal tissue at time points from 24 h to 7d. We also fabricated composite fibers containing etravirine-loaded nanoparticles and evaluated the pharmacokinetics over 7d. We found that our composite materials provided approximately 30-fold greater retention of nanoparticles in the reproductive tract at 24 h compared to aqueous suspensions. Compared to nanoparticles in aqueous suspension, the nanoparticles in fiber composites exhibited sustained and higher etravirine concentrations after 24 h and up to 7d, demonstrating the capabilities of this new delivery platform to sustain nanoparticle release out to 3d and drug retention out to one week after a single administration. This is the first report of nanoparticle-releasing fibers for vaginal drug delivery, as well as the first study of a single delivery system that combines two components uniquely engineered for complementary interactions with mucus.

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1. Introduction

Recent progress has been made in engineering nanocarriers to overcome physiological barriers for intravaginal administration. Nanoparticles (NPs) have been designed to rapidly diffuse through the cervicovaginal mucus barrier by PEGylating the nanoparticle surface to impart a net neutral surface charge [1,2]. The variable conditions of the vaginal environment have been employed in the design of pH-responsive Eudragit nanoparticles [3] and hyaluronidase-responsive nanoparticles [4] that can release drug in response to changes in pH or enzyme concentration due to the presence of semen. NPs have also been demonstrated to improve drug delivery to vaginal tissue *in vivo* compared to free drug delivered as a suspension. For example, a study in mice showed 5-fold higher drug concentration in vaginal tissue when the drug was delivered by nanoparticles compared to free drug in suspension [5]. Greater protection against herpes simplex virus type 2 (HSV-2) has also been documented *in vivo* for nanoparticles even when administered at a 10-fold lower concentration than free drug [1]. These findings may have application in developing more effective products for the prevention and treatment of STIs, including microbicides for female-initiated HIV prevention.

However, current methods for vaginal mucosal administration of nanoparticles are limited by extensive leakage of the administered dose and poor retention. *In vivo* studies to date have used aqueous suspensions (water or PBS) to intravaginally administer nanoparticles in mice [1,2,5,6]. Significant leakage has been documented *in vivo* for aqueous suspensions, with over 50−70% of the

* Corresponding author.
E-mail address: woodrow@uw.edu (K.A. Woodrow).

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administered nanoparticle dose leaking out within 30 min, and <1–2% of the total nanoparticle dose retained at 24 h [5,6]. Such administration methods also often require maintaining mice in an inverted position for 1–10 min to reduce leakage [5,6], and practical translation of such methods to clinical use is unlikely. External leakage and messiness from liquid or gel dosage forms have been cited as reasons for poor adherence [7], and gel-based dosage forms used once-daily or pericoitally have been associated with poor adherence in clinical trials [8,9]. To realize the full potential of nanocarrier delivery systems for reproductive health applications, new platforms are needed to increase dose retention of nanoparticles in the reproductive tract and provide a more practical method for their administration.

Electrospun nanofibers have recently been investigated as a platform for vaginal drug delivery [10–18]. Nanofibers (NF) are a solid-state dosage form, which may overcome challenges with user adherence by reducing messiness and leakage that has been associated with liquid or gel-based dosage forms. Proof-of-concept of the application of electrospun fibers to vaginal drug delivery has previously been demonstrated, showing that fibers can deliver active antiretroviral drugs and contraceptive agents with diverse properties [10,11]. Further work has shown that electrospun nanofibers can incorporate a remarkably high drug content up to 60% by mass [14], and that fiber polymer ratios and core-shell structure can be tuned to control drug release kinetics over the time course of days to weeks [15,16,18]. Nanofibers offer many other advantages for vaginal drug delivery, including flexibility in processing parameters (polymer/solvent selection, controllable fiber diameter, thickness), a nearly unlimited material space for electrospinning, the ability to encapsulate diverse agents, and multiple conceptual geometries to achieve practical and user-friendly administration [12,19,20]. Electrospun fibers containing antiretroviral drugs [19,21] or microparticles [22] have also been fabricated using free-surface electrospinning, which is a scalable technique that provides a pathway to clinical translation of fiber-based medical products.

Here, we designed nanoparticle-releasing nanofiber (NP-NF) composites for increased nanoparticle retention in the reproductive tract by individually tailoring each component for optimal interaction with mucus. We hypothesized that because nanofibers are a solid dosage form and offer a high surface area-to-volume ratio for quick dissolution, they would provide enhanced retention and quick release of nanoparticles in the vaginal tract. For the fiber component, we selected two mucoadhesive polymers, poly (vinyl alcohol) (PVA) and poly (vinyl pyrrolidone) (PVP), aimed to increase retention in the vaginal tract through association with the mucosa. Both polymers are hydrophilic and expected to dissolve quickly to release nanoparticles, but PVP is slightly more mucoadhesive than PVA [23–26], providing an interesting comparison to study how mucoadhesivity affects NP delivery. Building on recent work published on mucus-penetrating particles [1], we synthesized PEGylated PLGA nanoparticles designed to rapidly penetrate cervicovaginal mucus and deliver the drug payload to vaginal tissue. Although electrospun fibers containing nanoparticles have been used previously for drug or protein release [27–30], ours is the first study to design and investigate nanofiber composites for optimal delivery and retention of nanoparticles for vaginal applications. In this work, we aim to study the release and biodistribution of nanoparticles from composite fibers after intravaginal administration. To demonstrate the utility of the NP-NF composite platform for application as a topical microbicide for HIV prevention, we also compare the pharmacokinetics of the antiretroviral drug etravirine (ETR) after delivery in nanoparticles from nanofiber composites compared to aqueous suspensions. We show that NP-NF composites dramatically enhance both nanoparticle and drug retention in the reproductive tract relative to aqueous suspensions and sustain nanoparticle release out to three days after a single administration. This composite platform overcomes a major challenge in vaginal drug delivery by significantly prolonging both nanoparticle and drug residence time in the vaginal tract.

2. Materials and methods

2.1. Ethics statement

Animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Washington (Protocol # 4260-01). All animals were obtained and cared for in accordance with the IACUC guidelines.

2.2. Materials

Poly lactic-*co*-glycolide (PLGA) (50:50 L:G, ester-terminated, inherent viscosity = 0.55–0.75 dL/g in HFIP) was purchased from Lactel Absorbable Polymers. Rhodamine-B, Pluronic® F-127, agar, and poly (vinyl pyrrolidone) (Mw~1.3 MDa) were purchased from Sigma-Aldrich. Poly (vinyl alcohol) (Mw~105 kDa, P1180) was purchased from Spectrum Chemical. Other reagents used include acetone (Fisher), ethanol (Decon Laboratories, Inc.), dimethyl sulfoxide (DMSO) (BDH Solvents), sodium chloride (EMD Millipore), and PBS (1×, Mediatech, Inc.). All solvents used for high performance liquid chromatography (HPLC) were of HPLC grade, including water (Fisher), acetonitrile (ACN) (Fisher), and ammonium acetate (Sigma-Aldrich). Etravirine was purified by and given as a generous gift from I. Suydam at Seattle University (Seattle, WA).

2.3. Nanoparticle synthesis

PLGA nanoparticles were synthesized using a nanoprecipitation technique based on modifying previously described methods [31] for passive PEGylation with Pluronic® F-127 [1]. PLGA was dissolved in acetone at 20 mg/mL and added to 0.1% (w/v) Pluronic® F-127 at a 1:11 (v/v) ratio with a syringe pump at a flow rate of 1 mL/min. Acetone was evaporated from the aqueous phase over 4–6 h in a fume hood. Particles were then washed by centrifugation at 10,000g × 20 min and resuspended in water using alternating vortexing and water bath sonication as needed. Aliquots of NP suspension were lyophilized and analyzed for fluorescence or drug content. Remaining suspensions were stored at 4 °C until further use.

For fluorescent rhodamine-conjugated PLGA nanoparticles (Rho-NP), we first synthesized a rhodamine-B-PLGA conjugate using methods described by Costantino et al. [32]. We determined the conjugation efficiency to be 15.7% (loading of 0.169% (w/w) rhodamine B:PLGA) by dissolving polymer conjugate and measuring fluorescence. Rhodamine-B-PLGA conjugate was dissolved in acetone and NP formed as described above. To synthesize ETR-loaded nanoparticles (ETR-NP), we dissolved ETR at 10% (w/w ETR/PLGA) theoretical loading in the PLGA/acetone solution. ETR was passively loaded in NP during NP synthesis, not directly conjugated to PLGA like rhodamine-B. ETR-NP were synthesized as described above, except that the NP suspension was filtered after evaporation using 2 μm syringe filter to remove any drug precipitate before washing. Characterization of ETR-NP in terms of size, zeta potential, polydispersity index (PDI), drug loading, and encapsulation efficiency is described in the Supplementary Data (Supplementary Table S1).

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