Multipurpose Prevention Technologies for Global Health

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ABSTRACT SUMMARY

Multipurpose prevention technologies (MPT) that simultaneously prevent sexually transmitted infections (STIs) and unintended pregnancy are a global health priority. Here we show that drug-eluting fiber meshes designed for topical drug delivery can function as a combination chemical and physical barrier MPT. Nanofiber meshes were synthesized to encapsulate and elute antiviral agents that are effective against HIV-1 and HSV-2, and a contraceptive agent that targets sperm function. These drug-eluting nanofiber meshes represent an innovative new dosage form that may have immediate implications for the design of next generation MPTs to improve women’s sexual and reproductive health.

INTRODUCTION

The dual impacts of the HIV/AIDS pandemic and unintended pregnancies constitute a major health burden for women worldwide1,2. As a consequence, multipurpose protection technologies (MPT) combining safe, effective, and easily reversible options for contraception with a topical microbicide against sexual HIV-1 transmission are a global health priority3,4. To date, no single product exists that women can use discreetly for simultaneous and effective prevention of HIV and pregnancy.

Emerging technologies that integrate physical and chemical methods provide the greatest potential for new MPT designs. However, to be effective, these technologies must integrate five fundamental design specifications: 1) they must deliver multiple drugs with different physiochemical properties or pharmacokinetics in a single device, 2) they must provide extensive coverage of mucosal tissue, 3) contraceptive action must be fully reversible, 4) their application must be female-controlled and discreet, and 5) they must be inexpensive to reach the most relevant populations. Despite vigorous efforts, a bottleneck in the development of MPTs has been the integration of all these design specifications into a single device.

We propose a paradigm shift from existing MPT designs to a new platform technology that employs electrospun polymer fibers for topical drug delivery to the lower female reproductive tract. We fabricated fiber matrices in geometries suitable for intravaginal drug delivery, and show that the polymer fibers incorporate agents with differing aqueous solubility and mechanisms of action. Fibers deliver agents that inhibit both HIV and sperm in vitro in addition to physically preventing sperm penetration. We observe that drug-loaded meshes inhibit HIV-1 infection in vitro and block sperm migration. Furthermore, we report on a novel activity of glycerol monolaurate (GML) to potently inhibit sperm motility and viability. Thus, electrospun meshes may act as both a chemical and physical barriers to HIV transmission and pregnancy.

EXPERIMENTAL METHODS

We used polymer blends to electrospin biodegradable nanofibers encapsulating antiviral drugs with specific mechanisms of action against HIV-1 or HSV-2, and several non-hormonal chemical contraceptives. Electrospinning parameters were controlled to achieve high polymer recovery, tunable fiber diameter and controlled fiber degradation. Fiber matrices were characterized with scanning electron microscopy (SEM) to analyze morphology and fiber size. Fiber degradation was monitored by measuring change in mass and with SEM over a period of several weeks. Drug release kinetics were quantified using UV-HPLC and TLC methods. We assayed the drug-loaded vaginal matrices for cytotoxicity and anti-HIV-1 activity using the TZM-bL reporter
cell line, and for spermicidal activity with a sperm motility assay and barrier transwell assay. Uniaxial tension testing was used to study the moduli and yield stress/strain of fiber materials. Rheological measurements of hydrated materials were also measured. Finally, fibers were inserted vaginally into mice and histology analysis was performed to examine the effect of materials on the mucosal epithelium.

RESULTS AND DISCUSSION

Chemical agents with differing solubility and mechanisms of action against HIV-1, HSV-2 or sperm function were incorporated successfully into fibers at >95% drug encapsulation efficiency. ARVs incorporated in and eluted from the polymer fibers were identical to the unformulated drugs and showed potent anti-HIV activity. Drug-loaded fiber discs also significantly inhibited HIV-1 infection compared to vehicle control (blank) fibers (p<0.05). Fiber materials were shown to be nontoxic to cells and the vaginal epithelium of mice compared to commercial vaginal films containing nonoxynol-9. We also evaluated multiple strategies for controlling the release of ARV drugs from electrospun fibers by increasing fiber diameter and by modulating polymer fiber hydrophobicity and crystallinity. Our results provide proof of principle that electrospun fibers can sustain release of ARVs over multiple days.

We also report on a novel function of glycerol monolaurate (GML) to act as a spermicide and potential non-hormonal chemical contraceptive. GML nanofibers were electrospun reproducibly to achieve polymer recoveries of >70% and fiber diameters between 600-800 nm. GML showed significant inhibition of sperm motility at concentrations of 0.05 - 0.5 wt%, and reduced viability of human sperm in whole semen by 50% when used at a 5 wt% concentration. The potential function of GML as a non-hormonal contraceptive warrants greater attention given that the compound is recognized as safe, non-inflammatory, and has been shown to inhibit a variety of vaginal pathogens.

CONCLUSION

We demonstrate that drug-eluting nanofiber matrices can be effectively designed to provide chemical and physical barrier methods for multipurpose HIV-1 and HSV-2 prevention and contraception. Electrospun drug-loaded nanofiber matrices provide a novel MPT platform for topical delivery that may be a promising alternative for other sexual and reproductive health indications.

REFERENCES

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