International Journal of Pharmaceutics 475 (2014) 282–291

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

Manufacturing scale-up of electrospun poly(vinyl alcohol) fibers containing tenofovir for vaginal drug delivery

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ARTICLE INFO

Article history:
Received 3 April 2014
Received in revised form 18 July 2014
Accepted 19 August 2014
Available online 26 August 2014

Keywords:
Electrospinning
Scale-up
Microbicides
Tenofovir
Solid dispersions
Fibers

ABSTRACT

Electrospun fibers containing antiretroviral drugs have recently been investigated as a new dosage form for topical microbicides against HIV-1. However, little work has been done to evaluate the scalability of the fiber platform for pharmaceutical production of medical fabrics. Scalability and cost-effectiveness are essential criteria in developing fibers as a practical platform for use as a microbicide and for translation to clinical use. To address this critical gap in the development of fiber-based vaginal dosage forms, we assessed the scale-up potential of drug-eluting fibers delivering tenofovir (TFV), a nucleotide reverse transcriptase inhibitor and lead compound for topical HIV-1 chemoprophylaxis. Here we describe the process of free-surface electrospinning to scale up production of TFV fibers, and evaluate key attributes of the finished products such as fiber morphology, drug crystallinity, and drug loading and release kinetics. Poly(vinyl alcohol) (PVA) containing up to 60 wt% TFV was successfully electrospun into fibers using a nozzle-free production-scale electrospinning instrument. Actual TFV loading in fibers increased with increasing weight percent TFV in solution, and encapsulation efficiency was improved by maintaining TFV solubility and preventing drug sedimentation during batch processing. These results define important solution and processing parameters for scale-up production of TFV drug-eluting fibers by wire electrospinning, which may have significant implications for pharmaceutical manufacturing of fiber-based medical fabrics for clinical use.

1. Introduction

Women under the age of 24 years have three- to six-fold higher rates of HIV-1 infection than men in the same age category in some parts of sub-Saharan Africa (Gengiah and Abdool Karim, 2012; Glynn et al., 2001). Given the lack of an effective HIV-1 vaccine and no available options for effective female-initiated prevention, there is a need for a microbicide against HIV-1 that women can use discreetly to protect themselves from infection. Products such as vaginal rings, films, and gels are being investigated as potential dosage forms for the delivery of antiretroviral agents for the prevention of HIV-1. Pericoital dosage forms are preferred by some women, but challenges such as inadequate retention, low drug loading, and the lack of sustained release capabilities have limited their effectiveness. For example, challenges associated with low user adherence to daily gel use in some populations have been cited as a concern in the recent VOICE clinical trial (Microbicide Trials Network, 2013). Vaginal films are an alternative pericoital dosage form to gels and can be advantageous because of their compact size, ease of insertion without an applicator, and limited leakage or messiness (Garg et al., 2010; Nel et al., 2011). However, some vaginal films exhibit relatively long dissolution times (Multipurpose Prevention Technologies for Reproductive Health Think Tank, 2011), and the small dosing volume combined with the low drug loadings of $<\sim$1% (Akil et al., 2011; Sassi et al., 2011; Ham et al., 2012) may limit the effectiveness of vaginal films unless used with exceptionally potent drugs. As such, more options are needed for female-initiated protection against HIV-1 that are culturally acceptable, shelf-stable, effective, and inexpensive.

Electrospun fibers are a solid dosage form with versatility in terms of the diversity of polymers and antiviral agents that can be formulated, and they have recently been explored as a platform for vaginal drug delivery (Huang et al., 2012; Ball et al., 2012). Fibers can be formed into multiple geometries (sheets, tubes, coatings), and conceptual dosage forms have been identified for vaginal application of fibers that are similar to vaginal films or

Abbreviations: DSC, differential scanning calorimetry; HPLC, high performance liquid chromatography; PBS, phosphate buffered saline; PVA, poly(vinyl alcohol); R.H., relative humidity; SEM, scanning electron microscopy; TFV, tenofovir; TFA, trifluoroacetic acid; XRD, X-ray diffraction.

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http://dx.doi.org/10.1016/j.ijpharm.2014.08.039
0378-5173/

cervical barrier devices (Blakney et al., 2013). One criteria of an ideal microbicide platform is its ability to be scaled up inexpensively, which is of particular importance for low resource settings where HIV-1 is most prevalent. Methods for scaling up the electrospinning process have already been developed and are currently being used to produce products for filtration and purification (Persano et al., 2013). On the laboratory scale, small volumes of polymer solution are typically electrospun using a single needle electrode, syringe pump, voltage generator, and metal collector (Fig. 1). Formats used for large-scale electrospinning include multi-nozzle, centrifuge-based, and free surface instruments, which have been reported to increase productivity from 0.1–1 g/h (single needle electrode) to up to 6.5 kg/h (multi-nozzle) (Forward and Rutledge, 2012; Luo et al., 2012). The NS-1WS500U (Elmarco, Inc.) is the only commercially available production-scale electrospinning instrument that uses similar technology to existing manufacturing instruments, which is important for process transferability. The instruments employ free surface electrospinning, in which a high voltage is applied across either a wire or a rotating metal drum electrode. For the wire electrode used in this work, a moving carriage deposits polymer solution onto the wire. The polymer coating undergoes a Plateau–Rayleigh instability, resulting in the formation of many charged droplets on the wire (Forward and Rutledge, 2012). Numerous electrospinning jets emerge simultaneously from these droplets, producing a large sheet of fibers collected on a negatively charged parallel electrode. Such a system can process much larger volumes of solution than single needle electrode systems and has been reported to produce ~200 g of fibers/h, with potential for even greater productivity by combining multiple units in series (Persano et al., 2013). Evaluating the scale-up potential is the first step in evaluating cost-effectiveness of the fiber platform, and essential to determining its practicality as a microbicide platform and translation to clinical use.

In this report, we hypothesize that electrospun PVA fibers may be a good candidate for a quick-dissolving pericoital microbicide. The amorphous domains of partially hydrolyzed PVA allow for swelling and dissolution in water, and the large surface area of electrospun fibers may further promote fast dissolution and drug release. PVA has documented biocompatibility, being one of the primary components of the commercially available Vaginal Contraceptive Film® (Apothecus). Tenofovir (TFV), a nucleotide reverse transcriptase inhibitor, has been widely investigated for HIV-1 prevention. CAPRISA 004 was the first clinical trial in which a microbicide was shown to protect against HIV-1 acquisition, with a 39% overall reduction in HIV acquisition for women in the 1% TFV vaginal gel arm, and 54% reduction for women with high gel adherence (Karim et al., 2010). TFV has also been shown to be effective when administered orally for pre-exposure prophylaxis in three clinical trials (iPrEx, Partners PrEP, TDF2) (Grant et al., 2010; Baeten et al., 2012; Thigpen et al., 2012). Given its extensive use in antiretroviral-based prevention methods, we have selected TFV to evaluate in PVA fibers.

Here we present our work evaluating PVA fibers as a platform for vaginal drug delivery and their potential to be scaled up for mass production. We directly compare fiber morphology, drug loading, release kinetics, and crystallinity of TFV-loaded fiber meshes electrospun using a laboratory-scale needle instrument or a production-scale wire instrument. Using only water as a solvent, we encapsulated up to 60 wt% TFV (wt drug/wt fiber) into electrospun fibers without compromising fiber integrity or productivity on both needle and wire instruments. Additionally, we show the ability to electrospin solid dispersions of TFV. Surprisingly, we found that electrospun fibers containing solid dispersions of drug, even when highly crystalline, may not in fact alter release kinetics under sink conditions compared to electrospun fibers containing fully solubilized drug. Where limited solubility has previously precluded the use of some extremely hydrophobic drugs as microbicides, these results suggest that high crystallinity may not significantly impact release kinetics for electrospun fibers containing TFV. This is the first report to our knowledge of TFV fiber scale-up on a free-surface production-scale electrospinning unit with direct transferability to manufacturing scale.

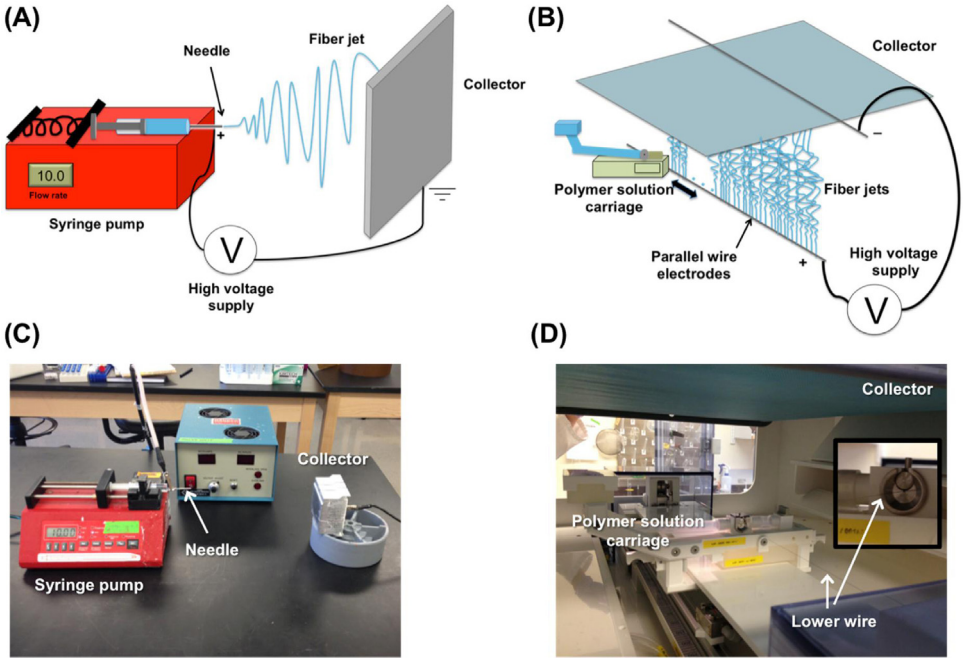

Fig. 1. Electrospinning instrumentation for needle and wire electrode instruments. Schematic (A) and photograph (C) of laboratory scale electrospinning in which a single fiber jet is electrospun from a needle/syringe pump. Schematic (B) and photograph (D) of scale-up free surface electrospinning, where numerous fiber jets are spontaneously produced from charged polymer droplets deposited on a wire electrode. A magnified inset view of the lower wire electrode is shown in (D).