A Hot-Melt Extruded Intravaginal Ring for the Sustained Delivery of the Antiretroviral Microbicide UC781

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ABSTRACT: Microbicide intravaginal rings (IVRs) are a promising woman-controlled strategy for preventing sexual transmission of human immunodeficiency virus (HIV). An IVR was prepared and developed from polyether urethane (PU) elastomers for the sustained delivery of UC781, a highly potent nonnucleoside reverse transcriptase inhibitor of HIV-1. PU IVRs containing UC781 were fabricated using a hot-melt extrusion process. *In vitro* release studies of UC781 demonstrated that UC781 release profiles are loading dependent and resemble matrix-type, diffusion-limited kinetics. The *in vitro* release methods employed over predicted the *in vivo* release rates of UC781 in rabbits. Accelerated stability studies showed good chemical stability of UC781 in prototype formulations, but surface crystallization of UC781 was observed following long-term storage at higher UC781 loadings, unless formulated with a polyvinylpyrrolidone/glycerol surface coating. Mechanical stability testing of prototype rings showed moderate stiffening upon storage. The PU and UC781 had minimal to no impact on viability, tissue integrity, barrier function, or cytokine expression in the tissue irritation model, and UC781 was shown to be delivered to and permeate through this tissue construct *in vitro*. Overall, UC781 was formulated in a stable PU IVR and provided controlled release of UC781 both *in vitro* and *in vivo*. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:576–587, 2012

Keywords: UC781; polyurethane; intravaginal ring; microbicides; controlled release; polymeric drug delivery system; extrusion; stability; *mucosal drug delivery, polymeric drug delivery system, extrusion, stability,* in vitro/in vivo release

INTRODUCTION

Approximately 33 million people worldwide currently are infected with the human immunodeficiency virus (HIV), with the majority of infected individuals residing in sub-Saharan Africa.[1] In some of these populations, women are approximately twice as likely as men to acquire HIV from an infected partner during sexual intercourse.[2] Although condoms can be an effective barrier against HIV transmission in both men and women,[3] condom use is unreliable and often not within the woman's control.[3] Therefore, there is an urgent need to develop safe, effective, and acceptable woman-controlled prophylactic methods that can prevent the sexual transmission of HIV.

Over the last two decades, there have been extensive efforts to develop topical microbicides for preventing HIV transmission.[4–8] Microbicides are agents that can be used by a woman to protect against sexually transmitted viral diseases during vaginal or rectal intercourse.[9] Efforts to date have culminated in recent clinical findings from the CAPRISA 004 trial,[10] demonstrating proof that a vaginally administered microbicide gel containing the antiretroviral tenofovir can significantly reduce the incidence of HIV acquisition. In the CAPRISA 004 trial, high adherers (gel adherence >80%) showed a 54% lower HIV incidence in the tenofovir arm. Intermediate (gel adherence 50%–80%) and low adherers (gel adherence <50%) showed a reduction in HIV incidence of 38% and 28%, respectively.[10]

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The efficacy of a microbicide product depends, in large part, on the ability of the product to deliver its drug at sufficiently prophylactic quantities to the right place (i.e., the site of the drug's activity) and at the right time (i.e., relative to a person's potential exposure to HIV). Most vaginal microbicides investigated clinically, thus far, have been pericoitally associated gels.[11–14] However, a compelling rationale exists for developing products capable of providing long-term, controlled-release of microbicides to afford prolonged protection against sexually transmitted HIV infection. Moreover, the coital independence of long-term dosage forms has the potential to improve user adherence, thereby increasing a product's potential efficacy.[10] Intravaginal rings (IVRs) are the leading dosage form being considered for the development of long-acting microbicide products.[15–17]

UC781 is a nonnucleoside reverse transcriptase inhibitor (NNRTI) that has undergone preclinical and clinical investigation as a microbicide.[18–20] UC781 demonstrates nanomolar potency *in vitro* against both wild-type and NNRTI-resistant HIV-1 strains.[21–23] Via the rapid and tight-binding inhibition of HIV-1 reverse transcriptase, UC781 is capable of inactivating both free and cell-associated virus directly, whereas NRTIs such as tenofovir require intracellular conversion to an active metabolite. Moreover, UC781 displays a prolonged protective effect *in vitro*, lasting several days after pretreatment with drug.[24] These unique attributes combine to make UC781 a potentially promising microbicide candidate.

UC781 presents several formulation challenges for development in an IVR due to poor aqueous solubility, rapid recrystallization, and significant aqueous and photo degradation,[25] thus making this an important test compound for developing hot-melt extrusion dosage forms and an important target in the HIV prevention field. The chemical structure of UC781 is shown in Figure 1a. The compound UC22, shown in Figure 1b, is the main degradation product of UC781 produced by desulfurization of the parent compound and possesses diminished antiviral activity compared with UC781.[26]

Successful formulation of antiretrovirals in IVRs requires appropriate polymer selection. An ideal polymer would have high drug solubilization capacity and loading-controllable drug release rates, maintain drug stability both chemically and physically, be biocompatible, and provide acceptable IVR mechanical properties. As the drug release rate is proportional to the dissolved concentration of the drug in the polymer, a polymer with a high drug solubilization capacity is desired to achieve loading-dependent release and deliver sufficient drug to the vaginal tract to inhibit viral replication.[27] We have observed higher solubilization of several hydrophobic small molecule pharmaceutical compounds, including UC781, in polyurethanes

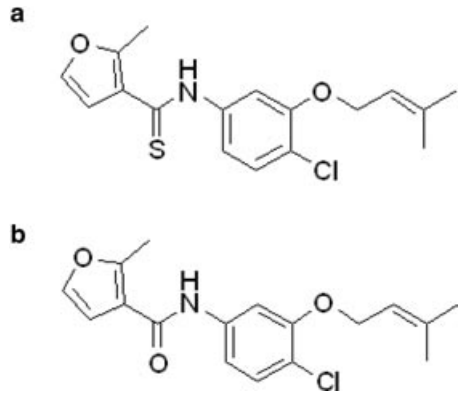

Figure 1. Chemical structure of (a) UC781 and (b) the desulfurated UC22.

compared with conventional IVR polymers such as polyethylene vinyl acetate or silicone (unpublished observations). Lastly, the mechanical properties of the IVR must be considered when selecting a polymer. A ring that is too stiff may be uncomfortable, disturb or damage the vaginal epithelium, or be difficult to insert, whereas a ring that is too soft may be displaced or expelled.[28–30] Polyurethane composition can be easily modified to possess different shore hardness or elastic modulus, and therefore modulate IVR stiffness. We evaluated a medical-grade aliphatic polyether urethane (PU) as an IVR matrix polymer for the sustained delivery of UC781.

Here, we report on the formulation development and fabrication of a physically and chemically stable PU matrix IVR capable of providing sustained delivery of UC781. Our report provides an assessment of the chemical, physical, and mechanical stability of prototypical IVR formulations, as well as *in vitro* and *in vivo* release characteristics of these formulations. In addition, this report presents the biocompatibility and drug permeability of UC781-loaded PU IVRs in the EpiVaginal™ tissue model.[31–33]

MATERIALS AND METHODS

Materials

Medical-grade aliphatic PU, Tecoflex® EG-85A, was obtained from Lubrizol (Wickliffe, Ohio). UC781 (lot #04-1803-02) and UC22 (lot #AC-1811-CMP-63) were provided by CONRAD (Arlington, Virginia). Loctite® super glue precision max and activator are products of Loctite (Westlake, Ohio) and were obtained from Henkel (Rocky Hill, Connecticut). High-density polyethylene was obtained from American Plastics (Arlington, Texas).

Fabrication of UC781-Loaded IVRs and Ring Segments

PU beads were cryo-ground with a Fritsch Pulverisette 14 (Idar-Oberstein, Germany) through a