Controlled 90-Day In Vitro and In Vivo Delivery of Tenofovir and Levonorgestrel from a Dual-Segment Reservoir Intravaginal Ring

Justin T. Clark¹, Meredith R. Clark², Todd J. Johnson¹, Namdev B. Shelke¹, Joel S. Nebeker¹, Gustavo F. Doncel², David R. Friend² and Patrick F. Kiser¹

¹Department of Bioengineering, University of Utah, Salt Lake City, Utah, 84112, USA; ²CONRAD, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Arlington, Virginia, 22209
justin.t.clark@utah.edu

ABSTRACT SUMMARY

We present in vitro drug release and in vivo pharmacokinetic results for a dual-segment reservoir-type polyurethane intravaginal ring designed for zero-order delivery of the hydrophilic HIV-1 nucleotide reverse transcriptase inhibitor tenofovir (TFV) and the hydrophobic contraceptive levonorgestrel (LNG) for 90 days.

INTRODUCTION

A majority of the world’s unintended pregnancies occur within resource-poor regions where HIV/AIDS is also prevalent. With the modest clinical success of the TFV vaginal gel as a topical method to prevent sexual transmission of HIV¹, there is global interest in topical drug delivery systems capable of simultaneously protecting women against HIV infection and unwanted pregnancy². We have developed the first segmented, reservoir-type polyurethane intravaginal ring (IVR) capable of simultaneous zero-order co-delivery of TFV and LNG for 90 days using polymers customized to the properties of each drug.

EXPERIMENTAL METHODS

Target release rates were defined as 10 mg TFV³ and 10 or 20 μg LNG per day (two IVRs with different LNG doses). Due to the differences in physicochemical properties of TFV (log D=-3.9 at pH 4) and LNG (c log P=+3.3), as well as the vast difference in desired release rates, it was necessary to design a segmented IVR utilizing three different custom-designed segmented polyether urethanes (PEUs). LNG was first dissolved into a low-modulus (75A durometer) PEU at 1.4% (w/w) by hot-melt extrusion and subsequently coaxially extruded into 5.5 mm cross-sectional diameter cylindrical strands with a 100 μm rate-controlling membrane (RCM) comprised of a high-modulus (60D durometer) PEU. A glycerin-based paste with 65% TFV (w/w) was loaded into melt-extruded hydrophilic polyurethane tubes (5.5 mm OD, 4.1 mm ID) with a high-pressure back-filling system. Tubing ends were sealed using a tip-forming induction welder. Ring assembly was performed by split-die induction welding of 10 or 20 mm LNG-loaded segments, with 141 or 131 mm TFV-filled tubes, respectively. 2 mm 60D PEU caps were welded in between segments to prevent diffusion of LNG into the TFV segment. IVRs were subjected to in vitro drug release testing in an aqueous buffer sink for both TFV and LNG. Drug concentration in release media was quantified by HPLC analysis periodically throughout 90 day testing. Because of anatomical similarity to women, IVRs were evaluated in a sheep pharmacokinetic model for 90 days. Weck-cel® swabs of vaginal fluid and pinch biopsies of vaginal and cervical tissue were taken periodically and drug content was determined by LC-MS/MS. Drug extraction from IVRs were used to estimate in vivo drug release rate.

RESULTS AND DISCUSSION

In vitro, IVRs released approximately 8 mg TFV per day in a zero-order fashion, as well as an average of 9 or 23 μg LNG per
day (from IVRs with 10 or 20 mm segments, respectively) for 90 days in a near-zero order fashion. By residual extractions, IVRs released 12-13 mg TFV per day and 14 or 31 μg per day LNG in vivo. Median TFV content ranged from 1-24 μg/g in vaginal tissue biopsies from day 14 to day 90 post-insertion, and was greater than 100 μg/g in vaginal fluid swabs from 24 hours post-insertion onward. Median LNG content ranged from 1-5 ng/g in cervical tissue for both doses from 8 hours post-insertion onward.

CONCLUSION
This is a unique IVR design which leverages polyurethane composition-property relationships for the controlled delivery of two chemically diverse compounds at very different release rates. The TFV levels observed in the sheep model show promise for HIV protection and our LNG release rate is similar to that used in most highly effective reversible contraceptive method currently available. This product will be tested in a phase I human trial later this year.

REFERENCES

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