



Cover story

An intravaginal ring for sustained and simultaneous delivery of 4 drugs



Human immunodeficiency virus Type 1 (HIV-1), discovered in the early 1980s, remains an incurable, yet manageable, disease. With the advent of highly active antiretroviral therapy, the quality of life of HIV-1 infected patients has improved significantly and mortality rates due to AIDS have been declining since 2000. The risk of acquiring HIV-1 increases significantly with prevalent sexually transmitted infections (STIs), such as Herpes simplex virus-2 (HSV-2) and human papillomavirus (HPV). Unfortunately, low income populations in Sub-Saharan Africa and South/West Asia, and women in particular, are still prone to HIV infections and other STIs. Unintended pregnancy also plagues women's reproductive health in resource limited settings. There is an urgent need to develop pharmaceutical formulations that meet the needs of these vulnerable populations.

Topical microbicides are woman-enabled, cost-effective products that can be used to prevent infection from HIV and other STIs that increase the risk of HIV acquisition. They show fewer side effects than systemically active products, and less systemic exposure minimizes the likelihood of developing mutant virus strains. Previously, microbicides had been used mainly for prevention of HIV-1, but they are now used in multipurpose prevention technologies (MPTs) that target HIV, other STIs, and unintended pregnancy at the same time.

In this issue, the paper by Dr. Ugaonkar and her colleagues describe a novel platform to deliver four active pharmaceutical ingredients (APIs): a combination microbicide composed of three antiviral APIs and a contraceptive that prevents HIV-1, HSV-2, HPV as well as unintended pregnancy for up to 90 days [1]. The author's primary challenge was to simultaneously deliver the four APIs with vastly different physicochemical properties. Often, the classical approach of "like dissolves like" where a hydrophobic (or hydrophilic) matrix used to deliver hydrophobic (or hydrophilic) APIs fails when the APIs have different water-solubilities and molecular sizes. Other challenges included maintaining the simplicity of the IVR design and offering protection for up to 90 days. To overcome the first challenge, the group used a combination of hot melt extrusion and *in situ* pellet technology to load the APIs. Ethylene vinyl acetate copolymer (EVA) was compounded with two hydrophobic, small molecular drugs, MIV-150 (a non-nucleoside reverse transcriptase inhibitor) and levonorgestrel (contraceptive). Carrageenan, a water soluble polysaccharide, and zinc acetate were compressed into a pellet in a hollow channel of the hydrophobic matrix. Thus, a prototype intravaginal ring (IVR) designed for macaques was made up of only one matrix but which enclosed a hydrophilic reservoir. The hydrophobic

APIs were released by diffusion from the EVA matrix and pores were created on the surface of the IVR to allow elution of the core APIs hydrated by *in vitro* release medium or vaginal fluid. The IVR was a simple toroid with no modifications made to the design itself to accommodate different APIs. All the drugs released continuously for 90 days *in vitro* and up to 28 days (the study duration) *in vivo*. The eluted drugs were active when tested in *in vitro* cell based assays.

The Ugaonkar team recognizes that this unique MPT IVR will face significant regulatory and manufacturing challenges. The US FDA has limited experiences with MPTs, so there will likely be regulatory delays as the approval process is sorted out. In addition, there are no processes in place to easily integrate non-extrudable technologies (e.g., tablet, pellet) with the routinely used hot-melt extrusion/injection molding processes for scale-up manufacturing of an IVR similar to the MPT IVR described by the Ugaonkar team. But once these hurdles are overcome, millions of women worldwide will have access to safe, effective, and low cost MPTs that simultaneously protect against HIV, other STIs, and unintended pregnancy. IVR formulations have a long history of use, but they are all limited to delivery of only one or two drugs. Sustained (90 days) and simultaneous delivery of four drugs having different physicochemical properties at the therapeutically effective levels is a challenge. Nonetheless, we need to overcome the product development challenges of these novel MPT IVRs so that they can be made available to the millions of women worldwide who urgently need them.

References

- [1] S.R. Ugaonkar, A. Wesenberg, J. Wilk, S. Seidor, O. Mizenina, L. Kizima, A. Rodriguez, S. Zhang, K. Levendosky, J. Kenney, M. Aravantinou, N. Derby, B. Grasperge, A. Gettie, J. Blanchard, N. Kumar, K. Roberts, M. Robbiani, J.A. Fernández-Romero, T.M. Zydowsky, A novel intravaginal ring to prevent HIV-1, HSV-2, HPV, and unintended pregnancy, *J. Control. Release* 213 (2015) 57–68.

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