Advances in vaginal drug delivery

David R. Friend

Published online: 10 May 2011
© Controlled Release Society 2011

Vaginal drug delivery has been of interest to scientists to varying degrees during the last century [1]. As a route of drug delivery, it offers a means to administer drugs for local benefit or systemic distribution. For years, antifungal and antibacterial agents have been administered vaginally to treat yeast and bacterial infections, respectively. Contraceptive gels and films containing nonoxynol-9 (N-9) represent other common products; however, the use of N-9-containing products is decreasing.

The introduction of intravaginal rings (IVRs) in the 1990s to administer steroid hormones for hormone replacement therapy represented a major advance in both vaginal drug delivery and the drug delivery field as a whole. These devices were designed to sustain the release of steroid hormones for up to 1 month in duration. A few years later, a contraceptive IVR product, NuvaRing®, was introduced. This product has been widely accepted as a once monthly vaginal contraceptive product.

Sexually transmitted infections (STIs) remain a significant problem, both in developed and developing world settings [2]. According to the latest statistics from UNAIDS/WHO, 33.3 million people are living with HIV-1 infection, with 2.6 million new infections in 2009. In addition, the WHO estimated 340 million new cases of gonorrhea, chlamydia, syphilis, and trichomoniasis throughout the world in 1999 in both men and women aged 15–49 years [3]. Herpes simplex virus 2 (HSV-2) is the most common cause of genital warts and is highly prevalent among sexually active individuals. Seroprevalence rates of HSV-2 range from 22% of sexually active adults in the USA to up to 60% in HIV-negative women in sub-saharan Africa and men who have sex with

men in Latin America. Additionally, more than 80% of individuals infected with HIV-1 are also infected with HSV-2 [4]. Unplanned pregnancies in both the developed and developing world remain a significant problem [5].

STIs and pregnancy are two drivers in the development of new vaginal drug delivery systems. Among STIs, the prevention of HIV-1 transmission has been a high funding priority for the National Institutes of Allergy and Infectious Diseases, the United States Agency for International Development, and the Bill and Melinda Gates Foundation. Early attempts to prevent transmission of HIV-1 from men to woman were based on the use of surfactants, polyanions, and acid buffers. Unfortunately, these compounds failed to protect women against HIV-1 infection. However, a recently completed study of women in South Africa using the nucleotide reverse transcriptase inhibitor tenofovir in a vaginal gel showed a significant reduction in HIV-1 transmission [6]. This success and the desire to reduce transmission of other sexually transmitted diseases has spurred the development of novel delivery systems for a wide range of drugs.

It was these recent advances in vaginal drug delivery that were highlighted in a scientific session held at the Controlled Release Society Annual Meeting held in Portland, Oregon in July 2010. This theme issue is based primarily on papers and posters presented at the meeting. A common theme throughout these papers is the use of microbicides, which are products designed to be administered vaginally to prevent HIV-1 transmission [7]. Jim Turpin reports on current gaps in the development of topical microbicide products such as formulation safety and the role of adherence to product use. The latter has been found to be correlated with product effectiveness since, unsurprisingly, a product not used is ineffective. Recent advances in IVRs for administration of contraceptives and a range of drugs potentially capable of

D. R. Friend (✉)
CONRAD, Eastern Virginia Medical School,
Arlington, VA 22209, USA
e-mail: dfriend@conrad.org

preventing transmission of STIs are reviewed. Chi Lee reviews the potential clinical application of intravaginal formulations containing nitric oxide. These formulations are based on biodegradable micro- or nanoparticles encapsulating nitric oxide prodrugs such as diethylenetriamine diazenium-diolate to treat vaginal blood flow abnormalities.

Quick dissolve film dosage forms represent a viable alternative to gels for vaginal administration of microbicides. Lisa Rohan and coauthors discuss the use of the nonnucleoside reverse transcriptase inhibitor (NNRTI) dapivirine as a prototype microbicide. In vitro bioactivity of dapivirine was also compared with that of UC781, another NNRTI considered for use as a vaginal microbicidal agent.

Vaginal gel products require an applicator, which requires disposal, even if the applicator is composed primarily of paper. The same is true for vaginal rings, although fewer used rings will be generated compared with vaginal applicators. Nonetheless, a degradable intravaginal ring would represent an advance in IVR design. Patrick Kiser and coauthors present the engineering of a degradable IVR for the delivery of dapivirine. The polymer tested incorporates degradable blocks of poly(ϵ -caprolactone) ester in a poly(tetramethylene ether) glycol ABA type polyurethane backbone. The mechanical properties of the IVR were comparable to NuvaRing. Release of dapivirine was constant during a 1-month period.

Two papers are presented on the performance of IVRs designed to release UC781 either alone or in combination with the contraceptive progestin levonorgestrel (LNG). In the first instance, Meredith Clark and coauthors present the in vivo pharmacokinetics of UC781 in rabbits. This study is interesting because it compares the release of UC781 from vaginally implanted ring segments composed of one of three different polymeric materials: silicone, ethylene vinyl

acetate copolymer (EVAc), and a hydrophobic polyurethane. Andrew Loxley and coauthors present additional data on the development of the UC781/LNG combination IVR based on the thermoplastic EVAc.

Finally, a paper by David Katz and coauthors review various mathematical models designed to predict microbicide delivery in vivo from different vaginal delivery systems. If appropriately designed and validated using clinical data, such models could be used to streamline the development of microbicide (and other) vaginal products.

References

1. Woolfson AD, Malcolm RK, Gallagher R. Drug delivery by the intravaginal route. *Crit Rev Ther Drug Carrier Syst.* 2000;17(5):509–55.
2. Friend DR, Doncel GF. Combining prevention of HIV-1, other sexually transmitted infections and unintended pregnancies: development of dual-protection technologies. *Antivir Res.* 2010;88 Suppl 1:S47–54.
3. World Health Organization: http://www.who.int/hiv/pub/sti/who_hiv_aids_2001.02.pdf (2001). Accessed 12 Apr 2011.
4. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;371(9630):2109–19.
5. Aitken RJ, Baker MA, Doncel GF, Matzuk MM, Mauck CK, Harper MJ. As the world grows: contraception in the 21st century. *J Clin Invest.* 2008;118(4):1330–43.
6. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010;329(5996):1168–74.
7. Friend DR. Pharmaceutical development of microbicide drug products. *Pharm Dev Technol.* 2010;15(6):562–81.