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Cover Story

A hydrophilic matrix approach for controlled vaginal drug delivery

Generally drug release from intravaginal rings occurs by drug diffusion through the ring elastomer, and thus, the chemical properties and dose requirements of the drug are typically coupled directly to the elastomer by selecting polymers that allow partition and diffusion of the drug. Until recently, this has limited intravaginal ring technologies to the delivery of hydrophobic, low molecular weight drugs like steroid hormones. Recently, new polymer ring designs have enabled the delivery of water soluble and macromolecular drugs with control that was previously unachievable. Other recent intravaginal ring designs have uncoupled the drug delivery requirements from the polymer characteristics of the ring elastomer by incorporating membrane controlled drug delivery systems that are inserted in the ring body. All these technologies, however, require the drug to diffuse through a rate controlling membrane layered on the inserts and the drug loading is limited in these designs.

In this issue, Professor Kiser and his colleagues describe an intravaginal ring technology where the mechanism of drug release is predominately controlled by hydration of a perforated hollow ring body and by dissolution of water-soluble polymer matrices contained within the core of the device. Modeling coupled to experimentation suggests that fluid entry largely controls the rate of polymer hydration and thereby mass transport of the hydrophilic polymer and its crystalline dispersion of drug from the device. These phenomena together allow for sustained and controlled delivery of substances contained in the ring for up to a month in duration with physiologically relevant doses. Instead of the drug release being controlled by the solubility and diffusivity of the drug in the ring elastomer, the orifice size and chemistry of the polymer pellets control the hydration rate and thereby release of the drug in the polymer matrix. The authors present a mechanistic model of drug release describing the hydration and diffusion of the hydrophilic polymers from the device supporting the authors' hypothesis of how drug release occurs, and enabling quantitative predictions of drug release.

By uncoupling the drug release mechanism from the interaction of the drug with the ring elastomer, this work conceptually enables the delivery of one or multiple drugs from a single or multiple compartments with diverse chemical properties at physiologically relevant release rates. This design can be integrated into an intravaginal ring with other known ring delivery systems. This should allow the design of fixed dose combination devices for the prevention of unwanted pregnancy, sexual transmission of HIV or other women's health issues requiring controlled drug delivery.

Since an effective HIV vaccine or cure remains elusive, there has been a significant effort to develop technologies to prevent male to female transmission of HIV. Here antiretrovirals are dosed intravaginally before potential sexual exposure to HIV. A number of recent clinical trials evaluating oral and topical administration of antiretrovirals have shown that pre-exposure prophylaxis strategies can be effective in reducing HIV acquisition rates. An important result of these clinical trials shows clearly that adherence correlates with effectiveness in reducing HIV incidence. This has driven a shift from daily or episodic topical dosing in the field towards long duration delivery systems, including intravaginal rings, in an attempt to increase adherence and to improve drug pharmacokinetics. The system described by the authors achieved relevant release rates of multiple antiretrovirals with disparate chemical properties that are being evaluated to prevent vaginal HIV transmission. In addition, it is possible to extend the duration of drug delivery longer than one month either by making the reservoir bigger or by utilizing different types of water-soluble polymers. The system developed by the Kiser team provides flexibility in delivering hydrophilic macromolecular drugs, greatly expanding the design space of clinically useful intravaginal ring formulations.

References

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