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Intravaginal Rings as a Novel Platform for Mucosal Vaccination

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The major reasons for the current lack of an effective vaccine include the fact that conventional vaccines are meant to protect against disease and not infections. In addition, the lack of understanding of the virus makes vaccine development even more challenging. In the absence of a vaccine, microbicides (products designed for vaginal or rectal application for the purpose of reducing or preventing sexually transmitted infections) are an excellent alternative strategy for protection against HIV. Over the past 20 years, numerous microbicidal formulations such as gels have been developed but all have shown limited efficacy. As the microbicide field evolves, there is an ever-increasing need for alternative dosage forms to deliver agents that can reduce or prevent the transmission of HIV. There are currently no approved microbicides that can effectively reduce or prevent HIV/AIDS.

Despite successful HIV prevention strategies such as condom use, monogamy, and abstinence, it has been reported by UNAIDS (Joint United Nations Programme on HIV/AIDS) that approximately 33.4 million people globally are living with HIV and 2 million have died in 2008 alone [1]. Biologically, women are twice more likely to become infected with HIV through unprotected heterosexual intercourse. According to Michel Sidibe, the Executive Director of UNAIDS, "This epidemic unfortunately remains an epidemic of women". As a result, there is a need to develop methods that provide female-controlled prevention of HIV infection.

Intravaginal rings (IVRs) are flexible, ring-shaped drug delivery devices typically made of medical grade elastomeric polymers intended for the sustained and controlled release of compounds into the vaginal tract. Unlike intrauterine devices, IVRs can be inserted and removed by the patient without the assistance of a medical practitioner. IVRs are an alternative dosage form that is currently approved by the FDA for use in contraceptives (i.e. NuvaRing®) and for hormone replacement therapy (i.e. Femring® and ESTRING®). Femring™ and Estring® are silicone-based rings for the delivery of estradiol and estradiol acetate, respectively. The ethylene-vinyl acetate ring, Nuvaring®, is designed to deliver etonogestrel and ethinyl estradiol. In an international study conducted using Nuvaring®, 14.1% of the women reported that they had temporarily removed the ring during the study period as a result of interference with intercourse and 4.1% removed the ring because the ring fell out [2]. Interestingly, at the completion of the study, overall acceptance was high with 96% of the patients satisfied with the ring and 97% would recommend the ring. This clinical trial along with others have demonstrated that IVRs are safe, relatively simple to use without the assistance of a healthcare professional, and IVR replacement is infrequent (once every 30 days as opposed to daily applications using vaginal gels). As a result, the concept of using an IVR as a microbicide or vaginal vaccine is not confounded due to the observed advantages.

There are numerous IVR designs with the simplest having the drug homogenously dispersed throughout the entire polymeric ring. The mechanism by which drug is released from these "matrix" IVRs typically involves diffusion of dissolved drug across the polymer. Conventional IVRs are typically fabricated using methods such as polymer curing, injection molding, or hot-melt extrusion (the polymer is melted, extruded into cylindrical rods, and then the ends are joined together using methods such as butt-welding or epoxies to form rings [3-5]. IVRs have been adapted for its applications in microbicide development for the sustained delivery of various anti-HIV drugs. The availability of various medical grade polymers with differing shore hardness, tensile strength, melting temperatures, and hydrophilicity makes it a suitable material for IVR fabrication and delivery of various small molecule drugs.

Recently, IVRs are being explored for their applications in mucosal vaccination. Mucosal membranes in the reproductive tract contain antibodies, T-cells, beta-defensins, lysozyme, and other enzymes that play a crucial role as the first line of defense against HIV-1 [6]. In a study by Kato et al., mice were immunized via the genital mucosa by an HIV peptide vaccine and cholera toxin as an adjuvant. HIV-1-specific IgA antibody was detected in vaginal washes [7]. In another study, a polymeric gel was used for the vaginal delivery of the HIV-1 gp140 protein. This delivery system was able to induce specific systemic and mucosal IgG and IgA antibody responses in genital secretions [8]. From these studies, it is clear that vaginal vaccination can induce HIV-specific antibody responses. It is believed that by developing a vaginal vaccine, a stronger, localized immune response may be mounted against HIV-1 in comparison to conventional intramuscular or intranasal routes of administration.

One of the major challenges in fabricating protein/peptide-loaded IVRs using conventional methods such as hot-melt extrusion is that the application of high heat will result in degradation/aggregation of the protein/peptides. In addition, the large molecular weight of proteins and peptides make it difficult to traverse across polymeric elastomers. To circumvent these issues, researchers have developed alternative IVRs whereby lyophilized proteins are inserted into the IVR rather than being incorporated during the IVR fabrication process [9,10]. Although these alternative designs overcome some of the challenges encountered with protein/peptide IVR fabrication and delivery, there are concerns associated with mass production of these devices for clinical evaluation due to the increased complexity in the design and increased cost.

Overall, the utility of IVRs as a microbicide and vaginal vaccine is very promising. Extensive research is still necessary to demonstrate its effectiveness in the reduction or prevention of HIV infection. Nonetheless, IVRs are interesting alternative platforms for inducing mucosal immunity to a variety of sexually transmitted pathogens and could be a significant breakthrough in women's health.

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