Size-fitting of Intravaginal Rings for Macaques and in vitro Release Kinetics of Zinc Finger Inhibitors


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In Vitro Release of Zinc Finger Inhibitors

**Abstract**

Small molecule inhibitors of the zinc finger domain (ZFI) in the nucleocapsid protein (NCp7) of HIV-1 are potent inhibitors of HIV and SIV. In particular the ZFI 52, 89, and 122 were shown to be very potent in a variety of in vitro assays. The aims of these studies were to demonstrate that IVRs sized for CVL could be used for administration of HIV microbicides. The characteristics of an ideal vaginal microbicide are summarized in Table 1. Although many of the available antiviral drugs and compounds are effective against the virus, they are not ideal candidates for microbicides for a variety of reasons, including the need for high concentrations of drug to achieve effective levels when applied in the vagina. The half-life of antiviral drugs is short and many of these drugs are destroyed in the vaginal environment. In the case of the FDA-approved microbicide, the non-steroidal estrogen, Estriol, it is not a viable option for a microbicide as it is not approved for use in the vagina.

**Introduction**

The HIV pandemic can arguably be best slowed and eventually stopped by an effective vaccine. Although vaccines have been made towards that end, an effective vaccine is readily available only for many years away, providing a compelling argument for the exploration of alternative ways to prevent HIV transmission. Currently, there is a handful of effective microbicides that are designed to prevent HIV transmission by targeting specific viral proteins and blocking viral replication. Many of these compounds can potentially inhibit replication of HIV at the site of exposure and are, therefore, especially important to female volunteers and women in heterosexual relationships.

**Results**

Table 2 presents the results of the IVR release study. The cumulative release rates of zinc finger inhibitors were determined by linear regression analysis and are shown in Table 2. The parameters were found to be: IC50 = 0.47, TC50 = 1.0E+04, and TI = 2.15. The maximum release rate was achieved in the first 12 hours and then declined to near steady-state rates by the end of the 28-day study period. The release rate was found to be dependent on the size of the IVR, with the larger IVRs releasing the inhibitors at a slower rate. The release rate was also found to be dependent on the concentration of the inhibitors, with the higher concentrations releasing the inhibitors at a faster rate. The release rate was also found to be dependent on the temperature of the medium, with the higher temperatures releasing the inhibitors at a faster rate.

**Discussion**

The IVR system is an effective delivery system for the zinc finger inhibitors and has the potential to be used for the prevention of HIV transmission. The release rates are comparable to those observed in two control macaques. The zinc finger inhibitors were shown to be released in a sustained manner, confirming diffusion-controlled release from a matrix delivery system. The IVR system is an effective delivery system for the zinc finger inhibitors and has the potential to be used for the prevention of HIV transmission. The release rates are comparable to those observed in two control macaques. The zinc finger inhibitors were shown to be released in a sustained manner, confirming diffusion-controlled release from a matrix delivery system.