Controlled Release of Antiretroviral Drugs from Ethylene-vinylacetate Intravaginal Rings to Protect Women From HIV Transmission

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INTRODUCTION

In the absence of an effective HIV vaccine, vaginally applied microbicides offer a promising approach to prevent male-to-female transmission of HIV during sexual intercourse. Various delivery options are in development including gels, films and intravaginal rings. Issues of patient compliance with daily-use or coitally-dependent gels are eliminated with IVRs which can be worn for 30 days at a time, and release drugs over that period. Therefore IVRs show promise for a simple, safe, covert and efficacious means to prevent HIV transmission. Ethylene-co-vinylacetate is a thermoplastic polymer that can be readily formed into devices using standard plastic processing techniques. We developed EVA intravaginal rings containing antiretroviral microbicides, and characterized their physical properties, 30-day *in vitro* drug delivery, and long term storage stability. We also developed a scalable manufacturing process to prepare rings.

METHODS

Four antiretroviral drugs (Dapivirine, Maraviroc, BMS793, CMPD167) were mixed at various levels with molten EVA (various grades) in a Banbury-style batch mixer or co-rotating twin screw hot-melt compounder. IVRs with 4mm cross-sectional diameter and 54mm overall diameter were prepared by injection molding of the pelletized API/EVA mixture into an aluminum or steel mold.

An EZ-Test apparatus fitted with a 10N load cell was used to determine physical properties of IVRs. IVRs were incubated under sink conditions in 100mL IPA:water (1:1 v/v) in a shaker (37° C, 1 Hz) for 30 d, and the medium assayed daily for API by HPLC.

RESULTS AND DISCUSSION

High quality antiretroviral-loaded IVRs were readily prepared by simple compounding and injection molding processes at lab scale and pilot scale.

All drugs were released from IVRs for at least 30d, with a burst on day-1 followed by first order kinetics (figure 1).

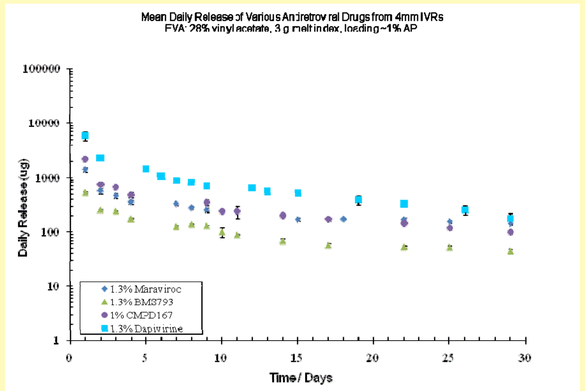

Figure 1: Release of various antiretroviral drugs from EVA IVRs.

Release was drug-loading dependent (as shown for Dapivirine in fig. 2), showed no dependence on polymer melt index (fig. 3), nor vinyl acetate content in the polymer (fig. 4) over 30d. IVRs containing combinations of two drugs released each drug independently of the other. The release of Dapivirine and Maraviroc from a combination IVR containing 25 mg Dapivirine (~1.3%) and 300 mg Maraviroc (~15%) is shown in fig. 5.

Drug assay and drug release kinetics for the 25 mg / 300 mg combination IVR remained within specification for at least 3 months at 40 °C / 75% RH, showing that the IVRs are stable under accelerated storage conditions (fig. 6). The acceptable release rates of drugs from the combination IVRs, coupled with their promising storage stability, make them ideal candidates for clinical trial.

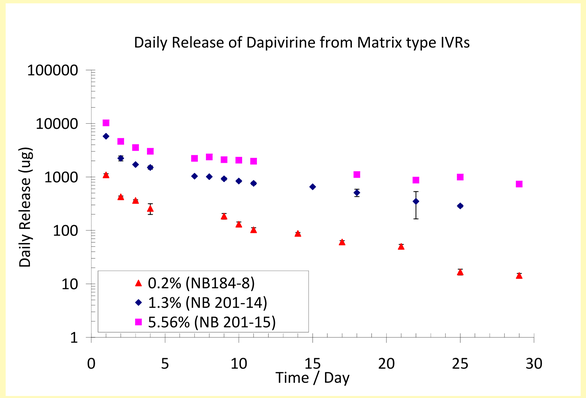

Figure 2: Release of Dapivirine from EVA matrix IVRs containing various Dapivirine loadings.

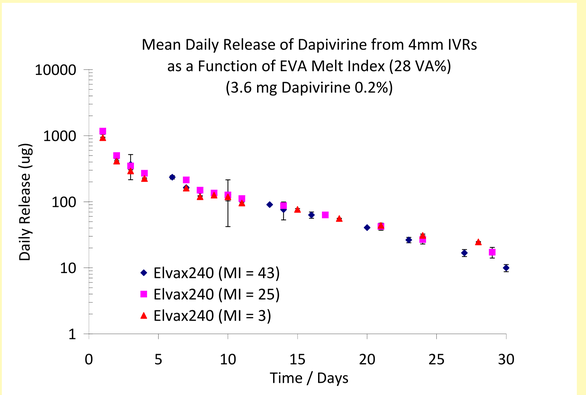

Figure 3: Release of Dapivirine from EVA matrix IVRs made from EVAs with 28% VA and various melt indices.

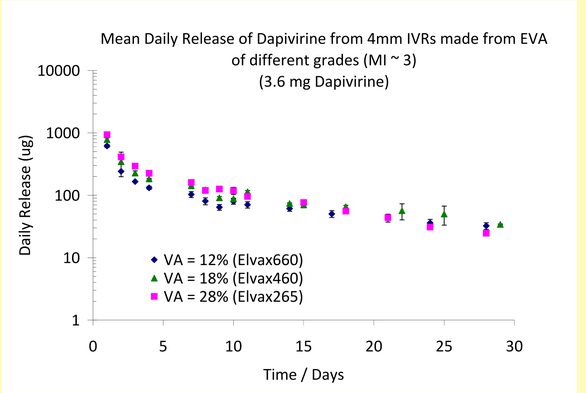

Figure 4: Release of Dapivirine from EVA matrix IVRs made from EVAs with a melt index of 3 g/10min and various VA contents

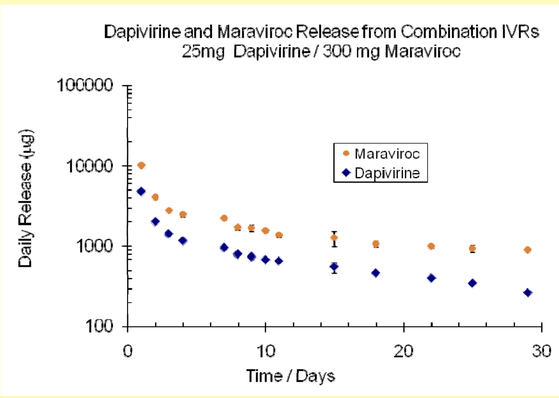

Figure 5: Release of Dapivirine and Maraviroc from combination IVRs containing 25 mg (~1.3%) Dapivirine and 300 mg (~15%) Maraviroc.

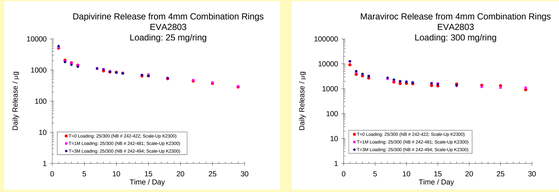

Figure 6: Release of Dapivirine (left) and Maraviroc (right) from combination IVRs containing 25 mg (~1.3%) Dapivirine and 300 mg (~15%) Maraviroc over a 3M stability study. Rings prepared using pilot equipment.

CONCLUSIONS

Hot-melt extrusion / injection molding of EVA is a robust and scalable route to preparing intravaginal rings that release appropriate levels of antiretroviral drugs for 30 days. A variety of antiretroviral drugs are released from EVA IVRs, at a high enough rate to be useful in a commercial device. The IVRs are stable under accelerated storage conditions – a key factor for product success in many developing countries where this device could have most impact.

A combination device containing 25 mg Dapivirine and 300 mg Maraviroc has been developed and is ready for clinical trial.

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