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Multipurpose vaginal rings for HIV prevention and non-hormonal contraception

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SUMMARY

Vaginal rings releasing antiretrovirals - either alone or in combination with contraceptive progestins - are being developed for contraception and prevention of human immunodeficiency virus (HIV) transmission via vagina. However, hormonal contraceptives are associated with numerous side effects and contraindications, and many women are interested in using hormone-free contraceptives. The aim of this project is to develop multipurpose vaginal rings to release copper and/or zinc ions and dapivirine over a month for contraception and HIV prevention. Ring manufacture, swell testing, and in vitro drug release testing have been conducted. The experimental results obtained currently are encouraging and support the continued development of these ring formulations as a novel and interesting multipurpose prevention technology strategy.

INTRODUCTION

Following recent marketing approval of the dapivirine (DPV)-releasing vaginal ring (VR) for HIV prevention, efforts are now underway to develop multipurpose ring formulations to simultaneously prevent HIV and unintended pregnancy. Currently, four vaginal hormone-releasing rings offering combination (progestin + estrogen) or progestin-only contraception are available (Boyd et al., 2019). Given the preference for continuous use of an antiretroviral ring for HIV prevention, it is not surprising that efforts towards multipurpose ring products have focused on incorporation of potent progestins, with levonorgestrel prioritized due to its well-established safety profile. However, hormonal contraceptives are associated with numerous side effects and contraindications, and many women are interested in using hormone-free contraceptive products. Copper (Cu) and zinc (Zn) ions have well documented spermicidal activity, and various Cu intrauterine devices are marketed and widely used by women. To date, there has been very limited research evaluating the potential of VRs releasing Cu/Zn ions for contraception.

MATERIALS AND METHODS

Matrix-type VRs (~7.8 g) containing 25 mg micronised DPV (mDPV) and/or 10% w/w of Cu/Zn nanoparticles (NP) or salts were prepared from medical grade addition-cure silicone elastomer dispersions (DDU4320, NuSil). Briefly, silicone parts A and B (1:1) were mixed (Speedmixer DAC-150) with the 25 mg mDPV and/or 10% w/w Cu/Zn compounds for 1 min at 3000 rpm, injected into custom ring molds fitted to an injection molding machine, and cured at 85℃ for 3 min. For in vitro release testing, VRs were incubated with 100 mL 2% W/V Kolliphor® HS 15 in 25 mM acetate buffer solution, pH 4.2 over 28 days (for formulations containing Zn NP, incubated with 2% W/V Kolliphor® HS 15, pH 4.2). Swell testing was conducted in parallel with release testing. On day 0,

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7, 14, 21 and 28, the ring was taken out from the flask within 15 min for measurement of ring weight.

RESULTS AND DISCUSSION

Across all formulations containing mDPV (Figure 1), a burst release of mDPV of ~0.6 mg on day 1 was observed, followed by a gradual decline in daily release quantities to ~0.1 mg/day on day 25. Cumulative mDPV released was 4.4 – 5.0 mg over 28 days. DPV release from matrix-type VRs is via a permeation-controlled mechanism. The presence of Cu or Zn compounds rings had only a small effect on mDPV release.

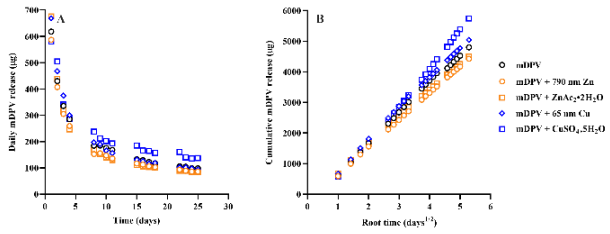

Fig. 1. *Mean daily release (μg) vs. time (A) and cumulative release vs. root time (B) profiles for release of mDPV from matrix-type VRs containing mDPV into release medium, over 28 days.*

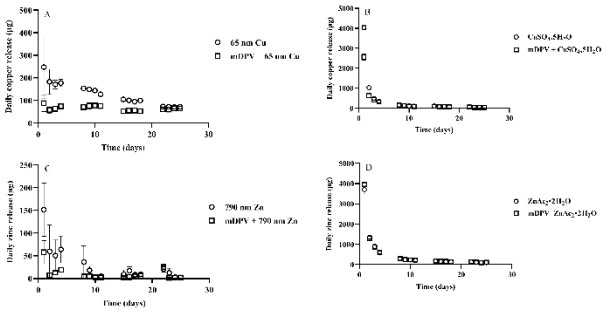

Fig. 2. *Daily Cu/Zn release from matrix-type VRs over 28 days.*

Small quantities of Cu/Zn ions were released from VRs over the 28-day study (less than 0.2 mg) (Figure 2), due to the dissolution of the metal compounds (Cu/Zn nanoparticles) at the surface of the VRs. Compared with NP VRs, relatively large amounts of Cu/Zn ions were released from salts VRs. This may be attributed to the relatively high solubility and diffusion of metal salts in the silicone and drug diffusion through water-filled pores in a partially swollen matrix. Specifically, 3.9 mg Zn ions were released from $ZnAc_2 \cdot 2H_2O$ VRs on day 1. VRs containing $CuSO_4 \cdot 5H_2O$ showed the same general trend for daily release, except for day 1 burst. Figure 3 presents that over 28 days, the maximum cumulative Zn release from rings containing $ZnAc_2 \cdot 2H_2O$ was ~11 mg, while the maximum cumulative Cu release from VRs containing $CuSO_4 \cdot 5H_2O$-only up to ~8.2 mg. Cumulative Cu release of ~6 mg was measured from VRs containing mDPV and $CuSO_4 \cdot 5H_2O$.

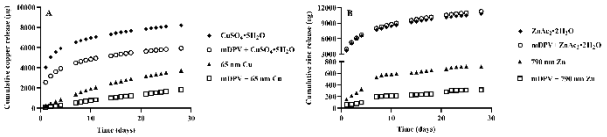

Fig. 3. *Cumulative release profiles for Cu (A) and Zn (B) release from matrix-type VRs over 28 days.*

The mean weight change measured is presented in figure 4. Not surprisingly, rings with hydrophilic APIs ($ZnAc_2 \cdot 2H_2O$ and $CuSO_4 \cdot 5H_2O$) have a significantly increase in weight over 28 days. The weight of rings has increased by 2 g ($CuSO_4 \cdot 5H_2O$) and 4 g ($ZnAc_2 \cdot 2H_2O$), respectively. The mass of other rings was mostly maintained during the 28-day release study.

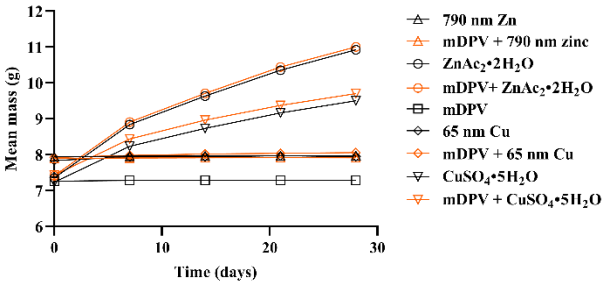

Fig. 4. *Mean weight change of VRs over 28-day release test.*

CONCLUSIONS

The results obtained currently are encouraging and support the continued development of these VR formulations as a novel and interesting multipurpose prevention technology strategy.

REFERENCES

Boyd, P., Variano, B., Spence, P.,2019. In vitro release testing methods for drug-releasing vaginal rings. J. Control. Release, 313, 54–69.