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Shen, X., Malcolm, K., Boyd, P., Dallal Bashi, Y., McCoy, C. F., Zhao, X., Lamb, D., Mitchell, L., Kumar, N., & Singer, P. (2023). *Poster abstract: A multipurpose vaginal ring releasing copper ions, zinc ions and dapivirine for HIV prevention and non-hormonal contraception*. 1. Abstract from United Kingdom & Ireland Controlled Release Society (UKICRS) Symposium 2023, London, United Kingdom.

Document Version:
Peer reviewed version

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A multipurpose vaginal ring releasing copper ions, zinc ions and dapivirine for HIV prevention and non-hormonal contraception

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Background: Following recent marketing approval of the 28-day dapivirine (DPV)-releasing vaginal ring for HIV prevention, efforts are now underway to develop new multipurpose rings that can simultaneously prevent HIV and unintended pregnancy. Efforts to date have primarily focused on incorporating potent progestin hormones, such as levonorgestrel, into antiretroviral-releasing ring products. Since progestins are associated with numerous side effects and contraindications, many women are interested in using hormone-free contraceptive products. Although copper (Cu) and zinc (Zn) ions have well documented spermicidal activity (and various Cu intrauterine devices are available), Cu and Zn actives have not previously been evaluated in vaginal ring formulations. The aim of this project is to develop a silicone elastomer vaginal ring offering sustained release of DPV, Cu ions and Zn ions with potential to prevent both HIV infection and unintended pregnancy.

Methods: Matrix-type LSR-4350 vaginal rings (~8.6 g) containing 25 mg DPV, 10% w/w anhydrous CuSO₄, 10% w/w ZnSO₄•H₂O and 10% w/w HPMC (DCZH) were prepared by injection molding (115 °C, 4 min) using a medical grade addition-cure silicone elastomer dispersion (LSR-4350). Rings were tested for *in vitro* release over 30 days by immersion in 100 mL 2% w/v Kolliphor® HS 15 in 25 mM acetate buffer solution pH 4.2. Samples were collected daily and DPV, Cu ions and Zn ions measured using HPLC and ICP-OES. Ring characteristics (weight, dimensions, shore M hardness, compression force, etc.) were recorded before and after *in vitro* release and after drying. Anhydrous CuSO₄, ZnAc and ZnSO₄•H₂O compounds were chosen to conduct anti-sperm motility test.

Results: The EC₅₀ for 50% sperm motility reduction were: ~12 mM for anhydrous CuSO₄, ~18 mM for ZnAc, ~65 mM for ZnSO₄•H₂O and ~6 mM for hydrogen peroxide as a positive control. Both anhydrous CuSO₄ and ZnSO₄•H₂O showed EC₅₀ values in expected ranges, which demonstrated that CuSO₄ and ZnSO₄•H₂O are potential candidates for contraception. For the *in vitro* test results, DPV showed a burst release on day 1 at ~815 µg, which decreased to ~285 µg by day 30. Over 30 days, the cumulative release of DPV was ~12.6 mg, which was ~7 mg higher than the 30-day *in vitro* release levels observed with a 25 mg DPV matrix ring. In terms of metal release from the ring, ~5.3 mg Cu and ~7.2 mg Zn were released on day 1. The 30-day cumulative release of Cu and Zn was ~18.2 mg and ~21.6 mg, respectively. After 30 days of release, the mass of DCZH rings increased from ~8.6 g (before release) to ~20.1 g. When the rings were put into the oven for evaporating the release medium, the mass of the ring decreased to ~8.5 g. The same change was observed for the cross-sectional diameter and outer diameter (CSD * OD) of the rings, which changed from 7.2 mm * 56.9 mm (before release) to 9.8 mm * 78.7 mm (after release), and then shrank back to 7.1 mm * 59.8 mm (after drying). Regarding the shore M hardness test, the value before release, after release, and after drying were about 64, 34, and 64, respectively. For the compression test at 20 mm, the forces required to compress the DCZH rings before and after release and after drying were approximately 3.4 N, 2.0 N, and 3.5 N, respectively.

Conclusions: The experimental results obtained currently are encouraging and support the continued development of the ring formulation as a novel and interesting multipurpose prevention technology strategy for HIV prevention and non-hormonal contraception.