Multipurpose vaginal rings for HIV prevention and non-hormonal contraception

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Background: Following recent marketing approval of the dapivirine (DPV)-releasing ring 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. 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) have well documented spermicidal activity, and various Cu intrauterine devices are marketed and widely used by women. However, to date, there has been very limited research evaluating the potential of vaginal rings containing Cu/Zn for contraception. The aim of this project is to develop a vaginal ring that can provide sustained release of both DPV and Cu/Zn to simultaneously prevent HIV infection and unintended pregnancy.

Methods: Matrix-type DDU-4320 vaginal rings (~7.8 g) containing 25 mg DPV and 10% w/w Cu/Zn compounds 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 required quantity of DPV and Cu/Zn compounds (65 nm Cu, 790 nm Zn nanoparticles; copper sulfate pentahydrate; zinc acetate dihydrate) for 1 min at 3000 rpm, and then injected into the injection molding machine and cured at 85℃ for 3 min. For i*n vitro* release testing, vaginal rings 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 nanoparticles, incubated with 2% W/V Kolliphor® HS 15, pH 4.2). Samples were collected daily and quantification of DPV and Zn/Cu release measured using HPLC and atomic absorption spectroscopy, respectively.

Results: In vitro release of Cu, Zn and DPV were affected the incorporation of other actives. Across all formulations, a burst release of DPV 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 DPV released 4.4–5.0 mg over 28 days. Small quantities of Cu/Zn were released from nanoparticles over 28-day incubation (~1.8 and ~0.3 mg, respectively), a possible consequence of the relatively low solubility and diffusion of metal nanopowders in the hydrophobic silicone. The release of Cu/Zn from metal nanoparticles rings is mostly due to the dissolution of active pharmaceutical ingredients (Cu/Zn nanoparticles, copper oxide, zinc oxide, et al.) on the surface of rings. Compared with metal nanoparticles, relatively large amount of metal salts was released from matrixes. Specifically, ~2.5 mg Cu/~3.9 mg Zn released from DPV and copper sulfate pentahydrate/zinc acetate dihydrate vaginal rings on day 1. And over 28 days, Cu/Zn cumulative release of ~6 mg and ~11 mg were observed from these rings. 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.

Conclusions: 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.