

## PRELIMINARY FORMULATION DEVELOPMENT OF SILICONE ELASTOMER VAGINAL RINGS FOR SUSTAINED RELEASE OF METRONIDAZOLE, SUCROSE AND LACTOBACILLUS

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**Background:** Bacterial vaginosis (BV) is a common dysbiosis of the human vagina in which commensal vaginal lactobacilli are displaced by mixed pathogenic bacterial populations. Current treatments for – including metronidazole (MET) and clindamycin – result in short-term cure but often lead to recurrence. New treatment options are needed. Lactobacilli are being actively developed as a probiotic treatment option for BV, given their ability to inhibit growth of pathogenic microorganisms and to maintain the health and stability of the vaginal tract microbiota. Also, prebiotic sucrose gels have shown promise for treatment of BV in clinical studies. Here, we report preliminary formulation work as part of our efforts to develop sustained-release vaginal ring formulations for simultaneous release of MET, a prebiotic lyoprotectant and lactobacillus. Specifically, the influence of incorporating various lyoprotectants into silicone elastomer rings is investigated.

**Methods:** Silicone elastomer matrix-type rods (as prototype vaginal rings) were prepared having various antibiotic and prebiotic components incorporated, including: MET, maltodextrin (MD), mannitol (MT), sucrose (SC), polyethylene glycol 4000 (PEG) and 20% freeze-dried sucrose (FDSC). Briefly, MET and lyoprotectant were added to Parts A and B of medical-grade silicone elastomer and mixed (3000 rpm, 10 s, SpeedMixer DAC-150 FVZ-K). Rods were prepared by injecting the mix into PVC tubing and then curing in an oven at 40 °C. Manufactured rods were demolded and then cut into 5 cm lengths. Rods containing lyoprotectant only (n=4) underwent in vitro swelling testing in simulated vaginal fluid medium for 14 days. Rods containing MET + lyoprotectants were also tested for in vitro MET release in 200 mL water over 14 days (37 °C and 60 rpm), with quantification by reverse-phase UPLC (ACQUITY UPLC).

**Results:** Swelling ratio values ( $Q_{wt}$ ) were calculated following the swelling experiment. The addition of lyoprotectants increased the swelling ratio (hydrophilicity) of the silicone elastomer rods. As the concentrations of lyoprotectants MT, MD and SC increased, the hydrophilicity of silicone elastomer increased. From 5% to 10% of PEG4000, the hydrophilicity also increased. The FDSC rods absorbed more water than the corresponding SC rods ( $Q_{wt}$  increase from 0.0 to 0.4). All rods indicated a burst MET release on day 1 followed by a slightly decreasing daily release with time and a linear cumulative release vs. square root time (all  $R^2 > 0.9$ ), indicative of a permeation-control drug release mechanism from a polymeric matrix device containing excess solid drugs. In this 14-day release study, cumulative release for all rods increased as the lyoprotectant loading increased, consistent with hypothesis that the prebiotic lyoprotectant can facilitate the release of metronidazole by absorbing fluid.

**Conclusions:** Incorporation of hydrophilic prebiotic lyoprotectants (for the future purpose of also incorporating live lactobacillus) into silicone elastomer vaginal rings containing MET causes swelling of the rings and facilitates release of the MET. Moving forward, it will be important to minimize swelling of the ring device while still achieving sufficient release of MET, the prebiotic and the lactobacillus. In future work, freeze-dried lactobacillus will also be incorporated into the rings.