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 disease that widely affects women's health. More than 50% of all women globally experience vaginitis of varying severity. The most common treatments of BV include antibiotics, and the current gold standard drugs are metronidazole (MET) and clindamycin. Lactobacilli are being actively developed as a treatment option for BV, given their ability to inhibit growth of pathogenic microorganisms and to maintain the health and stability of the vaginal tract biofilm. This project involves freeze-drying of lactobacillus with different categories of lyoprotectant and incorporate both together with metronidazole into silicone elastomer vaginal rings. One study has reported that the lactobacillus can increase the cure rate of BV and help to restore the lactobacillus-dominated flora. Therefore, the treatment of BV by lactobacillus is worth exploring further.

Methods: Matrix-type MED-4870 vaginal rings (VRs) loaded with (i) no active ingredients (blank), (ii) four lyoprotectants (MT, MD, SC and PEG) of three different concentration (5%w/w, 10%w/w and 20%w/w), were manufactured by injecting into injection mold and then curing at 120 ºC. Blank MED-4870 VRs and matrix-type MED-4870 VRs formulations with various components incorporated maltodextrin (MD), mannitol (MT), sucrose (SC), polyethylene glycol 4000 (PEG) were prepared. Appropriate quantities of lyoprotectant were added to MED-4870 Parts A and B in an appropriately sized container and mixed at 3000 rpm for 10 s in a SpeedMixer (DAC-150 FVZ-K). Two 25 g premixes of each of parts A and B were prepared and stored at 4 ºC for each rod batch. The parts were then combined, and the material hand mixed for 30 s and speed mixed at 2350 rpm for 20 s in SpeedMixer (DAC 600 VAC-P). Rings were made by injecting the combined mixture into injection mold and cured at 120 ºC. Manufactured rods were demolded, weighed and measured the outer diameter and cross-section diameter. Four rings were randomly selected from each groups: (i) MT, （ii） MD, (iii) SC ,(iv) PEG and (vi) Blank for (i) mechanical tests (compression test, twist test and Shore M Hardness test) (ii) swelling test and (iii) *in vitro* release test into reverse osmosis water (pH = 5.5). The release test and swelling test lasted for 12 days. On day 0, each rod was into a 250 mL DURAN flask with 100 mL reverse osmotic pressure water and stored in a shaking incubator at 37 ºC and 60 rpm. The release medium was sampled and replaced by another 50 mL medium on rest 11 days. The release amount of lyoprotectants were quantified by HPLC coupled with evaporative light scattering detection (ELSD).

Results: In mechanical tests, as the increase of the concentration of lyoprotectants, the resistance force of VRs increase, while the rotational angle decreased. However, there are only limited differences between the Shorehardness values. In the swelling test, addition of lyoprotectant can increase the potential of silicone vaginal rings to absorb water. Of four lyoprotectants, the mannitol produced the greatest swelling. In the *in vitro* release test, the length of releasing time was dependent on the concentration of lyoprotectants. Of 12 formulations, 20%w/w mannitol and 20% sucrose indicated longest release duration.

Conclusions: The concentration of lyoprotectants have effect on the mehanical characteristic and hydrophilicity of MED-4870 vaginal rings. The lyoprotectants can release from the VRs and. The release amount relies on categories of lyoprotectants and concentration. The experimental results obtained to date are encouraging, and support the continued development of these ring formulations as a novel and interesting strategy for improving treatment of BV.