A SPOONFUL OF SUGAR (OR ACID) HELPS THE MEDICINE GO DOWN: A MULTIPURPOSE VAGINAL RING STRATEGY FOR TREATMENT OF BACTERIAL VAGINOSIS.

Xinyu Zhao[1], Peter Boyd[1], Laura Domenici[1], Sophie Ervine[1], Karl Malcolm[1]

[1] School or Pharmacy, Queen's University Belfast, BT9 7BL, UK

Background: Bacterial vaginosis (BV) is a common dysbiosis of the human vaginal microbiome associated with depletion of the normally dominant Lactobacillus species and overgrowth of facultative anaerobic bacteria. Although most women diagnosed with BV do not suffer complications, BV can lead to preterm birth, risk of infection after gynecologic surgery, pelvic inflammatory disease, and increased risk of acquiring a sexually transmitted infection, including infection with human immunodeficiency virus (HIV). Following the significant advances in recent years in developing antiretroviral-releasing vaginal rings (VRs) for HIV prevention, there is now considerable interest in developing new multipurpose prevention technology (MPT) VRs aimed at treating/preventing BV in addition to delivering an antiretroviral drug. Here, we describe formulation efforts to develop a MPT VR offering simultaneous release of two or more of the following actives: dapivirine (DPV, a potent experimental antiretroviral); 5-nitroimidazole antibiotic drug, including metronidazole (MET), tinidazole (TNZ), secnidazole (SNZ) and ornidazole (ONZ); sucrose (selectively promotes the growth of lactobacilli), and boric acid (antimicrobial and anti-biofilm properties).

Methods: Matrix-type silicone elastomer VRs containing various combinations of DPV, MET, sucrose and BA were manufactured. In vitro testing of rings included: rheological assessment of cure properties; drug release; thermal analysis (DSC, TGA); mechanical testing (compression, Shore Hardness); swelling studies in aqueous medium; surface imaging using scanning electron microscope.

Results: All of the active agents, both singly and in various combinations, were successfully incorporated into silicone elastomer matrix-type vaginal rings. For rings loaded with 250 mg 5-nitroimidazole drugs, rank order *in vitro* release was SNZ>ONZ>MET>TNZ. The incorporation of sucrose in MET rings increased MET release. DPV release was readily modulated by changing the drug loading or combining with MET. Mechanical properties of these vaginal ring formulations were acceptable. Release of boric acid from rings decreased the pH of the release medium. Incorporation of sucrose and boric acid caused surface roughness of the rings. The incorporation of up to 25% w/w sucrose and boric acid caused the vaginal ring to swell by 70% and 12.5% of the original mass, respectively.

Conclusions: Despite challenges in developing a VR device offering simultaneous release of multiple actives, the data support the further development of combining a 5-nitroimidazoile antibacterial drug with sucrose, boric acid and an antiretroviral drug.