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], R. Karl Malcolm[1]

School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK

E: xzhao11@qub.ac.uk

E: k.malcolm@qub.ac.uk

QUEEN'S UNIVERSITY BELFAST

Key points

1. The release of MET, SNZ, ONZ and TNZ from matrix-type DDU-4320 silicone elastomer vaginal rings conforms to root time kinetics.
2. DPV, MET, sucrose, boric acid and different combinations of these four compounds are compatible with DDU-4320 silicone elastomer.
3. The incorporation of boric acid and sucrose did not negatively influence the release of DPV and MET in the 28-day *in vitro* release testing.

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, potentially therapeutic substances) to prevent HIV infection and, at the same time, treat or prevent BV.

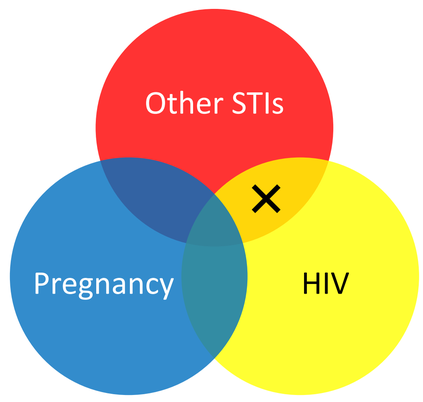
Objectives

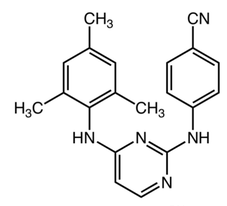
- To test the compatibility of candidate active ingredients with silicone elastomer.
- To manufacture matrix-type vaginal rings.
- *In vitro* release testing of vaginal ring formulations.

Methods

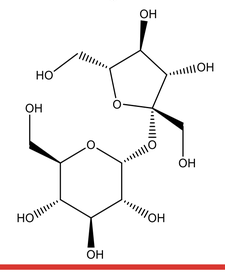
- DSC analysis: active ingredients (API) powders, physical mixtures of two and three APIs, DDU-4320 silicone elastomer loaded with APIs (10% w/w) and combinations of APIs.
- Ring manufacture by reaction injection molding: matrix-type DDU-4320 silicone elastomer vaginal rings loaded with ONZ, TNZ, SNZ, MET, DPV, sucrose, boric acid, DPV + MET, and the combination of DPV, MET, sucrose and boric acid.
- *In vitro* release testing (28 days): release media – 0.2% w/w Tween 80 (pH=4.2, 100/200 mL), release condition – 60 rpm and 37 ˚C.

Multipurpose Prevention Technologies (MPTs)

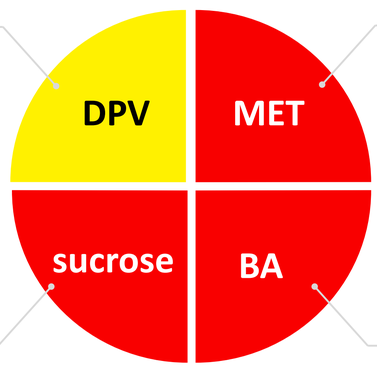




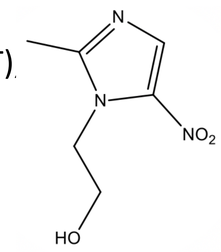
Dapivirine (DPV), a potent experimental antiretroviral



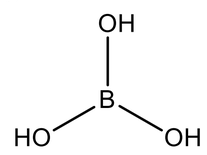
Sucrose, prebiotic promoting the growth of lactobacilli



Metronidazole (MET), a 5-nitroimidazole antibiotic drug



Boric acid (BA), biofilm disruptor candidate



Results & Discussion

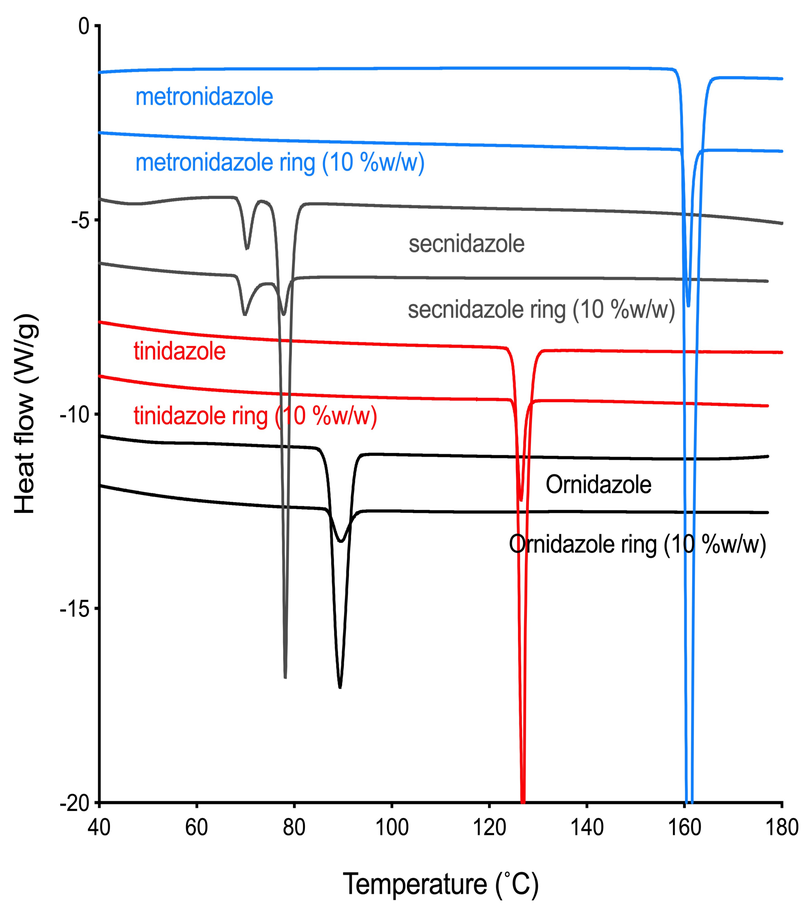


Figure 1. Representative DSC traces showing thermal behaviour of MET, SNZ, TNZ and ONZ and corresponding ring samples containing MET, SNZ, TNZ and ONZ (10% w/w each). The thermal transitions of MET, TNZ and ONZ are melting peaks at 160, 127 and 89 ˚C respectively. SNZ shows two endotherms at 70 ˚C and 78 ˚C, attributed to dehydration and melting. The same thermal transitions are also observed for silicone elastomer samples.

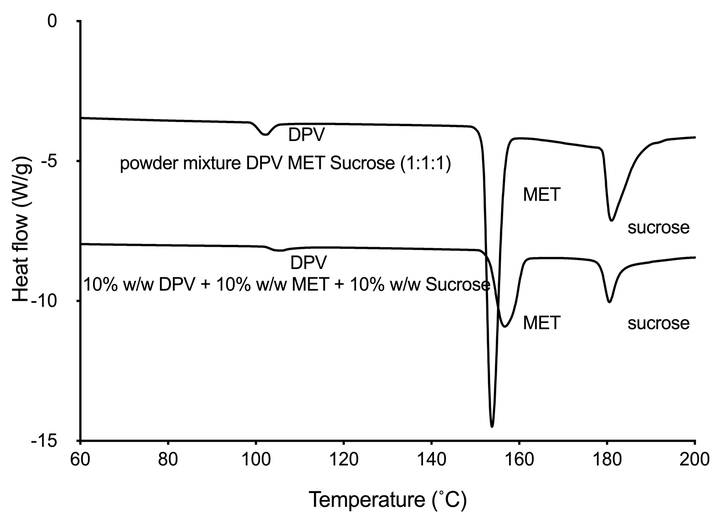


Figure 2. DSC thermograms showing thermal behaviours of physical mixtures of DPV, MET and sucrose (1:1:1) and silicone elastomer ring samples containing the mixture (10% w/w x 3).

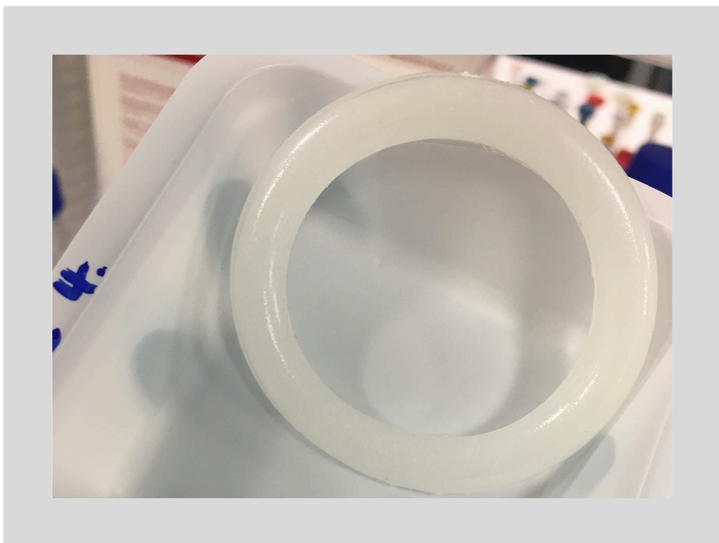


Figure 3. Representative photo of matrix-type silicone elastomer DDU-4320 vaginal rings.

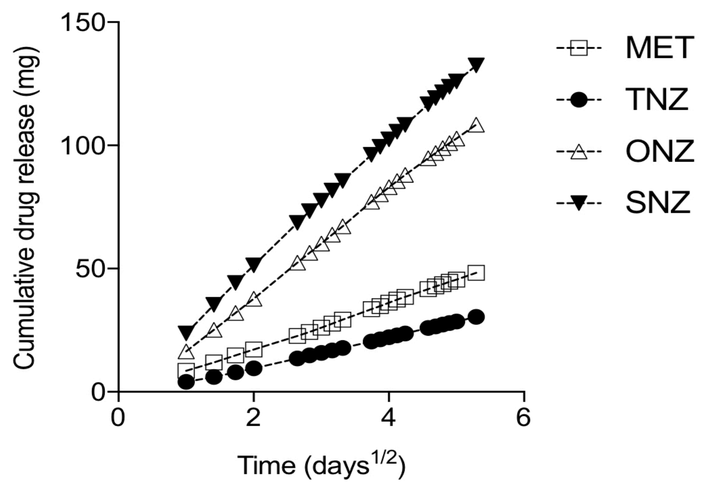


Figure 4. Cumulative release vs. root time profiles for release into 0.2% w/w Tween (pH=4.2) for MET, TNZ, ONZ and SNZ (250 mg) from DDU-4320 matrix-type vaginal rings over 28 days.

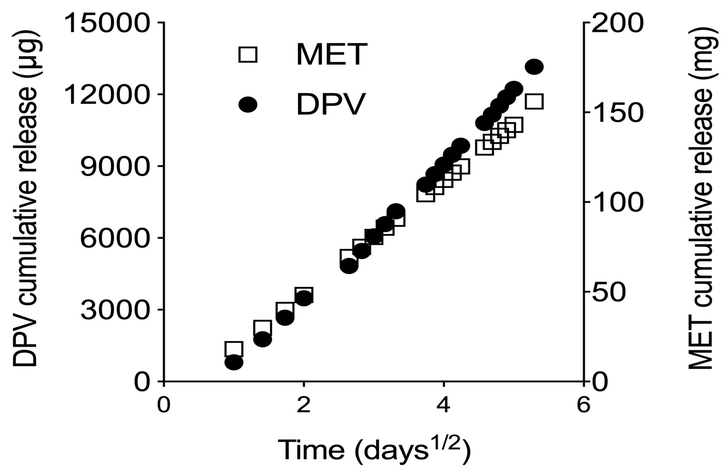


Figure 5. Cumulative release versus root time profiles for release into 0.2% w/w Tween (pH=4.2) of DPV and MET from MPT matrix-type vaginal rings (DPV, MET, sucrose and boric acid (400 mg *4)) over 28 days.