ABSTRACT SUMMARY

New multi-purpose prevention technology (MPT) products that prevent both unintended pregnancy and sexually transmitted infections (STIs) are required to address women’s reproductive health needs. Here, various vaginal ring (VR) designs are described that provide controlled release of dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed as an HIV microbicide, and levonorgestrel, a contraceptive agent.

INTRODUCTION

Unintended pregnancy, HIV, and other STIs all pose major reproductive health issues for women worldwide, particularly in developing countries where access to appropriate medication / contraceptives is limited. In recent years, there has been renewed interest in so-called multipurpose prevention technologies (MPTs) that can simultaneously address two or more clinical indications around reproductive health. MPTs may offer a number of advantages, including a reduced overall cost compared to individual products with a single indication, and potentially increased user adherence.

VRs are widely acknowledged as a useful technology platform for development of MPTs, since they can readily accommodate multiple drugs and provide long-term controlled release (Figure 1). Single indication VRs are commercially available for use in hormonal contraception (e.g. NuvaRing®), and estrogen replacement therapy (e.g. Estring®). They are also being developed for delivery of single and combination microbicides to prevent sexual transmission of HIV. Recent studies have demonstrated the potential efficacy of these devices in macaques**, and a matrix-type VR loaded with dapivirine is currently in a Phase III clinical trial.

Figure 1. Isometric projections of various types of vaginal ring, with a section cut away. A: matrix [consists of a single compartment with drug(s) uniformly distributed throughout the entire body of the ring]. B, C and D: reservoir [consists of a central core, which is completely surrounded by a separate sheath layer; drug(s) may be distributed within a single core (B), or multiple, partial-length cores may be used (C); drug(s) may also be located in both compartments, i.e. the core and sheath (D); the core length and cross-sectional diameter are readily adjusted].

Here, we report on the preclinical development of a range of vaginal ring configurations, each capable of providing long-term (up to 60 days) controlled release of dapivirine (DAP; an HIV microbicide) and levonorgestrel (LNG; a contraceptive progestogen).

EXPERIMENTAL METHODS

Four different ring configurations, each containing both DAP and LNG, were manufactured by injection molding using medical-grade, addition-cured, silicone elastomer:

i) Configuration 1 (C1)
Matrix ring; loaded with both DAP (0.3125 % w/w) and LNG (0.1, 0.3 or 1.0 % w/w); Figure 1A.

ii) Configuration 2 (C2)
Reservoir ring; DAP and LNG formulated within a single full-length core (both 2% w/w), overmolded with a blank sheath; Figure 1B.

iii) Configuration 3 (C3)
Reservoir ring; DAP and LNG formulated within two separate half-length cores (both 2% w/w), overmolded with a blank sheath; Figure 1C.

iv) Configuration 4 (C4)
Reservoir ring; LNG formulated in a full-length core (1% w/w), overmolded with a DAP-loaded sheath (0.3125 % w/w); Figure 1D.

In vitro release was assessed over 30 or 60 days. Each VR (n=6 per formulation) was placed in a stoppered bottle containing 200 mL (C1, day 0, decreased to 100 mL from day 1 onwards) or 100 mL (C2, C3 and C4, day 0, decreased to 50 mL from day 1 onwards) of release medium (1:1 mixture of isopropanol and water). Bottles were stored in an orbital shaking incubator (37 °C, 60 rpm) and the release medium was sampled and completely replaced on a daily basis.

Drug release was quantified using reverse-phase HPLC with UV detection (DAP: 210nm; LNG: 240 nm). A 25 µL aliquot of each sample was injected onto a Thermo Scientific BDS Hypersil C18 column (150 mm x 4.6 mm, 3 µm particle size) held at 25 °C, and isocratic elution was performed: mobile phase 55% 7.7 mM phosphate buffer (pH 3.0) / 45% HPLC-grade acetonitrile,
flow rate 1.2 mL/min, run time 9 min. DAP and LNG were eluted after 6.2 and 7.7 min, respectively.

The cumulative mass of DAP and LNG released from the various formulations was compared using a one-way ANOVA, followed by post-hoc analysis with the Tukey-Kramer multiple comparisons test when appropriate. A p value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION
Cumulative release data for DAP and LNG from each ring configuration are presented in Figure 2.

![Figure 2](image)

Figure 2. Mean cumulative in vitro release of DAP (A and C) and LNG (B and D) from each ring configuration.

DAP and LNG were released from matrix rings (C1) according to root time kinetics (Figures 2A and 2B). DAP and LNG release both increased significantly with LNG loading (p < 0.05). DAP was released from C2 and C3 at a constant daily rate (i.e. zero order release), since it was formulated in the core of these reservoir rings (102 and 56 µg/day respectively, p < 0.05) (Figure 2C). All reservoir rings (C2, C3 and C4) provided zero order release of LNG (135, 53 and 118 µg/day from C2, C3 and C4 respectively, p < 0.05) (Figure 2D). The rate of release of DAP and LNG from reservoir rings increased significantly as the core length increased from half-length (C3) to full-length (C2). For C4 (where DAP was formulated in the sheath of the ring, i.e. similar to a matrix-type ring), DAP release followed root time kinetics, but the total cumulative release was significantly lower than C1 (p < 0.05), indicating that the presence of LNG in the same compartment increases the release of DAP.

Target release profiles of both DAP and LNG (and indeed other anti-STI/contraceptive agents) can be easily achieved through rational adjustment of the ring design, demonstrating the versatility offered by this drug delivery platform. For example, by increasing the initial drug loading in the core compartment of C2 and C3 (reservoir rings) the duration of drug release could be readily extended, such that a single ring device could be used for a period of one year or more; this would be beneficial from the perspectives of user adherence and cost. Core length and/or the number of cores, and their cross-sectional diameter, can all be readily modified to dial in the desired release rate of each individual agent. A matrix ring design (such as C1), provides less options for fine-tuning of release rates, and the duration of use will be reduced compared to a reservoir design, but this type of VR is likely to incur the lowest manufacturing costs of all the ring configurations investigated.

CONCLUSION
Different ring configurations provide a range of options when considering a vaginal ring addressing both HIV prevention and contraception. The ring design(s) chosen for further development and Phase I studies will be selected on the basis of desired drug release profiles, duration of release, cost of manufacture, and suitability for target market.

REFERENCES

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