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Matrix and reservoir-type multipurpose vaginal rings for controlled release of dapivirine and levonorgestrel

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ABSTRACT

A matrix-type silicone elastomer vaginal ring providing 28-day continuous release of dapivirine (DPV) – a lead candidate human immunodeficiency virus type 1 (HIV-1) microbicide compound – has recently demonstrated moderate levels of protection in two Phase III clinical studies. Here, next-generation matrix and reservoir-type silicone elastomer vaginal rings are reported for the first time offering simultaneous and continuous *in vitro* release of DPV and the contraceptive progestin levonorgestrel (LNG) over a period of between 60 and 180 days. For matrix-type vaginal rings comprising initial drug loadings of 100, 150 or 200 mg DPV and 0, 16 or 32 mg LNG, Day 1 daily DPV release values were between 4132 and 6113 μg while Day 60 values ranged from 284 to 454 μg. Daily LNG release ranged from 129 to 684 μg on Day 1 and 2–91 μg on Day 60. Core-type rings comprising one or two drug-loaded cores provided extended duration of *in vitro* release out to 180 days, and maintained daily drug release rates within much narrower windows (either 75–131 μg/day or 37–66 μg/day for DPV, and either 96–150 μg/day or 37–57 μg/day for LNG, depending on core ring configuration and ignoring initial lag release effect for LNG) compared with matrix-type rings. The data support the continued development of these devices as multi-purpose prevention technologies (MPTs) for HIV prevention and long-acting contraception.

1. Introduction

Vaginal rings offering sustained or controlled release of antiretroviral drugs have been at the forefront of efforts over recent years to develop microbicide products for prevention of sexual transmission of human immunodeficiency virus type 1 (HIV-1) (Malcolm et al., 2016). A matrix-type silicone elastomer vaginal ring containing dapivirine (DPV; Fig. 1A) – an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) – and intended for 28-day continuous use is being developed by the International Partnership for Microbicides (IPM) (Malcolm et al., 2012a; Nel et al., 2011, 2009). This DPV ring recently completed two Phase III clinical studies (the Aspire Study and The Ring Study) designed to support licensure of the ring for preventing infection with HIV in women (Baeten et al., 2016; Nel et al., 2016b). Results from these studies showed that the ring reduced HIV infection by 27% and 31%, respectively, compared with a placebo ring (Baeten et al., 2016; Nel et al., 2016b). Post hoc sub-group analyses in the Aspire Study revealed a 37% reduced risk after excluding two sites with the lowest rates of retention and adherence, a 56% reduced risk when only women older than 21 years were considered, and a 61% reduction in women aged 25 and older (Baeten et al., 2016). In The Ring Study, sub-analysis by age revealed no significant benefit for women younger that 21 years, and a 37.5% reduced risk in women aged >25 years (Nel et al., 2016b).

Despite the fact that a safe and effective vaginal microbicide product to protect against HIV infection has yet to reach market, there is already considerable interest and early-stage development

Abbreviations: DAC, dual asymmetric centrifuge; DPV, dapivirine; DSC, differential scanning calorimetry; HIV-1, human immunodeficiency virus type 1; HPLC, high performance liquid chromatography; LNG, levonorgestrel; IPM, International Partnership for Microbicides; MPT, multipurpose prevention technology; NNRTI, non-nucleoside reverse transcriptase inhibitor; STI, sexually transmitted infection; SVF, simulated vaginal fluid.

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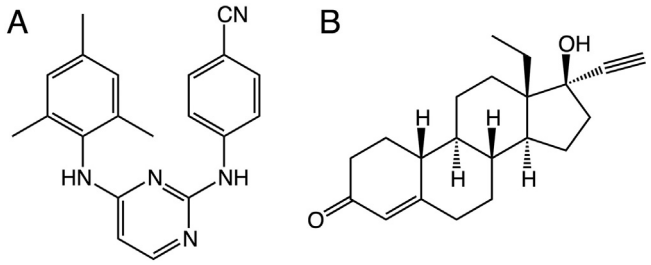

Fig. 1. Chemical structures for dapivirine (A) and levonorgestrel (B).

activity around next-generation multipurpose prevention technology (MPT) products that seek to combine HIV prevention with contraception and/or prevention/treatment of other sexually transmitted infections (STIs) (Fernández-Romero et al., 2015; Malcolm and Fetherston, 2013; Malcolm et al., 2016, 2014; Romano et al., 2013; Woodsong et al., 2015). With 86 million unintended pregnancies (Sedgh et al., 2014) and 2.1 million new HIV cases around the world every year (Joint United Nations and HIV/AIDS, 2016), reformulation of the DPV ring to additionally include a continuous-use progestin-only contraceptive is an obvious next step, especially since most existing hormonal birth control methods offer no protection against HIV or other STIs. Furthermore, a vaginal ring with a use indication for both prevention of pregnancy and HIV infection may result in increased user adherence compared with a product preventing only HIV, since women's perceived risk of pregnancy is usually higher than that for HIV infection (Woodsong and Holt, 2015).

Many of the MPT products currently undergoing development, including a number of vaginal ring devices, have prioritised use of levonorgestrel (LNG; Fig. 1B) as the contraceptive hormone component based on its historical record of safety and effectiveness and its suitability for continuous use without need for a monthly withdrawal period (Mansour, 2012; Romano et al., 2013; Ugaonkar et al., 2015; Woodsong et al., 2015). In addition to its current use as a long-acting contraceptive in intrauterine devices and subdermal implants (Eisenberg et al., 2015; Gonzalo et al., 2002; Koetsawang et al., 1990a,b,c; Rose et al., 2009), LNG has also previously been investigated extensively for delivery from silicone elastomer vaginal rings (Bounds et al., 1993; Koetsawang et al., 1990a,b; Mishell et al., 1975; Murphy et al., 2016b). Recently, as part of continued efforts to develop a MPT vaginal ring offering simultaneous release of DPV and LNG, we reported on various formulation strategies to reduce the extent of LNG binding to addition cure silicone elastomer materials (Murphy et al., 2016b). Here, we report for the first time assessment of the preclinical feasibility of matrix-type and reservoir-type silicone elastomer vaginal rings offering continuous release of both DPV and LNG for at least 60 days and preferably at least 90 days in quantities anticipated to offer clinical effectiveness.

2. Materials and methods

2.1. Materials

Micronised DPV was supplied by S.A. Ajinomoto OmniChem N. V. (Wetteren, Belgium). Non-micronised LNG (Batch No: 120101) was supplied by Haorui Pharma-Chem Inc. (Irvine, CA, US). MED-4870 and DDU-4320 silicone elastomer kits were purchased from NuSil Technology LLC (Carpinteria, CA, US). HPLC-grade acetonitrile, HPLC-grade isopropanol and potassium dihydrogen orthophosphate (AnalaR analytical reagent) were purchased from VWR International Ltd. (Dublin, Ireland). Phosphoric acid (85% w/w in water) was purchased from Sigma-Aldrich (Gillingham, UK). A Millipore Direct-Q 3 UV Ultrapure Water System (Watford, UK) was used to obtain HPLC-grade water.

2.2. Ring release rate targets

The aim of this study was to develop a MPT vaginal ring offering at least 60-day *in vitro* release, and preferably 90-day release, of DPV and LNG at levels likely to be effective for HIV prevention and contraception. In comparison, the existing Dapivirine Vaginal Ring-004 contains only 25 mg DPV and is intended for 28 days of use (Nel et al., 2009). For the DPV component of the MPT ring, the *in vitro* release rate on Day 60 or Day 90 was targeted to be equal to or greater than the Day 28 *in vitro* release value from the Dapivirine Vaginal Ring-004 (*i.e.* 200 μg). This value was determined from historical data across multiple batches of Ring-004 and measured experimentally under the same *in vitro* release conditions as those used to test the MPT rings described in this study. Two target (lowest acceptable) *in vitro* release rates – 35 μg/day and 70 μg/day – were defined for LNG based on our analysis of previously reported data in the scientific literature (Clark et al., 2014; Eisenberg et al., 2015; Jackanicz, 1981; Koetsawang et al., 1990a; Landgren et al., 1994a,b; Xiao et al., 1985). Vaginal rings with *in vitro* LNG release rates ranging from 20 to 30 μg/day have been investigated previously (Clark et al., 2014; Jackanicz, 1981; Koetsawang et al., 1990a; Landgren et al., 1994a,b; Xiao et al., 1985). Systemic LNG levels peaked at between 300–800 pmol/L shortly after ring insertion and remained relatively stable with an average decline of 23–26% during the 3 months of use (Koetsawang et al., 1990a,b,c; Landgren et al., 1994b; Xiao et al., 1985). However, new ring designs targeting higher LNG *in vitro* release rates (*e.g.* 35 μg/day) have been advocated due to concern with the higher pregnancy rates observed among heavier women in clinical trials (Brache et al., 2000).

2.3. Differential scanning calorimetry

Samples of micronised DPV, non-micronised LNG and physical mixtures of the two drugs at 10% w/w intervals were prepared for DSC analysis. Each mixture was mixed thoroughly, first by hand using a spatula and then in a Speedmixer™ at 3000 rpm. Samples were analyzed by DSC (TA Instruments 2920 modulated DSC) in standard heating ramp mode. Approximately 5–10 mg of each sample was accurately weighed into an aluminum pan and heated from 20 to 250 °C at a rate of 10 °C per min alongside an empty reference pan. For each sample, the following parameters were noted for any melting transitions that were observed: onset temperature (°C), peak temperature (°C) and enthalpy (ΔH, J/g). A minimum of four replicates was used to calculate mean values for each sample mixture. DSC analysis was similarly performed on silicone elastomer samples loaded with various concentrations and ratios of DPV only, LNG only and DPV + LNG in order to characterize the nature of the drugs in the rings.

2.4. Matrix-type vaginal ring manufacture

The DPV-only matrix-type vaginal ring (Ring-004) that recently completed being tested in two Phase III clinical trials in Africa contains 25 mg DPV and is intended for 28-day use (Baeten et al., 2016). In order to extend DPV release from a matrix-type device out to at least 60 days, it was necessary to increase the DPV loading in the matrix-type ring, in accordance with the relevant theory of drug release kinetics (Malcolm et al., 2003; Siepmann and Peppas, 2011). Three higher DPV loadings were selected for further investigation in this study: 100 mg, 150 mg and 200 mg. Two LNG loadings – 16 mg and 32 mg – were also selected, based on previous data generated as part of the project (data not published).