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Controlling levonorgestrel binding and release in a multi-purpose prevention technology vaginal ring device

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ABSTRACT

Despite a long history of incorporating steroids into silicone elastomers for drug delivery applications, little is presently known about the propensity for irreversible drug binding in these systems. In this study, the ability of the contraceptive progestin levonorgestrel to bind chemically with hydrosilane groups in addition-cure silicone elastomers has been thoroughly investigated. Cure time, cure temperature, levonorgestrel particle size, initial levonorgestrel loading and silicone elastomer type were demonstrated to be key parameters impacting the extent of levonorgestrel binding, each through their influence on the solubility of levonorgestrel in the silicone elastomer. Understanding and overcoming this levonorgestrel binding phenomenon is critical for the ongoing development of a number of drug delivery products, including a multi-purpose technology vaginal ring device offering simultaneous release of levonorgestrel and dapivirine – a lead candidate antiretroviral microbicide – for combination HIV prevention and hormonal contraception.

1. Introduction

Silicone elastomers have been widely used in controlled release drug delivery applications since Dziuk and Cook first demonstrated in 1966 that various steroid molecules were capable of effectively permeating and releasing from silicone rubber capsules subcutaneously implanted in ewes [1]. Numerous steroid-releasing silicone elastomer devices, including subdermal implants, vaginal rings and intrauterine systems, have since reached market (Table 1). The past ten years have seen considerable interest in silicone elastomer vaginal ring technology for controlled release of antiretroviral (ARV) drug molecules for prevention of sexual transmission of human immunodeficiency virus (HIV) (Table 1) [2–9]. The International Partnership for Microbicides (IPM) and the Microbicide Trial Network (MTN) are currently in Phase III clinical trials in Africa with a matrix-type silicone elastomer vaginal ring developed by IPM. This ring device provides controlled release of dapivirine (Fig. 1A), a non-nucleoside reverse transcriptase inhibitor, over 28 days and has already been shown to be safe and well tolerated in vivo. If successful, the dapivirine ring will likely provide both further impetus and a viable technology platform for development of multi-purpose prevention technologies (MPTs) aimed at combining HIV prevention with prevention of unintended pregnancy and prevention/treatment of other sexually transmitted infections (STIs) through use of a single formulation or drug-device combination product [10–13]. Many of the MPT products currently undergoing development have prioritized use of levonorgestrel (Fig. 1A) as the contraceptive hormone component, based on its historical record of safety and efficacy [12–14].

Silicone elastomers for use in medical and pharmaceutical applications are prepared through the chemical crosslinking of functionalised, linear, polydimethylsiloxane molecules. The most important chemical crosslinking mechanisms involve either condensation-cure or addition-cure chemistries. Condensation-cure systems involve the tin-catalyzed reaction between hydroxy-terminated polydimethylsiloxane molecules and a tetraalkoxysilane, resulting in the formation of the cured elastomer and an alcohol by-product [15,16]. Although the chemistry of this silicone elastomer crosslinking reaction is generally compatible with a very wide range of chemical functional groups, the alcohol produced can be problematic when the incorporated drug(s) is highly soluble in the alcohol [17,18]. Crosslinking of addition-cure silicone elastomer systems relies on the platinum-catalyzed hydrosilylation reaction between hydride- and vinyl-functionalised polydimethylsiloxane molecules (Fig. 1B). No by-product is formed with this reaction. However, the platinum catalyst is particularly sensitive to poisoning by certain chemical functional groups, most notably organotin, organosulfur and certain amine containing compounds.

It is well established that small molecules containing ethylenic (C═C) and acetylenic (C≡C) functional groups can undergo hydrosilylation reaction with molecules containing hydrosilane (Si—H) groups (Fig. 1C

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Table 1
Controlled release drug delivery devices for humans that use silicone elastomer as the rate controlling material. Marketed products (current or previous), discontinued development products and products presently undergoing clinical testing are included. VRs — vaginal rings.

Product name	Product type	Drug(s)	Indication/duration of action	Developer	Stage
Norplant®	Reservoir-type subdermal implant	Levonorgestrel	Female contraception/5 years	Population Council	Discontinued
Jadelle® (Norplant II)	Reservoir-type subdermal implant	Levonorgestrel	Female contraception/5 years	Population Council	Marketed
Mirena®	Reservoir-type intrauterine system	Levonorgestrel	Female contraception/5 years	Bayer	Marketed
Skyla®	Reservoir-type intrauterine system	Levonorgestrel	Female contraception/5 years	Bayer	Marketed
Femring®	Reservoir-type VR	17β-Estradiol-3-acetate	Estrogen replacement therapy/3 months	Warner Chilcott	Marketed
Estring®	Reservoir-type VR	17β-Estradiol	Estrogen replacement therapy/90 days	Pfizer	Marketed
Progering®	Matrix-type VR	Progesterone	Female contraception/1 year	Population Council	Marketed (South America only)
Fertiring®	Matrix-type VR	Progesterone	In vitro fertilization/hormone replacement therapy/3 months	Population Council	Marketed
–	Matrix-type VR	Progesterone	Luteal phase support	Italfarmaco	Phase I/II
–	Matrix-type VR	Progesterone	Luteal phase support	TEVA	Discontinued
–	Reservoir-type VR	Oxybutynin	Overactive bladder	TEVA	Discontinued
–	Reservoir-type VR	Nestorone and ethinyl estradiol	Female contraception	Population Council	Phase III
–	Matrix-type VR	Dapivirine	HIV prevention/30 days	IPM	Phase III
–	Matrix-type VR	Dapivirine and maraviroc	HIV prevention/30 days	IPM	Phase I
–	Matrix-type VR	Dapivirine and levonorgestrel	HIV prevention/90 days	IPM	Phase I

and D, respectively) [19–23]. In general, the alkyne hydrosilylation reaction catalyzed by platinum proceeds at a faster rate compared to alkenes, and is less susceptible to many electronic and structural factors that may impede alkene hydrosilylation [19]. Given the large number of steroid molecules containing ethylenic or acetylenic functional groups that have been previously formulated in silicone elastomers, it is rather surprising that only a single article (a 1980 US patent) has reported the potential for covalent binding of such steroids to the silicone elastomer [24]. Furthermore, the patent states that the quantity of drug that reacts with the silicone elastomer is "negligible for the sustained drug release rate". On the contrary, here we report that levonorgestrel, a common contraceptive progestin, reacts with addition-cure silicone elastomer systems such that a very significant fraction of the incorporated levonorgestrel can be irreversibly bonded to the silicone elastomer impacting levonorgestrel release rates. The extent of binding is dependent on the silicone elastomer cure conditions and the particle size of the levonorgestrel material used. Aside from recent U.S. patent applications by IPM [25,26], this issue has not been reported previously for levonorgestrel, despite its long history of incorporation into addition-cure silicone elastomer drug delivery systems (Table 1).

2. Methods and materials

2.1. Materials

Medical grade, addition-cure silicone elastomers DDU-4320 and MED-4870, condensation-cure silicone elastomer MED-6382, and MED-360 silicone oil were supplied by NuSil Silicone Technology Inc. (Carpinteria, CA, USA). Micronized dapivirine was supplied by S.A. Ajinomoto OmniChem N.V. (Wetteren, Belgium). Micronized levonorgestrel was supplied by CHEMO Group (Saronno, Italy). Non-micronized and sieved fractions of non-micronized levonorgestrel (non-micronized levonorgestrel) were supplied by Tecoland (Irvine, CA, US) and CHEMO Group (Saronno, Italy); except where explicitly stated, non-micronized levonorgestrel in the text refers to material sourced from Tecoland. Particle size data (d_{10}, d_{50} and d_{90}; measured via laser diffraction) for each of the levonorgestrel materials was provided by the suppliers (Table 2). HPLC-grade acetonitrile, isopropanol and dichloromethane, and phosphoric acid (85% *w*/*w* in water) were purchased from Sigma Aldrich (Gillingham, UK). HPLC-grade water was obtained using a Millipore Direct-Q 3 UV Ultrapure Water System (Watford, UK). 19-Norethindrone was supplied by LGM Pharma (Boca Raton, Florida, USA) and used as an internal standard for HPLC. Analytical grade potassium dihydrogen orthophosphate was obtained from VWR (Dublin, Ireland).

2.2. Manufacture of silicone rings and slabs

Matrix-type, silicone elastomer vaginal rings containing 200 mg micronized dapivirine and 32 mg levonorgestrel (either micronized or non-micronized) and measuring 57 mm overall diameter × 7.8 mm cross-sectional diameter were manufactured by reaction injection molding of active silicone elastomer mixes using a Babyplast 6/10P injection-molding machine in semi-automatic mode fitted with custom, stainless steel, single-cavity injection molds. These rings were cured at 160 °C for 90 s. Briefly, the appropriate quantities of dapivirine and levonorgestrel powders were added to both Parts A and B of the addition-cure silicone elastomer system MED-4870 and mixed at 3000 rpm for 3 min using a SpeedMixer DAC 150 FVZ-K (Synergy Devices, UK). These active premixes were stored at 4 °C until use. Prior to combining the premixes, they were first hand-mixed with a spatula for 30 s and then speedmixed for 120 s at 3000 rpm. Equal weights of Part A and Part B active premixes were then combined, handmixed for 30 s, speedmixed for 30 s at 3000 rpm, and then transferred to a 65 cm^3 low-density polyethylene Semco 220316 cartridge system (Polymer Systems Technology Ltd., Buckinghamshire, UK) that operates with the dosing meter fitted to the Babyplast injection molder.

Silicone elastomer slabs (20.0 × 30.0 × 2.0 mm) or vaginal rings containing levonorgestrel or dapivirine were also manufactured in a similar fashion using a custom, aluminum, multi-cavity mold fitted to an electrically-heated, laboratory-scale injection molding machine. For rings and slabs prepared using the DDU-4320 silicone elastomer (a low temperature cure system), cure time and temperature were varied between 1.5–120 min and 60–160 °C, respectively. For slabs prepared with the MED-4870 silicone elastomer (a high temperature cure system), cure time and temperature were varied between 1.5–120 min and 120–200 °C, respectively. Levonorgestrel-loaded silicone elastomer slabs were also prepared using condensation-cure MED-6382 silicone elastomer using cure conditions of 80 °C/5 min. For some silicone elastomer slabs, the drug powder was first dispersed in MED-360 silicone oil prior to preparing the silicone elastomer premixes.

2.3. Quantification of levonorgestrel by HPLC

Levonorgestrel concentrations were quantified by HPLC using a BDS Hypersil C18, 3 μm column (150 × 4.6 mm; Thermo Scientific, UK), fitted with an Analytical Guard Cartridge System (Phenomenex, UK),