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Published in:
International Journal of Pharmaceutics

Document Version:
Peer reviewed version

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Intravaginal rings for continuous low-dose administration of cervical ripening agents

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Abstract

Intravaginal rings (VRs) have been widely reported for administration of pharmaceutical drugs – most notably estrogens, progestogens and antiretrovirals – to the vagina for clinical benefit. Here, for the first time, we describe the design, manufacture and preclinical testing of VRs for sustained/controlled release of the cervical ripening agents isosorbide mononitrate (ISMN) and misoprostol (MP), either singly or in combination. Matrix-type silicone elastomer VRs containing ISMN showed declining daily release rates, ranging from 31–168 mg (Day 1) to 3–25 mg (Day 11). Novel orifice-type rings, in which a MP-containing silicone elastomer core is partially exposed to the external environment by overmolding with a non-medicated silicone elastomer sheath containing orifices, provided relatively constant daily MP release rates over 14 days (~20 or 60 μg/day depending on the formulation type). Combination vaginal rings offered simultaneous release of both ISMN and MP over 14 days, with an almost constant MP release rate (60 μg/day) and steadily declining daily ISMN release (295 mg on Day 1 and 24 mg on Day 11). The VR design can be readily tailored to provide sustained or controlled release of ISMN and MP at rates potentially useful for cervical ripening.

Keywords

induction of labour; silicone elastomer drug delivery device; vaginal drug administration; controlled release; sustained release; out-patient.
1. Introduction
Flexible polymeric ring-shaped devices have been investigated since the 1970s for sustained or controlled release of drug substances to the human vagina. To date, six vaginal ring (VR) products have reached market, each offering release of one or more steroid molecules for estrogen replacement therapy (Estring® and Femring®), contraception (Nuvaring®, Progering® and Ornibel®) or hormone supplementation and pregnancy maintenance during in vitro fertilization (Fertiring®) (Brache et al., 2013; Friend, 2011; Malcolm et al., 2015, 2012). Since 2002, great progress has been made in the design and development of various antiretroviral-releasing VRs for reducing HIV acquisition (Kiser et al., 2012; Malcolm et al., 2015, 2010; Thurman et al., 2013), with a dapivirine-releasing silicone elastomer ring having recently completed late-stage clinical testing and currently under regulatory review by the European Medicines Agency (Baeten et al., 2016; Devlin et al., 2013; Nel et al., 2016b). A major impetus for continued innovation in VR design has been the growing interest in combination HIV microbicide and multipurpose prevention technology products for which release needs to be individually tailored for each drug molecule (Baum et al., 2012; Boyd et al., 2016; Derby et al., 2017; Fetherston et al., 2013; Friend et al., 2013; Malcolm et al., 2015, 2014; Moss et al., 2016; Murphy et al., 2014; Smith et al., 2017; Shweta R. Ugaonkar et al., 2015; Shweta R Ugaonkar et al., 2015). However, other clinical indications within women’s health are also likely to benefit from enhanced drug administration using existing or new VR technologies.

Induction of labour (IOL) is a widely-used practice in obstetrics to prevent maternal and fetal morbidity and mortality. However, a major complication of IOL is hyperstimulation of the
uterus, which can lead to the sudden onset of powerful, frequent and painful contractions which women may find unbearable or frightening. These uterine contractions can damage the fetus due to hypoxia as the placenta cannot be fully revascularised if the uterus is contracting too frequently. Despite these concerns, there is increasing demand to deliver IOL in an outpatient setting where women can be more comfortable and relaxed and reduce their length of stay in hospital. Here, we describe a potential new IOL method involving slow and continuous administration of cervical ripening agents from VRs. This approach has the potential to more closely mimic the natural cervical ripening process and spontaneous onset of labour and reduce the incidence of hyperstimulation, making it safer and more acceptable to women, particularly in an out-patient setting.

Cervicovaginal administration of pharmacological agents – most notably dinoprostone and misoprostol – has been widely used to ripen the cervix as a method for initiating IOL (Agarwal et al., 2012; Alfìrevic et al., 2015; Calder et al., 2008; MacKenzie, 2006; Vogel et al., 2017; Zhang et al., 2015). Two forms of vaginal dinoprostone are already used routinely. Prepidil® is a non-aqueous gel containing 0.5 mg dinoprostone in 3 g triacetin which is administered to the endocervix every 6 h up to a maximum of three doses in 24 h. Cervidil®/Propress® is a pessary-type dosage form comprising 10 mg dinoprostone dispersed within a hydrogel copolymer inserted in a mesh pouch. The insert is placed in the posterior fornix of the vagina and provides sustained release of dinoprostone over 12 h, after which the pouch is removed. Thus, use of modified release formulations for cervical ripening is already well established and offers certain advantages over more conventional immediate-release products (Embrey et al., 1980; Lyrenäis et al., 2001).
Vaginal administration of the synthetic prostaglandin misoprostol, often in the form of fractionated tablet doses (25 µg) of the anti-ulcer product Cytotec®, has also been widely reported for cervical ripening (Furukan et al., 2007; Rodrigues et al., 1998; Sanchez-Ramos et al., 1998; Sharma et al., 2005; Zieman et al., 1997). As with dinoprostone, a hydrogel insert for sustained-release vaginal administration of misoprostol has also been developed, marketed under the brand names Mysodelle®/Myspess®/Misodel® and offering administration rates of approximately 7 µg/h misoprostol (Miller et al., 2016; Powers et al., 2008; Stephenson and Wing, 2015; Wing, 2008; Wing et al., 2013).

Although more commonly used for the treatment of angina pectoris, there has also been interest in the use of the nitric oxide donor isosorbide mononitrate (ISMN) for cervical ripening (Agarwal et al., 2014, 2012; Bollapragada et al., 2009; Bullarbo et al., 2007; Chanrachakul et al., 2002, 2000; Chwalisz et al., 1997; Habib et al., 2008; Ledingham et al., 2000; Norman, 1996; Tschugguel et al., 1999; Väisänen-Tommiska et al., 2003). In contrast to prostaglandins, nitric oxide donors induce cervical ripening without causing uterine contractions, making them particularly interesting for use in out-patient settings where fetal monitoring is not possible.

Here, for the first time, we report that silicone elastomer VRs can offer sustained/controlled release of misoprostol and ISMN at rates likely to be clinically effective for cervical ripening (Amorosa and Stone, 2015; Leopold and Sciscione, 2017; Sharp et al., 2016). A combination
VR device offering release of both agents at significantly different release rates is also described.

2. Materials and methods

2.1. Materials
ISMN (70% w/w in lactose) and pure ISMN (98%) were purchased from Clariant (Leeds, UK) and iChemical Technologies Inc. (Shanghai, China), respectively. Misoprostol (MP, 1% w/w dispersion in HPMC) was purchased from Sequoia Research Products Ltd. (Pangbourne, UK). DDU-4320 silicone elastomer kits were purchased from NuSil Technology LLC (Carpinteria, CA, US). HPLC-grade acetonitrile, HPLC-grade acetone, sodium chloride, potassium hydroxide, calcium hydroxide, bovine serum albumin, lactic acid, acetic acid and glucose were bought from Sigma (Gillingham, UK). Urea and hydrogen chloride (37% w/w in water) were obtained from VWR International Ltd. (Dublin, Ireland). Millipore Direct-Q 3 UV Ultrapure Water System (Watford, UK) was used to obtain HPLC-grade water.

2.2. Manufacture of vaginal rings
Silicone elastomer matrix-type VRs (Fig. 1A) containing various loadings of ISMN (100, 500 and 1000 mg per ring) were manufactured on a laboratory-scale injection molding machine, according to well-established and previously reported manufacturing protocols (Boyd et al., 2016; Fetherston et al., 2013). Briefly, the required amounts of ISMN were added to both Parts A and B of the MED-4320 addition-cure silicone elastomer system contained in custom screw-cap polypropylene containers, and the contents of each container individually mixed using a Dual Asymmetric Centrifuge (DAC) mixer (SpeedMixerTM DAC 150 FVZ-K, Hauschild, Germany) for 30 s at 3000 rpm. The Part A and B premixes were combined in a
1:1 ratio in a polypropylene container, hand-mixed using a spatula, and then speedmixed (30 s, 3000 rpm) to produce the active silicone elastomer mixture. The active mix was manually injected into a heated (60 °C) matrix ring mold assembly fitted to the molding machine using a SEMCO® injection cartridge and cured for 10 min producing matrix-type rings (dimensions: 7.6 mm cross-sectional diameter and 55.0 mm external diameter).

Silicone elastomer reservoir-type VRs (Fig. 1B) – comprising ISMN (7% w/w) or MP (0.2% w/w) in a central core, with the core encapsulated with a silicone elastomer sheath – were similarly manufactured by injection molding via a previously described three-step process (Boyd et al., 2016). Briefly, active silicone elastomer mixtures, prepared as described for the matrix-type rings, were injected into a core ring mold assembly (Fig. 1D) and cured at 60 °C for 10 min to produce ISMN-loaded cores with 4.5 mm cross-section diameter and 51.9 mm external diameter. Full-length or half-length cores were then placed in a custom mold assembly and overmolded with non-medicated MED-4320 silicone elastomer in two (top and bottom) additional injection molding steps. The resulting reservoir-type rings had the following dimensions: 4.5 mm core diameter, 7.6 mm cross-sectional diameter, 55.0 mm external diameter and 1.55 mm membrane thickness.

Silicone elastomer orifice-type VRs (Fig. 1C) – comprising ISMN or MP in a central silicone elastomer core and partially encapsulated with a silicone elastomer sheath containing various orifices exposing the underlying core – were manufactured in a similar manner to reservoir rings except using custom-designed injection molds with pins designed to partially expose the
drug-loaded central core to the external environment via orifices in the membrane (Figure 1E, 1).

2.3. Differential scanning calorimetry
Thermal analysis of ISMN, MP and samples taken from the drug-loaded rings was performed using differential scanning calorimetry (DSC; TA Instruments Q100; 50 mL min\(^{-1}\) nitrogen flow; –70 °C to 150 °C at a rate of 10 °C min\(^{-1}\)) to probe the nature of the drugs within the rings, following established methods (Boyd et al., 2016; Fetherston et al., 2013).

2.4. Quantification of ISMN in the rings
Individual VRs were cut into 2 mm slices and placed in a 250 mL glass bottle (Duran \(\text{GLS 80}\)) containing 100 mL acetone. The bottles were placed in a shaking orbital incubator (Infors HT Unitron, Switzerland; 37 °C, 60 rpm, 25 mm orbital throw). After 7 d, the supernatants were collected and diluted 20-fold with water-acetonitrile (90:10, v/v). The amount of ISMN in each VR was analysed by ultra-performance liquid chromatography (UPLC).

2.5. In vitro release testing
Individual VRs were placed into 250 mL glass bottles (Duran \(\text{GLS 80}\)) containing 50 mL pH 4.2 simulated vaginal fluid (SVF). SVF mimics the chemical composition of vaginal fluid (Owen and Katz, 1999). The bottles were placed in the shaking orbital incubator (Infors HT Unitron, Switzerland; 37 °C, 60 rpm, 25 mm orbital throw) for 14 days. Sampling (1 mL) followed by complete replacement of the release medium was performed daily except on Fridays when the flask was refilled with 100 mL SVF and no sampling was performed again until the following Monday. The amount of drug in each sample was quantified by UPLC,
and the data used to construct release vs time plots. All release testing experiments were conducted n=4.

2.6. Quantification of ISMN and MP using UPLC

ISMN and MP were quantified using a Waters ACQUITY UPLC® system fitted with an ACQUITY UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm) and an in-line filter (0.2 μm). ISMN samples were injected (1.0 μL) onto the column (40 °C) and isocratic elution was performed with a mobile phase of water-acetonitrile (90/10, v/v) at flow rate of 0.6 mL/min. ISMN was detected at 210 nm with a 0.76 min retention time. MP samples were injected (2.0 μL) onto the column (40 °C) and isocratic elution was performed using a water-acetonitrile (50/50, v/v) mobile phase at 0.6 mL/min flow rate. MP was detected at 210 nm with a 0.69 min retention time. Linear ranges for ISMN and MP were 25–800 μg/mL and 0.5–25 μg/mL, respectively.

2.7. Statistical analyses

Statistical analyses were performed using one-way ANOVA, followed by post-hoc analysis using the Tukey-Kramer multiple comparisons test. Statistical significance is defined as p < 0.05. Analysis was conducted using GraphPad Prism.

3. Results

3.1. Design and manufacture of rings

Matrix-type rings containing ISMN (F1–F4, Table 1), reservoir and orifice-type rings containing ISMN (F5–F8, Table 1), and matrix-type and orifice-type rings containing MP (F9–F13, Table 1) were manufactured successfully; Fig. 2 shows representative photographs.
The different ring designs are intended to offer different drug release rates. Matrix-type rings contain the drug distributed uniformly throughout the entire volume of the ring (Fig. 1A), and typically exhibit declining release rates with time (Boyd et al., 2016; Fetherston et al., 2013; Malcolm et al., 2016). Reservoir rings contain a drug-loaded core and a non-medicated membrane (Fig. 1B) that controls the drug release rate from the core via a permeation mechanism, and typically results in constant release rates (Boyd et al., 2016; Malcolm et al., 2016, 2005). Orifice-type rings (Fig. 1C) – reported here for the first time – are similar in construction to reservoir-type rings except that the core containing the drug active(s) is partially exposed to the external environment by orifices extending through the rate-controlling membrane, intended to further modulate the drug release rate.

3.2. Thermal analysis of rings

DSC analysis was performed to investigate the physical state of the drugs within the rings, since this impacts the release mechanism. The thermograms of the non-medicated silicone elastomer sample and each of the representative ring formulations F1, F2, F3, F6, and F8 (Fig. 3A) show an endothermic peak close to −45°C, due to crystalline melting of the silicone elastomer. Ring samples F1, F2, F3 and F6 show an additional endothermic peak at ~90°C, attributed to melting of crystalline ISMN. Thus, these ring devices are shown to contain solid crystalline ISMN (i.e. the drug is incorporated above its solubility limit in the silicone elastomer). The peak size associated with the ISMN melting transition correlates with the ISMN loading in the ring. Melting enthalpies associated with the ISMN were linearly correlated with the mass fraction of ISMN in the rings (Fig. 3B). From the x-intercept of the fitted line, the solubility of ISMN at its melting point in the silicone elastomer ring was determined to be 0.62% w/w (Gramaglia et al., 2005; Woolfson et al., 2003). This is important,
as diffusion of drugs through silicone elastomers (and therefore release of drugs from VRs) requires at least some of the incorporated drug to be in the dissolved state (Malcolm et al., 2003, 2016).

No discernible thermal transition related to crystalline melting of MP was observed for either the supplied MP material (a 1% dispersion in HPMC) or the ring loaded with 0.2% w/w MP (F8, Table 1, Fig. 3A). This is due to the very low concentration of MP in the supplied material, which is significantly below the DSC detection limit. However, a very broad endothermic peak (30–130 °C) was observed for MP (1% in HPMC) (Fig. 3A), due to dehydration of HPMC during heating (Chandak and Verma, 2008). This broad peak was greatly suppressed in the thermogram of the MP-containing ring (F8) due to dilution of the MP material within the silicone elastomer.

3.3. Release of ISMN from VRs

ISMN was effectively released from matrix-type rings F1–F4 into the SVF release medium, displaying typical ‘burst and decline’ release profiles (Fig. 4A). Release rates were dependent on the initial ISMN loading in the rings, with Day 1 values ranging between 31 and 168 mg. By Day 4, the daily quantities of ISMN released from the rings had declined to between 8–57 mg, and to 3–25 mg by Day 11. These daily release quantities administered from the rings are of an entirely similar order of magnitude to doses reported previously for vaginal administration of ISMN tablets in both out-patient and in-patient settings (Agarwal et al., 2014, 2012; Bollapragada et al., 2009; Bullarbo et al., 2007; Chanrachakul et al., 2002; Habib et al., 2008; Vidanagamage and Goonewardene, 2011). The continuous dosing of ISMN offered by the rings may be clinically more effective and enhance compliance compared to
the periodic dosing regimen used for the tablets (48, 32 and 16 h prior to the scheduled time
of admission for induction).

Release of ISMN from the VRs obeys root time ($t^{0.5}$) kinetics, as evidenced by linear
cumulative release versus root-time graphs (Fig. 4B). Increasing the ISMN loading from 100
(F1) to 1000 mg (F3) significantly increased the ISMN release rate from 24.6 to 176.0
mg/day$^{0.5}$ (Table 1).

Rings F3 and F4 both contained 1000 mg ISMN per ring, however, F3 contained ISMN
diluted with 30% lactose (as supplied), while F4 contained pure ISMN (i.e. no lactose). The
presence of the lactose diluent serves to significantly increase the rate of release of ISMN
from the rings (176.0 vs. 121.8 mg/day$^{0.5}$; Table 1 and Fig. 4B).

Release of ISMN from reservoir and orifice-type rings is presented in Figs. 4C and 4D. Here,
daily ISMN release is relatively constant over the study period (Fig. 3C), at least compared to
the matrix-type rings (Fig. 3A), resulting in linear cumulative release vs. time profiles (Fig.
4D). Daily ISMN release from the reservoir ring containing a full-length ISMN-loaded core
(F6) decreased from 7.2 mg on Day 1 to 4.4 mg on Day 11. The half-core ring (F5) provided
Day 1 release of 3.7 mg and 2.2 mg on Day 11, approximately half the values for the full-core
ring (F6). Compared with Ring F6, the orifice-type ring (F7) had a relatively large amount of
ISMN release on Day 1 (10.3 vs. 7.2 mg) and a higher daily ISMN release rate (6.29 vs. 5.22
mg/day), clearly illustrating the impact of partly exposing the drug-loaded core to the SVF.
Unlike the matrix-type ring design, formulating the reservoir-type ring to contain pure ISMN (F8; no lactose diluent) produced ISMN release rates identical to the reservoir ring containing ISMN+lactose (F6) (Figs 4C and 4D). The water-soluble lactose is unable to modulate the ISMN release from reservoir rings, since the lactose is contained only in the core of the device and is not directly exposed to the SVF release medium. After 14 days, cumulative ISMN release from the reservoir rings was 37.5, 74.2, 92.0 and 73.8 mg, F5–F8 respectively, equivalent to 39.7%, 39.3%, 48.7% and 39.0% of the initial loadings (Table 1).

3.4. Release of MP from VRs

Ring F9 is the core component used to manufacture the orifice-type MP rings (F10–F13). Not surprisingly, it displayed release behaviour typical of a matrix-type ring, including relatively high Day 1 release (779 μg), declining amounts of MP released on subsequent days (233 μg on Day 4 and only 26 μg on Day 11, Fig. 4E), and root-time kinetics (Fig. 4F). The quantities of MP released during Day 1 and Day 4 were much higher than the safe clinical doses (25–200 μg) reported for vaginal administration of MP in IOL (Ambika et al., 2017; Calder et al., 2008; Chaudhuri et al., 2011; Frohn, 2002; Oboro and Tabowei, 2005).

When this F9 core was incorporated into a conventional reservoir-type ring, no release of MP was observed. However, rings having either small circular orifices (F10, F11, F13) or larger window-style orifices (F12) exposing an underlying full-length (F11 and F13) or a partial-length (F10 and F12) MP-loaded core showed significant MP release (Fig. 4G and 4H, Table 1). In general, the daily release profiles (Fig. 4G) do not show the burst-and-decline behaviour of matrix-type rings (Fig. 4E); instead, greater constancy of release is observed, similar to a conventional reservoir-type ring (Fig. 4C). Moreover, MP release is clearly shown to depend
upon the length of the core, the type of orifices (circular vs. elongated), and the number of orifices. Inevitably, given that only part of the core in these rings is exposed to the SVF, the release rates are reduced compared to ring F9. However, daily MP release rates tend to hover around either 20 or 60 μg/day (Fig. 3G), conveniently straddling the dosing range currently used in vaginal administration of MP for cervical ripening (Ambika et al., 2017; Calder et al., 2008; Chaudhuri et al., 2011; Frohn, 2002; Oboro and Tabowei, 2005).

Finally, ring formulation F13 – containing 5.4 mg MP in the core and 1209.8 mg ISMN in the sheath (Table 1) – effectively demonstrates the utility of vaginal ring technology in offering simultaneous and independent release of multiple cervical ripening agents over extended time periods. For this combination drug ring, MP is released from the core of the device at an almost constant rate of 60 μg/day (Figs. 4G and 4H), while the ISMN incorporated into the sheath component provides Day 1 release of 295 mg followed by declining daily release on each subsequent day and reaching 24 mg on Day 11 (Fig. 4I). After 14 days, the cumulative amount of MP and ISMN released was 780 μg and 870 mg (Fig. 4J), respectively, equivalent to 14.4% and 72.2% of the initial loadings, respectively (Table 1).

4. Discussion

In general, the silicone elastomer matrix-type rings are best suited to administration of daily IMSN doses in the relatively high 1–200 mg range. The administered dose of ISMN was readily modulated by adjusting the initial drug loading. Matrix rings provided an initial burst release followed by declining release on subsequent days; as such, the release range would need to carefully tailored for optimal clinical efficacy. However, constant low milligram-per-day release of ISMN was achieved with silicone elastomer reservoir rings, with the daily
release rate proportional to the length of the IMSN-loaded core. According to well-established design principles for reservoir-type rings, the thickness of the rate-controlling membrane could also be adjusted to further modulate release; for example, adjusting the membrane thickness of the F5 and F6 rings to 0.78 mm (half of the current 1.55 mm) would result in a two-fold increase in the daily ISMN release rate. Incorporating orifices in the membrane also significantly increased the ISMN release rate and offered release kinetics intermediate between conventional matrix and reservoir rings.

Much lower microgram-per-day doses of MP are required for IOL. Since conventional reservoir-type VRs containing MP provided no release, we focused our attention on ring designs including orifices in the membrane so as to expose, to varying extents, the MP-loaded core to the release medium. By controlling the number of orifices, the size of orifices and the length of the MP-loaded core, near-constant release rates in the range 20–60 µg/day could be easily achieved.

This is the first study reporting VRs for sustained or controlled delivery cervical ripening agents. The release rates of ISM and MP from VRs could be readily tailored by drug loading and ring designs to meet the clinical requirements for IOL. This study is based on in vitro testing of VRs, and therefore the release data may not correlate with performance in vivo. However, for other VRs – most notably the dapivirine-releasing silicone elastomer VR for prevention of sexual transmission of the human immunodeficiency virus (HIV) – in vitro testing of dapivirine release using SVF correlated closely with in vivo release, based on
residual drug analysis content post-use (Baeten et al., 2016; Malcolm et al., 2016; McCoy et al., 2017; Nel et al., 2016a).

VRs are already used successfully for estrogen replacement therapy and hormonal contraception, and an antiretroviral-releasing VR will likely soon be available in Africa for HIV prevention (Baeten et al., 2016; Nel et al., 2016a). The ring devices described in this study are of similar size and fabricated from similar materials as other marketed vaginal ring products (most notably Estring®, Femring® and the dapivirine-releasing ring). In general, VRs are user-friendly, are easily inserted and removed by the woman, and are highly acceptable (Mulders and Dieben, 2001; Novák et al., 2003).

As with other sustained/controlled release drug formulations, increased user acceptability and compliance/adherence with VRs is often mooted as a potential advantage over more conventional immediate release vaginal dosage forms (Malcolm et al., 2015). Previous studies have reported high user acceptability and/or adherence of VRs for contraception and estrogen replacement therapy (Ayton et al., 1996; Barentsen et al., 1997; Brache et al., 2000; Casper and Petri, 1999; Dieben et al., 2002; Faundes et al., 1981; Nachtigall, 1995; Novák et al., 2003; Roumen et al., 2001; Roumen and Dieben, 1999; Stifani et al., 2018; Vartiainen et al., 1993; Weisberg et al., 1995). Yet, lower-than-expected adherence has been reported in late-stage clinical trials of the dapivirine ring, particularly among young women (Baeten et al., 2016; Montgomery et al., 2017; Nel et al., 2016b, 2016a; Spence et al., 2016). However, the observed low adherence with the dapivirine may reflect various sociocultural issues particularly pertinent to Sub-Saharan Africa and HIV infection (Montgomery et al., 2017).
The relatively short use regime intended for a VR for cervical ripening coupled with its use in a managed primary care health setting should lead to high levels of user adherence.

The combination ISMN+MP ring described in this study is particular interesting, since synergistic effects have previously been reported when administering the combination of ISMN and MP intravaginally for cervical ripening (Abdellah et al., 2011; Elsokary et al., 2015; Soliman, 2013).

4. Conclusions

The results of this proof-of-concept study highlight the potential for development of long-acting sustained or controlled release drug delivery devices for low dose vaginal administration of cervical ripening agents for IOL. The continuous dosing of small amounts of these agents might be particularly useful in out-patient settings, reducing the time spent in hospital, reducing health service costs, and offering increased user compliance compared to periodic dosing regimens. The results strongly support progress to clinical testing.

Transparency declarations

The authors declare no conflicts of interest.

Acknowledgements
This study was funded through the UK Medical Research Council’s ‘Confidence in Concept’ scheme (MC-PC-15035).
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**Table and figure captions**

**Table 1.** Parameters for DDU-4320 VRs loaded with cervical ripening agents. Standard deviation values were calculated based on four replicates.

**Fig. 1.** Cross-sectional views of (A) matrix rings, (B) reservoir rings and (C) orifice rings. D – core ring mold assembly. E – orifice ring mold assembly, showing the protruding pins for incorporation of orifices in the ring structure.

**Fig. 2.** Representative images of DDU-4320 VRs loaded with cervical ripening agents. F1-F4: matrix-type rings loaded with ISMN. F5-F6: reservoir-type or orifice-type rings loaded with ISMN; F9-F13: matrix-type or orifice-type rings containing MP.

**Fig. 3.** A: DSC thermographs of the non-medicated silicone elastomer (SE), ISMN (70% w/w dispersion in lactose), silicone elastomers loaded with ISMN, MP (1% w/w dispersion in HPMC) and silicone elastomers loaded with MP. Each concentration of ISMN or MP in the silicone elastomer is equivalent to the drug concentration in the ring formulation listed in the brackets. B: melting enthalpy of the crystalline ISMN as a function of the mass fraction of ISMN in silicone elastomer. The dotted line represents the result of the curve fitting.

**Fig. 4.** Daily release and cumulative release profiles for DDU-4320 VRs loaded with cervical ripening agents over 14 days in SVF. A and B: daily release versus time and cumulative release versus root time profiles of ISMN released from matrix-type rings loaded with 100
(F1), 500 (F2), 1000 (F3) and 1000 mg ISMN (without lactose, F4). C and D: daily release and cumulative release of ISMN from Ring F5 (reservoir-type ring with half-length core), F6 (reservoir-type ring with full-length core), F7 (orifice-type ring with full-length core) and F8 (reservoir-type ring with full-length core, formulated with pure ISMN). The plot of F8 in Graph B is not visible due to overlapping with the plot of F6. E and F: daily MP release versus time plots and cumulative MP release versus root time plots for Ring F9. G and H: daily and cumulative MP release versus time plots for Ring F10-13. I and J: daily ISMN release versus time plots and cumulative ISMN release versus root time plots for Ring F13.