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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; Alfirevic 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; Lyrenäs et al., 2001).

77

78 Vaginal administration of the synthetic prostaglandin misoprostol, often in the form of
79 fractionated tablet doses (25 μg) of the anti-ulcer product Cytotec®, has also been widely
80 reported for cervical ripening (Furukan et al., 2007; Rodrigues et al., 1998; Sanchez-Ramos
81 et al., 1998; Sharma et al., 2005; Zieman et al., 1997). As with dinoprostone, a hydrogel insert
82 for sustained-release vaginal administration of misoprostol has also been developed, marketed
83 under the brand names Mysodelle®/Myspess®/Misodel® and offering administration rates of
84 approximately 7 μg/h misoprostol (Miller et al., 2016; Powers et al., 2008; Stephenson and
85 Wing, 2015; Wing, 2008; Wing et al., 2013).
86

87 Although more commonly used for the treatment of angina pectoris, there has also been
88 interest in the use of the nitric oxide donor isosorbide mononitrate (ISMN) for cervical
89 ripening (Agarwal et al., 2014, 2012; Bollapragada et al., 2009; Bullarbo et al., 2007;
90 Chanrachakul et al., 2002, 2000; Chwalisz et al., 1997; Habib et al., 2008; Ledingham et al.,
91 2000; Norman, 1996; Tschugguel et al., 1999; Väisänen-Tommiska et al., 2003). In contrast
92 to prostaglandins, nitric oxide donors induce cervical ripening without causing uterine
93 contractions, making them particularly interesting for use in out-patient settings where fetal
94 monitoring is not possible.
95

96 Here, for the first time, we report that silicone elastomer VRs can offer sustained/controlled
97 release of misoprostol and ISMN at rates likely to be clinically effective for cervical ripening
98 (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 ºC 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 ºC to 150 ºC at a rate of 10 ºC 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® GLS 80®) containing 100 mL acetone. The bottles were placed in a shaking orbital incubator (Infors HT Unitron, Switzerland; 37 ºC, 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® 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 ºC, 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 ºC) 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 ºC) 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.

185 The different ring designs are intended to offer different drug release rates. Matrix-type rings
186 contain the drug distributed uniformly throughout the entire volume of the ring (Fig. 1A), and
187 typically exhibit declining release rates with time (Boyd et al., 2016; Fetherston et al., 2013;
188 Malcolm et al., 2016). Reservoir rings contain a drug-loaded core and a non-medicated
189 membrane (Fig. 1B) that controls the drug release rate from the core via a permeation
190 mechanism, and typically results in constant release rates (Boyd et al., 2016; Malcolm et al.,
191 2016, 2005). Orifice-type rings (Fig. 1C) – reported here for the first time – are similar in
192 construction to reservoir-type rings except that the core containing the drug active(s) is
193 partially exposed to the external environment by orifices extending through the rate-
194 controlling membrane, intended to further modulate the drug release rate.

195 *3.2. Thermal analysis of rings*

196 DSC analysis was performed to investigate the physical state of the drugs within the rings,
197 since this impacts the release mechanism. The thermograms of the non-medicated silicone
198 elastomer sample and each of the representative ring formulations F1, F2, F3, F6, and F8 (Fig.
199 3A) show an endothermic peak close to –45ºC, due to crystalline melting of the silicone
200 elastomer. Ring samples F1, F2, F3 and F6 show an additional endothermic peak at ~90°C,
201 attributed to melting of crystalline ISMN. Thus, these ring devices are shown to contain solid
202 crystalline ISMN (i.e. the drug is incorporated above its solubility limit in the silicone
203 elastomer). The peak size associated with the ISMN melting transition correlates with the
204 ISMN loading in the ring. Melting enthalpies associated with the ISMN were linearly
205 correlated with the mass fraction of ISMN in the rings (Fig. 3B). From the x-intercept of the
206 fitted line, the solubility of ISMN at its melting point in the silicone elastomer ring was
207 determined to be 0.62% w/w (Gramaglia et al., 2005; Woolfson et al., 2003). This is important,

208 as diffusion of drugs through silicone elastomers (and therefore release of drugs from VRs)
209 requires at least some of the incorporated drug to be in the dissolved state (Malcolm et al.,
210 2003, 2016).
211
212 No discernible thermal transition related to crystalline melting of MP was observed for either
213 the supplied MP material (a 1% dispersion in HPMC) or the ring loaded with 0.2% w/w MP
214 (F8, Table 1, Fig. 3A). This is due to the very low concentration of MP in the supplied
215 material, which is significantly below the DSC detection limit. However, a very broad
216 endothermic peak (30–130 ^{o}C) was observed for MP (1% in HPMC) (Fig. 3A), due to
217 dehydration of HPMC during heating (Chandak and Verma, 2008). This broad peak was
218 greatly suppressed in the thermogram of the MP-containing ring (F8) due to dilution of the
219 MP material within the silicone elastomer.

220 *3.3. Release of ISMN from VRs*
221 ISMN was effectively released from matrix-type rings F1–F4 into the SVF release medium,
222 displaying typical 'burst and decline' release profiles (Fig. 4A). Release rates were dependent
223 on the initial ISMN loading in the rings, with Day 1 values ranging between 31 and 168 mg.
224 By Day 4, the daily quantities of ISMN released from the rings had declined to between 8–57
225 mg, and to 3–25 mg by Day 11. These daily release quantities administered from the rings are
226 of an entirely similar order of magnitude to doses reported previously for vaginal
227 administration of ISMN tablets in both out-patient and in-patient settings (Agarwal et al.,
228 2014, 2012; Bollapragada et al., 2009; Bullarbo et al., 2007; Chanrachakul et al., 2002; Habib
229 et al., 2008; Vidanagamage and Goonewardene, 2011). The continuous dosing of ISMN
230 offered by the rings may be clinically more effective and enhance compliance compared to

231 the periodic dosing regimen used for the tablets (48, 32 and 16 h prior to the scheduled time
232 of admission for induction).
233
234 Release of ISMN from the VRs obeys root time ($t^{0.5}$) kinetics, as evidenced by linear
235 cumulative release versus root-time graphs (Fig. 4B). Increasing the ISMN loading from 100
236 (F1) to 1000 mg (F3) significantly increased the ISMN release rate from 24.6 to 176.0
237 mg/day$^{0.5}$ (Table 1).
238
239 Rings F3 and F4 both contained 1000 mg ISMN per ring, However, F3 contained ISMN
240 diluted with 30% lactose (as supplied), while F4 contained pure ISMN (i.e. no lactose). The
241 presence of the lactose diluent serves to significantly increase the rate of release of ISMN
242 from the rings (176.0 vs. 121.8 mg/day$^{0.5}$; Table 1 and Fig. 4B).
243
244 Release of ISMN from reservoir and orifice-type rings is presented in Figs. 4C and 4D. Here,
245 daily ISMN release is relatively constant over the study period (Fig. 3C), at least compared to
246 the matrix-type rings (Fig. 3A), resulting in linear cumulative release vs. time profiles (Fig.
247 4D). Daily ISMN release from the reservoir ring containing a full-length ISMN-loaded core
248 (F6) decreased from 7.2 mg on Day 1 to 4.4 mg on Day 11. The half-core ring (F5) provided
249 Day 1 release of 3.7 mg and 2.2 mg on Day 11, approximately half the values for the full-core
250 ring (F6). Compared with Ring F6, the orifice-type ring (F7) had a relatively large amount of
251 ISMN release on Day 1 (10.3 vs. 7.2 mg) and a higher daily ISMN release rate (6.29 vs. 5.22
252 mg/day), clearly illustrating the impact of partly exposing the drug-loaded core to the SVF.
253

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

300 release rate proportional to the length of the IMSN-loaded core. According to well-established
301 design principles for reservoir-type rings, the thickness of the rate-controlling membrane
302 could also be adjusted to further modulate release; for example, adjusting the membrane
303 thickness of the F5 and F6 rings to 0.78 mm (half of the current 1.55 mm) would result in a
304 two-fold increase in the daily ISMN release rate. Incorporating orifices in the membrane also
305 significantly increased the ISMN release rate and offered release kinetics intermediate
306 between conventional matrix and reservoir rings.
307
308 Much lower microgram-per-day doses of MP are required for IOL. Since conventional
309 reservoir-type VRs containing MP provided no release, we focused our attention on ring
310 designs including orifices in the membrane so as to expose, to varying extents, the MP-loaded
311 core to the release medium. By controlling the number of orifices, the size of orifices and the
312 length of the MP-loaded core, near-constant release rates in the range 20–60 μg/day could be
313 easily achieved.
314
315 This is the first study reporting VRs for sustained or controlled delivery cervical ripening
316 agents. The release rates of ISM and MP from VRs could be readily tailored by drug loading
317 and ring designs to meet the clinical requirements for IOL. This study is based on *in vitro*
318 testing of VRs, and therefore the release data may not correlate with performance *in vivo*.
319 However, for other VRs – most notably the dapivirine-releasing silicone elastomer VR for
320 prevention of sexual transmission of the human immunodeficiency virus (HIV) – *in vitro*
321 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).

345 The relatively short use regime intended for a VR for cervical ripening coupled with its use in
346 a managed primary care health setting should lead to high levels of user adherence.
347
348 The combination ISMN+MP ring described in this study is particular interesting, since
349 synergistic effects have previously been reported when administering the combination of
350 ISMN and MP intravaginally for cervical ripening (Abdellah et al., 2011; Elsokary et al.,
351 2015; Soliman, 2013).
352

353 # 4. Conclusions

354 The results of this proof-of-concept study highlight the potential for development of long-
355 acting sustained or controlled release drug delivery devices for low dose vaginal
356 administration of cervical ripening agents for IOL. The continuous dosing of small amounts
357 of these agents might be particularly useful in out-patient settings, reducing the time spent in
358 hospital, reducing health service costs, and offering increased user compliance compared to
359 periodic dosing regimens. The results strongly support progress to clinical testing.
360

361 # Transparency declarations

362 The authors declare no conflicts of interest.
363

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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

693 (F1), 500 (F2), 1000 (F3) and 1000 mg ISMN (without lactose, F4). C and D: daily release
694 and cumulative release of ISMN from Ring F5 (reservoir-type ring with half-length core), F6
695 (reservoir-type ring with full-length core), F7 (orifice-type ring with full-length core) and F8
696 (reservoir-type ring with full-length core, formulated with pure ISMN). The plot of F8 in
697 Graph B is not visible due to overlapping with the plot of F6. E and F: daily MP release versus
698 time plots and cumulative MP release versus root time plots for Ring F9. G and H: daily and
699 cumulative MP release versus time plots for Ring F10-13. I and J: daily ISMN release versus
700 time plots and cumulative ISMN release versus root time plots for Ring F13.