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Wang, Y., Boyd, P., Hunter, A., & Malcolm, R. K. (2018). Intravaginal rings for continuous low-dose administration of cervical ripening agents. *International Journal of Pharmaceutics*, 549, 124–132. <https://doi.org/10.1016/j.ijpharm.2018.07.053>

Published in:
International Journal of Pharmaceutics

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Intravaginal rings for continuous low-dose administration of cervical ripening agents

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10 **Abstract**

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

26

27 **Keywords**

28 induction of labour; silicone elastomer drug delivery device; vaginal drug administration;
29 controlled release; sustained release; out-patient.

30

31 **1. Introduction**

32 Flexible polymeric ring-shaped devices have been investigated since the 1970s for sustained
33 or controlled release of drug substances to the human vagina. To date, six vaginal ring (VR)
34 products have reached market, each offering release of one or more steroid molecules for
35 estrogen replacement therapy (Estring[®] and Femring[®]), contraception (Nuvaring[®],
36 Progering[®] and Ornibel[®]) or hormone supplementation and pregnancy maintenance during *in*
37 *vitro* fertilization (Fertiring[®]) (Brache et al., 2013; Friend, 2011; Malcolm et al., 2015, 2012).
38 Since 2002, great progress has been made in the design and development of various
39 antiretroviral-releasing VRs for reducing HIV acquisition (Kiser et al., 2012; Malcolm et al.,
40 2015, 2010; Thurman et al., 2013), with a dapivirine-releasing silicone elastomer ring having
41 recently completed late-stage clinical testing and currently under regulatory review by the
42 European Medicines Agency (Baeten et al., 2016; Devlin et al., 2013; Nel et al., 2016b). A
43 major impetus for continued innovation in VR design has been the growing interest in
44 combination HIV microbicide and multipurpose prevention technology products for which
45 release needs to be individually tailored for each drug molecule (Baum et al., 2012; Boyd et
46 al., 2016; Derby et al., 2017; Fetherston et al., 2013; Friend et al., 2013; Malcolm et al., 2015,
47 2014; Moss et al., 2016; Murphy et al., 2014; Smith et al., 2017; Shweta R. Ugaonkar et al.,
48 2015; Shweta R Ugaonkar et al., 2015). However, other clinical indications within women's
49 health are also likely to benefit from enhanced drug administration using existing or new VR
50 technologies.

51

52 Induction of labour (IOL) is a widely-used practice in obstetrics to prevent maternal and fetal
53 morbidity and mortality. However, a major complication of IOL is hyperstimulation of the

54 uterus, which can lead to the sudden onset of powerful, frequent and painful contractions
55 which women may find unbearable or frightening. These uterine contractions can damage the
56 fetus due to hypoxia as the placenta cannot be fully revascularised if the uterus is contracting
57 too frequently. Despite these concerns, there is increasing demand to deliver IOL in an
58 outpatient setting where women can be more comfortable and relaxed and reduce their length
59 of stay in hospital. Here, we describe a potential new IOL method involving slow and
60 continuous administration of cervical ripening agents from VRs. This approach has the
61 potential to more closely mimic the natural cervical ripening process and spontaneous onset
62 of labour and reduce the incidence of hyperstimulation, making it safer and more acceptable
63 to women, particularly in an out-patient setting.

64

65 Cervicovaginal administration of pharmacological agents – most notably dinoprostone and
66 misoprostol – has been widely used to ripen the cervix as a method for initiating IOL (Agarwal
67 et al., 2012; Alfirevic et al., 2015; Calder et al., 2008; MacKenzie, 2006; Vogel et al., 2017;
68 Zhang et al., 2015). Two forms of vaginal dinoprostone are already used routinely. Prepidil®
69 is a non-aqueous gel containing 0.5 mg dinoprostone in 3 g triacetin which is administered to
70 the endocervix every 6 h up to a maximum of three doses in 24 h. Cervidil®/Propress® is a
71 pessary-type dosage form comprising 10 mg dinoprostone dispersed within a hydrogel
72 copolymer inserted in a mesh pouch. The insert is placed in the posterior fornix of the vagina
73 and provides sustained release of dinoprostone over 12 h, after which the pouch is removed.
74 Thus, use of modified release formulations for cervical ripening is already well established
75 and offers certain advantages over more conventional immediate-release products (Embrey et
76 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

99 VR device offering release of both agents at significantly different release rates is also
100 described.

101 **2. Materials and methods**

102 *2.1. Materials*

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

112 *2.2. Manufacture of vaginal rings*

113 Silicone elastomer matrix-type VRs (Fig. 1A) containing various loadings of ISMN (100, 500
114 and 1000 mg per ring) were manufactured on a laboratory-scale injection molding machine,
115 according to well-established and previously reported manufacturing protocols (Boyd et al.,
116 2016; Fetherston et al., 2013). Briefly, the required amounts of ISMN were added to both
117 Parts A and B of the MED-4320 addition-cure silicone elastomer system contained in custom
118 screw-cap polypropylene containers, and the contents of each container individually mixed
119 using a Dual Asymmetric Centrifuge (DAC) mixer (SpeedMixer™ DAC 150 FVZ-K,
120 Hauschild, Germany) for 30 s at 3000 rpm. The Part A and B premixes were combined in a

121 1:1 ratio in a polypropylene container, hand-mixed using a spatula, and then speedmixed (30
122 s, 3000 rpm) to produce the active silicone elastomer mixture. The active mix was manually
123 injected into a heated (60 °C) matrix ring mold assembly fitted to the molding machine using
124 a SEMCO® injection cartridge and cured for 10 min producing matrix-type rings (dimensions:
125 7.6 mm cross-sectional diameter and 55.0 mm external diameter).

126

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

138

139 Silicone elastomer orifice-type VRs (Fig. 1C) – comprising ISMN or MP in a central silicone
140 elastomer core and partially encapsulated with a silicone elastomer sheath containing various
141 orifices exposing the underlying core – were manufactured in a similar manner to reservoir
142 rings except using custom-designed injection molds with pins designed to partially expose the

143 drug-loaded central core to the external environment via orifices in the membrane (Figure 1E,
144 1).

145 *2.3. Differential scanning calorimetry*

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

150 *2.4. Quantification of ISMN in the rings*

151 Individual VRs were cut into 2 mm slices and placed in a 250 mL glass bottle (Duran® GLS
152 80®) containing 100 mL acetone. The bottles were placed in a shaking orbital incubator (Infors
153 HT Unitron, Switzerland; 37 °C, 60 rpm, 25 mm orbital throw). After 7 d, the supernatants
154 were collected and diluted 20-fold with water-acetonitrile (90:10, v/v). The amount of ISMN
155 in each VR was analysed by ultra-performance liquid chromatography (UPLC).

156 *2.5. In vitro release testing*

157 Individual VRs were placed into 250 mL glass bottles (Duran® GLS 80®) containing 50 mL
158 pH 4.2 simulated vaginal fluid (SVF). SVF mimics the chemical composition of vaginal fluid
159 (Owen and Katz, 1999). The bottles were placed in the shaking orbital incubator (Infors HT
160 Unitron, Switzerland; 37 °C, 60 rpm, 25 mm orbital throw) for 14 days. Sampling (1 mL)
161 followed by complete replacement of the release medium was performed daily except on
162 Fridays when the flask was refilled with 100 mL SVF and no sampling was performed again
163 until the following Monday. The amount of drug in each sample was quantified by UPLC,

164 and the data used to construct release vs time plots. All release testing experiments were
165 conducted n=4.

166 *2.6. Quantification of ISMN and MP using UPLC*

167 ISMN and MP were quantified using a Waters ACQUITY UPLC[®] system fitted with an
168 ACQUITY UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm) and an in-line filter (0.2 μm).
169 ISMN samples were injected (1.0 μL) onto the column (40 °C) and isocratic elution was
170 performed with a mobile phase of water-acetonitrile (90/10, v/v) at flow rate of 0.6 mL/min.
171 ISMN was detected at 210 nm with a 0.76 min retention time. MP samples were injected (2.0
172 μL) onto the column (40 °C) and isocratic elution was performed using a water-acetonitrile
173 (50/50, v/v) mobile phase at 0.6 mL/min flow rate. MP was detected at 210 nm with a 0.69
174 min retention time. Linear ranges for ISMN and MP were 25–800 μg/mL and 0.5–25 μg/mL,
175 respectively.

176 *2.7. Statistical analyses*

177 Statistical analyses were performed using one-way ANOVA, followed by post-hoc analysis
178 using the Tukey-Kramer multiple comparisons test. Statistical significance is defined as $p <$
179 0.05. Analysis was conducted using GraphPad Prism.

180 **3. Results**

181 *3.1. Design and manufacture of rings*

182 Matrix-type rings containing ISMN (F1–F4, Table 1), reservoir and orifice-type rings
183 containing ISMN (F5–F8, Table 1), and matrix-type and orifice-type rings containing MP
184 (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 -45°C , due to crystalline melting of the silicone
200 elastomer. Ring samples F1, F2, F3 and F6 show an additional endothermic peak at $\sim 90^{\circ}\text{C}$,
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 °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

254 Unlike the matrix-type ring design, formulating the reservoir-type ring to contain pure ISMN
255 (F8; no lactose diluent) produced ISMN release rates identical to the reservoir ring containing
256 ISMN+lactose (F6) (Figs 4C and 4D). The water-soluble lactose is unable to modulate the
257 ISMN release from reservoir rings, since the lactose is contained only in the core of the device
258 and is not directly exposed to the SVF release medium. After 14 days, cumulative ISMN
259 release from the reservoir rings was 37.5, 74.2, 92.0 and 73.8 mg, F5–F8 respectively,
260 equivalent to 39.7%, 39.3%, 48.7% and 39.0% of the initial loadings (Table 1).

261 *3.4. Release of MP from VRs*

262 Ring F9 is the core component used to manufacture the orifice-type MP rings (F10–F13). Not
263 surprisingly, it displayed release behaviour typical of a matrix-type ring, including relatively
264 high Day 1 release (779 µg), declining amounts of MP released on subsequent days (233 µg
265 on Day 4 and only 26 µg on Day 11, Fig. 4E), and root-time kinetics (Fig. 4F). The quantities
266 of MP released during Day 1 and Day 4 were much higher than the safe clinical doses (25–
267 200 µg) reported for vaginal administration of MP in IOL (Ambika et al., 2017; Calder et al.,
268 2008; Chaudhuri et al., 2011; Frohn, 2002; Oboro and Tabowei, 2005).

269

270 When this F9 core was incorporated into a conventional reservoir-type ring, no release of MP
271 was observed. However, rings having either small circular orifices (F10, F11, F13) or larger
272 window-style orifices (F12) exposing an underlying full-length (F11 and F13) or a partial-
273 length (F10 and F12) MP-loaded core showed significant MP release (Fig. 4G and 4H, Table
274 1). In general, the daily release profiles (Fig. 4G) do not show the burst-and-decline behaviour
275 of matrix-type rings (Fig. 4E); instead, greater constancy of release is observed, similar to a
276 conventional reservoir-type ring (Fig. 4C). Moreover, MP release is clearly shown to depend

277 upon the length of the core, the type of orifices (circular vs. elongated), and the number of
278 orifices. Inevitably, given that only part of the core in these rings is exposed to the SVF, the
279 release rates are reduced compared to ring F9. However, daily MP release rates tend to hover
280 around either 20 or 60 $\mu\text{g}/\text{day}$ (Fig. 3G), conveniently straddling the dosing range currently
281 used in vaginal administration of MP for cervical ripening (Ambika et al., 2017; Calder et al.,
282 2008; Chaudhuri et al., 2011; Frohn, 2002; Oboro and Tabowei, 2005).

283

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

293 **4. Discussion**

294 In general, the silicone elastomer matrix-type rings are best suited to administration of daily
295 ISMN doses in the relatively high 1–200 mg range. The administered dose of ISMN was
296 readily modulated by adjusting the initial drug loading. Matrix rings provided an initial burst
297 release followed by declining release on subsequent days; as such, the release range would
298 need to carefully tailored for optimal clinical efficacy. However, constant low milligram-per-
299 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

322 residual drug analysis content post-use (Baeten et al., 2016; Malcolm et al., 2016; McCoy et
323 al., 2017; Nel et al., 2016a).

324

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

332

333 As with other sustained/controlled release drug formulations, increased user acceptability and
334 compliance/adherence with VRs is often mooted as a potential advantage over more
335 conventional immediate release vaginal dosage forms (Malcolm et al., 2015). Previous studies
336 have reported high user acceptability and/or adherence of VRs for contraception and estrogen
337 replacement therapy (Ayton et al., 1996; Barentsen et al., 1997; Brache et al., 2000; Casper
338 and Petri, 1999; Dieben et al., 2002; Faundes et al., 1981; Nachtigall, 1995; Novák et al.,
339 2003; Roumen et al., 2001; Roumen and Dieben, 1999; Stifani et al., 2018; Vartiainen et al.,
340 1993; Weisberg et al., 1995). Yet, lower-than-expected adherence has been reported in late-
341 stage clinical trials of the dapivirine ring, particularly among young women (Baeten et al.,
342 2016; Montgomery et al., 2017; Nel et al., 2016b, 2016a; Spence et al., 2016). However, the
343 observed low adherence with the dapivirine may reflect various sociocultural issues
344 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

364 **Acknowledgements**

365 This study was funded through the UK Medical Research Council's 'Confidence in Concept'
366 scheme (MC-PC-15035).

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670 **Table and figure captions**

671

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

674

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

678

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

682

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

689

690 **Fig. 4.** Daily release and cumulative release profiles for DDU-4320 VRs loaded with cervical
691 ripening agents over 14 days in SVF. A and B: daily release versus time and cumulative
692 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.