



## Silicone elastomer formulations for improved performance of a multipurpose vaginal ring releasing dapivirine and levonorgestrel

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### ABSTRACT

A dapivirine-releasing silicone elastomer vaginal ring for reducing women's risk of HIV acquisition has recently been approved. A next-generation multipurpose vaginal ring releasing dapivirine and levonorgestrel is currently in development, offering hormonal contraception and HIV prevention from a single device. Previously, we reported challenges with incorporating levonorgestrel into rings manufactured from addition-cure silicone elastomers due to an irreversible chemical reaction between the levonorgestrel molecule and the hydride-functionalised crosslinker component of the silicone elastomer formulation, leading to low drug content assay, cure inhibition, and reduced ring mechanical properties (which may account for the increased incidence of ring expulsion *in vivo*). Here, we report on the development and testing of various custom silicone elastomer materials specifically formulated to circumvent these issues. After extensive testing of the custom silicones and subsequent manufacture and testing (Shore M hardness, pot life, content assay, oscillatory rheology, mechanical testing) of rings containing both dapivirine and levonorgestrel, a lead candidate formulation was selected that was amenable to practical ring manufacture via injection molding, exhibited no substantial levonorgestrel binding, and offered suitable mechanical properties.

### 1. Introduction

Silicone elastomers based on polydimethylsiloxane (PDMS) are used to fabricate a diverse range of products for healthcare applications, including medical devices (e.g., contact lenses, catheters, drains, shunts and stents) and drug delivery devices (e.g., vaginal rings, transdermal patches and intrauterine devices) (Aliyar and Schalau, 2015; Bao et al., 2020; Kim et al., 2018; Malcolm et al., 2016; Tighe, 2013; Wildgruber et al., 2016). Unlike thermoplastic polymers, silicone elastomer formulations are relatively complex, comprising multiple components that contribute to the function and properties of the cured elastomer (Delebecq and Ganachaud, 2012; Harkous et al., 2016; Lambert, 2006; Malcolm et al., 2016; Shim and Isayev, 2004). Silicone elastomers for use in healthcare are commonly produced through the chemical crosslinking of functionalised linear PDMS molecules via either addition-type or condensation-type curing reactions (Malcolm et al., 2016, 2005).

Chemical crosslinking of addition-cure silicones occurs via a platinum-catalysed hydrosilylation reaction between vinyl-functionalised and hydride-functionalised PDMS molecules. This cross-linking reaction does not create any by-products and is the preferred material for manufacture of silicone elastomer vaginal rings (Malcolm et al., 2016) and medical devices. However, the platinum catalyst may be inhibited, most notably by tin, sulfur and amine-containing organic compounds (Jerschow, 2001; Karlsson and Albertsson, 2001). Also, we have previously reported that steroid drug molecules containing specific unsaturated chemical moieties – including ethynyl or enone groups – can undergo irreversible chemical bonding with addition-cured silicone elastomers, such that the drugs are no longer able to be released (Dallal Bashi et al., 2019; McCoy et al., 2018; Murphy et al., 2016).

Over the past 15–20 years, there has been much interest in vaginal ring technologies for sustained or controlled release of microbicidal compounds for prevention of sexually-acquired HIV infection (Malcolm

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et al., 2016; Thurman et al., 2013). A silicone elastomer vaginal ring developed by the International Partnership for Microbicides (IPM) and offering continuous release of dapivirine (DPV) over 28 days has demonstrated effectiveness in reducing the incidence of HIV acquisition in two Phase III clinical trials and has recently received a positive opinion/approval from the European Medicines Agency (EMA) and the World Health Organization for use in developing countries (Baeten et al., 2016; European Medicines Agency, 2020; Nel et al., 2016). There is also considerable interest in next-generation multipurpose prevention technology (MPT) products aimed at combining HIV prevention activity with contraception and/or prevention/treatment of other sexually transmitted diseases (Friend et al., 2013; Malcolm et al., 2014; Thurman et al., 2013). These multipurpose products potentially offer increased convenience and appeal to women. To this end, IPM is developing a new vaginal ring designed to simultaneously release dapivirine and the contraceptive progestin levonorgestrel (LNG). LNG has a well-established safety profile and is widely used in numerous marketed contraceptive products, including progestin-only oral pills for emergency contraception, combined oral contraceptive pills, and long-acting intrauterine devices (e.g., Kyleena®, Jaydess®, Mirena®).

In previous studies describing development of a combination DPV-LNG silicone elastomer ring, we reported a significant chemical reaction between LNG molecules and the hydride-functionalised polydimethylsiloxane crosslinker component of addition-cure silicone elastomers. Under some circumstances, all of the LNG contained in the formulation was irreversibly bonded to the silicone elastomer (Fig. 1) such that no LNG release was measured (Dallal Bashi et al., 2019; McCoy et al., 2018; Murphy et al., 2016). This binding reaction can be partially mitigated through (i) use of LNG material having a larger particle size, (ii) careful control of the cure temperature and cure time during ring manufacture, and/or (iii) use of alternative silicone elastomers having different stoichiometry of hydrosilane and vinyl functional groups (Dallal Bashi et al., 2019; Murphy et al., 2016).

Since the LNG binding reaction competes with the normal silicone crosslinking reaction (Fig. 1), rings containing LNG often display lower than expected mechanical strength (Murphy et al., 2016). The mechanical characteristics of vaginal rings are critical, since they impact the retention of the device in vivo; involuntary expulsion of rings is reported by users of all marketed ring products and can influence user comfort and acceptability (Boyd et al., 2020; McCoy et al., 2019). The mechanical properties of marketed rings have been reported and depend on the ring design and type of polymer used (Fetherston et al., 2013; McCoy et al., 2019). Here, custom silicone elastomer formulations were

developed and tested as part of efforts to optimise the mechanical performance of the DPV-LNG ring while seeking to reduce the extent of LNG binding.

## 2. Materials and methods

### 2.1. Materials

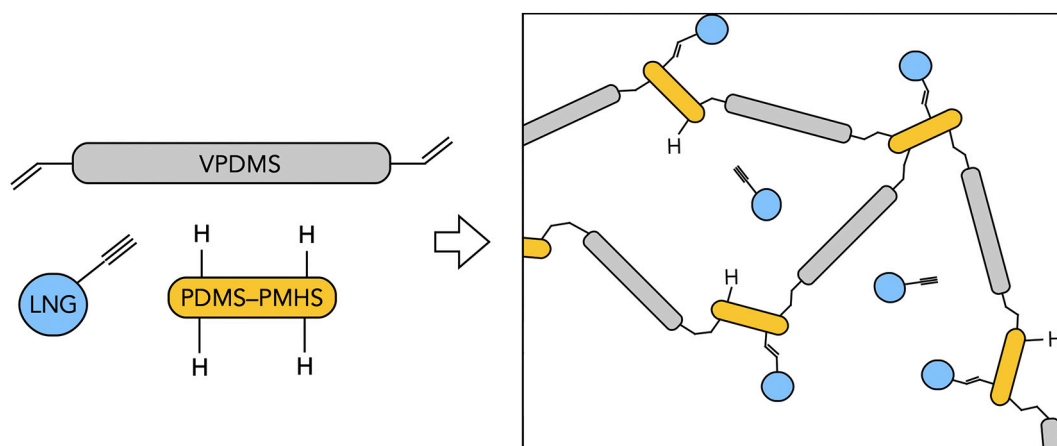
Seven custom silicone elastomer formulations were supplied by Elkem (Elkem Silicones, NJ, USA) (Table 1), varying in the percentage composition of (i) silica (which acts as a reinforcing filler), (ii) silicone elastomer base (containing vinyl-functionalised polydimethylsiloxane molecule VPDMS; Fig. 1), (iii) crosslinker (the hydride-functionalised polydimethylsiloxane molecule PDMS-PMHS; Fig. 1), (iv) a functional additive, and (v) the molecular weight of the silicone base polymer. A commercial comparator addition-cure silicone elastomer formulation (DDU-4320, NuSil Technology, Carpinteria, CA, USA) – reported previously for manufacture of DPV-LNG rings (Boyd et al., 2016; Malcolm et al., 2016) – was also tested. Micronized DPV was supplied by Ajinomoto OmniChem n.v. (Wetteren, Belgium). Non-micronized LNG (nmLNG) was supplied by CHEMO Group (Industriale Chimica s.r.l., Saronno, Italy). Potassium dihydrogen orthophosphate and sodium hydroxide were purchased from VWR International Ltd. (Dublin, Ireland). Phosphoric acid (85% w/w in water) and HPLC-grade methanol, acetonitrile and acetone were purchased from Sigma-Aldrich (Gillingham, UK). A Millipore Direct-Q 3 UV Ultrapure Water System (Watford, UK) was used for HPLC-grade water.

**Table 1**

Formulation changes for each silicone elastomer compared to the composition of the addition-cure silicone elastomer Silbione™ LSR D135-QB.

Silicone elastomer formulation	Silica filler (%)	Base (%)	Crosslinker (%)	Polymer MW	Functional additive (%)
I	–	–	↑↑	↓	–
II	–	↑↑	↑	↓	↑
III	↑	–	↑↑	–	–
IV	↑	↑	↑	↓	–
V	↑	–	↑↑	↓	–
VI	↑	↑	↑↑	–	–
VII	↑	↑	↑↑	↓	↑

↑ moderately increased, ↓ moderately decreased, ↑↑ significantly increased, – unchanged.



**Fig. 1.** Representation of the typical silicone elastomer addition-cure reaction (i.e., a hydrosilylation reaction between the PDMS-PMHS and VPDMS components) and the competing reaction between levonorgestrel (LNG; note the ethynyl group) and the hydride-functionalised crosslinker component (PDMS-PMHS). PDMS-PMHS represents the poly(dimethylsiloxane)-co-poly(methylhydrosiloxane) component, and VPDMS the vinyl-terminated poly(dimethylsiloxane) component of the elastomer formulation. The size of the coloured items in the figure represent the relative molecular weight of the components (VPDMS > PDMS-PMHS > LNG), but are not to scale.

## 2.2. Preparation of silicone elastomer slabs

For preliminary tests, silicone elastomer slabs (45 g target weight, ~65 mm diameter, ~14 mm height) were prepared instead of rings. Slabs contained either no drug ('blank slabs') or 2.5% w/w DPV and 4.0% w/w nmLNG ('active slabs'). Active slabs were prepared as follows: (i) the required amounts of the drugs and the Part A and Part B silicone components were weighed into polypropylene Speedmixer® containers; (ii) each silicone part was spun down at 3000 rpm for 5 s using a DAC-150 FVZ-K Speedmixer™ (Hauschild, Germany) followed by addition of the drugs; (iii) the silicone + drug combination was then mixed with a spatula for 30 s before sealing the container and mixing at 3000 rpm for 30 s; (iv) the containers (with lids removed to allow evaporation of the cure inhibitor) were cured at room temperature for at least 60 h. For post-cure heat treatment, slabs were placed in an oven at 100 °C for 3 h. Preparation of blank slabs was similar but without addition of the drug powders.

## 2.3. Manufacture of vaginal rings

Matrix-type vaginal rings – either containing no drug ('blank rings') or containing 200 mg DPV and 320 mg nmLNG ('active rings') – were manufactured for selected silicone elastomer formulations using a Babyplast™ 6/10P injection molding machine (Chronoplast, Spain). The procedure is described here for drug loaded 'active rings'; the procedure was similar for blank ring manufacture without drug powder addition. The steps required to prepare the mixture before transferring to the injection cartridge are displayed schematically in Fig. 2. Part A and B silicone components were stored at -20 °C for at least 10 min prior to use. Active pre-mixes (i.e., silicone part + drugs; 50 g) were prepared by weighing the required quantity of Part A or B into a 100 g polypropylene container. The container was mixed at 3000 rpm for 5 s before the required amount of DPV was added and mixed with a spatula for ~30 s to ensure the powder was fully wetted. The mixture was further mixed at 3000 rpm for 30 s using a DAC-150 FVZ-K Speedmixer™ (Hauschild, Germany) before storing at -20 °C for at least 10 min. nmLNG added was then added following the same protocol, and the active Part A and Part B mixes stored at -20 °C for 10 min before further

use.

Equal quantities of the Part A and B active mixes (~50 g) were sequentially added to a large plastic polypropylene Speedmixer® container until ~200 or ~400 g in total had been transferred. The contents were mixed with a spatula (10 s) and then using a DAC-600 Speedmixer™ (Hauschild, Germany; 1500 rpm for 30 s). The container was cooled at -20 °C for 10 min, further mixed with a spatula for 10–20 s, and the contents transferred into a modified E1000 cartridge (Fiscbach, Germany). The cartridge was inserted into a pre-chilled (-20 °C; > 30 min) cartridge holder, the assembly fitted in the Babyplast™ machine, and rings manufactured at 100 °C for 95 s using pre-defined injection molding parameters optimised for this elastomer: shot size (7.70 g); first and second injection pressures 50 and 15 bar, respectively; clamping pressure 100 bar.

## 2.4. Qualitative pot-life assessment

Qualitative assessment of the pot-life at room temperature (~20 °C) was evaluated for selected silicone active mixes. Silicones parts containing DPV and nmLNG were added to polypropylene containers, mixed (30 s by hand followed by 20 s at 3000 rpm using the Speedmixer™) and allowed to cure at room temperature. Extent of cure was determined every 30 min using a spatula, with materials classified as 'cured', 'partially cured' or 'uncured'. Partially cured materials were tacky and could be manipulated with a spatula; cured materials were not tacky, and the spatula could not be easily inserted into the material.

## 2.5. Mechanical testing

### 2.5.1. Shore M hardness test

Shore M hardness testing of rings and slabs was performed using a Checkline Europe® RX-DD-M Shore M durometer held in an OS-3 stand and conforming with ASTM D-2240 (Type M scale). A pen mark was used to identify the test sites on the surface of the ring or slab samples. Six measurements were performed per ring or slab.

### 2.5.2. Static 28-day compression test

Rings were placed in a custom-designed multi-cavity compression jig

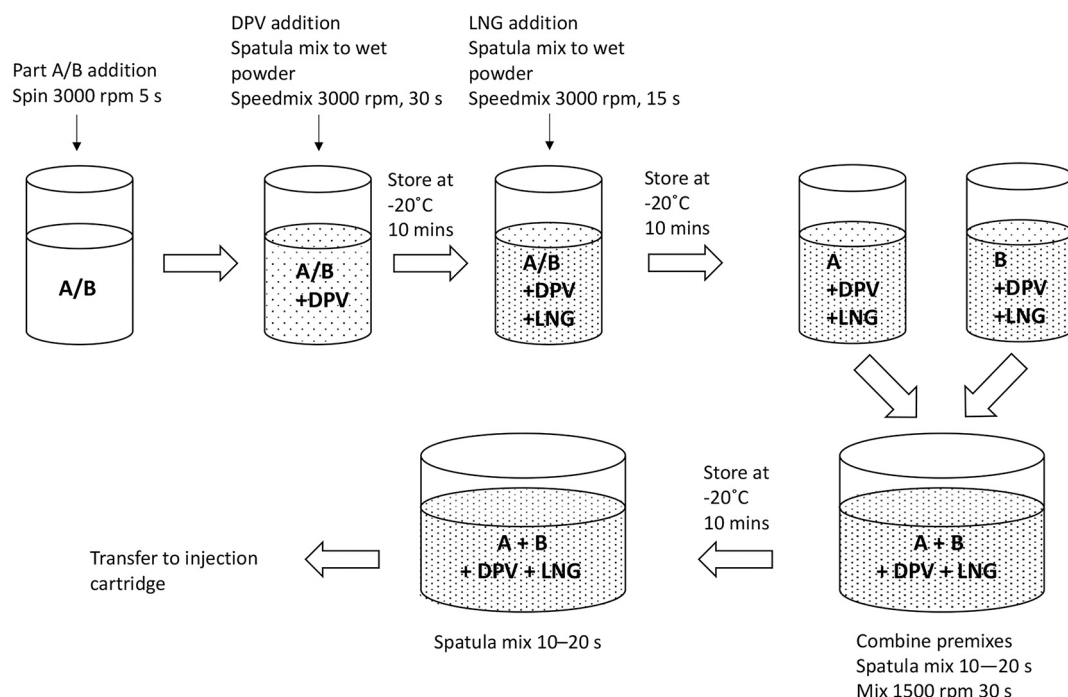


Fig. 2. Method for preparation of DPV-LNG active elastomer mixes prior to ring manufacture.

and each ring compressed until the ring sides touched. After 28 days, the rings were removed from the jig and allowed to recover for 15–20 s before the percentage recovery values relative to the original ring diameter were measured using a custom gauge (McCoy et al., 2019).

### 2.5.3. Twist during compression test

A custom twist-testing jig – described in a previous article (McCoy et al., 2019) – was fitted to an EZ Test Universal Tester (Shimadzu, UK). Rings were mounted on the jog and compressed by lowering the tester cross-arm. The distance between the cross-arm and the ring holder was determined based on the external diameter for each ring formulation. Maximum angular rotation values during the compression cycle were measured for each ring.

### 2.5.4. 1000-cycle compression test

A custom aluminium plate having multiple rectangular grooves in which rings can be vertically positioned was mounted on the lower fixed platform of a Shimadzu EZ Test Universal Tester. An upper Perspex® plate with identical grooves was mounted on the upper moveable arm of the tester, such that the lower and upper grooves were aligned. The upper plate was lowered until it touched the top of the rings, and all rings were held in a vertical position under minimal pre-compression. Rings were cyclically compressed 1000 times at a test speed of 15 mm s<sup>-1</sup> until their sides touched. Ring diameters were assessed using a custom gauge and percentage recovery values expressed relative to the original external diameter of the ring.

### 2.5.5. Elongation at break test

Rings were tested for elongation at break using an EZ Test Universal Tester fitted with a 5000 N load cell and custom O-ring grips. Rings were placed around the upper and lower ring grips, with the distance between the grips adjusted according to the internal diameter of each ring such that the rings were initially under minimum tension. Each ring was stretched using a test speed of 500 ± 50 mm/min until fracture occurred.

## 2.6. Rheological evaluation of silicone elastomer cure

The cure characteristics of the silicone elastomer formulations were evaluated by oscillatory rheology using an AR-2000 rheometer (TA Instruments, Leatherhead, UK) fitted with a 40 mm crosshatch parallel plate geometry and using a 1000 µm gap. Under an oscillatory stress of 50 Pa at a frequency of 10 Hz, samples were heated from 30 to 100 °C at 30 °C/min and then held at 100 °C for 10 min. Isothermal oscillatory stress experiments (50 Pa, 10 Hz) were performed at 15 and 30 °C for 6 h with a reduced sampling frequency to investigate the pot life/working time of the silicone elastomer formulations. Similar oscillatory stress experiments were also performed at 15 °C for 5 min to give a point measure of the curing status of blank and active mixes sampled from the E1000 injection cartridge at various times during ring manufacture.

## 2.7. Drug content assay

Selected slabs and rings were sectioned into small pieces, weighed, and added to individually labelled 250 mL glass flasks. Acetone (200 mL) was added to each flask before placing the sealed flasks in an orbital shaking incubator (37 °C, 60 rpm). After 72 h, flasks were removed and allowed to cool for at least 1 h before a 1 mL aliquot of the acetone extraction solution was diluted to 100 mL with 1:1 acetonitrile/water. The extraction samples were run against point standards of equivalent or similar concentration.

## 2.8. Quantification of DPV and LNG by HPLC

Quantification of DPV and LNG was performed on a Waters HPLC system (Waters Limited, Elstree, UK) consisting of a 1525 Binary HPLC pump with an in-line degasser AF unit, column heater, 717 Plus

Autosampler and a 2487 dual wavelength absorbance detector. Samples (25 µL) were injected onto a Thermo Scientific BDS Hypersil™ C18 HPLC column (150 mm × 4.6 mm, 3 µm particle size) fitted with a guard column. The column was held at 25 °C and isocratic elution was performed using a mobile phase of 58% HPLC-grade acetonitrile and 42% pH 2.4 phosphate buffer (prepared using 7.7 mM, pH 3 phosphate buffer modified by addition of 2.2 mL of 85% phosphoric acid and 1.0 mL of 10 M sodium hydroxide), a flow rate of 1.2 mL/min and a run time of 5 min. DPV was detected at 210 nm at ~2.7 min and LNG at 240 nm at ~3.7 min (Dallal Bashi et al., 2019).

## 3. Results and discussion

### 3.1. Initial formulation screening

We have previously reported the irreversible chemical binding of LNG to silicone elastomers during the manufacture of vaginal rings (Dallal Bashi et al., 2019; Murphy et al., 2016). Based on our requirements around the critical material attributes for LNG binding and the mechanical properties of the resultant cured elastomer, Elkem provided seven new custom silicone elastomer materials based on modifications to a healthcare grade silicone formulation (Silbione™ LSR D135-QB). The formulation changes described in Table 1 were primarily selected to increase the durometer hardness and include various combinations of the following strategies: (i) increased concentration of the silica reinforcing filler, (ii) increased concentration of the silicone elastomer base material (VPDMS, Fig. 1; to compete with LNG reaction), (iii) increased crosslinker concentration (PDMS–PHMS, Fig. 1; to mitigate low cure and low hardness), (iv) decreased molecular weight (MW) of the silicone polymer (to increase Shore hardness), and (v) increased concentration of a functional additive (to improve cure characteristics). Component parts of silicone elastomer compositions are described in previously published research (Delebecq and Ganachaud, 2012; Lambert, 2006; Malcolm et al., 2016). Most of the formulation changes do not introduce any new components into the elastomer formulations. Rather, they are based on modifications to existing, commercially available, healthcare-grade silicone systems. Therefore, the modified silicone products discussed here will have comparable biocompatibility to other healthcare grade silicones.

As part of an initial screening exercise, the custom silicone elastomer materials (with and without DPV + LNG) were cured at room temperature for 60 h and the extent of LNG binding and mechanical properties measured. Preparing samples at room temperature allowed preliminary comparison of the extent of LNG binding for the various materials without considering cure temperature; silicone elastomer rings are normally manufactured by injection molding at elevated temperatures (typically 80–170 °C, depending upon silicone type and formulation). Subsequent post-curing of samples at 100 °C for 3 h was performed to drive the LNG binding reaction to completion, after which further assessment of LNG binding and mechanical properties was performed.

A wide range of Shore M values was recorded; the highest post-cure values were obtained for silicone formulations III, V and VI (Table 2). The post-curing process typically increased the Shore M value of the silicone elastomer slabs by 5–14%, except for formulation VII which increased by ~50% from a very low initial value. Formulations I, II and VII gave Shore M values either borderline with or below the target value range of 50–70 units. Marketed vaginal rings typically have Shore M hardness values within this target range (McCoy et al., 2019).

Relatively high LNG recovery was measured for each of the custom silicone elastomer formulations, even after the post-curing heat treatment (Table 2). Much lower LNG recovery values have been reported previously with other silicone elastomer materials (Dallal Bashi et al., 2019; Murphy et al., 2016). Therefore, from the perspective of LNG binding, all formulations provided adequate values. However, formulations I, II and VII were not investigated further due to Shore M values being below or close to the lower limit of the target range.



**Table 2**

Shore M hardness (mean  $\pm$  SD of  $n = 6$  measurements for a single slab) of blank slabs (B) and active slabs (A) (2.5% w/w DPV + 4% w/w nmLNG), and drug content recovery values for active formulations cured at room temperature (RT) for 60 h and then post-cured at 100 °C for 3 h. LNG recovery values were calculated with respect to weight-corrected percentage loadings.

Silicone elastomer formulation	Shore M		DPV recovery (%)	LNG recovery (%)
	RT cure	Post-cured		
I B	Not cured	55.3 $\pm$ 0.8	–	–
I A	Not cured	47.3 $\pm$ 1.6	101 $\pm$ 1	98 $\pm$ 2
II B	45.4 $\pm$ 1.9	51.5 $\pm$ 1.0	–	–
II A	47.0 $\pm$ 0.9	50.0 $\pm$ 0.8	101 $\pm$ 1	99 $\pm$ 1
III B	59.4 $\pm$ 0.5	62.2 $\pm$ 1.0	–	–
III A	58.0 $\pm$ 1.9	63.1 $\pm$ 1.0	101 $\pm$ 2	95 $\pm$ 1
IV B	51.5 $\pm$ 0.9	55.4 $\pm$ 0.5	–	–
IV A	49.5 $\pm$ 0.4	55.0 $\pm$ 1.4	103 $\pm$ 1	101 $\pm$ 2
V B	58.5 $\pm$ 1.2	62.8 $\pm$ 0.5	–	–
V A	55.0 $\pm$ 2.5	61.1 $\pm$ 0.7	103 $\pm$ 1	97 $\pm$ 1
VI B	58.6 $\pm$ 1.4	62.4 $\pm$ 1.8	–	–
VI A	58.9 $\pm$ 2.1	62.8 $\pm$ 1.1	104 $\pm$ 1	98 $\pm$ 1
VII B	18.3 $\pm$ 1.0	27.6 $\pm$ 0.7	–	–
VII A	19.3 $\pm$ 1.5	25.5 $\pm$ 0.5	101 $\pm$ 0.4	100 $\pm$ 1

Qualitative assessment of room-temperature cure time for each formulation is reported in Table 3. From the perspective of room temperature pot-life, prototypes IV, V and VI all performed at least as well as the commercial comparator. Formulation III was excluded from further investigation due to its pot-life being considered too short to be compatible with commercial processes.

### 3.2. Rheological assessment of cure characteristics

Oscillatory rheometry was used to assess the real-time cure characteristics of lead candidate formulations IV, V and VI compared to the commercial comparator. Plots of storage modulus vs. time are presented in Fig. 3; storage modulus is a measure of the amount of energy that must be inputted into a sample in order to distort it, and is indicative of the extent of cure within the sample (Murphy et al., 2016). In the plots, the dashed vertical line indicates the time when the plate temperature reached 100 °C, a typical cure temperature for these systems; we found it easier to apply the silicone samples to the parallel plate geometry at room temperature and then ramp the temperature as quickly as possible to match the cure temperature used during the injection molding

**Table 3**

Time to different states of cure at room temperature for active (A) Elkem formulations and the commercial comparator.

Silicone elastomer formulation	Last uncured timepoint (h)	Partially cured timepoint (h)	Fully cured timepoint (h)
III A	2.0	2.5	3.0
IV A	5.0	Not cured	Not cured
V A	3.0	3.5	Not cured
VI A	5.0	Not cured	Not cured
Commercial comparator	3.0	3.5	4.5

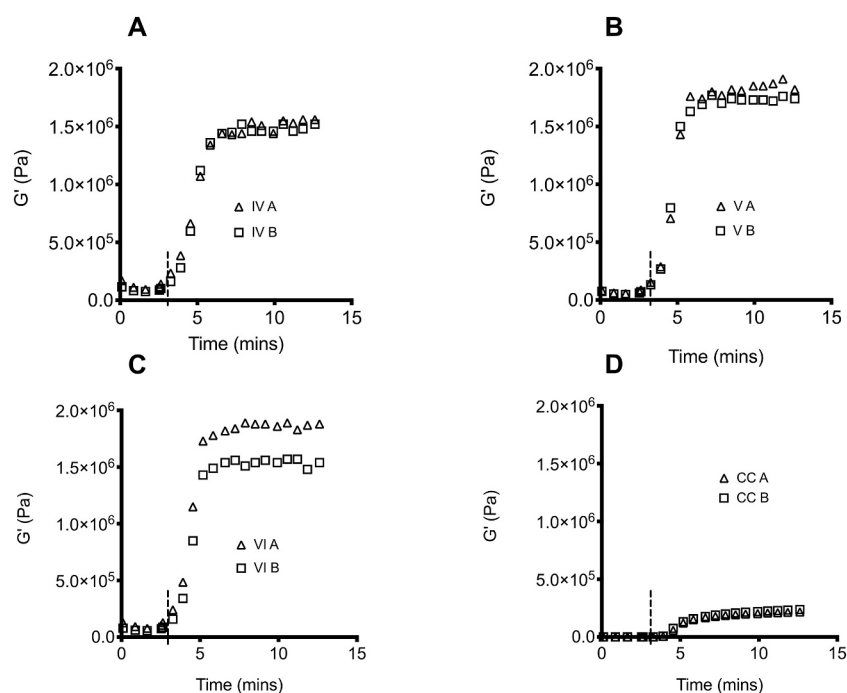
process. For each silicone formulation, representative cure profiles for both blank (B) and active (A; 2.5% DPV + 4% nmLNG) silicones are displayed on the same plot.

As expected, the storage modulus increased rapidly upon heating. Cure profiles were similar for blank and active silicone materials. The maximum storage modulus value for each new formulation (Fig. 3A–C) was almost an order of magnitude larger than that measured for the commercial comparator material (Fig. 3D), reflecting the higher durometer specifications for the new materials and the changes made to the silicone formulations (Table 1). For each of the lead candidate silicone elastomer formulations, the maximum storage modulus value was  $\sim 1.5 \times 10^6$  Pa. Similar values were measured for blank and drug-loaded elastomers, except for formulations VI A and VI B (Fig. 3A–C).

To better model and assess cure characteristics during high temperature injection molding manufacture of rings, the times required to achieve 10, 50 and 90% of the final plateau storage modulus value were measured (Table 4). Values determined for each custom silicone formulation and the commercial comparator – both with and without DPV + nmLNG – indicated almost complete cure of each new elastomer formulation within 3 min at 100 °C (Table 4), significantly faster than for the commercial comparator formulation. Small differences were observed between active and blank silicones, but trends were inconsistent and not considered practically significant.

Having established an approximate storage modulus value at full cure, the extent of cure at room temperature was then monitored at 15 °C and 30 °C to provide insights into the pot-life when the silicone elastomer mixes are prepared and stored prior to injection molding (Fig. 4A–D). Several notable observations were made. As expected, the rate of increase in storage modulus at these temperatures was much lower than observed at higher temperatures. Also, active mixes showed higher storage modulus values compared with blank mixes due to an increased proportion of solid material within the elastomer mix. Modulus values were also dependent on temperature, with the 30 °C profiles showing greater increase in moduli compared with the 15 °C profiles. For each custom formulation, increasing the temperature from 15 to 30 °C led to the storage modulus more than doubling over the six-hour period for both blank and active materials. The effect of temperature increase was greater than the effect of drug addition (comparing active elastomer at 15 °C with blank elastomer at 30 °C), and the impact of both drug addition and temperature increase was at least additive, with substantial further increases in storage modulus recorded for each active formulation at 30 °C. Some of these increases may be attributed to the impact of adding a high proportion of solids to the elastomer. However, the active samples may also be curing more quickly than the blank samples, evidenced by their line gradients, since the impact of addition of solids would be expected to result in a uniform increase in viscosity throughout. In Fig. 4D, only the 30 °C blank and active samples are visible in the plot; the storage modulus plots for the 15 °C samples barely register above the x-axis. Interestingly, in this instance, addition of DPV and LNG does not greatly impact the storage modulus, presumably due to their relatively low concentrations.

Comparing the storage modulus values obtained for formulations tested at 15 and 30 °C with values obtained after complete cure gives some indication as to the extent of curing which has occurred at these temperatures. These values – expressed as a percentage of the mean nominal final storage modulus value from the previous temperature ramp experiments – are presented in Table 5. By this analysis, formulations IV and V show a similar extent of cure during 6 h at 15 and 30 °C, whereas formulation VI shows more complete cure over the same period. These data suggest a limited work time ( $\sim 2$  h) at room temperature for these materials once Parts A and B are combined. Note that the 15 °C and 30 °C rheology measurements were performed on single replicates.



**Fig. 3.** Plot of storage modulus vs. time for blank and active silicone formulations (A for formulation IV, B for formulation V, C for formulation VI and D for commercial comparator (CC) formulation) upon heating to 100 °C (denoted by the dashed vertical line) and holding for 10 min. Experimental parameters: 50 Pa oscillatory stress, 10 Hz frequency. In the legends, A refers to active, and B to blank formulations.

**Table 4**

Time to 10, 50 and 90% of complete cure for custom silicone elastomer formulations IV, V, and VI, as determined from temperature ramp oscillatory rheology. A – active, B – blank.

Silicone elastomer formulation	Mean time (min, $\pm$ SD) to reach stated percent of max storage modulus value		
	10%	50%	90%
IV B	0.5 $\pm$ 0.1	2.2 $\pm$ 0.1	3.0 $\pm$ 0.1
IV A	0.1 $\pm$ 0.1	2.1 $\pm$ 0.1	3.3 $\pm$ 0.1
V B	1.0 $\pm$ 0.1	2.2 $\pm$ 0.2	3.0 $\pm$ 0.5
V A	0.7 $\pm$ 0.1	2.1 $\pm$ 0.1	3.0 $\pm$ 0.1
VI B	0.7 $\pm$ 0.1	1.9 $\pm$ 0.0	2.7 $\pm$ 0.2
VI A	0.5 $\pm$ 0.0	1.9 $\pm$ 0.0	2.6 $\pm$ 0.1
Commercial comparator B	1.6 $\pm$ 0.0	2.3 $\pm$ 0.0	4.6 $\pm$ 0.3
Commercial comparator A	1.7 $\pm$ 0.1	2.4 $\pm$ 0.1	4.3 $\pm$ 0.1

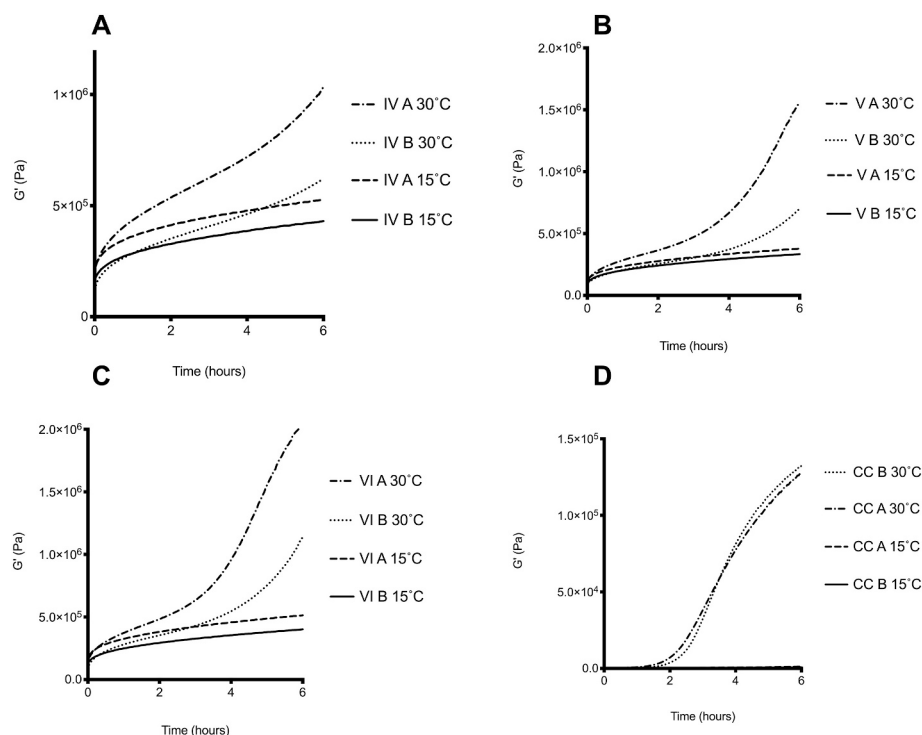
### 3.3. Manufacture and testing of rings using lead candidate silicone elastomer formulations

To better monitor the cure state of the new silicone elastomers during the manufacture of a single batch of vaginal rings using the Babyplast™ injection molding machine, silicone elastomer mix was sampled from the injection cartridge at different timepoints throughout the manufacturing run and the storage modulus measured immediately using oscillatory rheology. The first sample ( $T_0$ ) was taken just after the combined material was added to the cartridge; the next sample ( $T_1$ ) was taken just prior to performing the first injection; subsequent samples were taken at approximate 30 min intervals throughout the manufacturing run ( $T_2$ – $T_4$ ). Blank and active mixes for formulations IV, V and VI were tested (Table 6). In agreement with the preliminary rheological data (Fig. 4, Table 5), batch manufacture of blank rings was consistently completed in under 120 min without issue. Rheological assessment of samples taken at the end of the manufacturing run showed storage modulus values less than 20% of the value at complete cure. Smaller active mix batch sizes were necessary for the custom formulations since manufacturing runs could not be extended to longer times

due to premature cure. The most favourable profile was for formulation V, falling within the workable range for 115 min (Table 6). By comparison, formulation IV required operator intervention to ensure satisfactory dosing of the of the injection cylinder during the semi-automatic cycle to complete ring manufacture and was considered unworkable after less than 50 min. Formulation VI also required similar intervention to complete ring manufacture and was approaching an unworkable state at the end of the manufacturing run.

A full suite of mechanical tests was performed for all blank and active ring types. A summary of the mechanical testing results is provided in Table 7. Values for the 25 mg DPV-only ring and the marketed product Femring® are also presented for context. Drug assay was also measured for six rings from each batch run (Table 8). Mean drug content recoveries for all batches were within 3% of the target value for both DPV and LNG.

Mean Shore M values for blank rings (Table 7) were broadly similar to those measured for post-cured slabs (Table 2). Shore M values were reduced for each active ring compared to its blank equivalent; this was most pronounced for formulation VI (17% reduction) and lowest for formulation V rings (3% reduction). This reduction is consistent with previous reports of LNG addition affecting the curing and mechanical properties of addition-cure silicone elastomers (Dallal Bashi et al., 2019; Murphy et al., 2016). The values measured for active rings are similar to those measured here for Femring® (Table 7) and previously reported values for Femring® and Estring® (McCoy et al., 2019). The mean angular rotation values were generally similar across all of the new elastomer formulation rings and in line with values recorded for the 25 mg DPV ring and a commercially available ring (Femring®), as well as previously published values for these rings (Boyd et al., 2019). The percentage recovery values after 28-day static compression were in the 80–90% range for formulation IV and VI active rings, compared to 90–100% for the equivalent blank rings and all other comparators. There is likely no practical significance associated with this reduction. Results from the 1000-cycle compression and elongation at break testing were in line with expectations, with the new formulations showing measured values between those for Femring® and the 25 mg DPV ring.



**Fig. 4.** Increase in the storage modulus of the blank and active new silicone formulations and a commercial comparator under oscillatory stress at 15 and 30 °C over 6 h; **A** formulation IV, **B** formulation V, **C** formulation VI, **D** commercial comparator (CC). In the legends, A refers to active, and B to blank formulations.

**Table 5**

Summary of the extent of silicone curing (% cure) using storage modulus values obtained after 1, 3 and 6 h under oscillatory stress at 15 or 30 °C compared with storage modulus values representing full cure. A refers to active, and B to blank formulations.

Silicone formulation	% cure at 1 h		% cure at 3 h		% cure at 6 h	
	15 °C	30 °C	15 °C	30 °C	15 °C	30 °C
IV B	19	18	24	25	29	31
IV A	26	31	32	44	38	74
V B	12	13	17	19	20	44
V A	14	17	18	27	22	89
VI B	17	19	23	30	28	81
VI A	17	20	23	34	27	110
Commercial comparator B	0	0	0	17	0	69
Commercial comparator A	0	0	0	21	1	71

**Table 6**

Manufacturing and rheological information relating to batch manufacture of blank and active vaginal rings using lead candidate silicone elastomer formulations IV, V and VI.

Silicone formulation <sup>a</sup>	Batch size (g)	Manufacturing run time (min)	G' of T <sub>4</sub> /last available sample (Pa) <sup>b</sup>	% Cure <sup>c</sup>	Active mix status at end of run	Comments
IV B	400	<120	228,000	15.6	Workable	No issues
V B	400	<120	140,000	8.3	Workable	No issues
VI B	400	<120	224,000	15.7	Workable	No issues
IV A	200	<50	327,000	22.7	Not workable	Refill time 60 to >95 s <sup>e</sup>
V A	200	<50	175,000	9.9	Workable <sup>d</sup>	Refill time 49 to 60 s
VI A	200	<50	275,000	14.9	Borderline	Refill time 69 to >95 s <sup>e</sup>

<sup>a</sup> A – active, B – blank formulations.

<sup>b</sup> Calculated as the mean of the storage modulus values obtained under oscillatory rheometry at 50 Pa stress and a frequency of 10 Hz over 5 min (typically 3 values).

<sup>c</sup> Calculated as a percentage of the measured maximum G' value representing full cure.

<sup>d</sup> The active mix was in the workable range for 115 min. <sup>e</sup> Automatic refill incomplete after at least some injections, further manual refill required.

Overall, the mechanical testing data reflect the formulation changes (Table 1) introduced to improve the mechanical properties of the elastomer and reduce LNG binding. Formulation V demonstrated the optimal combination of mechanical properties and manufacturability for a vaginal ring containing DPV and LNG and was selected for further investigation.

#### 3.4. Prototype DPV/LNG rings manufactured using formulation V

Prototype vaginal rings containing 200 mg DPV combined with different LNG loadings (80, 160, 240 or 320 mg) were manufactured using custom silicone elastomer formulation V. Rings were assessed for drug content and mechanical performance. The results of mechanical testing (Table 9) showed good consistency with values obtained in the screening experiments (Table 7). In particular, the mean Shore M value was very close to the target value of 60, and all rings displayed complete recovery after 1000 cycles of compression. Measured DPV content values were consistently close to 100% of the nominal ring loading

**Table 7**

Summary of the mechanical testing results (mean  $\pm$  standard deviation) for blank and active rings with data for the 25 mg DPV ring and a commercially available ring (Femring®) included for comparison ( $n = 6$  rings per formulation). A – active, B – blank.

Formulation	Mean Shore M $\pm$ SD	Mean angular rotation ( $^{\circ}$ ) $\pm$ SD	% Recovery original OD post 28-day static compression	% Recovery original OD post 1000-cycle compression	Mean maximum load at maximum extension (N)	Mean tensile extension at maximum load (mm)	Mean elongation at break (%)
IV B	57.7 $\pm$ 0.7	71 $\pm$ 1	90–100	100	314 $\pm$ 66	167 $\pm$ 29	402 $\pm$ 70
V B	62.2 $\pm$ 0.2	74 $\pm$ 1	90–100	100	582 $\pm$ 17	197 $\pm$ 6	478 $\pm$ 14
VI B	59.4 $\pm$ 0.6	71 $\pm$ 2	90–100	100	438 $\pm$ 14	216 $\pm$ 7	523 $\pm$ 16
IV A	52.4 $\pm$ 0.7	71 $\pm$ 1	80–90	100	334 $\pm$ 8	239 $\pm$ 7	580 $\pm$ 16
V A	60.3 $\pm$ 0.2	74 $\pm$ 1	90–100	100	404 $\pm$ 17	167 $\pm$ 6	405 $\pm$ 15
VI A	49.1 $\pm$ 0.3	66 $\pm$ 1	80–90	100	396 $\pm$ 11	216 $\pm$ 7	523 $\pm$ 16
Femring®	59.8 $\pm$ 0.5	69 $\pm$ 3	90–100	90–100	283 $\pm$ 33	109 $\pm$ 11	267 $\pm$ 20
25 mg DPV ring	ND	63 $\pm$ 2	90–100	100	721 $\pm$ 50	307 $\pm$ 21	749 $\pm$ 52

**Table 8**

Summary (mean  $\pm$  standard deviation) drug content assay data for the DPV-LNG rings, expressed as a percentage of the target loading ( $n = 6$ ).

Silicone elastomer formulation <sup>a</sup>	DPV target loading % recovery <sup>b</sup>	LNG target loading % recovery <sup>b</sup>
IV A	101.3 $\pm$ 2.7	102.7 $\pm$ 2.4
V A	101.3 $\pm$ 1.5	100.7 $\pm$ 3.4
VI A	101.5 $\pm$ 2.3	100.3 $\pm$ 2.5

<sup>a</sup> A – active.

<sup>b</sup> Target loading % recovery – the amount calculated relative to an expected ring content of 200 mg DPV, 320 mg LNG.

**Table 9**

Properties of prototype rings having different DPV/LNG loadings and prepared using formulation V. All values reported as means  $\pm$  standard deviations.

Target DPV + LNG loading per ring (mg)	Mean DPV recovery (%; $n = 3$ )	Mean LNG recovery (%; $n = 3$ )	Mean Shore M ( $n = 6$ )	Mean twist during compression ( $^{\circ}$ ; $n = 6$ )	Ring outer diameter recovery post 1000-cycle compression (%; $n = 3$ )
200 + 80	98.4 $\pm$ 0.6	94.2 $\pm$ 2.5	60.5 $\pm$ 0.1	69.3 $\pm$ 0.8	100
200 + 160	99.8 $\pm$ 0.7	96.7 $\pm$ 1.5	60.5 $\pm$ 0.4	69.8 $\pm$ 1.2	100
200 + 240	101.4 $\pm$ 1.0	99.7 $\pm$ 1.4	59.9 $\pm$ 0.7	69.3 $\pm$ 1.0	100
200 + 320	101.2 $\pm$ 0.4	99.1 $\pm$ 1.6	62.5 $\pm$ 0.5	68.8 $\pm$ 1.2	100

(Table 9). Measured LNG values were lower for rings having a lower nominal LNG loading (94% for the 200 mg DPV + 80 mg LNG ring compared to 99% for the 200 mg DPV + 320 mg LNG ring), a finding consistent with previous data (Dallal Bashi et al., 2019; Murphy et al., 2016).

#### 4. Conclusions

Use of custom grades of addition-cure silicone elastomer materials was useful in achieving practical manufacture, optimal mechanical properties and reduced tendency of LNG to chemically bind with the silicone elastomer. The mechanical properties of the cured rings were improved through addition of silica filler and increasing the concentration of crosslinker to give rings with mechanical properties similar to other commercially available products. This should make the ring more comfortable to use and less likely to be accidentally expelled. There may be substantial scope for further elastomer development to tailor the properties of the formed silicone to the requirements of the formulation.

#### Author contribution to manuscript

All authors contributed to the design of experiments and analysis of data. DJM, YDB and CFM conducted the experimental work. The manuscript was drafted by DJM, YDB and RKM, with input from the other authors. All authors approved submission of the manuscript.

#### Declaration of Competing Interest

Leeanne Brown, Matthew Kihara, François Martin and Nicole McMullen are employees of Elkem Silicones. The other authors declare no competing financial or personal interest.

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