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Manufacturing and characterization of long-acting levonorgestrel intrauterine systems

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Abstract

Mirena® is long-acting (5 years) contraceptive intrauterine device. It is composed of a hollow cylindrical drug reservoir (containing Levonorgestrel and polydimethylsiloxane), which is covered with a release rate controlling silicone membrane. This structure presents a manufacturing challenge and to date, there have been no literature reports on the manufacturing, product design and quality evaluation of these hollow cylindrical intrauterine devices. It is vital to develop a reproducible and robust manufacturing process for these long-acting intrauterine devices or systems to obtain an understanding the *in vitro* and *in vivo* performance of such drug-device combinations. In this study, a twin-syringe method with a customized mold was developed to manufacture hollow cylindrical polydimethylsiloxane (PDMS)-based levonorgestrel intrauterine systems (LNG-IUSs). Different mold materials, curing temperatures and times were screened to fabricate PDMS-drug reservoirs with good quality characteristics (easy demolding, good appearance and appropriate physicochemical characteristics). The prepared PDMS-drug reservoirs were covered with the release rate controlling membrane to fabricate the LNG-IUSs.

Physicochemical characterization (drug content and content uniformity, powder X-Ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Fourier-transform infrared spectroscopy (FTIR) of the PDMS-drug reservoirs with different drug loadings (10%, 25% and 50% w/w) was conducted. Real-time *in vitro* drug release testing of LNG-IUSs with different drug loading was performed in normal saline (0.9% w/v NaCl) at 37 °C using a water bath shaker rotating at 100 rpm. The prepared PDMS-drug reservoirs demonstrated good and reproducible quality characteristics including appearance (smooth surfaces), targeted drug loading and good drug content uniformity in the PDMS matrix. The PXRD showed that the crystallinity of the API was maintained inside the PDMS matrix. DSC, TGA and FTIR confirmed the structure of the drug and the PDMS, indicating no interaction between the drug and the PDMS matrix in the prepared LNG-IUSs. Real-time *in vitro* drug release from the LNG-IUSs with different drug loadings showed zero-order release kinetics, and the drug release rate (based on daily release percentage) was inversely proportional to the drug loading.

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Keywords

Intrauterine device; Intrauterine systems; Polydimethylsiloxane; Levonorgestrel; Mirena®; Manufacturing; *In vitro* drug release

1. Introduction

Unintended or unplanned pregnancies can have a serious impact on numerous social, economic, and cultural aspects of modern life (Brown and Eisenberg, 1995). In the United States, the unintended pregnancy rate was 45% of all pregnancies in 2011, which is a slight decline from 51% in 2008 (Finer and Zolna, 2016). There are several effective contraceptive methods suggested by the World Health Organization (WHO) (World Health Organization, 2006) including: one-time procedures (implants, intrauterine devices or systems (IUDs or IUSs), female sterilization or vasectomy); injectables that must be repeated every one to three months; and birth control pills, that are taken daily. Among all these methods, the Centers for Disease Control and Prevention (CDC) has reported that long-acting reversible contraception (LARC) including IUDs or IUSs and implants are highly effective (less than 1% failure rate (Winner et al., 2012) because they do not depend on regular compliance from the users. In addition, the LARC methods are appropriate for most women, including adolescents and nulliparous women (Gavin, 2014). Currently there are six LARC products approved by the U.S. FDA (Table 1), one hormonal implant and five IUD/IUSs (a copper IUD and four levonorgestrel (LNG) IUSs). The levonorgestrel IUSs (LNG-IUSs) have been more widely used and have higher continuation rates than the copper T380A IUD since the copper T380A IUD has higher bleeding and pain risk (Rivera et al., 1999; Lyus et al., 2010).

The LNG-IUSs deliver a small amount of progesterone locally over periods of three to five years. Mirena® is the first FDA approved (in 2000) LNG-IUS and the number one prescribed IUS in the US. The Mirena® drug reservoir is made up of a mixture of 52 mg LNG and polydimethylsiloxane (PDMS) polymer covered by a release rate controlling silicone membrane. The hollow cylindrical reservoir is mounted on the stem of a T-shaped polyethylene frame (32 mm × 32 mm). Mirena® has an average daily release of 20 µg of LNG over the first year (Nelson, 2017) and the daily release declines slightly over time. However, the release of LNG is maintained at about 10 µg per day (50% rate decrease) at the end of 5 years (Lähteenmäki et al., 2000; Mirena.com, 2017). LNG (Fig. 1) is a potent, synthetic hormonal medication used in a number of birth control methods including oral tablets (e.g. Plan B one-step) for emergency contraception, transdermal implants (e.g. Norplant® or Jadelle®, discontinued on the US market) and IUSs (Table 1) for long-acting contraception. LNG has poor water solubility with a LogP of 3.8 (Drugbank, 2018). Polydimethylsiloxane (PDMS) $[(CH_3)_2SiO]_n$ is the simplest silicone, a polymer having a repeat unit of $-Si(CH_3)_2-O-$. PDMS has been widely used as a drug carrier in different drug delivery medical devices (Mashak and Rahimi, 2009) (implants (Abbasi et al. (2006)); intravaginal rings (Malcolm et al., 2003; Malcolm et al., 2003), transdermal devices (Aliyar and Schalaus, 2015), etc.) for controlled drug delivery due to its good biocompatibility and non-biodegradability (Andreopoulos and Plytaria, 1998).

These LNG-IUSs contain substantial amounts of LNG and consequently, dose dumping or unanticipated changes in the *in vivo* release characteristics may potentially lead to toxicity. Therefore, the manufacturing process of LNG-IUSs must be carefully designed and controlled to ensure product quality. To date, there have been no previous reports on the manufacturing, physicochemical characterization, and/or *in vitro* drug release testing of LNG-IUSs such as Mirena®, other than the Mirena® patent. This may be due, at least in part, to the challenges associated with the development of such formulations: 1) the long-term investment in the drug development cycle of Mirena® (approximately 25 years) (Friend, 2016) due to the long-acting nature of this product (up to 5 years); 2) the high cost associated with the long research and development time associated with such long-acting products; and, 3) the lack of regulatory guidelines for performance evaluation of this type of product.

The first patent of Mirena® came off patent in 2015 (Wired.com, 2017; Emedtv.com, 2017), and, therefore, it is likely that companies will be investigating the possibility of introducing generic equivalents. For this, it is important to have a good understanding of the formulation, potential processing methods, as well as appropriate evaluation approaches. The first step is to develop an appropriate and reproducible manufacturing process that achieves the expected drug loading.

Here, a simple and reproducible manufacturing process for LNG-IUSs is reported. A twin-syringe system was designed and utilized to fabricate hollow cylindrical LNG drug reservoirs using silicone rubber and LNG. The LNG drug reservoirs were then covered with release controlling silicone membranes previously swollen in organic solvent. Physicochemical characterization (drug loading and uniformity, PXRD, DSC/TGA, FTIR) of the LNG drug reservoirs was performed. In addition, real-time *in vitro* drug release over a period of 300 days was performed on the LNG-IUSs to understand the release kinetics. Correlation between the release rate and drug loading of the prepared LNG-IUSs was also investigated.

2. Materials and methods

2.1. Materials

Levonorgestrel with a particle size of 16 µm was purchased from Tecoland Corporation (Irvine, CA, USA). Liquid silicone rubber (MED-4840 Part A and Part B) was purchased from NuSil™ (Carpinteria, CA, USA). Sodium chloride and sodium dodecyl sulfate (SDS) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Unless otherwise specified, all materials were of analytical grade.

2.2. Preparation of levonorgestrel intrauterine systems

2.2.1. Material screening for mold fabrication—Different commonly used materials (stainless steel, Teflon coated stainless steel, polycarbonate, glass, black 3-D printing resin and polyethylene) were screened for their application as molds for reservoir fabrication. The PDMS base, curing agent and levonorgestrel (50% drug loading) were mixed and placed in

contact with these materials to allow curing. The ease of demolding and completion of curing were determined to evaluate the material compatibility with the fabrication process.

2.2.2. Preparation of levonorgestrel intrauterine reservoir—The LNG reservoir was prepared using a customized designed extrusion device composed of one polycarbonate mold (3.18 mm I.D. × 9.53 mm O.D. × 2.80 mm height), two 3-ml plastic syringes (9.53 mm I.D.) with the needle part removed, a metal rod (1.50 mm in diameter) inserted into one piece of the centering device A (1.50 mm I.D. × O.D. 9.53 mm × 8.00 mm height, and hole depth: 6.00 mm) and another centering device B (same size as device A except with a hole depth of 8.00 mm) (Fig. 2). Before preparation, all the devices and items were cleaned with ethanol. To fit in the mold, the total weight of all components was 300 mg for one batch. The drug reservoir was prepared using liquid silicone rubber (MED 4840 from NuSil™, Part A:Part B = 1:1) and a certain amount of LNG according to the drug loading required. For example, for the preparation of a reservoir with 50% drug loading, 75 mg of Part A, 75 mg of Part B and 150 mg of LNG were added into one syringe and mixed inside the syringe with a steel tool. After homogeneous blending, the matrix was left under vacuum for 5 h to remove any air bubbles generated during the mixing process. The polycarbonate mold was then fitted onto the ends of two syringes. A metal rod with a centering device A was pushed into one end of the syringe until it reached the mold followed by insertion of the plunger at the same side. The mixture of the polymer and LNG was transferred to the other end of the syringe followed by insertion of the centering device B. The steel rod of the centering device A must be inserted into the cavity of centering device B to ensure the system is completely centered. Another plunger was then inserted into the barrel of the syringe and used to extrude the polymer and LNG mixture into the mold to form the tubular shaped drug reservoir. This step must be conducted rapidly with sufficient force to allow the formation of smooth cylinders. The two plungers at each end of the syringes were then removed prior to the curing step at 80 °C for 20 h. The cured reservoir was then peeled off the mold and the steel rod was removed for further fabrication.

2.2.3. Preparation of the levonorgestrel intrauterine systems—The resultant LNG intrauterine reservoirs were cut into 100 mg pieces and enveloped onto plastic rods (diameter: 1.57 mm). Silastic® silicone tubes (Dow Corning, 1.57 mm I.D. × 2.41 mm O.D.) were cut into 24 mm-long pieces. The tube segments were soaked in hexane at room temperature for 5 min to swell. The swollen tubes were then coated onto the drug reservoirs in a symmetrical way. The coated LNG intrauterine units were placed into a desiccator under vacuum at room temperature overnight to remove the residual hexane solvent. The resultant intrauterine systems are shown in Fig. 1E.

2.3. HPLC analytical methods

The concentration of LNG was determined using an Agilent 1290 Infinity HPLC system with a UV detector set at 240 nm. The mobile phase was a mixture of acetonitrile and water (60/40, v/v). A Synergi C18 column (250 × 4.6 mm, 4 μm, Phenomenex®) was used with a flow rate at 1.5ml/min. The column temperature was set at 30 °C and the injection volume was 50 μl. The chromatographs were analyzed using Agilent OpenLAB CDS ChemStation.

2.4. Drug loading and content uniformity of the reservoir

The drug loading of the prepared reservoirs was determined using a tetrahydrofuran (THF) extraction method. In brief, the drug reservoirs were cut into small pieces (with a weight of approximately 8 mg) and each piece was soaked in a 25-ml volumetric flask with THF. The flasks were kept sealed and left at room temperature for 2 days. An appropriate volume of THF was added to the flasks to achieve a total volume of 25 ml. The samples were vortexed and mixed well. The resultant samples were diluted with the mobile phase (acetonitrile/water = 60/40 (v/v)) prior to being injected into the HPLC for analysis. Three batches of reservoirs with different drug loading (10%, 25% and 50% w/w) were tested. For each batch, three samples were cut from different regions of the reservoirs and tested for drug loading and content uniformity.

2.5. Powder X-ray diffraction (PXRD)

PXRD (wide-angle X-ray scattering) was utilized to test the crystallinity of the drug particles in the prepared intrauterine drug reservoirs. X-ray diffraction patterns were obtained using an X-ray diffractometer (Model D2 phaser, Bruker AXS Inc., Madison, WI) with Cu- α radiation, a voltage of 30 kV, and a current of 10 mA. All the scans were performed from 5° to 45° at 2 θ ranges with a step increment of 0.02°/step and 0.2 s/step.

2.6. Thermal analysis

2.6.1. Differential scanning calorimetry (DSC)—DSC of the drug reservoirs was performed using a TA Q1000 and TA Q20 calorimeter (TA instruments, New Castle, DE, USA) equipped with a refrigerated cooling accessory. The instrument was calibrated for enthalpy and heat capacity using indium and sapphire, respectively. To examine the API thermal events, the samples were sealed in non-hermetic pans and heated to 250 °C at a heating rate of 10 °C/min. To investigate the thermal events of the PDMS matrix, the samples were equilibrated at – 90 °C and then heated up at 10 °C/min to 50 °C. Nitrogen gas was used for purging at a flow rate of 50 ml/min. Data were analyzed using TA universal analysis software.

2.6.2. Thermogravimetric analysis (TGA)—TA Q500 (TA instruments, New Castle, DE, USA) was used to analyze the thermal changes along with temperature. The samples were loaded to the platinum pan and heated to 600 °C at a ramp rate of 20 °C/min.

2.7. Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy was performed using a Nicolet FTIR (iS5 FTIR, Thermo Scientific) spectrometer with an attenuated total reflectance (ATR) accessory. The samples were placed on the crystal window (Germanium) and compressed lightly using the pressure clamp. Spectra were recorded over a range of 400–4000 cm^{-1} with a resolution of 4 cm^{-1} , for 128 parallel scans. Data analysis was performed using Omnic® 6.0a software (Thermo Nicolet Corporation).

2.8. Real-time *in vitro* drug release

Real-time *in vitro* release testing for the LNG-IUSs (with the outer release controlling membrane) was performed using a water bath shaker at 37 °C and a rotation speed of 100 rpm. Two small steel clips were clamped on the plastic rod of the IUSs to make sure the IUSs sink to the bottom of the glass bottles (Fig. 3). Normal saline (0.9% sodium chloride) was selected as the release testing media. The volume of the release media and the sampling procedures were designed to ensure sink conditions. The volume of real-time *in vitro* drug release testing was 100 ml, 250 ml and 300 ml for IUSs with drug loadings of 10%, 25% and 50%, respectively. At Day 3, 1 ml of the samples was with-drawn and 1 ml of fresh media was replenished. At Day 7, 1 ml of the samples was withdrawn and the rest of the media was emptied and replenished with the same volume of release media. The samples were withdrawn weekly thereafter. All release testing was performed in triplicate ($n=3$).

2.9. Statistical analysis

The linear regression and fitting were performed using OriginPro 2017 software (OriginLab Corporation).

3. Results

3.1. Material screening of mold fabrication

In the preliminary trials of the drug reservoir preparation process, incomplete curing of the PDMS and difficult demolding were encountered. To select proper molds for drug reservoir preparation, different materials were screened (Table 2). The Black 3-D printing resin slowed down the curing process significantly. This is possibly due to the presence of residual amine groups in this material which can slow down PDMS cross linking. Stainless steel (with or without Teflon coating) and glass were not suitable as the cured reservoirs stuck to them creating difficulties during demolding. Polycarbonate and polyethylene proved to be the most suitable mold materials for reservoir fabrication. Based on these results, polycarbonate was utilized as the mold material to prepare hollow cylindrical drug reservoirs.

3.2. Drug loading and content uniformity

Drug loading and content uniformity of the prepared LNG reservoirs are critical to drug product quality. To test the uniformity, samples cut from different regions of the prepared drug reservoirs were used (four batches were tested). All the formulations showed good uniformity ($RSD < 3\%$) and the drug loading tested using the THF extraction method was close to the target drug loading of the prepared drug reservoirs (Fig. 4).

3.3. PXRD patterns

To determine the crystalline state of LNG in the poly-dimethylsiloxane (PDMS) matrix, the PXRD patterns of the original drug and the drug reservoirs were compared (Fig. 5). The PXRD pattern of the prepared drug reservoirs was the same as the starting API, indicating no polymorphic form change during the manufacturing process. Compared with the pure API, the intensity of PXRD of the prepared LNG reservoirs was weaker, due to the large

amount of amorphous PDMS matrix in the reservoirs. In addition, the intensity of the PXRD peak was proportional to the drug loading of the reservoirs. As the drug loading of the prepared LNG reservoirs decreased from 50% to 10% (w/w), the intensity of the PXRD characteristic peaks decreased correspondingly.

3.4. Thermal analysis

3.4.1. DSC—Following the preparation of the drug reservoirs using the liquid silicone rubber, the thermal properties of the API in the matrix (Fig. 6A) and the matrix itself (Fig. 6B) were characterized using DSC. The PDMS based drug reservoirs with different drug loadings showed the same melting point ($\sim 240^{\circ}\text{C}$) as the pure API, indicating no polymorphic form change during the manufacturing process. In addition, the enthalpy of the API (139.80 J/g) and the drug reservoirs with different drug loading (70.94 J/g for 50% w/w drug loading, 29.50 J/g for 25% w/w drug loading and 6.29 J/g for 10% w/w drug loading) were linearly proportional to the amount of API in the system. Fig. 6B showed the melting point of the PDMS matrix in the drug reservoirs. When the PDMS drug reservoirs were cooled to -90°C , an exothermal peak at -80°C was observed (data not shown). The exothermal peak was the crystallization peak of the PDMS matrix. When heating from -90°C at $10^{\circ}\text{C}/\text{min}$, the melting peak (approximately -40°C) of the matrix was observed. The enthalpy of the matrix melting peak was linearly proportional to the amount of the PDMS polymer in the system. From the DSC profiling, no molecular interaction between the API and PDMS polymer was observed since both components showed their respective characteristics.

3.4.2. TGA—From the TGA profiles (Fig. 7), the API began to decompose at around 200°C and completely degraded at $\sim 350^{\circ}\text{C}$. LNG reservoirs with different drug loading at 350°C showed similar weight loss (%) to their drug loading, which is consistent with the drug loading results.

3.5. FTIR

The characteristic peaks of LNG are at 3300 cm^{-1} (O—H stretching) and 1652 cm^{-1} (C=O stretching). The characteristic peaks of the PDMS matrix are at 2962 cm^{-1} (C—H stretching), 1260 cm^{-1} (Si—CH₃ stretching), doublet peak (1072 cm^{-1} and 1007 cm^{-1}) (Si—O—Si stretching) and 785 cm^{-1} (Si—CH₃ wagging) (Fig. 8). The lower the drug loading, the API characteristic peaks become weaker; whereas the PDMS matrix peaks become stronger. The API and PDMS matrix in the LNG-IUSs with different drug loading showed their respective characteristic peaks and no obvious peak shift or widening was observed, indicating no molecular interaction between the API and the PDMS matrix.

3.6. Real-time *in vitro* drug release testing of the prepared LNG-IUSs

The real-time *in vitro* drug release testing over a period of 300 days for the prepared LNG-IUSs with different drug loading was performed using the water bath method. The release profiles (Fig. 9) of the LNG-IUSs with different drug loading showed similar release trends. Model fitting showed that release from the LNG-IUSs followed zero-order release kinetics with high R^2 values (> 0.9995) (Table 3). The small standard deviation (SD) implies a robust methodology and the reproducible quality of the prepared LNG-IUSs. To better understand

the release results, two release profiles (release amount vs. time (Fig. 9A) and release % vs. time (Fig. 9B)) and their modeling parameters were displayed separately. The daily drug release of the IUSs with 10%, 25% and 50% w/w drug loading were 6.57, 8.85 and 10.05 µg, respectively. The daily drug release percentage of the IUSs with 10%, 25% and 50% w/w drug loading were 0.07%, 0.04% and 0.02%, respectively.

4. Discussion

4.1. Manufacturing of LNG-IUSs

The challenges of manufacturing drug-device combination products using PDMS are dependent on the device shape, mold materials, drug properties (thermosensitive or reactivity), as well as drug loading.

One of the challenges for hollow cylindrical drug reservoir preparation, as reported here, is that the inner rod should be well-centered. The design of the centering device (A and B) is critical in the current study, allowing the metal rod to be exactly in the center. Compared to other non-hollow cylindrical devices, the current design is much more challenging.

The material used for mold construction may affect the demolding process and hence cause coarse or uneven device surfaces, leading to poor product quality such as irregular *in vitro* as well as *in vivo* drug release. Molds with different materials were investigated in the mold design and screening stage. However, molds prepared with polycarbonate resulted in the best product appearance due to the ease of curing and demolding.

Curing conditions (temperature and duration) are another critical factor in the manufacturing process. The vendors suggest operational temperature and time for curing silicone rubber, however, the recommended curing conditions may not be appropriate for the API (e.g., thermally liable drugs may become degraded after curing at high temperature). Some drug molecules may also react with the silicone rubber under the curing conditions, leading to incomplete curing, difficult demolding, and poor drug release behavior (e.g., the drug cannot be released completely or change in the release mechanism). The suggested curing conditions of the liquid silicone (Nusil™ MED-4840) used in the current study is 5min at 150 °C and then stabilized at room temperature for a minimum of 3 h (Nusil.com, 2014). Since the API, as well as the selected mold material (polycarbonate) and the syringes used to secure the mold cannot tolerate high temperature, the curing conditions were optimized at 20 h and 80 °C. In the pharmaceutical manufacturing process, lower operational temperature (e.g., less than 50 °C) may be preferred for other APIs that are physically (crystalline form changes) or chemically (degradation) unstable at high temperatures.

Lastly, the drug loading in the PDMS matrix may also affect the device manufacturing. In our preliminary screening process, it was observed that a lower curing temperature of 37 °C for 24 h, resulted in low drug loading (less than 30% w/w). Otherwise, the PDMS drug matrix cannot be cured as there will be insufficient amount of crosslinking agent for such low temperature. LNG reservoirs with different loading (between 10% and 50% w/w drug loading) were successfully manufactured under the optimized conditions (20 h at 80 °C) using the twin-syringe method.

4.2. Real-time release testing

In vitro drug release testing is the most important tool to monitor drug release under different conditions, to ensure robust and reliable drug product quality. For long-acting drug products such as Mirena®, drug release testing is much more challenging since drug release lasts for several years. In the current study, the release testing of the long-acting LNG-IUSs was performed using screw-capped bottles (to avoid release media evaporation) in a water bath shaker.

Robust release data from the LNG-IUSs with different drug loading over a 300-day period (close to one year) were obtained using this method. Constant daily drug release rates (zero-order release kinetics) for all of the LNG-IUSs with different drug loading were obtained. A plot of the reciprocal of the daily release rate (%) against the drug loading of the IUSs, yielded a straight line (Fig. 10), indicating the release rate (daily percentage) of the LNG-IUSs is inversely proportional to the drug loading. This result will be valuable in the design of LNG-IUSs since different target daily release rates can be obtained by adjusting the drug loading in the PDMS matrix.

5. Conclusions

For the first time, PDMS-based hollow cylindrical long-acting intrauterine systems (similar to Mirena®) with different drug loading (up to 50% w/w) were successfully manufactured using a well-designed twin-syringe mold system. Mold material, curing conditions (temperature and time) and drug loading have a great impact on the quality of the LNG drug reservoirs. Consequently, it is critical to comprehensively evaluate these three factors to ensure good drug product quality (appropriate appearance as well as reproducible drug content and content uniformity). No drug-PDMS molecular interaction was observed in any of the current characterization methods since the API and PDMS in all of the drug reservoirs showed their respective characteristic properties. Drug release from the LNG-IUSs showed zero-order release kinetics regardless of the drug loading. In addition, the daily drug release rate (as of percentage) is inversely proportional to the drug loading of the LNG-IUSs, which will be valuable in the design of PDMS-based LNG-IUSs with different targeted daily drug release rates.

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Abbreviations:

LNG	levonorgestrel
IUD	intrauterine device

IUS	intrauterine system
LNG-IUS	levonorgestrel intrauterine system
PDMS	polydimethylsiloxane
LARC	long-acting reversible contraception
PXRD	powder X-ray diffraction
DSC	differential scanning calorimetry
TGA	thermogravimetric analysis
FTIR	Fourier-transform infrared spectroscopy
DL	drug loading
CDC	centers for disease control and prevention

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Fig. 1.
The chemical structure of levonorgestrel.

Fig. 2. Pictorial demonstration of LNG-IUS manufacturing: A) devices used for preparation of IUS drug reservoirs; B) the processes of extrusion of PDMS polymer and LNG mixture to form the drug reservoirs; C) the resultant LNG drug reservoir with steel rod; D) 100 mg standard LNG reservoir with plastic rod; and E) LNG-IUS (with release controlling membrane).

Fig. 3.
Pictorial representation of LNG-IUS sample during *in vitro* drug release testing.

Fig. 4. The drug loading of reservoirs prepared with 10, 25 and 50% of LNG ($n = 3$) (The standard deviation is so small that the error bars are barely visible).

Fig. 5.
PXRD profiles of levonorgestrel and the prepared drug reservoirs.

Fig. 6. DSC thermal profiles of the prepared drug reservoirs: A) thermal event of the crystalline LNG; and B) thermal event of the PDMS matrix.

Fig. 7.
TGA profiles of LNG drug reservoirs with different drug loading.

Fig. 8.
FTIR profiles of the LNG drug reservoirs with different drug loading.

Fig. 9. Release profiles of LNG-IUSs with different drug loading: A) cumulative release amount against time; and B) release percentage against time ($n = 3$).

Fig. 10.
Linear regression profile of the reciprocal of daily release percentage against drug loading of the prepared LNG-IUSs.

IUDs and implants approved by the U.S. FDA (FDA, 2018; Mirena-us.com, 2018; Liletta.com, 2018).

Table 1

Active Ingredient	Proprietary Name	Dosage Form	Strength	Effective Duration	Applicant Holder	Year of Approval
Levonorgestrel	KYLEENA	IUD	19.5 MG	5 years	BAYER	2016
Levonorgestrel	LILETTA	IUD	52 MG	4 years	MEDICINES360	2015
Levonorgestrel	SKYLA	IUD	13.5 MG	3 years	BAYER	2013
Levonorgestrel	MIRENA	IUD	52 MG	5 years	BAYER	2000
Copper	PARAGARD T 380A	IUD	309 MG/COPPER	10 years	COOPERSURGICAL	1984
Etonogestrel	NEXPLANON®	Implant	68 MG/Implant	3 years	ORGANON	2011

Table 2

Material screening results for mold fabrication.

Mold material	Easy demolding	Curing completion
Stainless steel	no	yes
Teflon coated stainless steel	no	yes
Polycarbonate	yes	yes
Glass	no	yes
3-D printing resin (black color)	yes	no
Polyethylene	no	yes

Table 3

Parameters of zero-order fitting for the *in vitro* release profiles based on cumulative release amount and release percentage.

LNG-IUSs	Equation (Cumulative release amount)	Equation (Release %)	Adj. R ²
10% DL	$y = 6.57 \times -1.84$	$y = 0.07 \times -0.02$	0.9998
25% DL	$y = 8.85 \times +1.54$	$y = 0.04 \times +0.01$	0.9995
50% DL	$y = 10.05 \times +13.98$	$y = 0.02 \times +0.03$	0.9997