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In Vitro Release Testing of Long-Acting Levonorgestrel Intrauterine System

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PURPOSE

- During the past few decades, long-acting drug products (such as intrauterine devices/systems and subdermal implants) have been successfully used to deliver contraceptive steroids in a controlled manner over periods of years.
- Among these drug products, the Levonorgestrel intrauterine system (IUS) is considered a highly effective and reversible contraception option and is preferred by women of all ages.
- Currently, the manufacturing processes as well as the release testing methods of IUS are not well established and understood. It is crucial to develop appropriate *in vitro* release testing methods to ensure product quality as well as streamline the regulatory review process. For long-acting (five years) IUS, a reliable accelerated *in vitro* release testing method can reduce time and cost to a great extent.
- An accelerate release method could be very useful for QC purpose provided discriminatory powder has been demonstrated. An accelerated release method could significantly shorten the development time only if the accelerated release profile can directly correlate with the real time profile.
- The purposes of the current study are to: *1*) reproducible manufacturing process of intrauterine drug reservoirs; and *2*) develop real-time and accelerated drug release of the Levonorgestrel intrauterine system.

MATERIALS & METHOD

❑ Materials

The liquid silicone rubber MED 4840 (polydimethylsiloxane, PDMS) was purchased from Nusil®. Levonorgestrel of different particle size was purchased from Tecoland Corporation. The syringes were purchased from Fisher. Unless otherwise specified, all materials were of analytical grade.

❑ Methods

- Drug reservoir preparation: a well-designed in-house mold method was utilized to prepare reproducible batches of polydimethylsiloxane-based Levonorgestrel IUS (**Fiugre 1**). The LNG API (150 mg) and liquid silicone rubber (75 mg Part A and 75 mg Part B) were well mixed in one barrel of the syringe followed by application of vacuum at room temperature to remove bubbles generated during the mixing process. The mixture was then injected into the mold using a twin syringe system. The mold with the mixture was then cured at 80°C for 20 hours.

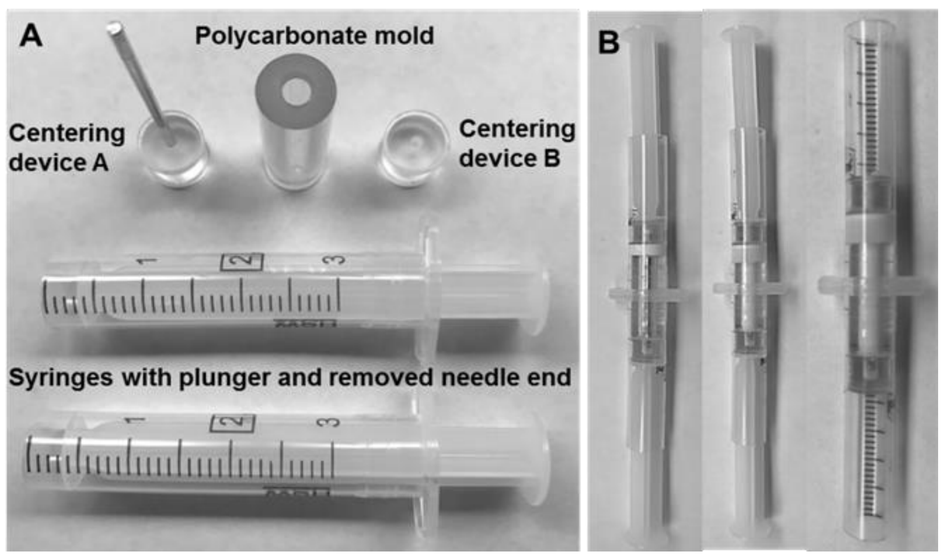

Figure 1. Pictorial demonstration of LNG IUS reservoir and unit preparation: **A**) devices used for preparation of IUS drug reservoirs; and **B**) the processes of extrusion of the PDMS polymer and LNG mixture to form the IUS reservoir.

- IUS unit preparation: the drug reservoir obtained as described above was cut into 100 mg pieces for fabrication of the IUS units. A Dow Corning silicone tube was used to coat the drug reservoirs by swelling in hexane.
- *In vitro* release testing of the LNG drug reservoir and the LNG IUS unit were performed using a shaker bath. Real-time release testing was conducted in 300 ml of saline (0.9% sodium chloride) at 37°C in a screw-capped bottle. Accelerated release was carried out in two conditions: *1)* 50 ml of 20% ethanol in pH 7.4 PBS with 0.25% of sodium dodecyl sulfate (SDS) at 45°C; and *2)* 100 ml of 20% tert-butanol (TBA) in pH 7.4 PBS with 0.25% SDS at 45°C. Following each sample withdrawal, the release media was drained and replenished with the same volume of fresh media to maintain sink conditions.

RESULTS

❑ Reproducible and good quality LNG-IUS units were manufactured using the in house designed molds and preparation methods (curing time and temperature) (**Figure 2**).

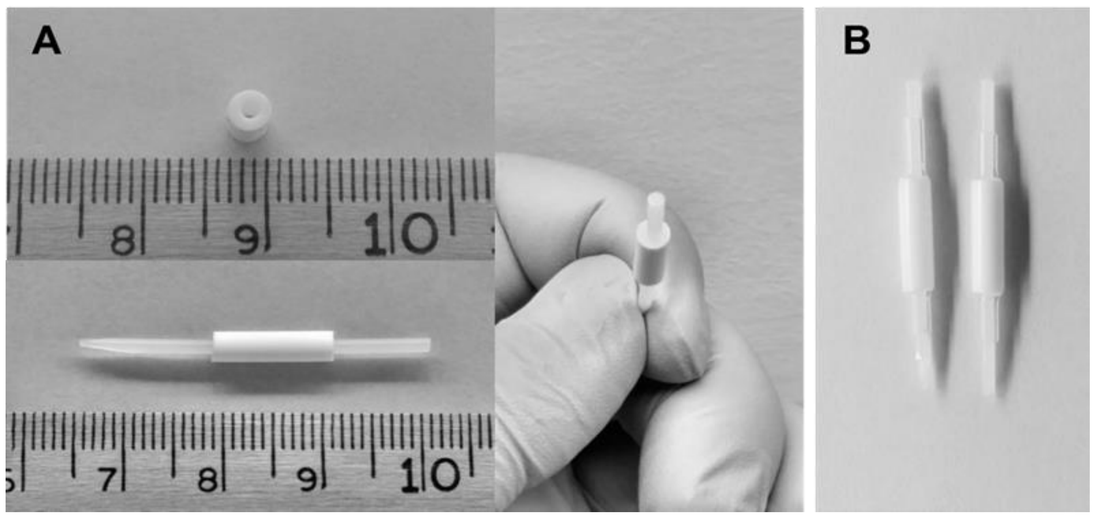

Figure 2. Images of **A**) the PDMS based Levonorgestrel intrauterine drug reservoir and **B**) the final IUS unit (with release rate controlling membrane).

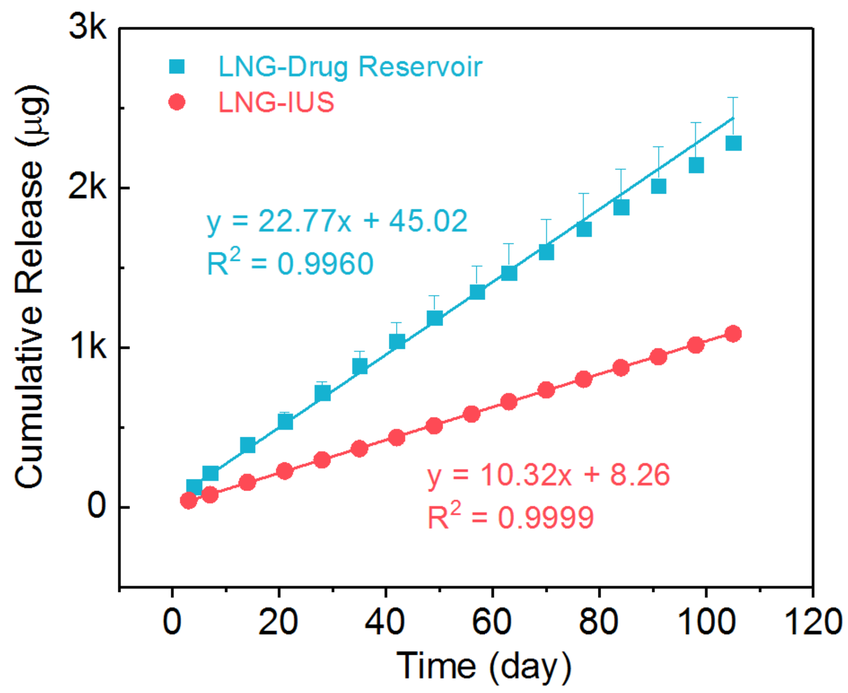

Figure 3. Cumulative drug release from LNG drug reservoirs and LNG-IUS units (with outer membrane) (*n*=3)

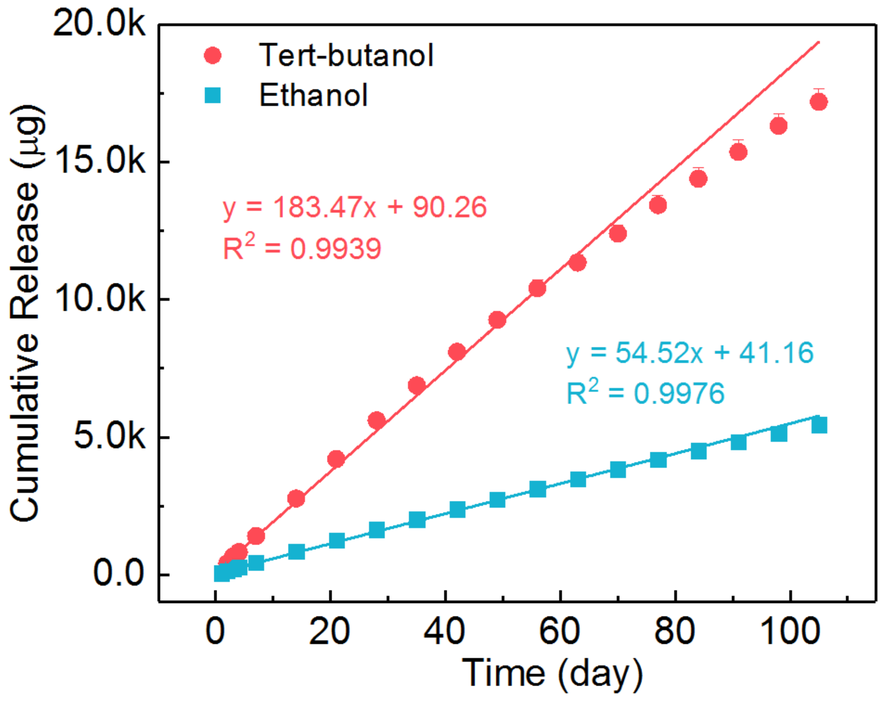

Figure 4. Accelerated drug release of LNG-IUS in 20% v/v organic solvents (Ethanol or Tert-butanol) and 80% v/v pH7.4 PBS with 0.25% w/v of SDS. (*n*=3)

CONCLUSIONS

❑ The in-house designed mold and manufacturing method rendered reproducible IUS units with smooth surfaces. The outer membrane coated onto the drug reservoirs significantly reduces the drug release rate. Addition of organic solvent with an increase of temperature can accelerate the drug release to as high as 20 fold, which would tremendously reduce development time for long-acting IUSs. The longer chain alcohol, tert-butanol, has a greater capability to accelerated drug release from the IUSs compared to ethanol, which may be due to the higher swellability of PDMS in tert-butanol.

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