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Source Variation of Outer Membranes on Drug Release from Intrauterine Systems

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PURPOSE

- Performance testing of long-acting (*e.g.*, 3-5 years) levonorgestrel (LNG) intrauterine systems (IUSs) such as Mirena® is challenging due to their complex formulation, local acting, and long duration of drug release.
- Currently all of the LNG-IUSs consist of a T-shaped polyethylene frame (T-body) with a steroid reservoir which is made of a mixture of LNG and polydimethyl-siloxane (PDMS) and covered by a PDMS-based outer membrane (release rate-controlling membrane).
- It is critical to understand the physicochemical properties of the outer membrane and their impact on the drug release characteristics. In this part of the study, PDMS membranes from different sources were evaluated.

MATERIALS AND METHODS

- **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.
- **METHODS**
  - PDMS-based cylindrical LNG-IUS drug reservoirs with 50% w/w LNG were prepared using a mold and were cured at 80°C for 20 hours. The cured drug reservoirs were cut to form pieces that weighed 100 mg.
  - Five PDMS outer membranes (A, B, C, D, and E) with the same dimensions, but from different sources, were swollen in hexane, and then pulled over the drug reservoirs.
  - Accelerated *in vitro* drug release testing of the prepared LNG-IUSs was performed at 45°C in a hydro-alcoholic media (containing 20% v/v tert-butanol (TBA), 80% v/v of pH 7.4 PBS and 0.25% w/v SDS. The *in vitro* release testing was performed using a water shaker bath with a rotation speed of 100 rpm.
  - The sampling plan was as follows: During the first 7-day, 1-mL sample was withdrawn on Days 1, 2, 3, 4 and 7, and replenished with fresh media. After that, all the media in the bottles were drained and replenished with fresh media. Thereafter samples were withdrawn weekly and all the media in the bottles were drained and replenished with fresh media following sampling.
  - The five outer membranes were characterized using a texture analyzer, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), energy dispersive X-Ray spectroscopy (EDS) and Fourier-transform infrared spectroscopy (FTIR) with attenuated total reflection (ATR).

RESULTS

- The LNG-IUSs prepared using different outer membranes showed the same release kinetics (zero-order), but different release rates with the following rank order: IUS-B>IUS-C>IUS-A≈IUS-D>IUS-E.

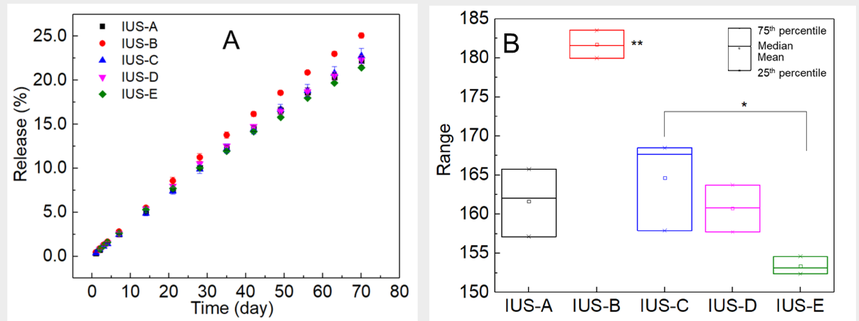


Fig.1. A) Release profiles of LNG-IUSs prepared using outer membranes from different sources under accelerated release conditions; and **B)** Box chart (25th percentile, mean, median and 75th percentile) of the release rate (µg/day) of the LNG-IUSs prepared using outer membranes from different sources. (The data are presented in mean ± SD, *n*=3).

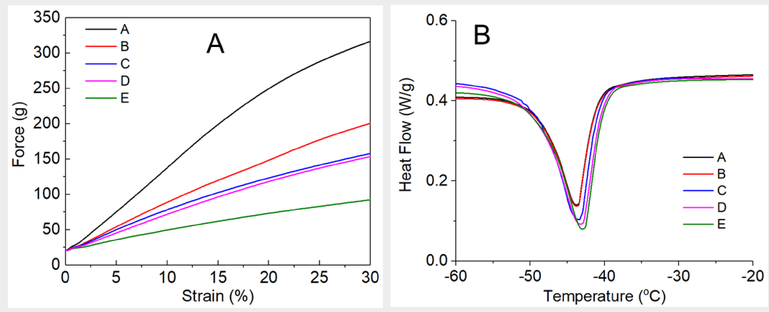
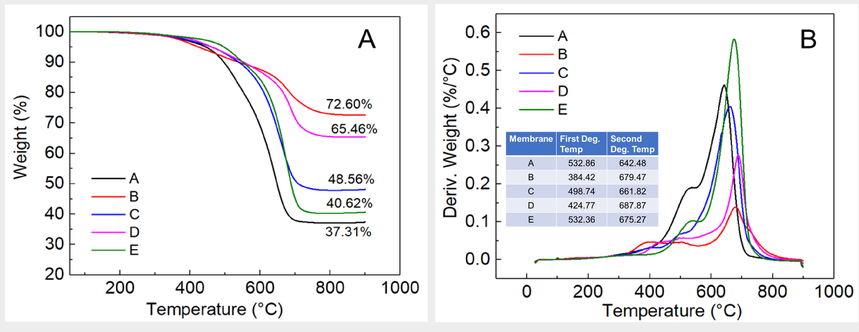


Fig.2. A) Mechanical strength; and **B)** DSC profiles of the outer membrane from different sources.



Membrane	First Deg. Temp	Second Deg. Temp
A	532.86	642.48
B	384.42	679.47
C	498.74	661.82
D	424.77	687.87
E	532.36	675.27

Fig.3. A) Thermogravimetric profiles; and **B)** Derivative of the TG profiles for the outer membrane from different sources.

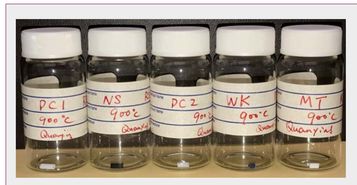


Fig.4. Pictorial images of the outer membrane from different sources following the TGA.

Table 1. Oxygen/silicon mass and molar ratio following TGA using EDS.

Membrane	O/Si (Conc.)	O/Si (Molar)
A	1.26	2.21
B	1.65	2.89
C	1.38	2.42
D	1.80	3.15
E	1.63	2.85

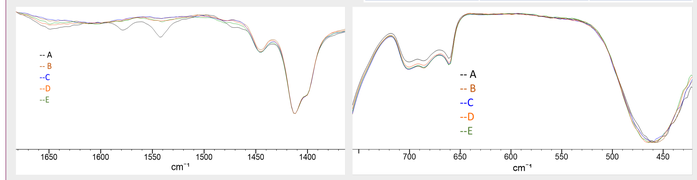


Fig.5. FTIR-ATR profiles of the outer membranes from different sources.

CONCLUSIONS

- Using outer membranes from different sources did not affect the release mechanisms, but had an impact on the drug release rates from LNG-IUSs.
- The outer membranes from different sources had different physicochemical properties (mechanical and thermal behavior, as well as elemental analysis), which may be responsible for the differences in drug release rates of LNG-IUSs.
- Therefore, selection of outer membranes for the manufacturing of LNG-IUSs should be carefully considered.

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