# Revolutionizing Women's Health by Enabling the Rational Development of Long-Acting Contraceptive Levonorgestrel Intrauterine Systems

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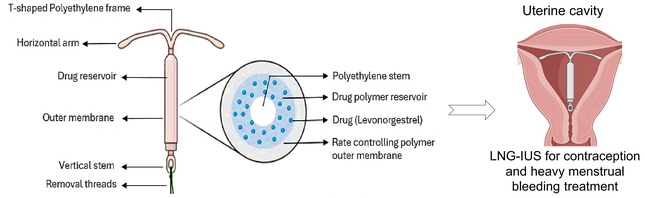
## PURPOSE

Levonorgestrel intrauterine systems (LNG-IUSs) are drug-device combination products releasing hormonal contraceptive drug for 3-8 years.







LNG-IUS for contraception and heavy menstrual bleeding treatment

Complex design combining monolithic & matrix systems of controlled release ⟹ Limited IUS products on market ⟹

**Challenges:**

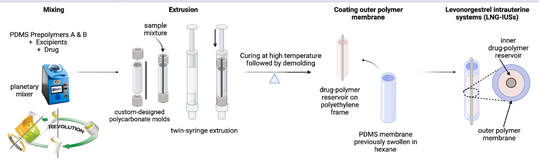
- Complex nature of excipients
- Intricate design and specialized manufacturing
- Incomplete product understanding
- Ultra long-acting nature (3-8 years)

## OBJECTIVE

To investigate the impact of the rate-controlling outer membrane on LNG-IUSs performance, with the goal of facilitating IUS product development.

## METHODS

**Lab-scale manufacturing process of LNG-IUSs**




**Approach: Studies with different outer membranes**

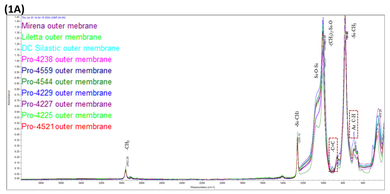
| Outer membranes | Details | Curing conditions |
|---|---|---|
| Pro-4238 | Standard control (Dimethyl PDMS with 20-40% w/w silica) | 80℃ for 24 h |
| Pro-4225 | Low silica PDMS (~1/3 lower amount of silica) | 80℃ for 24 h |
| Pro-4227 | Low MW PDMS (silica filler 20-40%, viscosity 100 kcP) | 80℃ for 24 h |
| Pro-4521 | Addition cure PDMS (silica filler 20-40%, contains benzoyl peroxide) | RT for 24 h |
| Pro-4229 | Phenyl-substituted PDMS (silica filler 20-40%, ~10% phenyl subst.) | 80℃ for 24 h |
| Pro-4544 | Condensation curing PDMS (no filler, alcohol by-product) | RT for 24 h |
| Pro-4559 | Addition curing PDMS (silica filler, optimized for low API binding) | RT for 24 h |
| DC silastic | Dow Corning® silastic premade PDMS outer membrane | NA |

**Drug reservoir:** 52% LNG in Pro-4238 standard control PDMS | * PDMS: Polydimethyl siloxane elastomer

**Molecular and mechanical properties, microstructure, and *in vitro* release studies**: DSC, TGA, FTIR, SEM, SEM-energy dispersive x-ray (SEM-EDX) analysis, UPLC, dynamic mechanical analysis (DMA), durometer hardness testing, *in vitro* release studies (*in vitro* release studies were conducted in 300 mL of 0.9% w/v saline at 37 °C and 100 rpm using the sample-and-separate method, with samples analyzed by UPLC.

## RESULTS

(1A)




(1B)

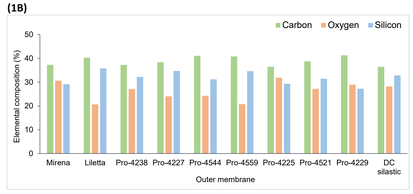
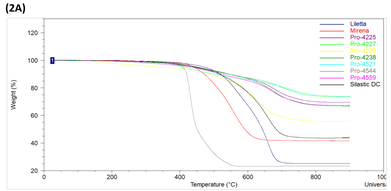



**Figure 1: (1A)** FTIR spectroscopic analysis: All PDMS outer membranes exhibit similar molecular structures, except Pro-4229 (phenyl-substituted PDMS), which shows a distinct chemical modification, **(1B)** SEM-EDX elemental analysis: All samples exhibit comparable elemental compositions, with minor variations, which attributed to differences in chemical composition, fillers.

(2A)




(2B)

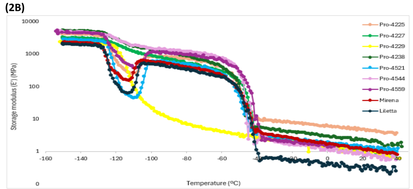
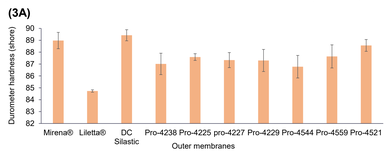
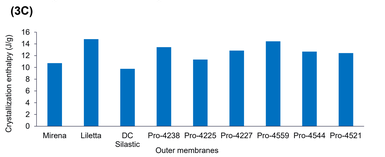



**Figure 2: (2A**) Thermogravimetric analysis: The differences in thermal properties (thermal degradation) are attributed to variations in chemical composition, fillers, and the degree of crosslinking, **(2B)** Dynamic mechanical analysis: The differences in mechanical properties are attributed to variations in chemical composition, fillers, and the degree of crosslinking.

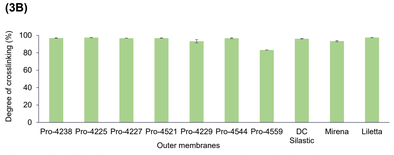
(3A)




(3C)




(3B)




(3D)

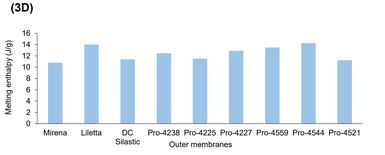



**Figure 3: (3A**) Durometer hardness testing: Liletta showed lowest hardness value which can be correlated with higher crystallization enthalpy (Figure 3C) and higher melting enthalpy (Figure 3D) (n = 3, mean ± SD), **(3B)** Degree of crosslinking: All samples showed more than 90% degree of crosslinking except Pro-4559 (addition cure, optimized for low API bonding) (showed ~83% degree of crosslinking), which could be due to chemical modifications (n = 3, mean ± SD), **(3C) & (3D)** Crystallization enthalpy and melting enthalpy, respectively: Higher crystallization enthalpy and melting enthalpy, attributed to lower degree of crosslinking, and variations in chemical composition, fillers.

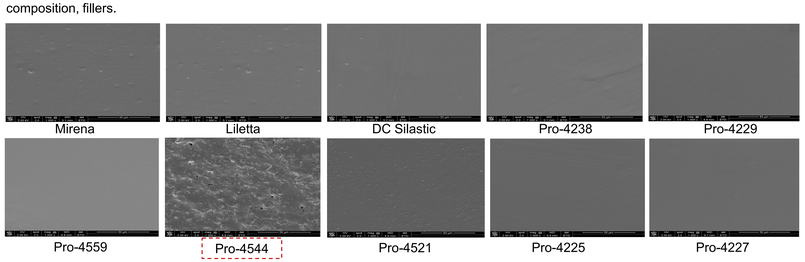
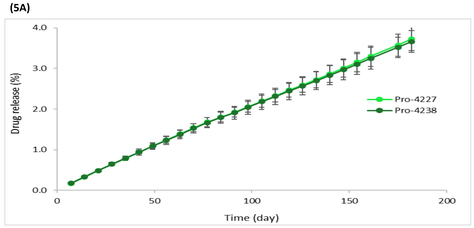



**Figure 4:** Microstructure analysis using scanning electron microscopy: All outer membrane showed similar microstructure except Pro-4544, which attributed to its chemical composition, and condensation curing process of preparation.

## RESULTS: Drug release studies

(5A)




(5B)

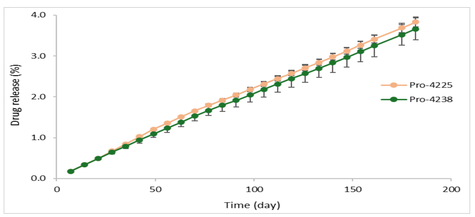
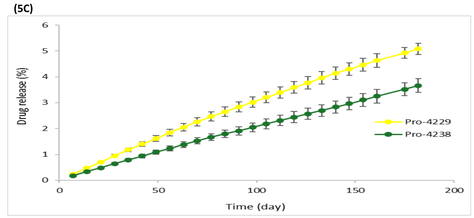



**Figure 5: (5A)** The differences in PDMS molecular weight did not impact release rates (n = 3, mean ± SD), **(5B)** The formulation with a high silica PDMS (Pro-4238) outer membrane showed decreased drug release compared to the low silica (Pro-4225) PDMS formulation, probably due to high silica content reducing polymer hydrophobicity and increasing API binding (n = 3, mean ± SD).

(5C)




(5D)

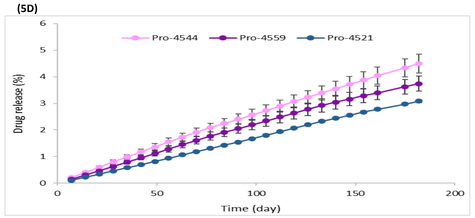
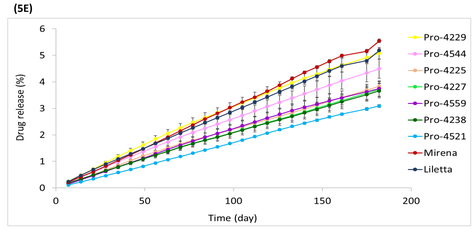



**Figure 5: (5C)** The phenyl-substituted PDMS (Pro-4229, non-polar) showed faster drug release than the dimethyl-substituted PDMS (Pro-4238, polar) (n = 3, mean ± SD), **(5D)** The formulation with condensation cured (Pro-4544) PDMS based membrane had a slightly higher release rate than the addition cured (Pro-4559, optimized for low API binding) PDMS and addition cure PDMS containing benzoyl peroxide (catalyst). This is attributed to the slightly higher solubility of LNG in the condensation cured PDMS (contains the by-product alcohol) (n = 3, mean ± SD).

(5E)




(5F)

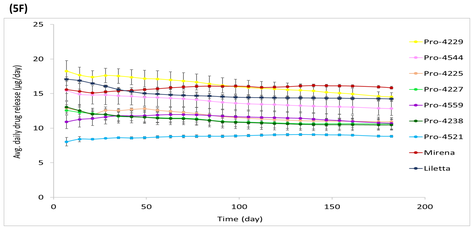



**Figure 5: (5E)** Cumulative drug release (%) (n = 3, mean ± SD), **(5F)** Average daily drug release (µg/day) (n = 3, mean ± SD).

## CONCLUSIONS

- Optimization of PDMS outer membranes such as chemical substitution changes (Pro-4229, 10% phenyl substitution) leads to comparable drug release to that of RLDs Mirena® and Liletta®.
- The differences in mechanical and thermal properties are attributed to variations in chemical composition, fillers, and the degree of crosslinking.
- SEM, SEM-EDX, and FTIR revealed both similarities and differences in the microstructure, elemental composition, and molecular structure.
- The knowledge gained is applicable to other PDMS-based controlled release products.

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