Enabling the Rational Development of Long-Acting Contraceptive Levonorgestrel Intrauterine Systems

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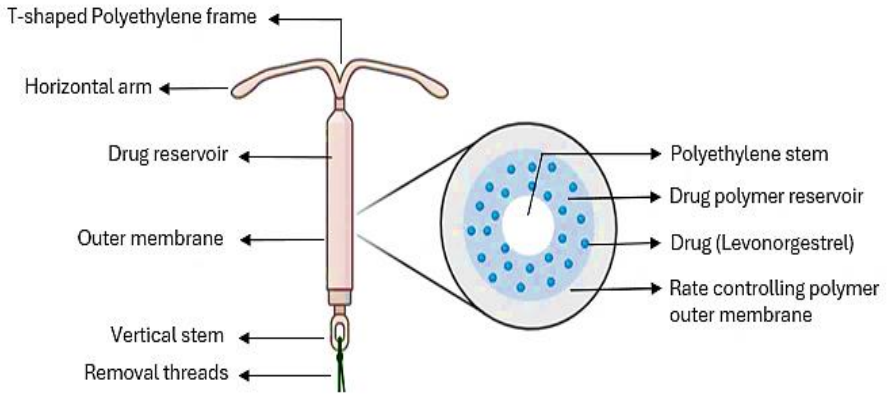
NEXT-GENERATION DELIVERY INNOVATIONS

Intrauterine drug delivery system

Levonorgestrel-releasing intrauterine systems (LNG-IUSs)



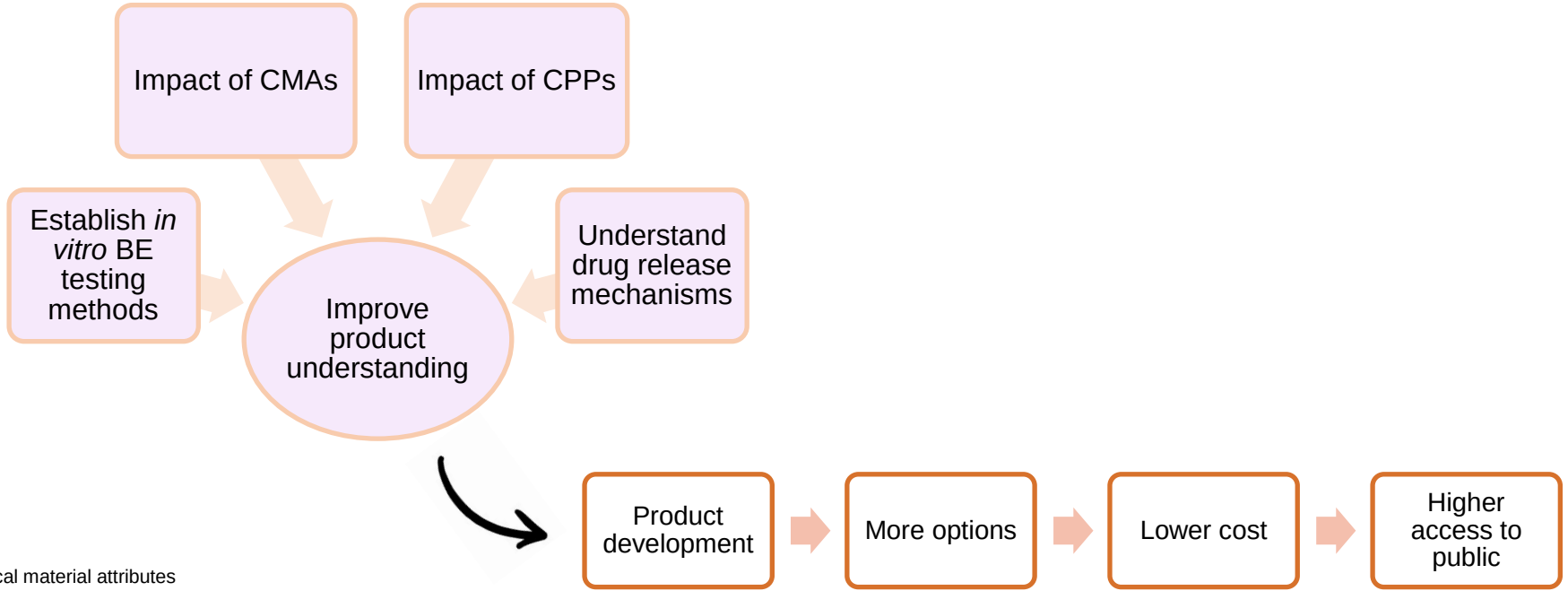
Why LNG-IUS product development is challenging?

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

Abhang *et al.*, Expert Opinion on Drug Delivery 2025, Fanse *et al.*, Advanced Drug Delivery Reviews 2023.

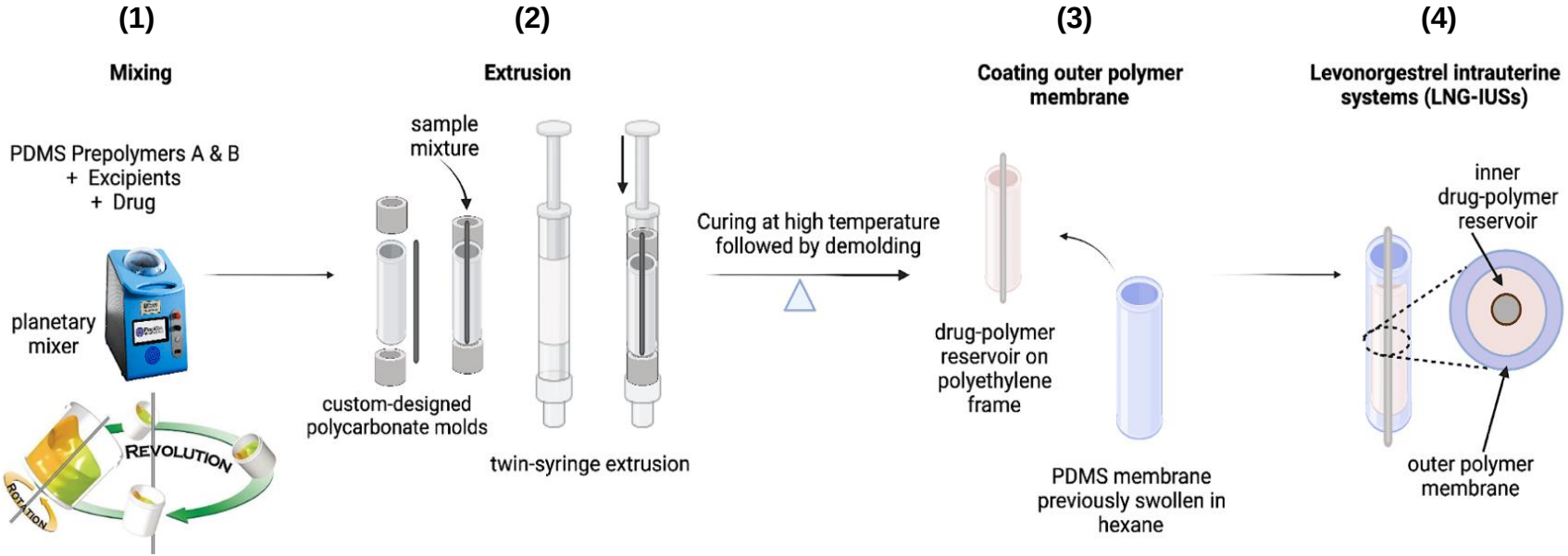
Fanse *et al.*, Advanced Drug Delivery Reviews 2023.

Objectives of current research



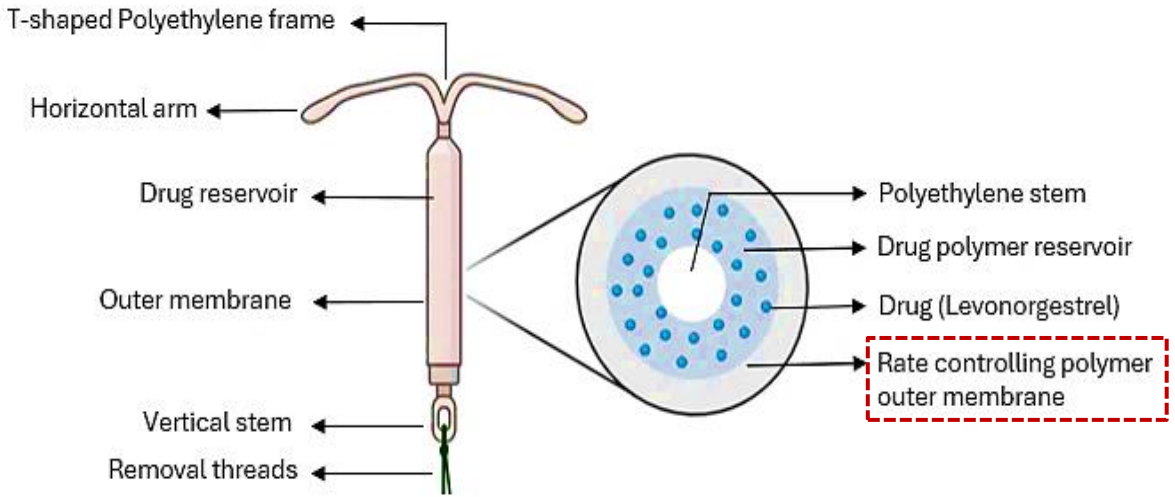
CMA: Critical material attributes
CPPs: Critical process parameters
BE: Bioequivalence

Lab-scale manufacturing process



Bao *et al*., International Journal of Pharmaceutics 2018.

Investigation of the effect of rate controlling outer membrane on LNG-IUSs performance



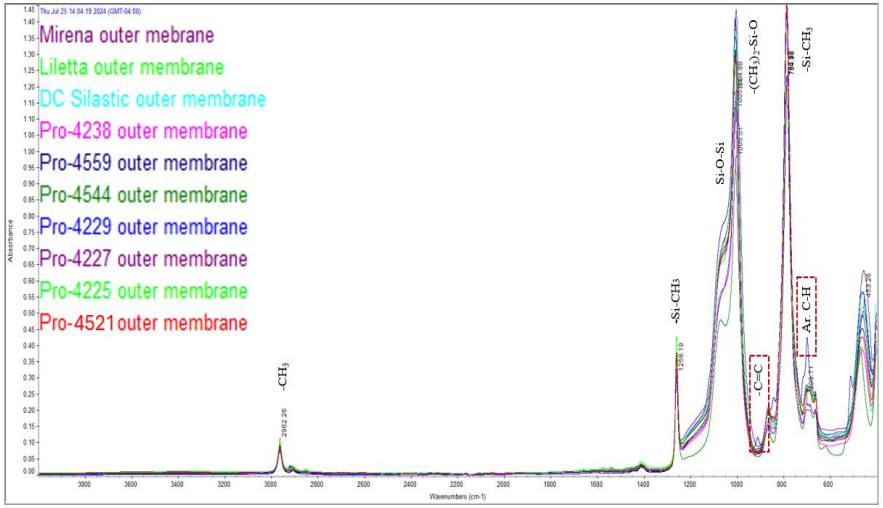
Studies with different outer membranes

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

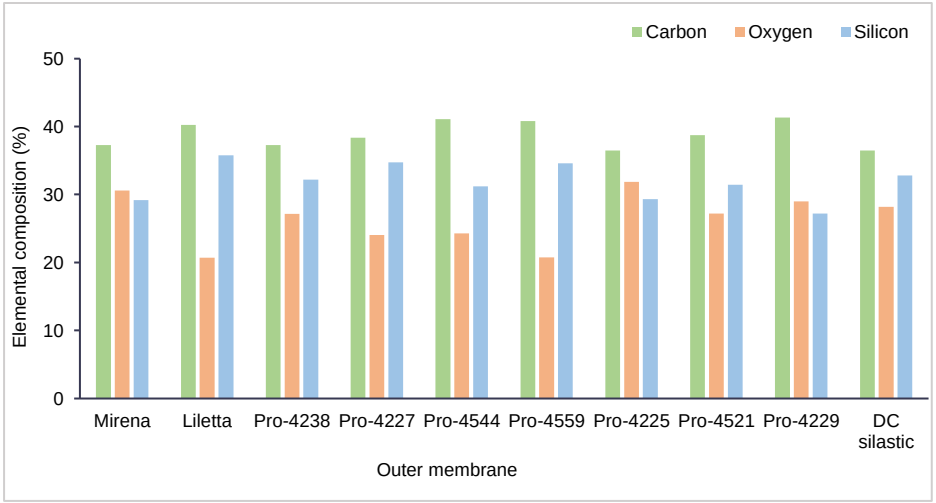
Drug reservoir: 52% Levonorgestrel in Pro-4238 standard control PDMS

FTIR and SEM-EDX Elemental analysis

FTIR spectroscopic analysis



SEM-EDX Elemental analysis

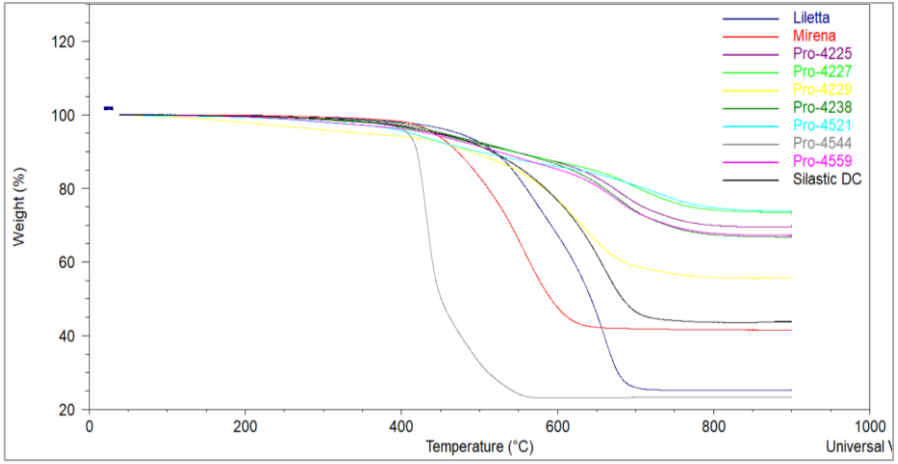


FTIR: Fourier transform infrared spectroscopy
SEM-EDX: Scanning electron microscopy – energy dispersive x-ray spectroscopy

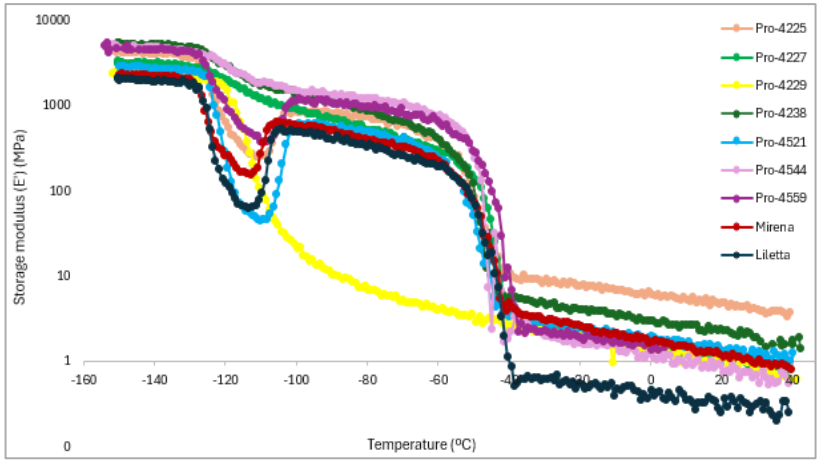
Pro-4238: Dimethyl PDMS (standard control)
Pro-4225: Low silica PDMS
Pro-4227: Low MW PDMS
Pro-4521: Addition cure (contains BPO)
Pro-4229: Phenyl-subs. PDMS
Pro-4544: Condensation curing
Pro-4559: Addition cure (optimized low API binding)

Thermogravimetric and dynamic mechanical analysis

Thermogravimetric analysis



Dynamic mechanical analysis



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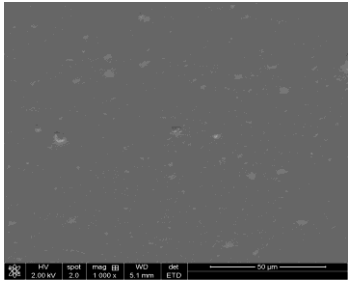
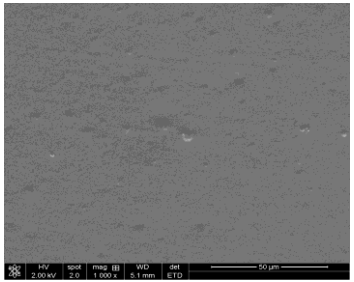
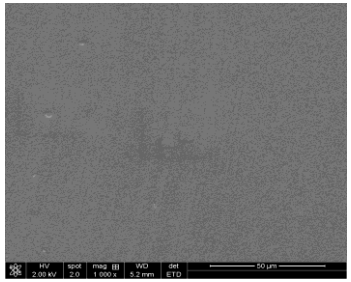
Microstructure analysis using SEM



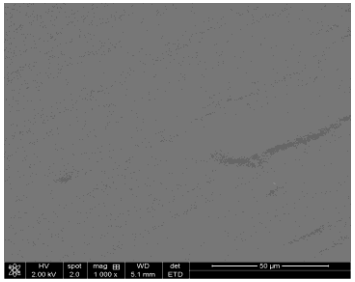
Mirena
(RLD (Bayer))



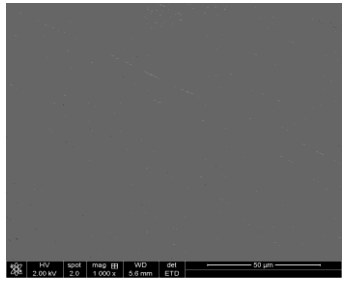
Liletta
(RLD (AbbVie))



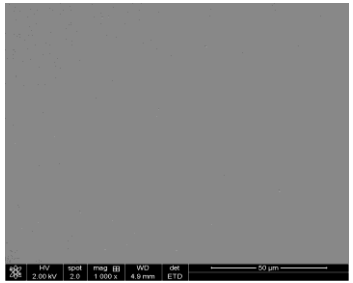
DC Silastic
(Premade)



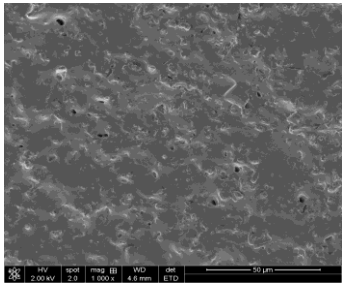
Pro-4238
(Standard/ Dimethyl-substituted)



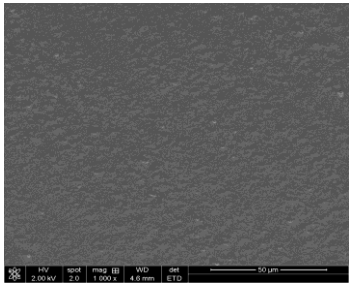
Pro-4229
(Phenyl-substituted)



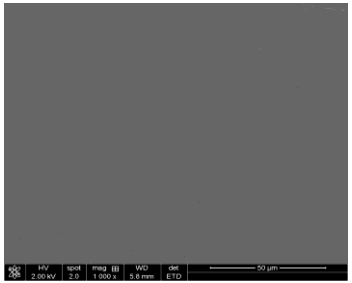
Pro-4559
(Low API binding)



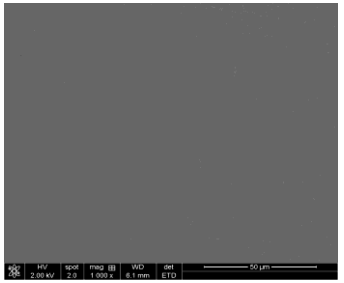
Pro-4544
(Condensation cure)



Pro-4521
(Benzoyl peroxide catalysts)



Pro-4225
(Low silica filler)

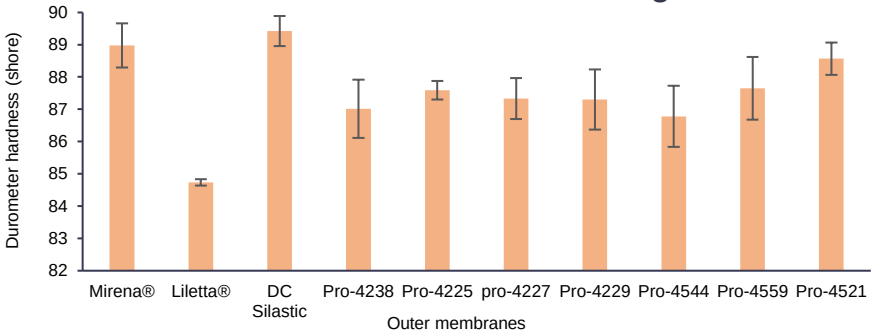


Pro-4227
(Low mol. weight)

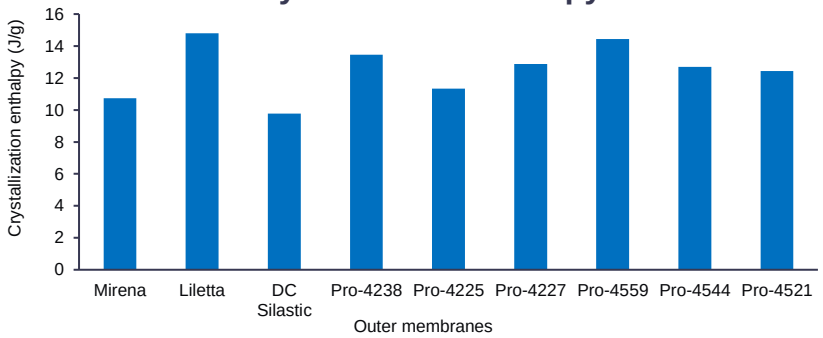
SEM: Scanning electron microscopy

Mechanical and thermal properties assessment

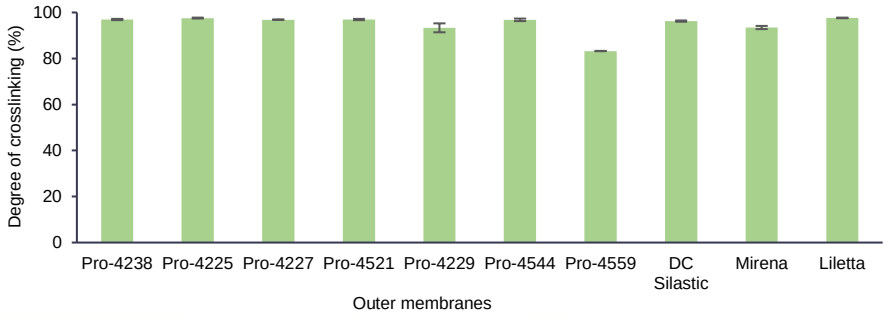
Durometer hardness testing



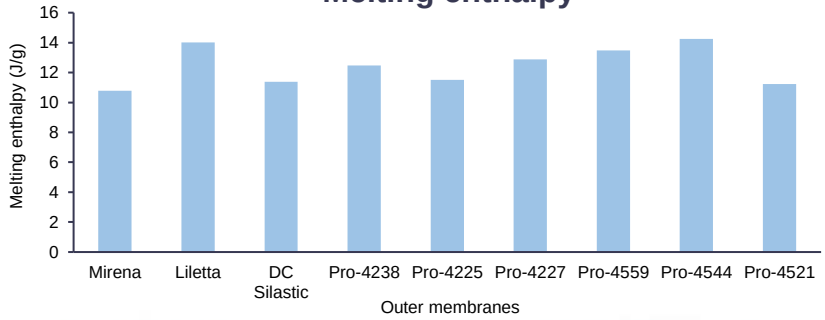
Crystallization enthalpy



Degree of crosslinking



Melting enthalpy



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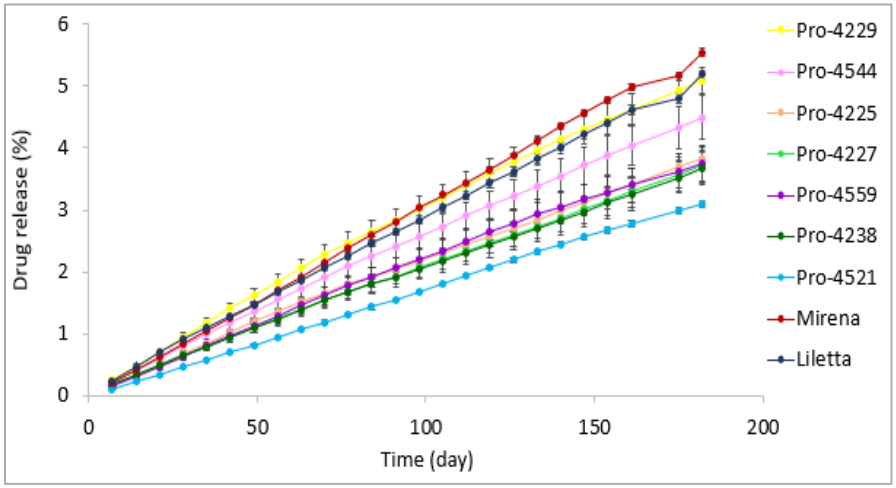
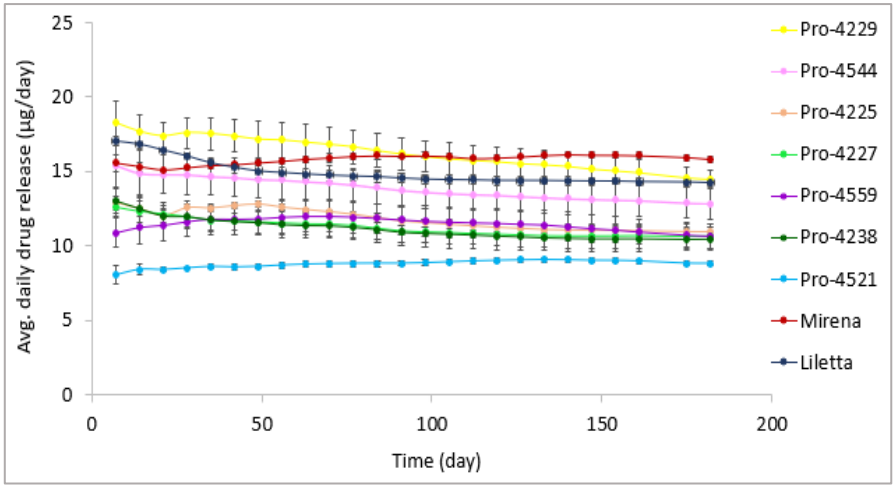
Release testing of LNG-IUSs with different outer membranes

Cumulative drug release (%)



Average daily drug release (µg/day)



Sample size, n = 3

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Summary and key take-aways

- Drug solubility and diffusion within PDMS are the key drivers of the drug release from LNG-IUSs.
- Following the initial faster release phase, the Pro-4229 PDMS formulation had the highest daily drug release, followed by Mirena® and Liletta®.
- By day 180, Mirena® had the highest daily drug release followed by Pro-4229 PDMS formulation and Liletta®.
- The differences in mechanical and thermal properties are due to variations in chemical composition, fillers, and the degree of crosslinking.
- SEM, SEM-EDX, and FTIR revealed similarities and differences in the microstructure, composition, and PDMS molecular structure.
- The knowledge gained may be applied to other PDMS-based controlled release products.

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