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

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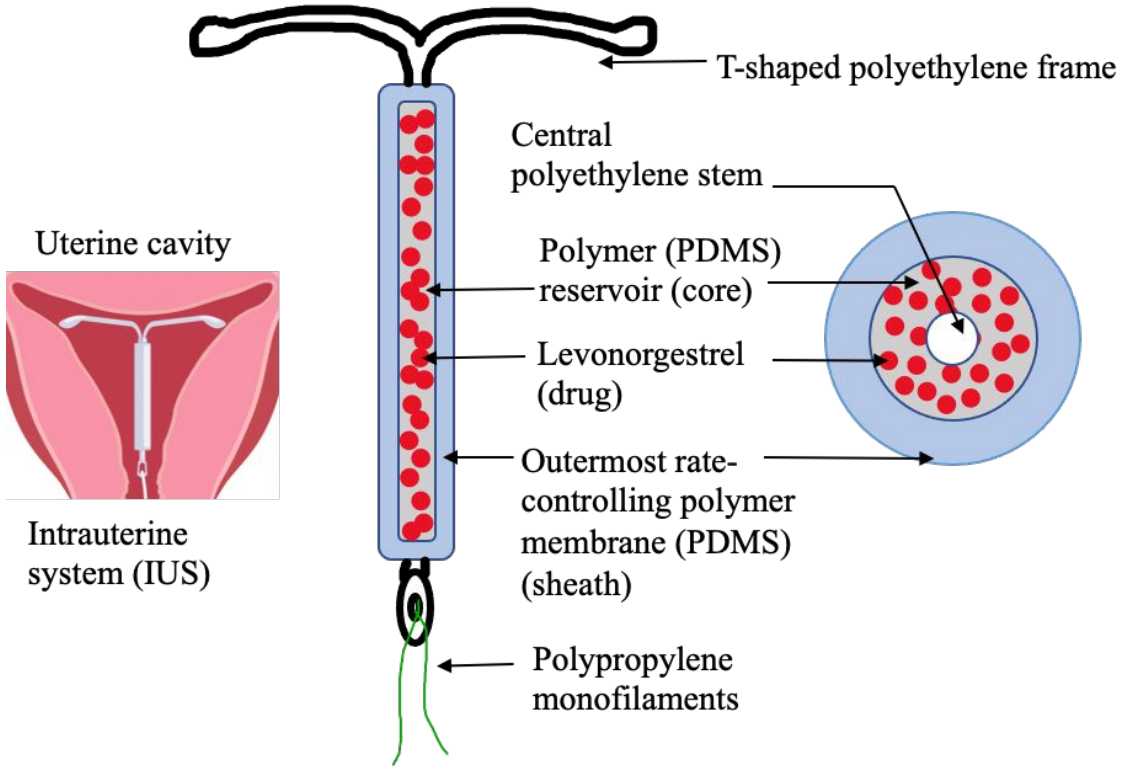
THE FUTURE OF DELIVERY SCIENCE

Levonorgestrel intrauterine systems



Levonorgestrel intrauterine systems (LNG-IUSs)
Long-Acting Reversible Contraceptives (LARCs)

Hormonal intrauterine systems for contraception

Advantages

- ✓ >99% effective
- ✓ Reversible
- ✓ Non-surgical
- ✓ Ultra long-acting (3-8 years)

Commercial LNG-IUS products

Product name	Strength	Effective duration	*In vivo* drug release rate at the end of first year of use	*In vivo* drug release rate at the end of approved year of use	Applicant holder	Year of approval
Mirena®	52 mg	7 years*	18.0 µg/ day	8.0 µg/ day (7 years)	Bayer	2000
Liletta®	52 mg	6 years	17.0 µg/ day	8.6 µg/ day (6 years)	Allergan/ Medicines360	2015
Kyleena®	19.5 mg	5 years	9.8 µg / day	7.4 µg/ day (5 years)	Bayer	2016
Skyla®	13.5 mg	3 years	6.0 µg/ day	5 µg/ day (3 years)	Bayer	2013

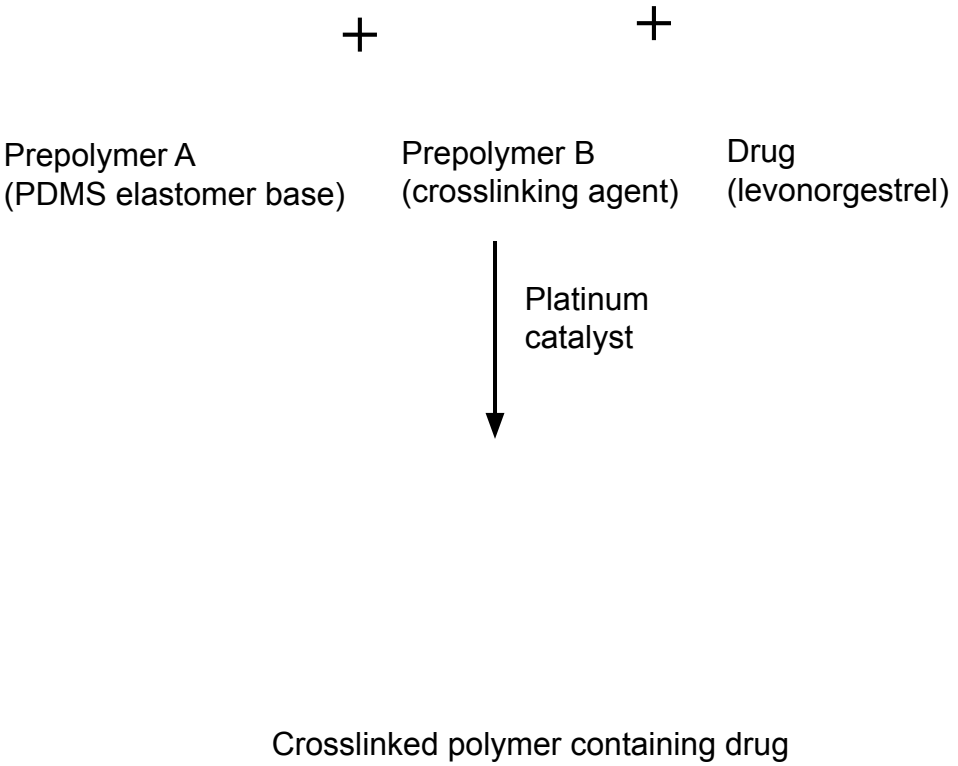
*The US FDA has extended the duration of use for Mirena® up to 8 years in 2022.

Generic drug product development of LNG-IUSs is challenging!!

Challenges

Why is generic product development of LNG-IUSs challenging?

- Complex nature of excipients
- Intricate design and specialized manufacturing process
- Incomplete product understanding and drug release mechanisms
- Extremely long-acting nature
- Qualitative sameness (Q1), Quantitative sameness (Q2), and Physicochemical similarity (Q3)



Objectives of current research

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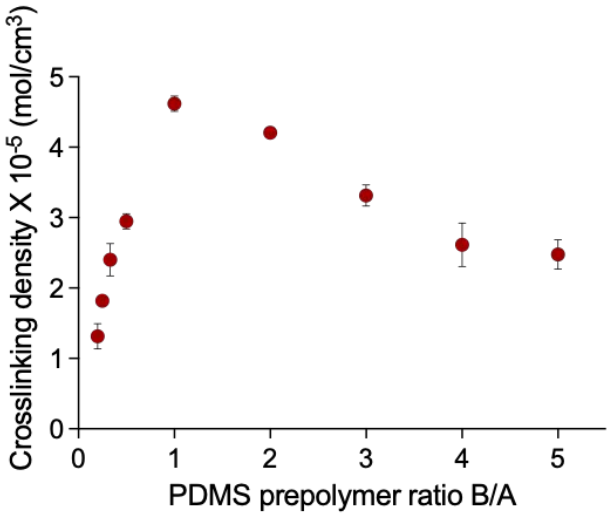
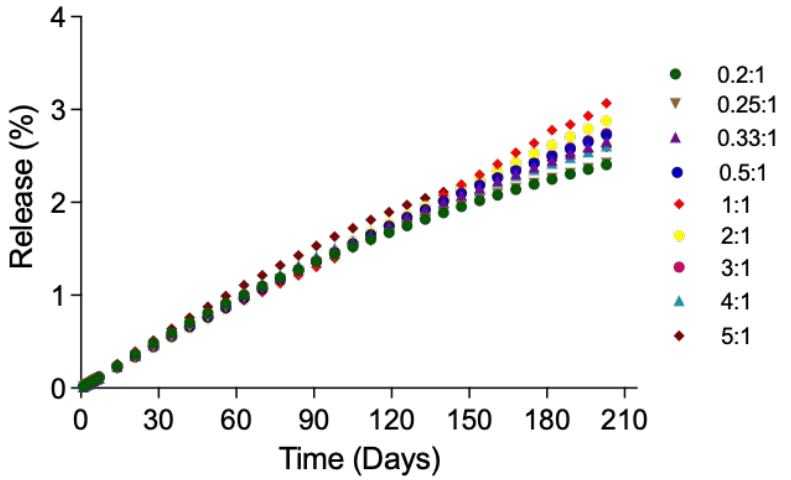
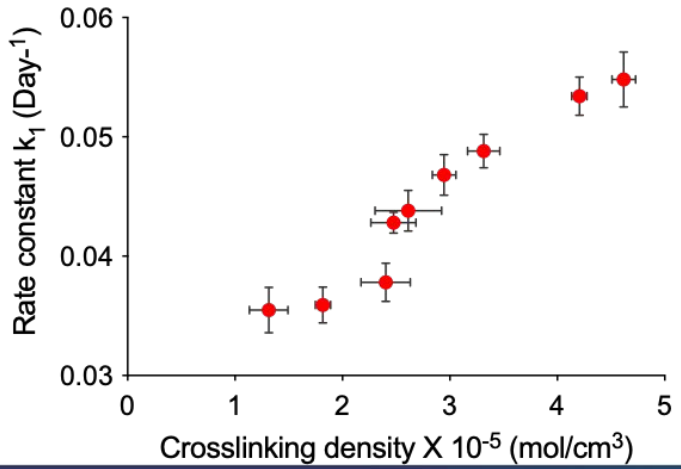
Improve product understanding and drive generic product development

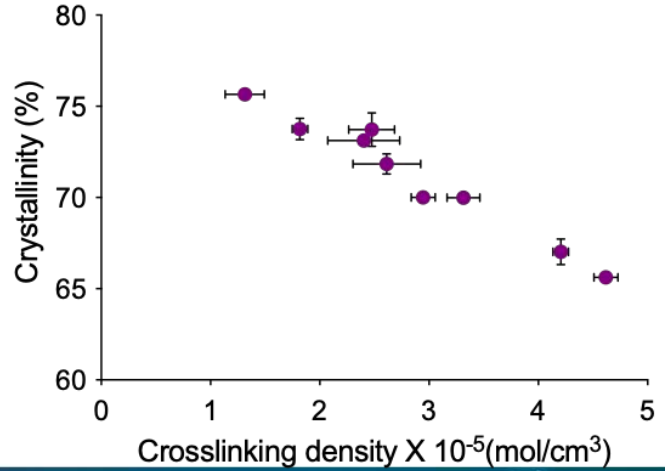
A. Impact of critical material attributes: crosslinking density





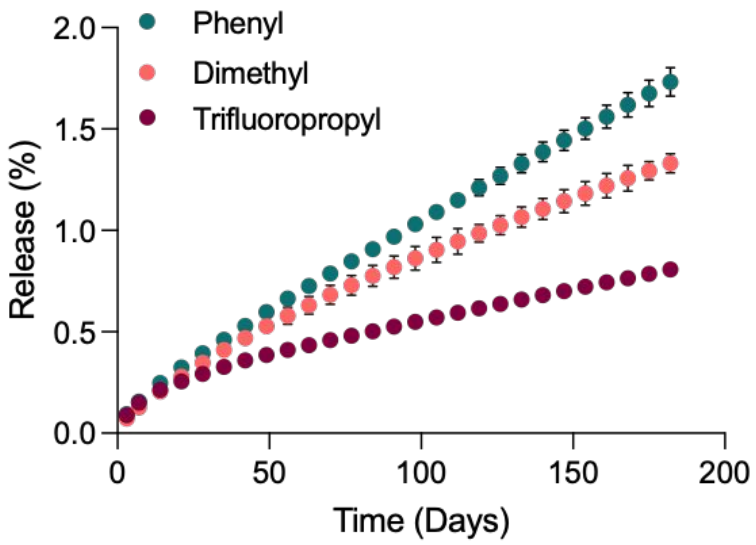
High polymer crosslinking density led to faster drug release





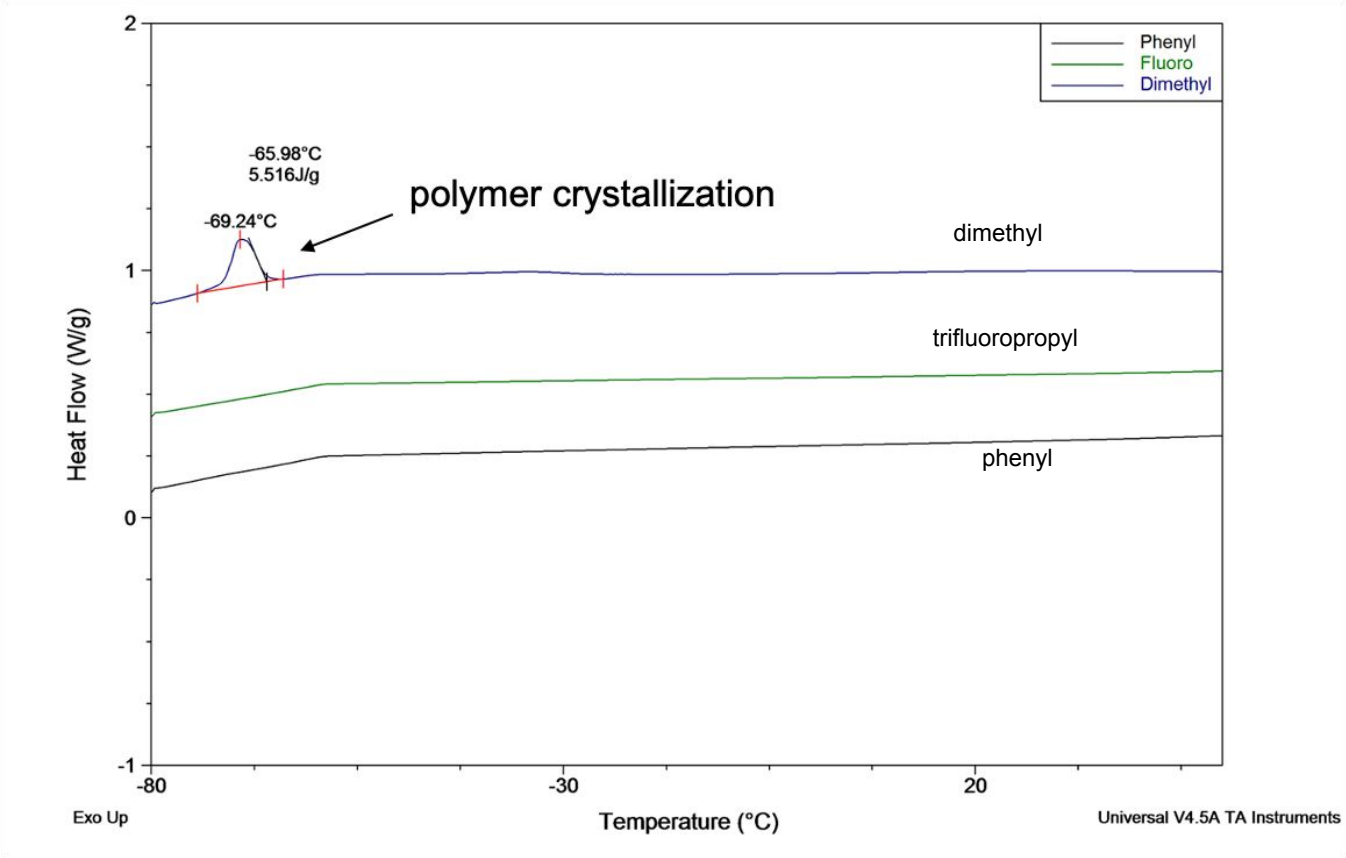
Reduced polymer crystallinity at high crosslinking densities

A. Impact of critical material attributes: polymer functionality



Key determinants?

1. Partition coefficient
2. Diffusion coefficient



A. Impact of critical material attributes: drug physicochemical properties

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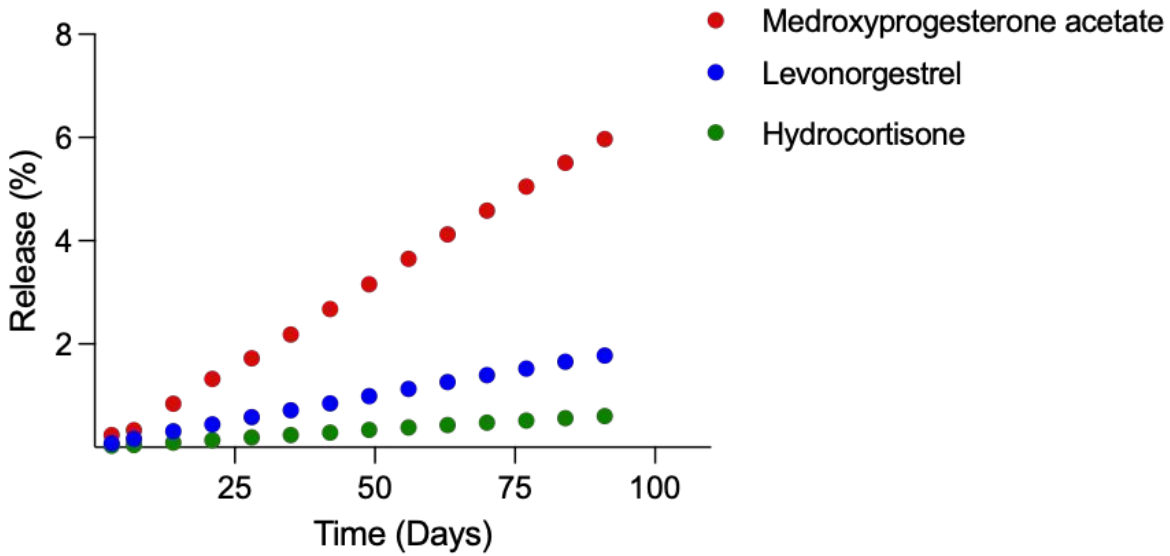
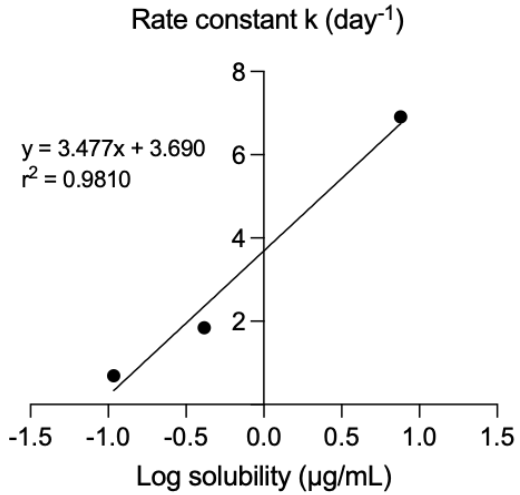
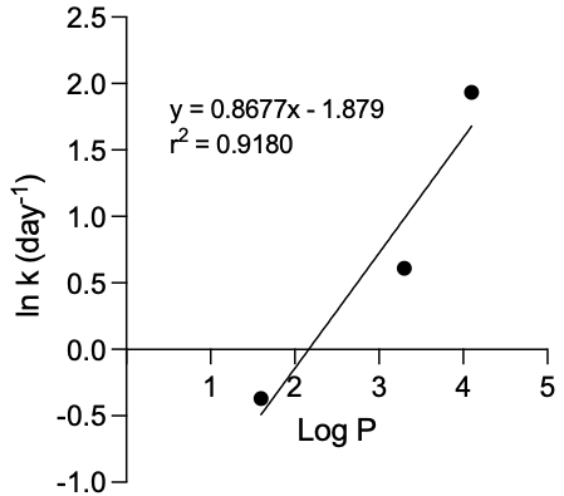
Evidence of diffusion-controlled release mechanism



Physicochemical attributes dictating drug release from IUSs

Drug	Log P	Mol. Wt (g/mol)	Solubility in polymer (µg/mL)	Melting point (℃)
Medroxyprogesterone	4.1	386.5	7.5730	214.5
Levonorgestrel	3.3	312.4	0.4139	240
Hydrocortisone	1.6	318.1	0.1084	220





A. Impact of critical material attributes: role of additives

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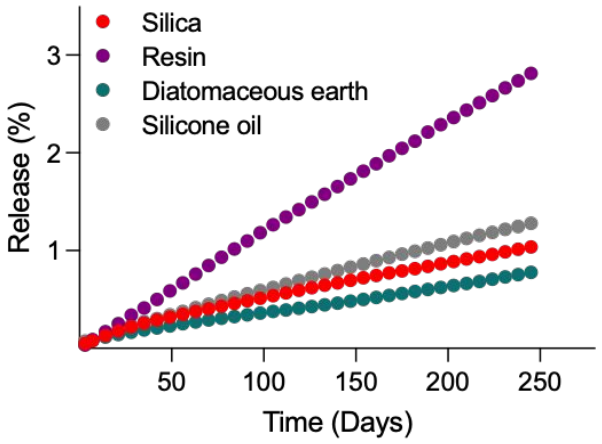
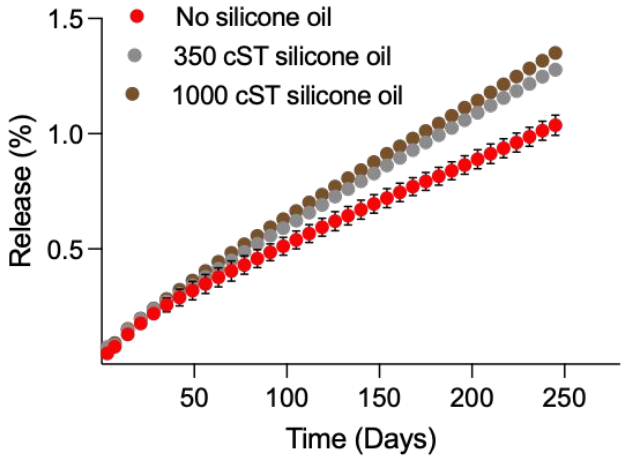
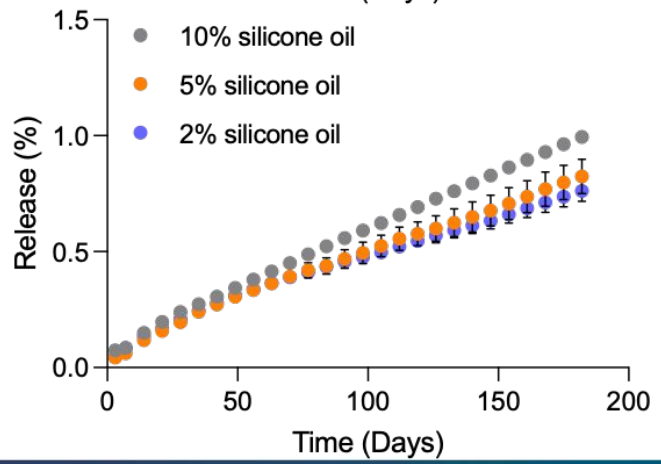
Matrix hydrophobicity and drug-excipient interactions are critical

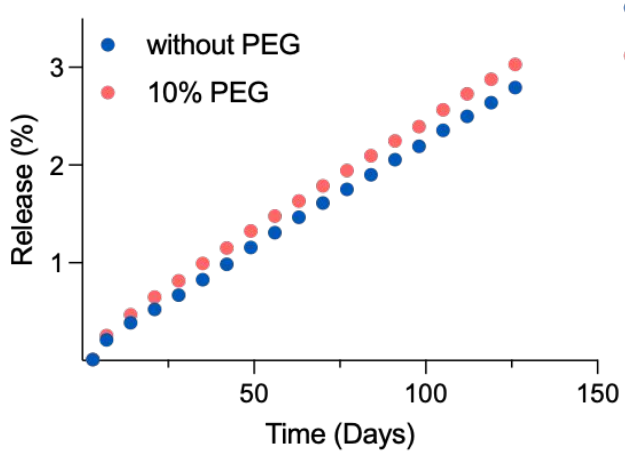


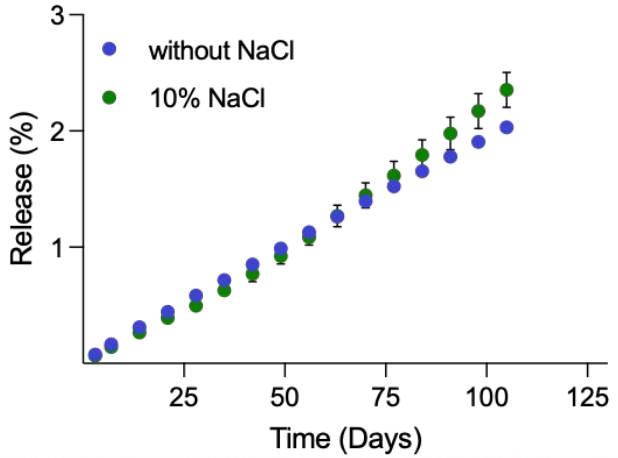
Excipients providing a low-viscosity matrix facilitate faster drug release



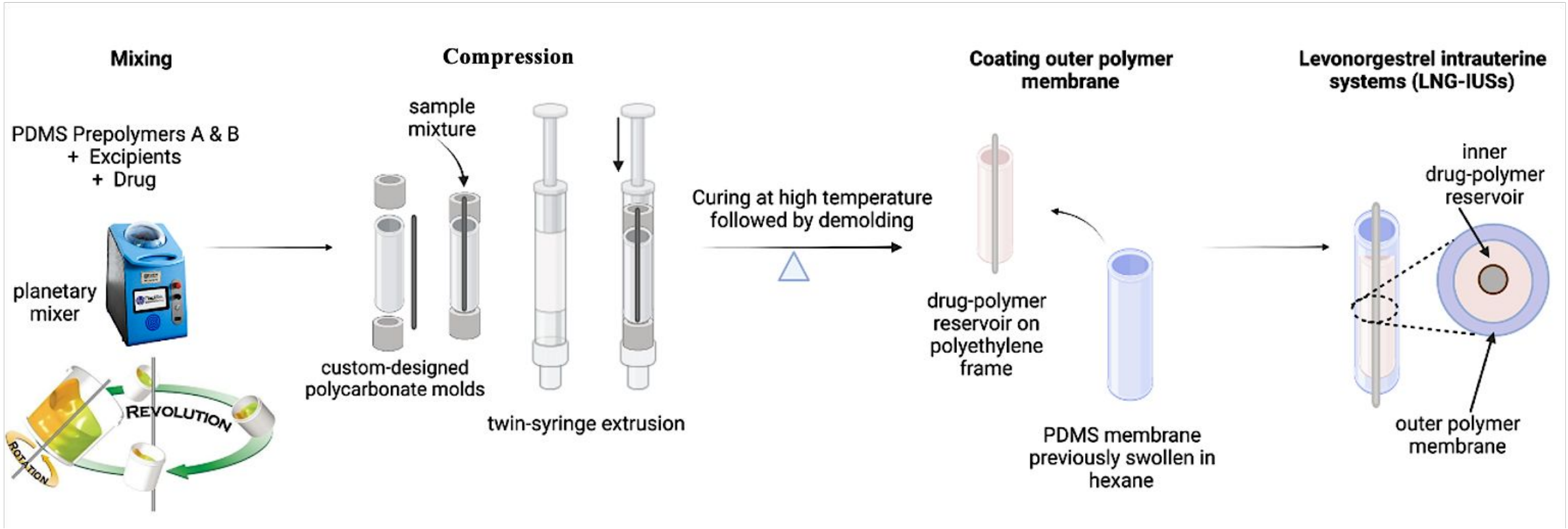


Porosity and osmosis may not be significant contributors to drug release





B. Influence of processing parameters



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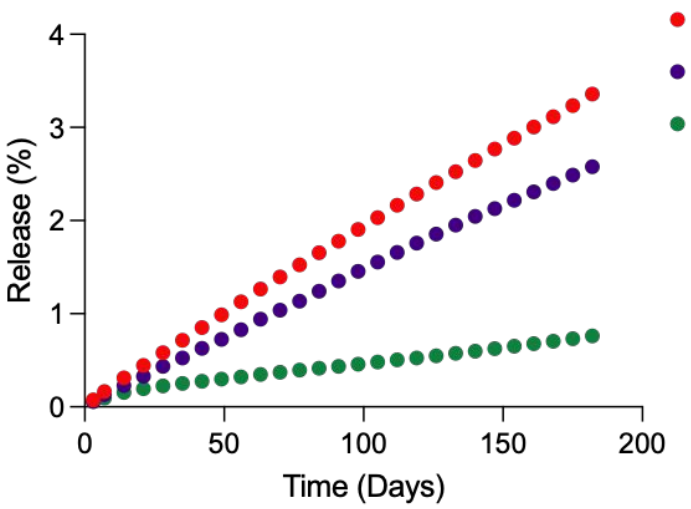
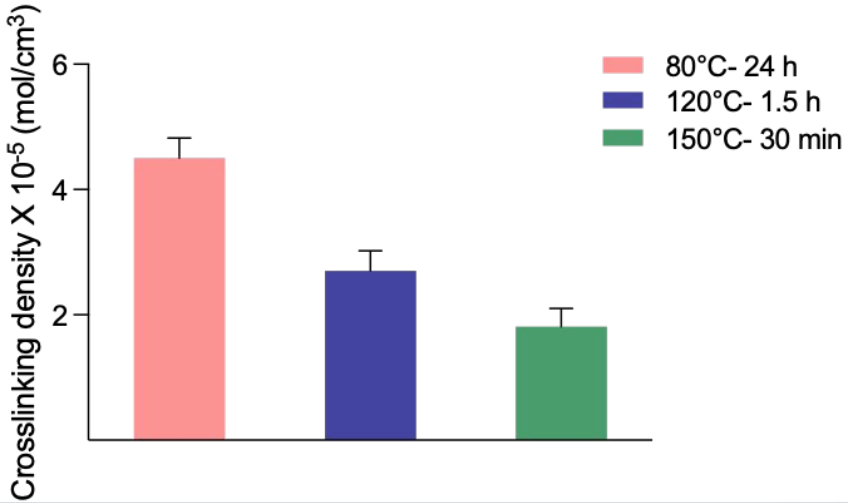
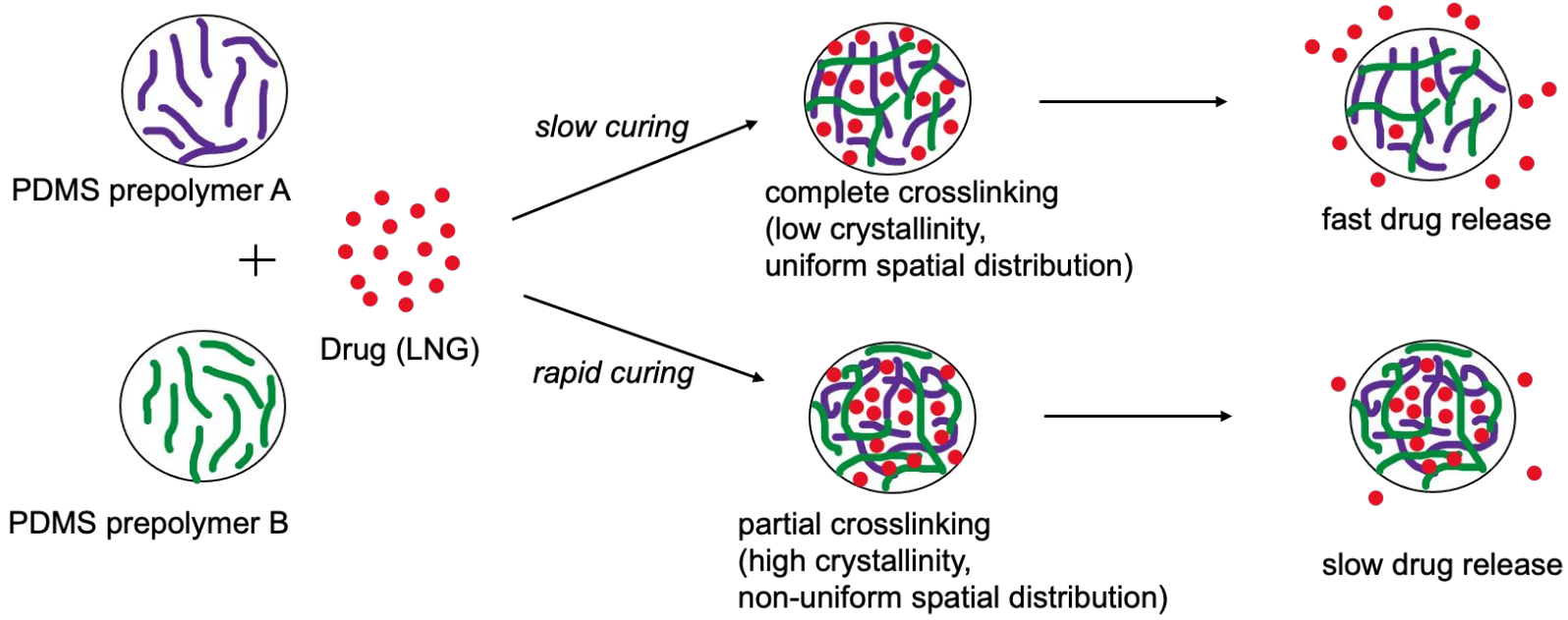
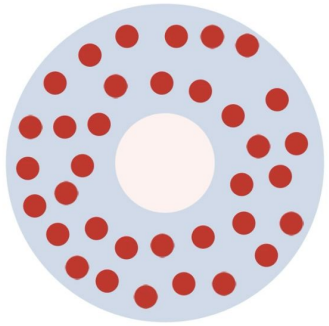




Degree of polymer crosslinking is dependent on curing rate



C. Elucidating drug release mechanisms



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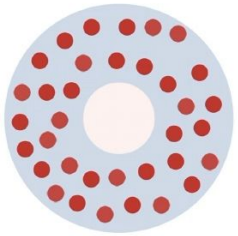
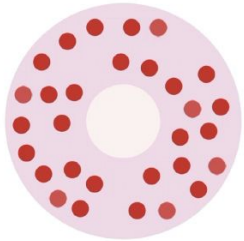
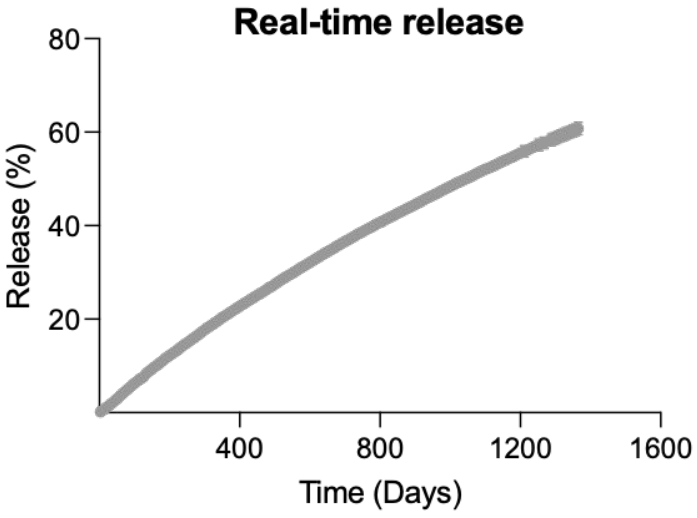


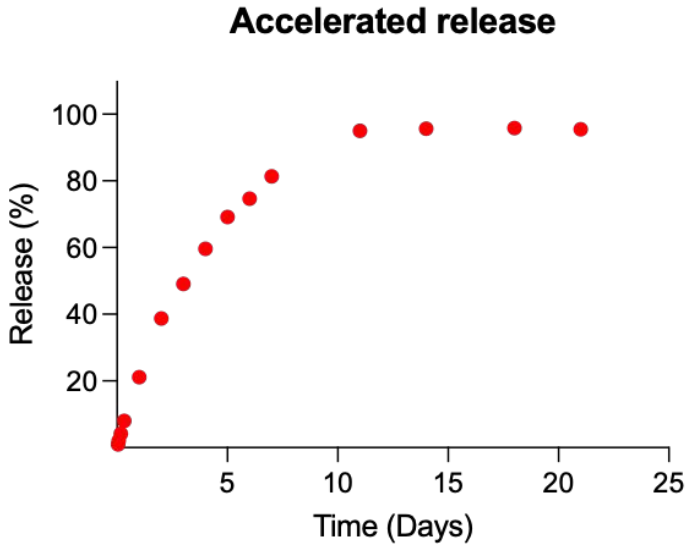
Hydrophobic drug in a Hydrophobic Matrix

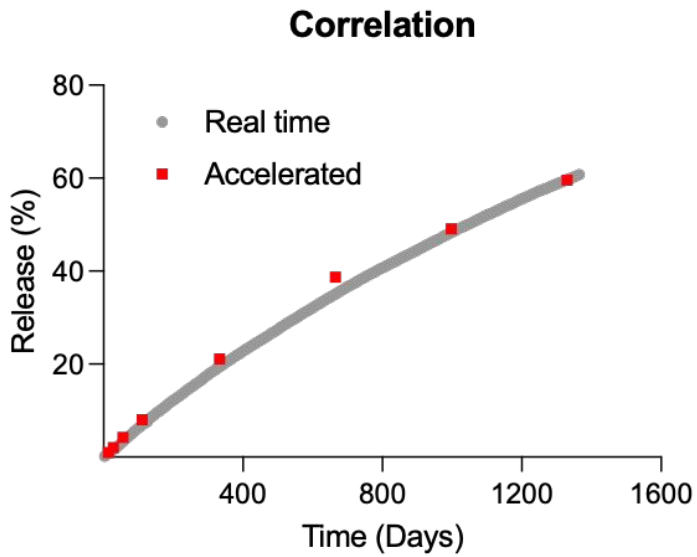


Hydrophobic drug in a Hydrophilic Matrix

D. Bioequivalence testing through *in vitro* approaches







IUS- 10% w/w drug loading
Saline, 37℃, 100 rpm

IUS- 10% w/w drug loading
45% v/v tert-butanol in PBS, 65℃, 100 rpm

Conclusions

- Tailoring drug release from IUSs □ Controlling polymer crosslinking density
  Curing conditions
  Excipient functionality
- Critical attributes □ matrix hydrophobicity, crystallinity, and viscosity.
- Drug release from IUSs □ drug solubility in polymer
  drug diffusivity in matrix
- Critical processing parameters □ curing temperature and time.
- Accelerated *in vitro* release tests □ quality control and batch testing

Impact

- Propel the development as well as approval of generic equivalent IUSs to advance women's health.
- Tailoring commercial polymers to suit the application.
- Development and optimization of other silicone based controlled release products.

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