

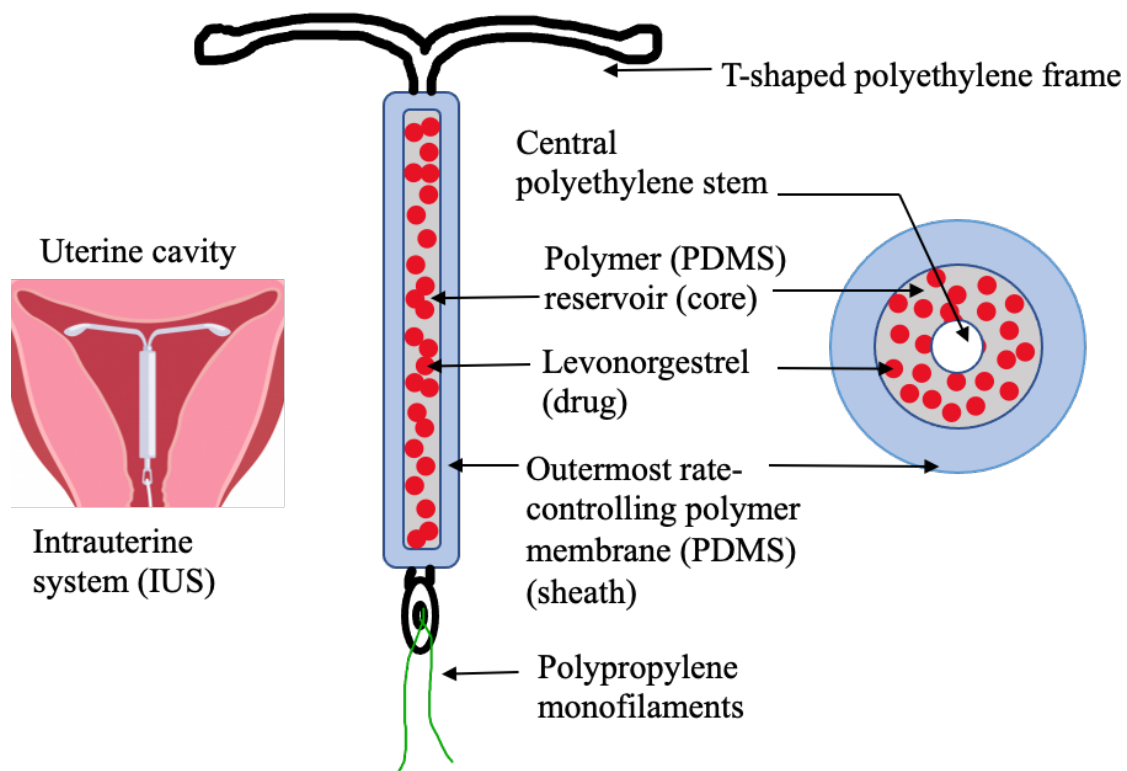
Enabling the Rational Development of Long-Acting Contraceptive Levonorgestrel Intrauterine Systems

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Disclaimer

This presentation reflects the views of the author and should
not be construed to represent FDA's views or policies

Levonorgestrel intrauterine systems



Hormonal intrauterine systems for contraception

Advantages

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

Levonorgestrel intrauterine systems (LNG-IUSs)

~~Long-Acting Reversible Contraceptives (LARCs)~~

Commercial LNG-IUS products

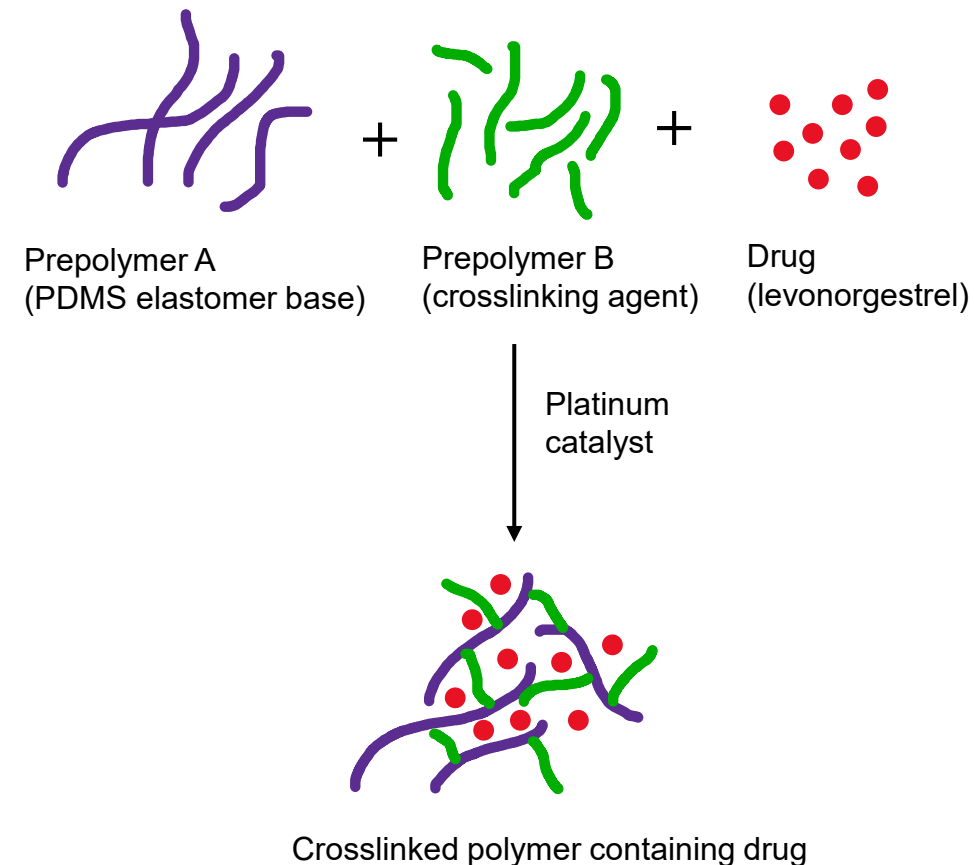
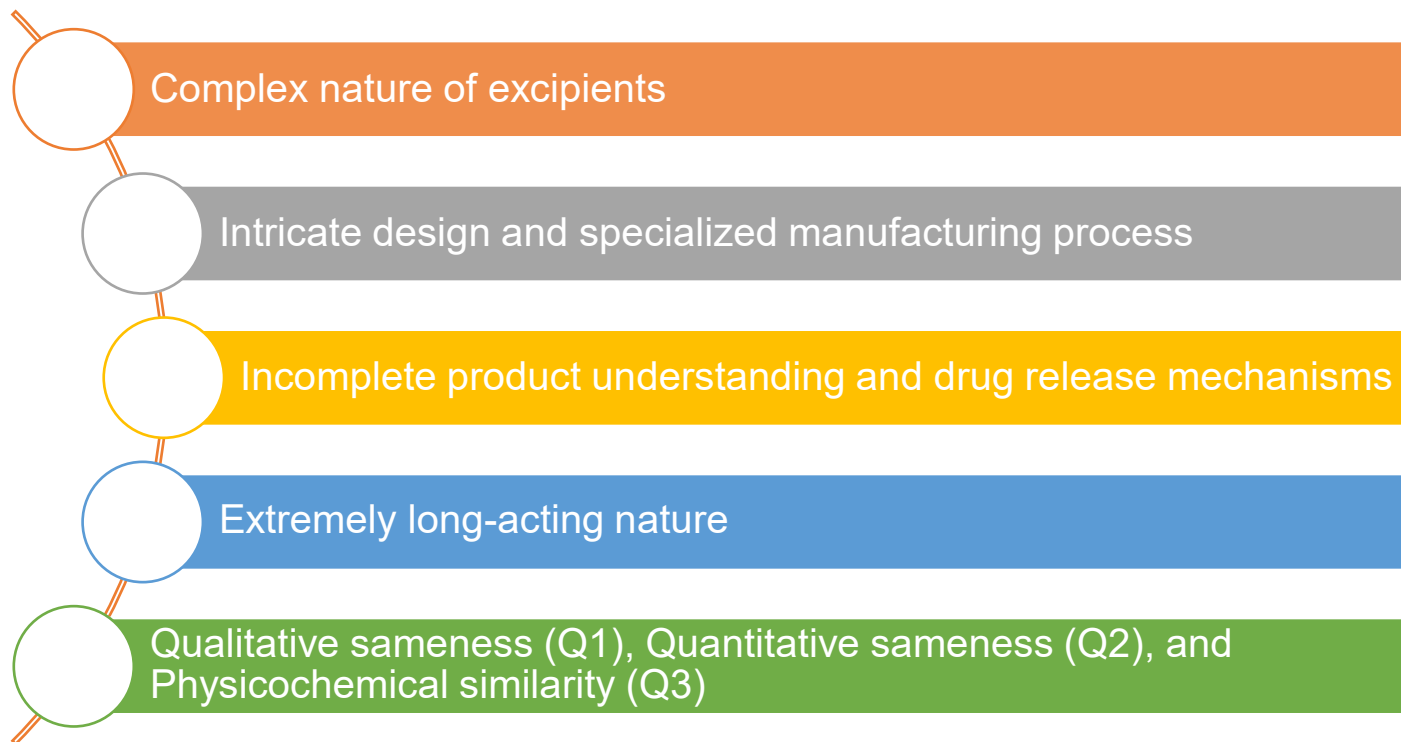
Product name	Strength	Effective duration	<i>In vivo</i> drug release rate at the end of first year of use	<i>In vivo</i> drug release rate at the end of approved year of use	Applicant holder	Year of approval
Mirena®	52 mg	7 years*	18.0 µg/ day	8.0 µg/ day (7 years)	Bayer	2000
Liletta®	52 mg	6 years	17.0 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?



Objectives of current research

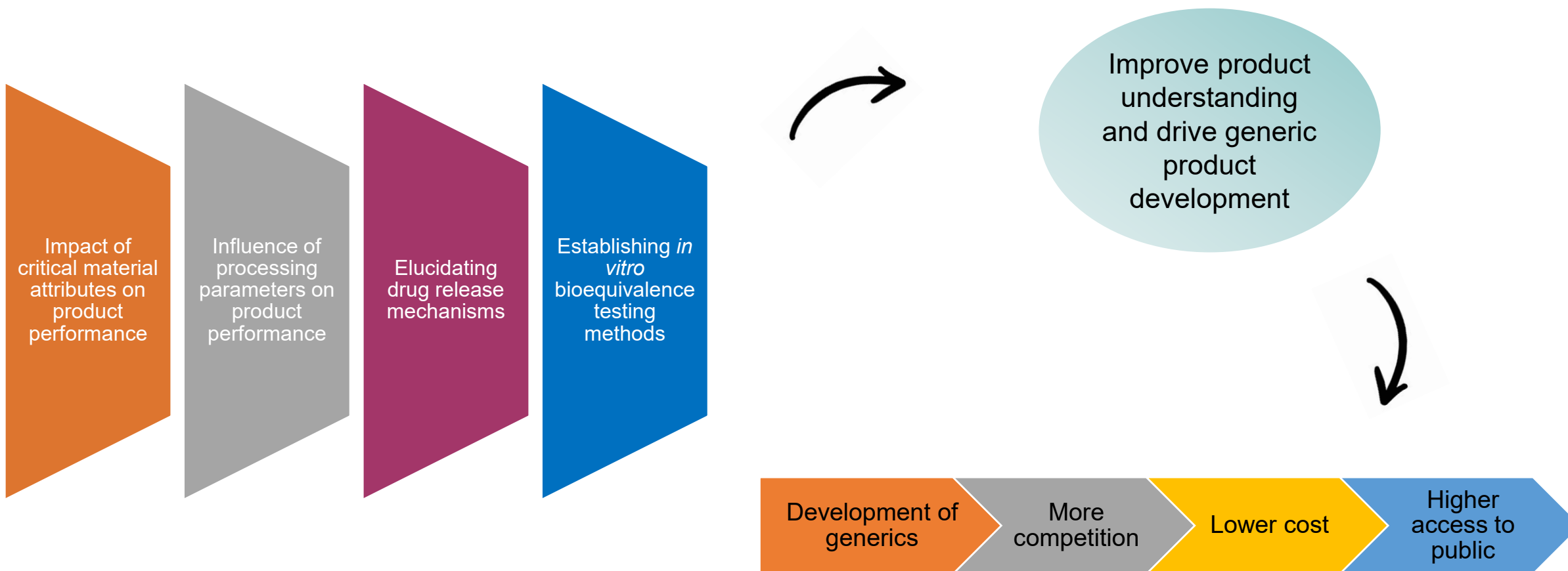
Impact of
critical material
attributes on
product
performance

Influence of
processing
parameters on
product
performance

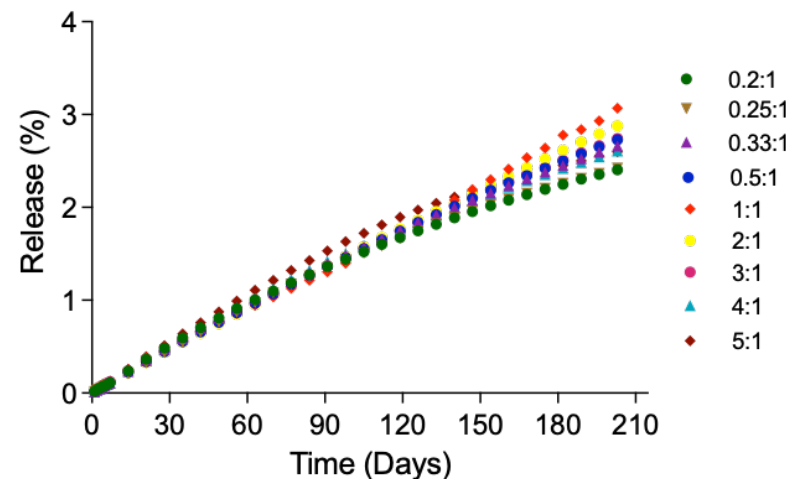
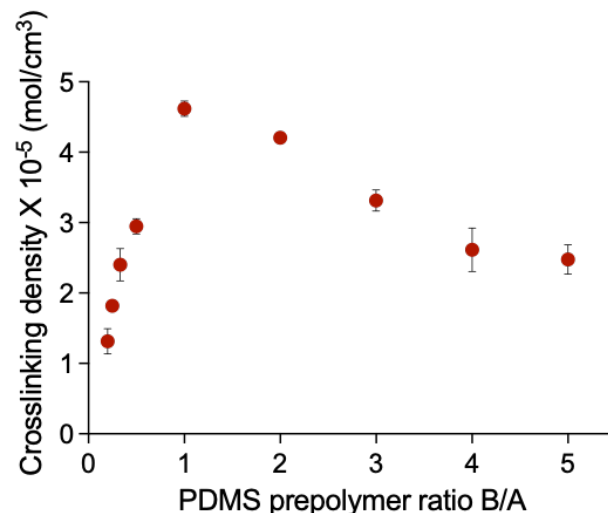
Elucidating
drug release
mechanisms

Establishing *in
vitro*
bioequivalence
testing
methods

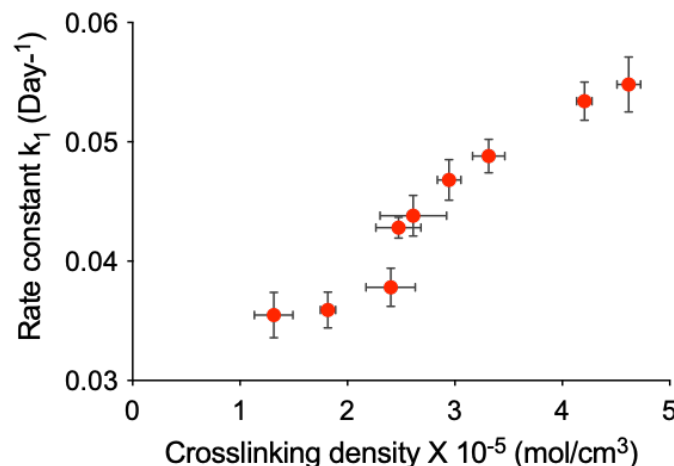
Objectives of current research



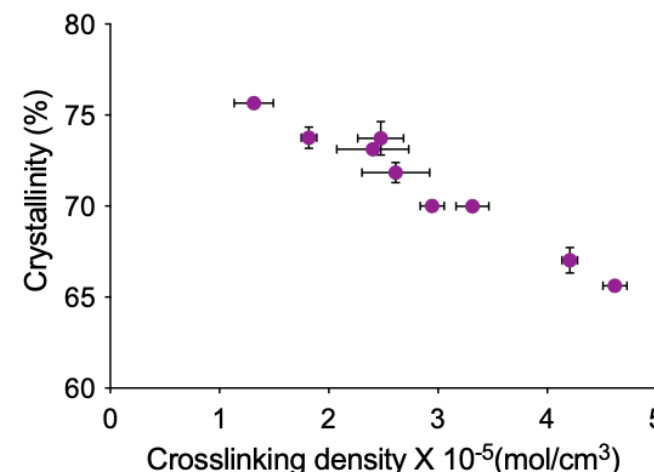
A. Impact of critical material attributes: crosslinking density



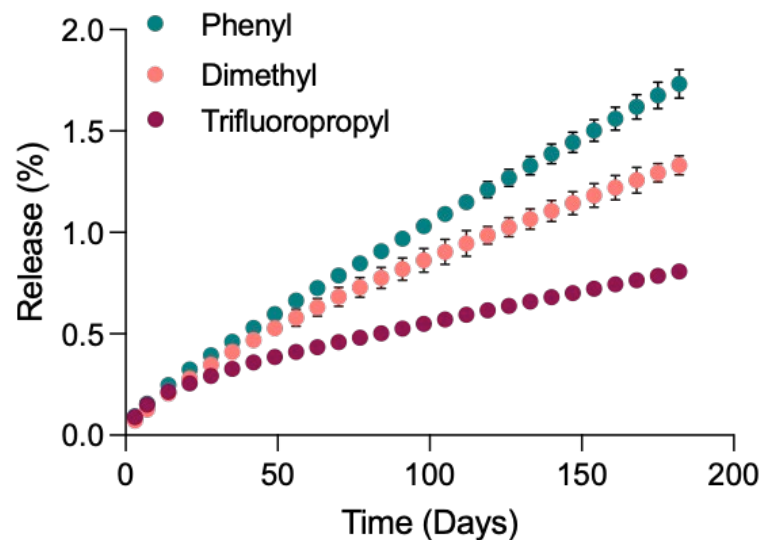
High polymer crosslinking density led to faster drug release



Reduced polymer crystallinity at high crosslinking densities

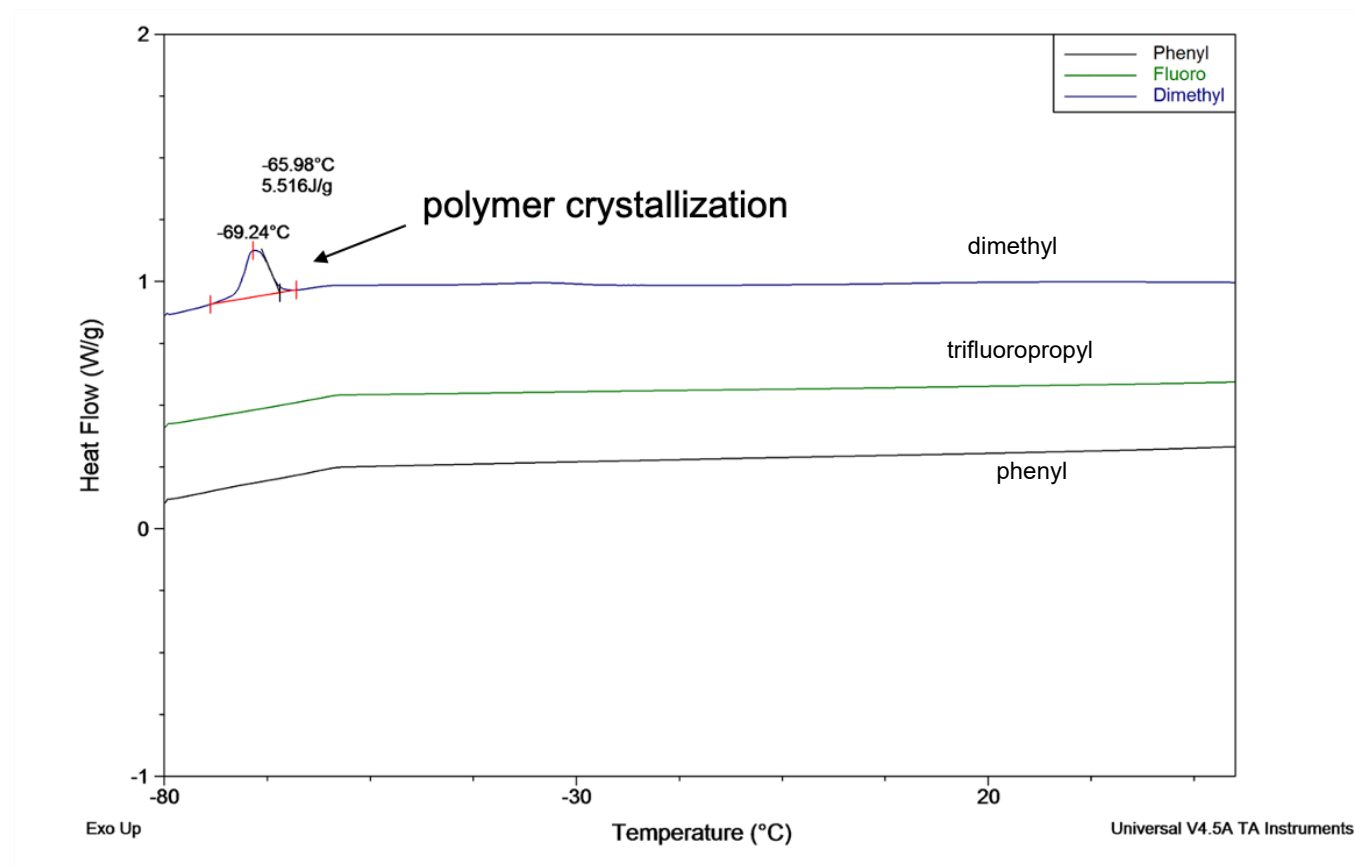


A. Impact of critical material attributes: polymer functionality



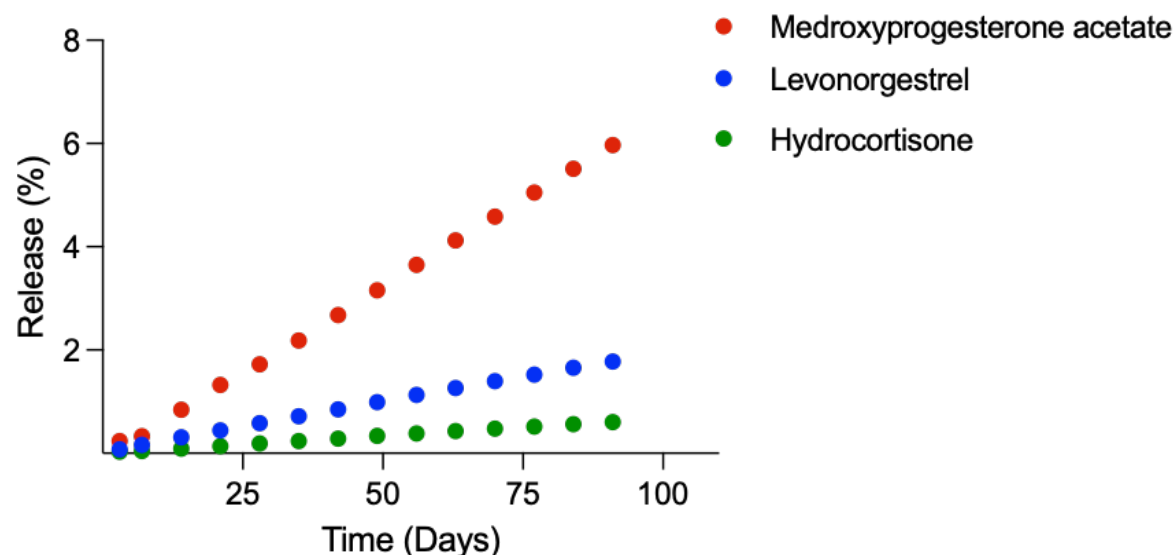
Key determinants?

1. Partition coefficient
2. Diffusion coefficient



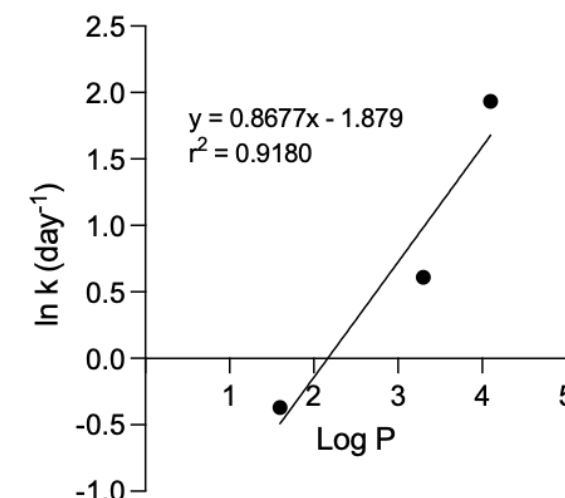
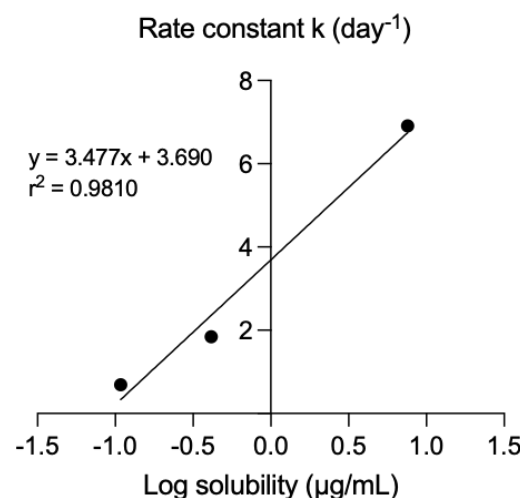
A. Impact of critical material attributes: drug physicochemical properties

Evidence of diffusion-controlled release mechanism



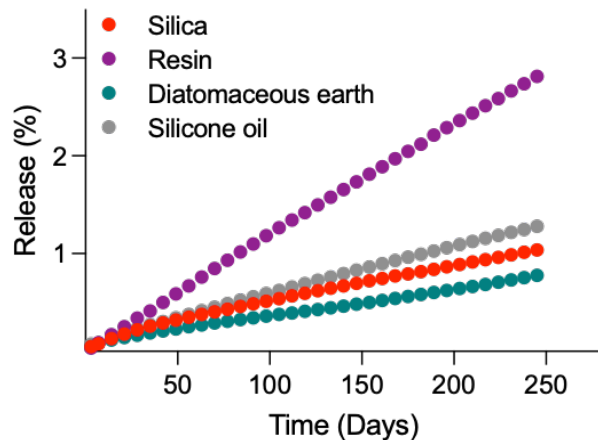
Physicochemical attributes dictating drug release from IUSs

Drug	Log P	Mol. Wt (g/mol)	Solubility in polymer (µg/mL)	Melting point (°C)
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

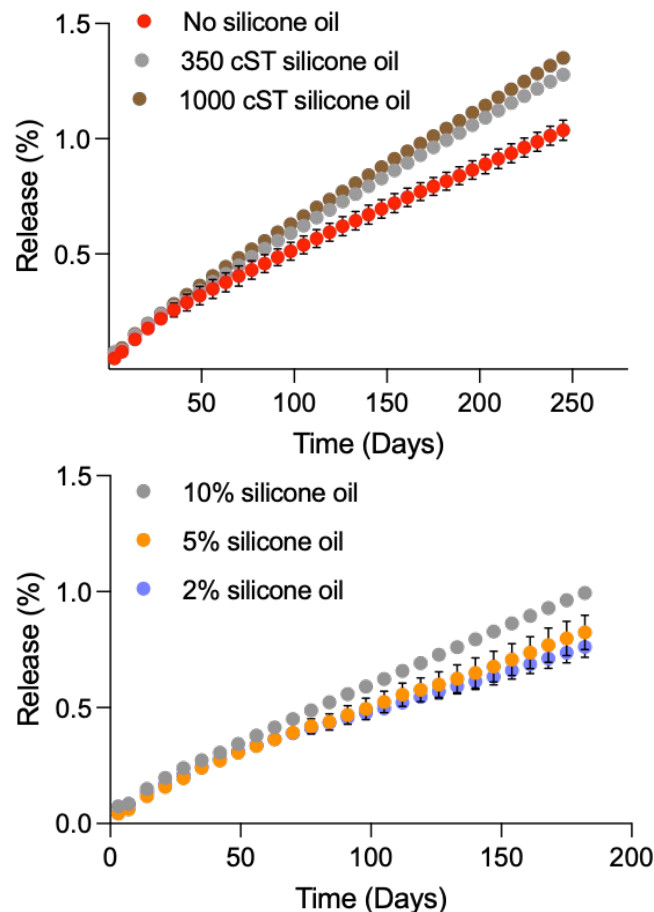


A. Impact of critical material attributes: role of additives

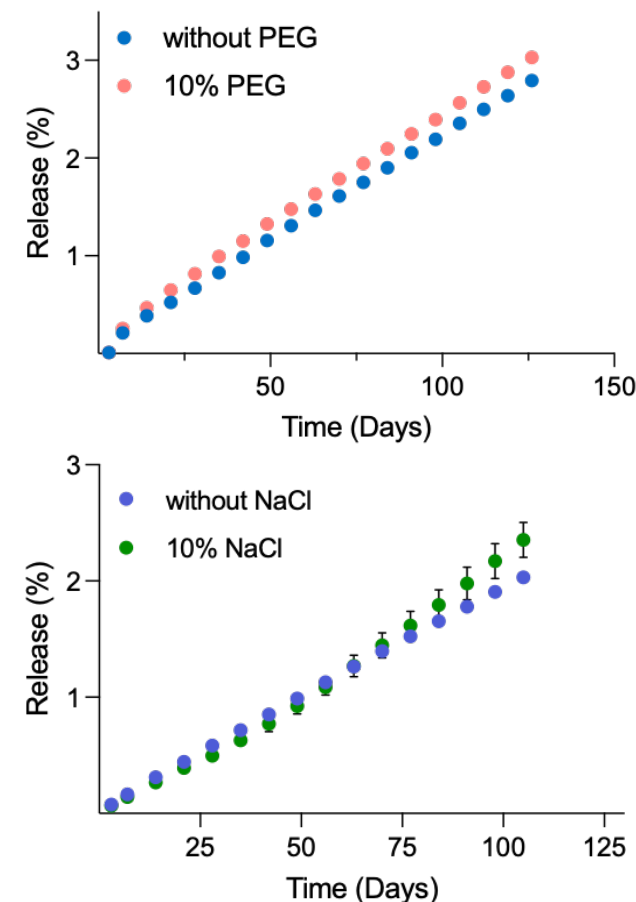
Matrix hydrophobicity and drug-excipient interactions are critical



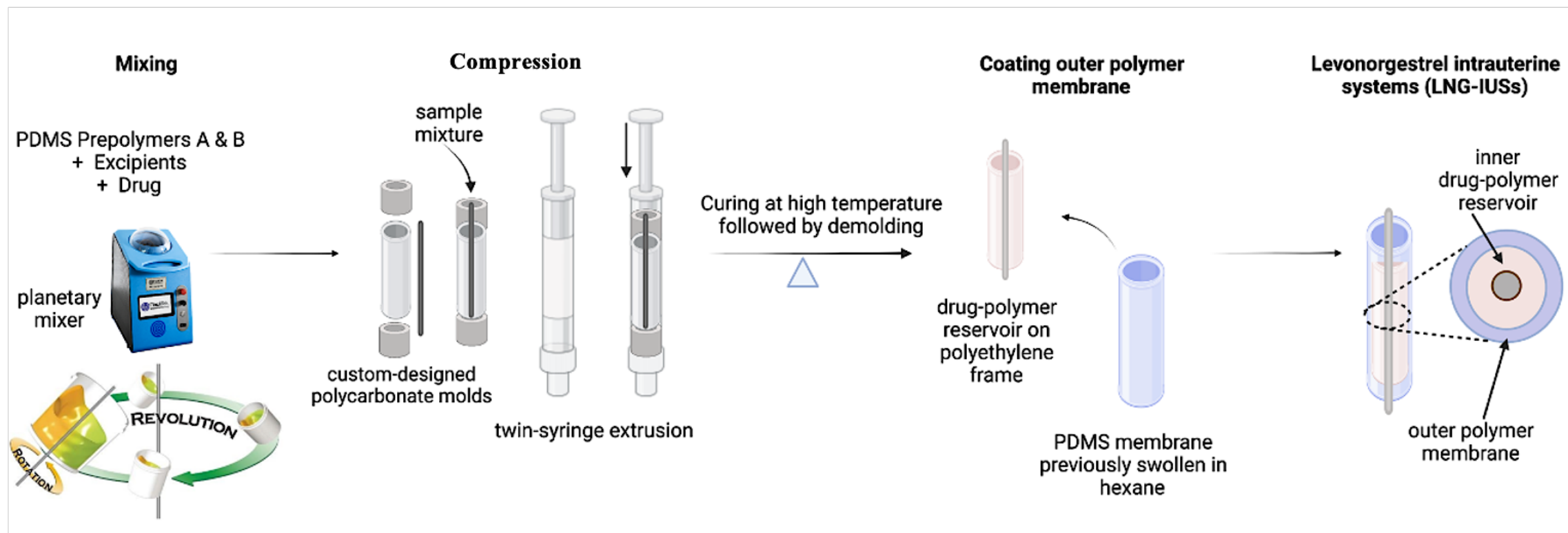
Excipients providing a low-viscosity matrix facilitate faster drug release



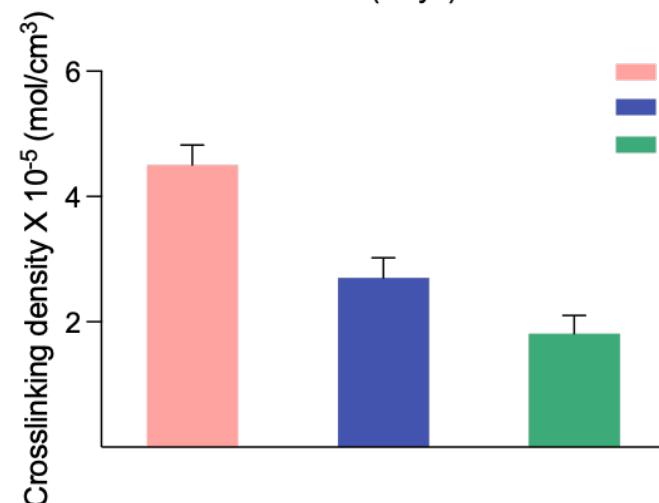
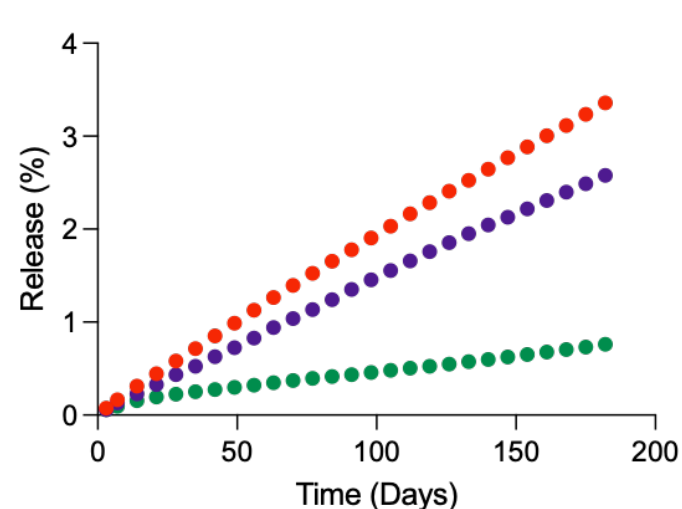
Porosity and osmosis may not be significant contributors to drug release



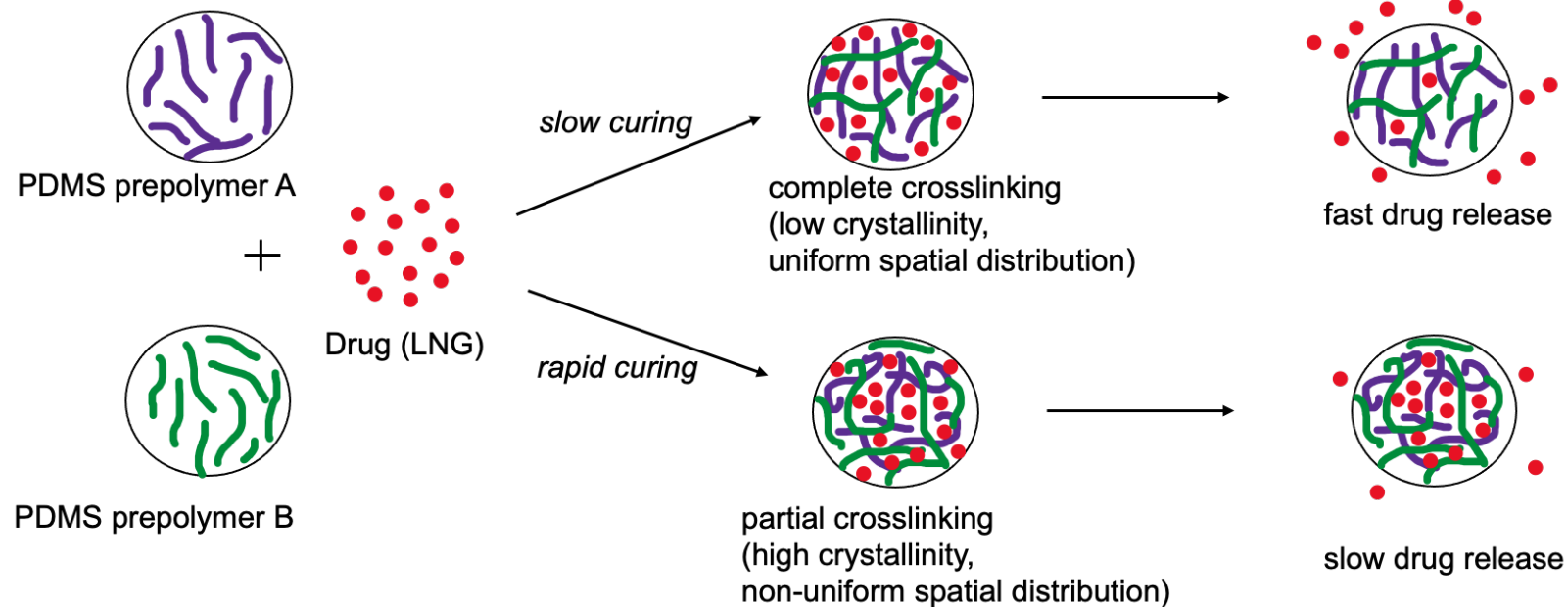
B. Influence of processing parameters



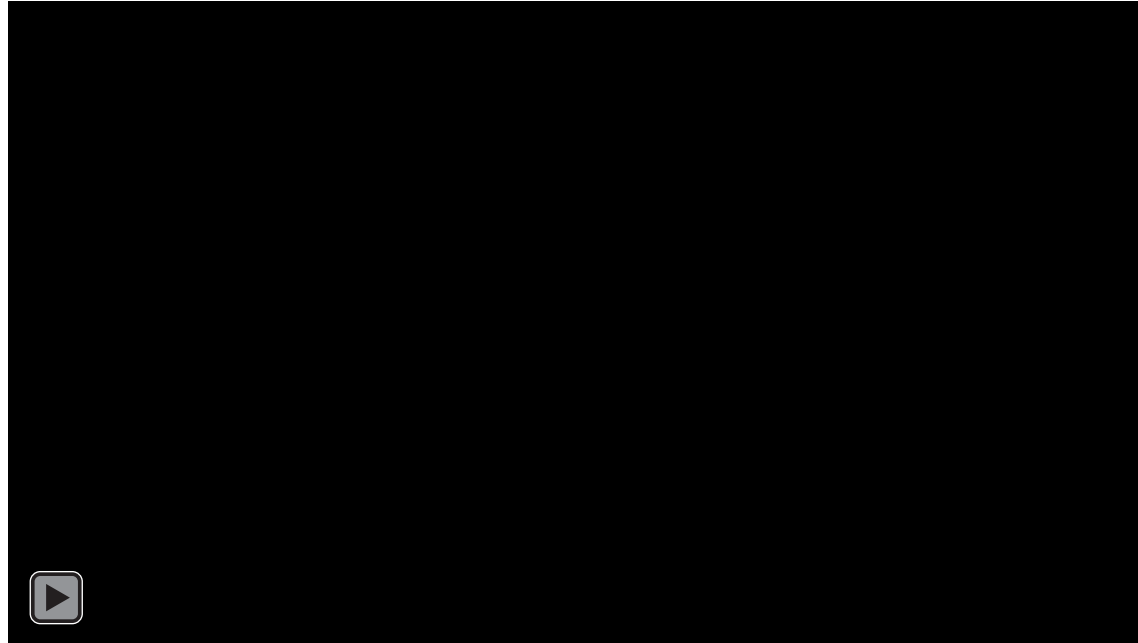
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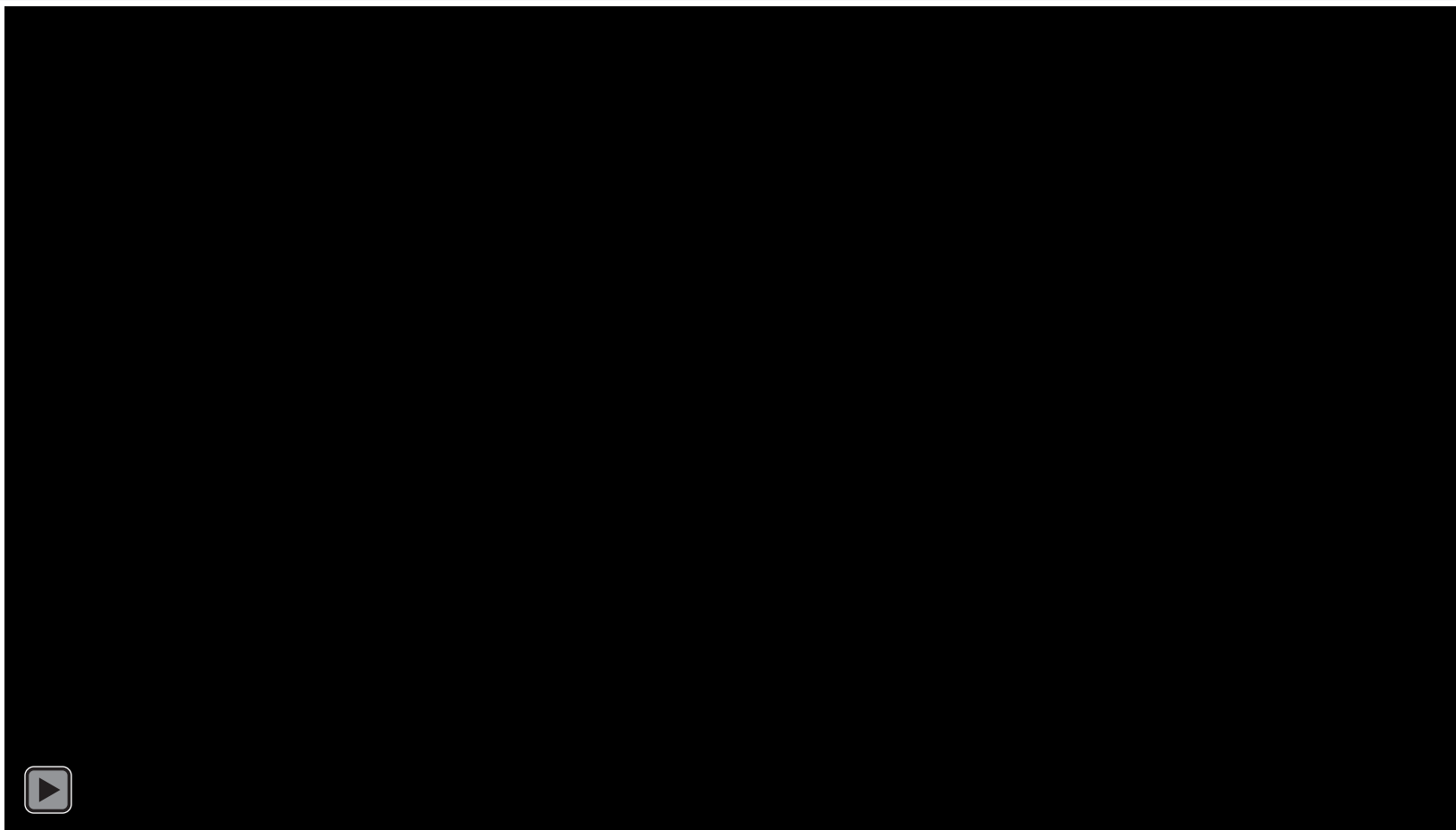
Degree of polymer crosslinking is dependent on curing rate



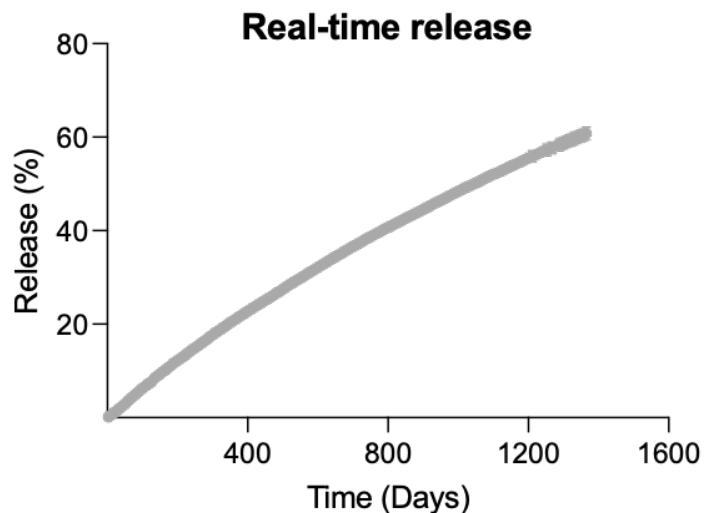
C. Elucidating drug release mechanisms



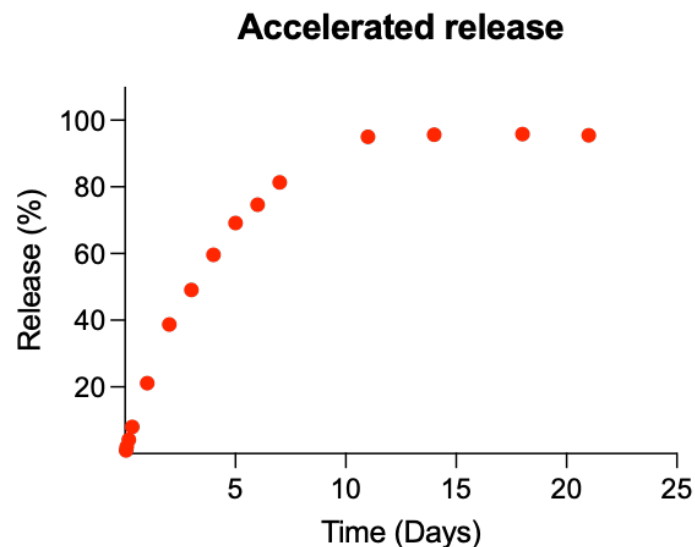
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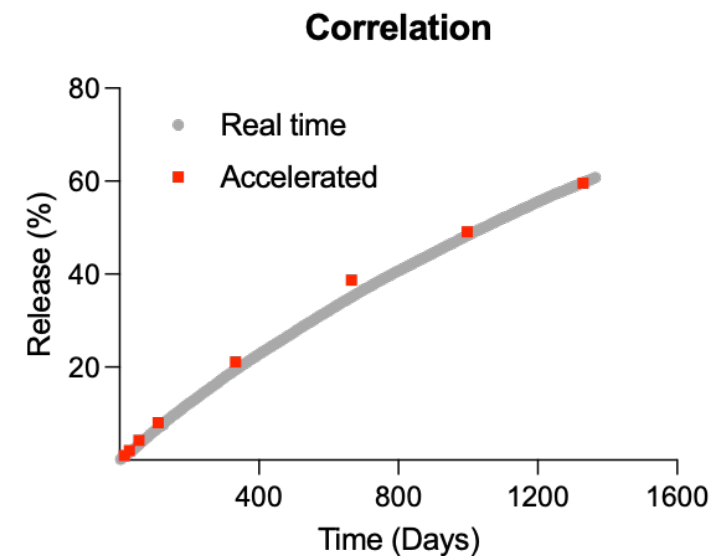
D. Bioequivalence testing through *in vitro* approaches



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



IUS- 10% w/w drug loading
45% v/v tert-butanol in PBS, 65°C, 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.

Acknowledgements

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CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

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