Effect of Polymer Crosslinking on Release Mechanisms from Long-acting Intrauterine Systems

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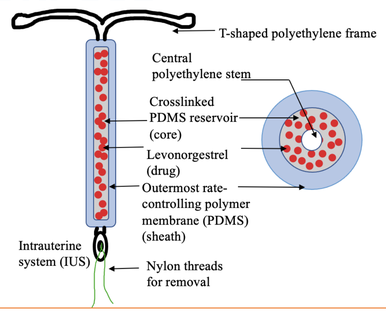
PURPOSE



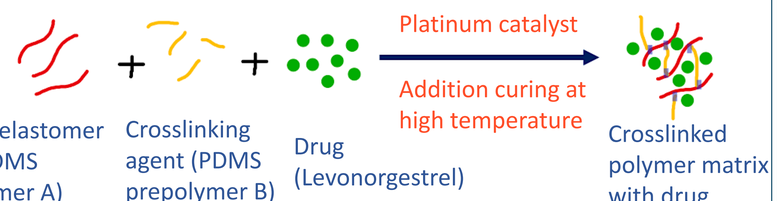
Contraceptive Levonorgestrel intrauterine systems (LNG-IUSs) such as Mirena® are long-acting complex drug-devices designed to provide drug release for 3 - 7 years.

Limited IUS products on market

Challenges:

- Polydimethylsiloxane (PDMS): complex excipient
- Impact of critical material attributes
- Drug release mechanisms

Critical attribute: polymer crosslinking density



Crosslinking density affects the physicochemical properties of the formulation and drug release

METHODS

Different prepolymer ratios → To achieve a range of polymer crosslinking densities in LNG-IUSs

- Mixing of prepolymers A and B
- Extrusion through custom designed polycarbonate molds to form cylindrical implants
- Outer PDMS coating (previously swollen in hexane)

Formulation characterization

DSC; wide-angle XRD; SEM; solid-state ^{29}Si NMR; mercury intrusion porosimetry polymer swelling studies

In vitro drug release

In vitro drug release using 45% v/v tert-butanol in PBS in a water shaker bath at 65°C at 100 rpm

RESULTS

High drug release rates with greater crosslinking density

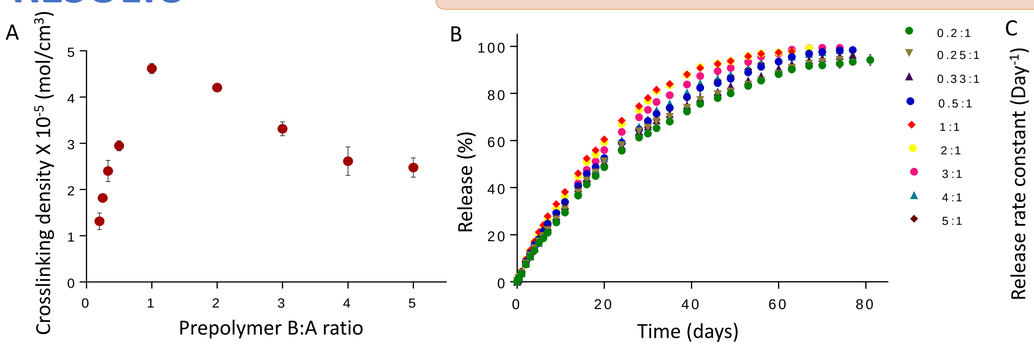


Fig. 1. A) PDMS crosslinking densities (mol/cm^3) of LNG-IUSs with different prepolymer ratios; **B)** *in vitro* drug release profiles of LNG-IUSs with different prepolymer B:A ratios; **C)** correlation between the first order release rate constant and PDMS crosslinking density in LNG-IUSs. (mean ± SD, n=3).

Polymer crystallinity decreases at high crosslinking density

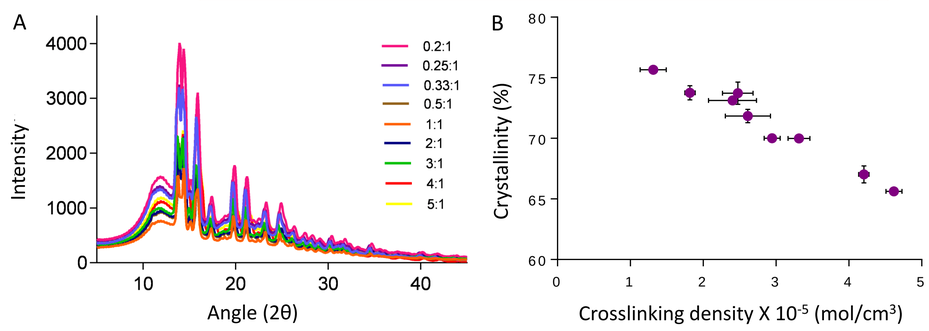


Fig. 2. A) Wide angle X-ray diffraction pattern of formulations with different crosslinking densities; **B)** relationship between polymer crystallinity and crosslinking density. (mean ± SD, n=3).

Molecular weight of polymer chains between two successive crosslink junctions is directly proportional to crosslinking density

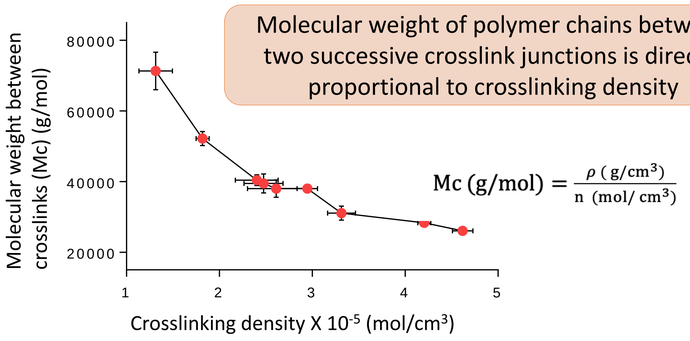
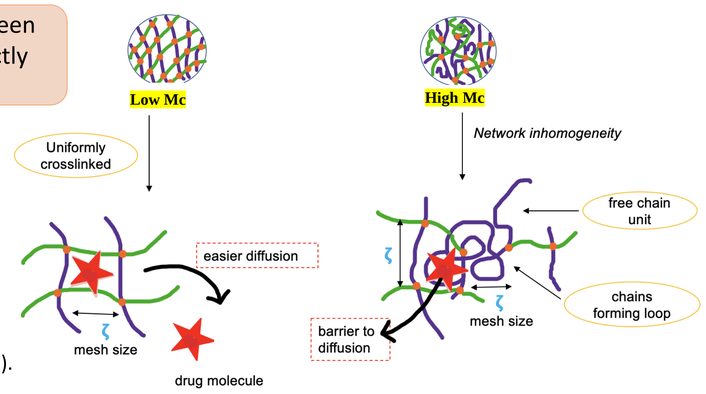


Fig. 3. Mc as a function of PDMS crosslinking densities in LNG-IUSs (mean ± SD, n=3).



High porosity: rapid solvent swelling: fast drug release

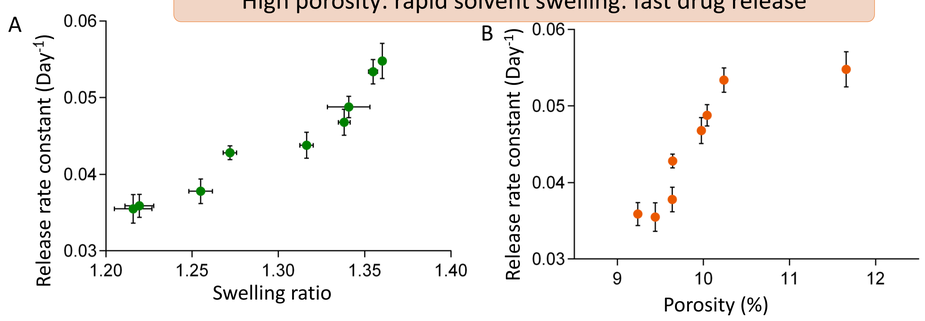


Fig. 4. A) Wide angle X-ray diffraction pattern of formulations with different crosslinking densities; **B)** Relationship between polymer crystallinity and crosslinking density. (mean ± SD, n=3).

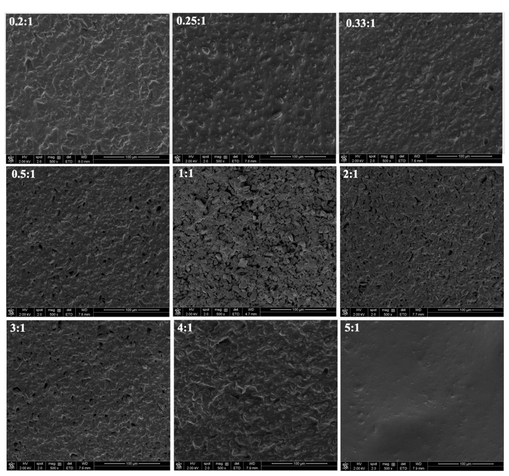
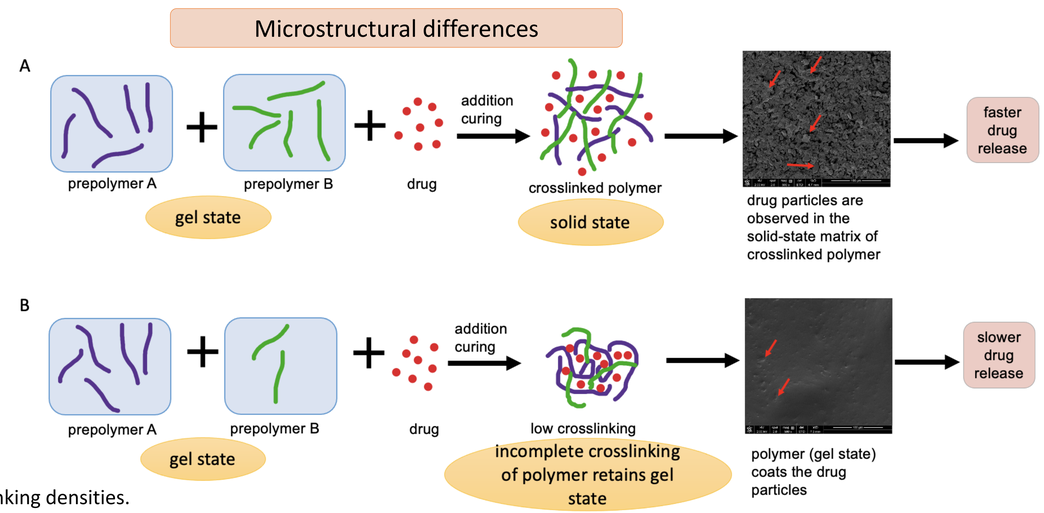


Fig. 5. SEM images (500X) of formulations with different crosslinking densities.

Microstructural differences



High polymer hydrophobicity: Rapid dissolution of lipophilic drug (LNG)

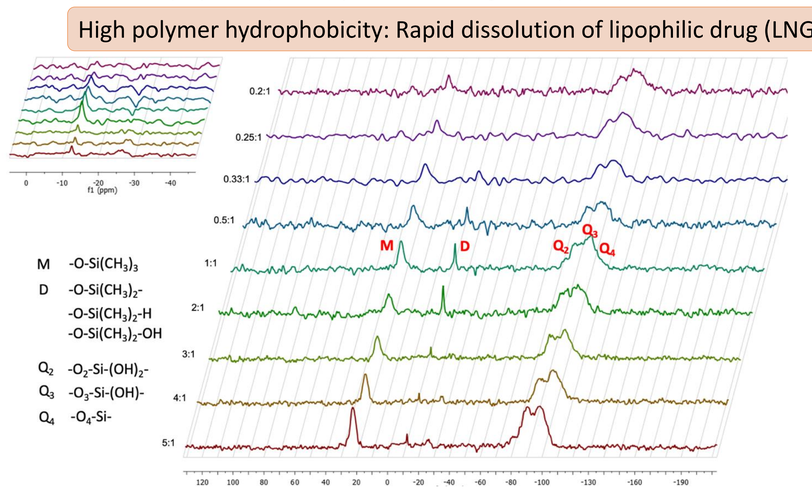


Fig. 6. Solid-state silicone NMR of formulations with different crosslinking densities.

CONCLUSIONS

- Controlling the degree of crosslinking of LNG-IUSs can be used to tune the drug release kinetics of these long-acting formulations.
- Drug release from LNG-IUSs was influenced by polymer crystallinity, porosity-controlled swelling, hydrophobicity, and the the diffusion barrier created by the polymer matrix.
- The current study provides enhanced understanding of drug release from LNG-IUSs and will facilitate the development of their generic equivalents.

ACKNOWLEDGEMENTS

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This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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