Tailoring Drug Release from Long-Acting Contraceptive Levonorgestrel-Containing Intrauterine Systems

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Suraj Fanse[1], Quanying Bao[1], Yuan Zou[2], Yan Wang[2], Diane J. Burgess[1]

[1]University of Connecticut, School of Pharmacy, Storrs, CT, USA
[2]Office of Research and Standards, Office of Generic Drugs, CDER, U.S. Food and Drug Administration, Silver Spring, MD, USA

CONTACT INFORMATION: suraj.fanse@uconn.edu; d.burgess@uconn.edu

PURPOSE

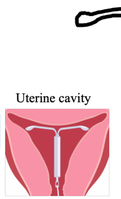
Levonorgestrel intrauterine systems (LNG-IUSs) are drug-device combination products releasing hormonal contraceptive drug for 3-8 years.

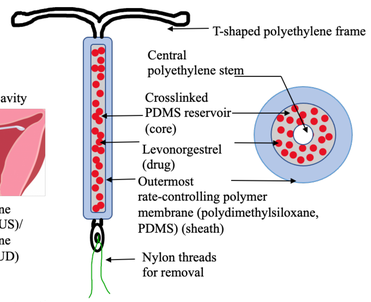
Complex design combining monolithic and matrix systems of controlled release

Limited generic IUS products on market

Challenges:

- Complex excipients
- Impact of critical material attributes
- Influence of processing parameters
- Drug release mechanisms





Objectives: *(i)* to identify and investigate the impact of critical material attributes (CMAs) and critical processing parameters (CPPs); *(ii)* to investigate the role of excipients on product performance; and *(iii)* to elucidate drug release mechanisms.

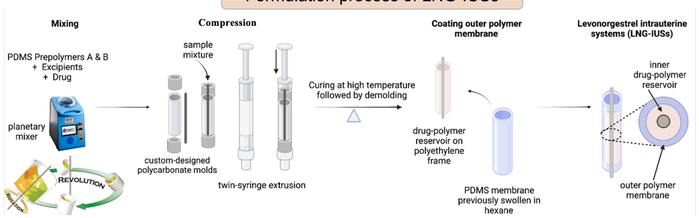
➡ Improve product understanding

⬇

Enable the rational development of LNG-IUS generics.

METHODS

Formulation process of LNG-IUSs



Approach

i. Manufacturing variables: mixing methods, polymer curing temperature and time.

ii. Material attributes: polymer molecular weight, polymer chemistries, additives and fillers.

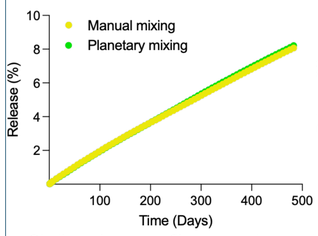
iii. Model drugs with different physicochemical properties (medroxyprogesterone acetate (MPA), levonorgestrel (LNG), hydrocortisone (HTC)

Microstructure and molecular properties: DSC, XRD, SEM, ^{13}C solid-state NMR, thermogravimetric analysis (TGA), ultra-performance liquid chromatography (UPLC) and dynamic mechanical analysis (DMA).

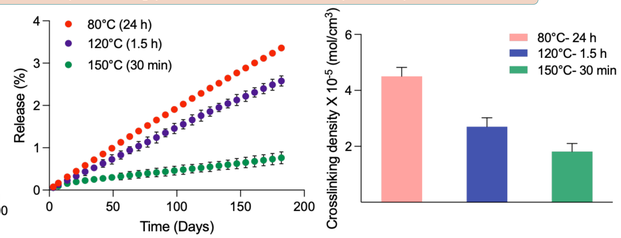
All the measurements were performed in triplicate. Results are reported as mean ±SD.

RESULTS

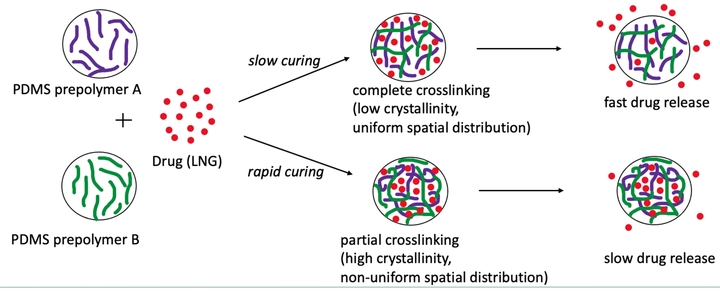
Influence of processing parameters on LNG-IUS product performance



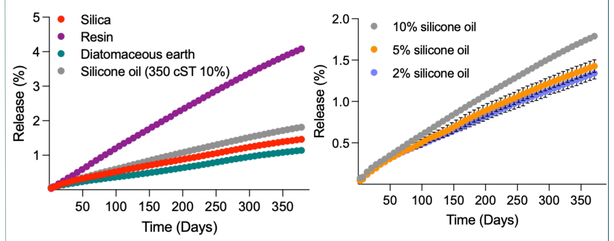
Similar release profiles were observed using different mixing methods.



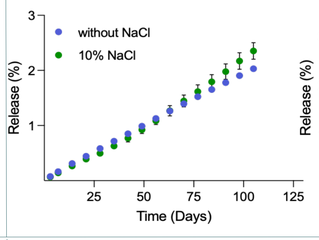
Changes in curing temperature and time have a significant impact on the crosslinking density and subsequent drug release.

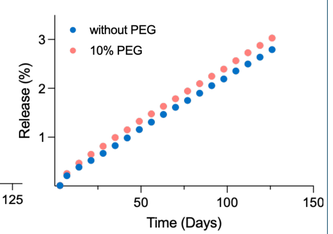


Drug release can be tuned using different additives

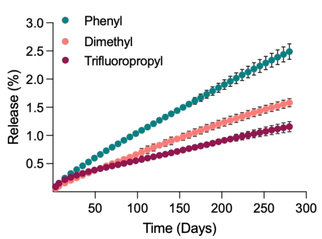


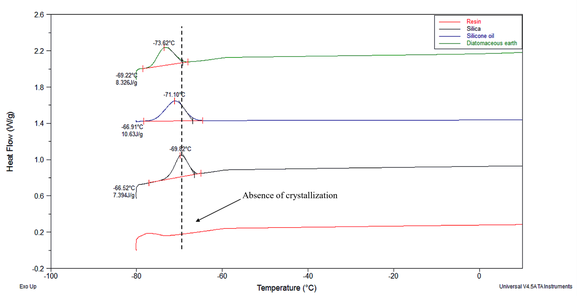
Porosity and osmosis may not be significant factors contributing to drug release





Investigation of critical polymer characteristics affecting drug release from LNG-IUSs

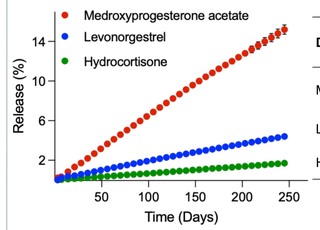




Polymer functional group substitution	Drug solubility in polymer (S)[1]	Drug diffusivity (D)[2]	Permeability K∝ S* D
Phenyl	High	High	High
Dimethyl	High	Low	Intermediate
Trifluoropropyl	Very low	High	Low

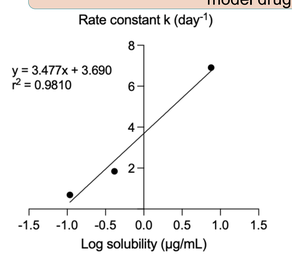
[1]Drug solubility (lipophilic LNG) in polymer was dictated by polymer hydrophobicity (difference in solubility parameter of drug and polymer).
[2] Drug diffusivity in polymer was dictated by polymer crystallinity and drug-polymer interactions.

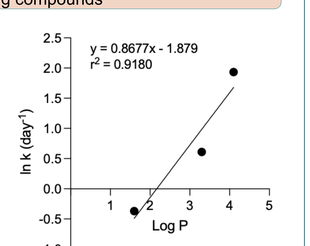
Evidence of diffusion-based release mechanism



Drug	Log P	Mol. Wt (g/mol)	Solubility in polymer (µg/mL)	Melting point (°C)
MPA	4.1	386.5	7.5730	214.5
LNG	3.3	312.4	0.4139	240
HTC	1.6	318.1	0.1084	220

Correlation between release rates and physicochemical properties of model drug compounds





CONCLUSIONS

CMAs ⟶ Polymer chemistry, additives
CPPs ⟶ Curing temperature and time

- Drug permeability (release) was dictated by a balance between drug solubility in the polymer matrix (partitioning) and drug diffusivity.
- Elucidating the material-property-processing relationship of LNG-IUSs will guide: ***(a)*** the rational selection of excipients; and ***(b)*** the optimum manufacturing design space.
- Allow tailoring of drug release to establish bioequivalence with commercial reference listed drugs (RLDs) to facilitate the development of generic IUSs and improve women's health.
- Furthermore, insights obtained from the current study will be beneficial to the development of other PDMS-based controlled-release products.

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