Role of Excipients on Drug Release from Long-Acting Intrauterine Systems

T0930-03-14

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PURPOSE

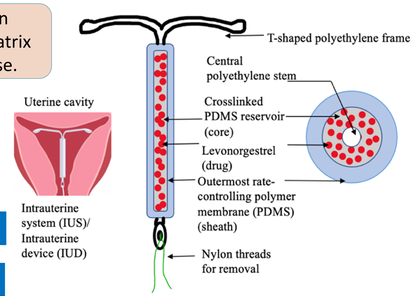
Levonorgestrel intrauterine systems (LNG-IUSs) are drug-device combination products releasing hormonal contraceptive drug for 3-8 years.

IUSs have a complex design combining monolithic and matrix systems of controlled release.

Limited IUS products on market

Challenges:

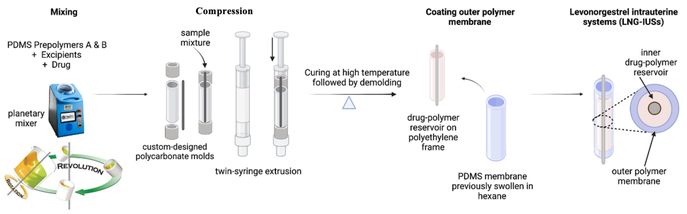
- Complex excipients
- Impact of critical material attributes
- Drug release mechanisms



Accordingly, **the objectives of this work** were to investigate the impact of excipients on formulation attributes and *in vitro* drug release from LNG-IUSs, elucidate drug release mechanisms, and thereby obtain improved product understanding.

METHODS

Formulation process of LNG-IUSs



Approach

i. Different additives: silica, silicone resin, diatomaceous earth, silicone oil

ii. Effect of osmotic agents (NaCl) and pore-formers (PEG)

iii. Model compounds with different Log P and molecular weight (Medroxyprogesterone acetate, levonorgestrel, diclofenac, metronidazole)

Impact of excipients and factors influencing drug release

Drug loading *via* UPLC, characterization *via* DSC and SEM, as well as *in vitro* drug release testing using 0.9% w/v sodium chloride in a water shaker bath at 37°C at 100 rpm were carried out for all the formulations.

RESULTS

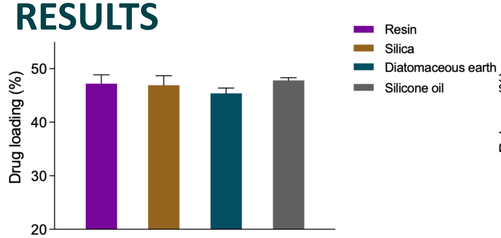


Fig. 1. Drug loading of LNG-IUSs containing different additives (n=3 ± SD).

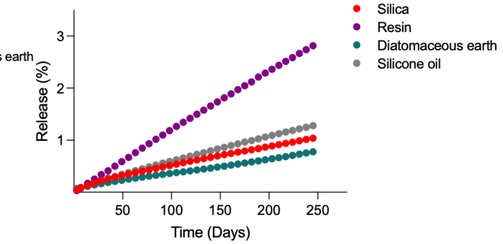


Fig. 2. *In vitro* release of LNG-IUSs containing different additives (n=3 ± SD).

Excipients affect matrix crystallinity

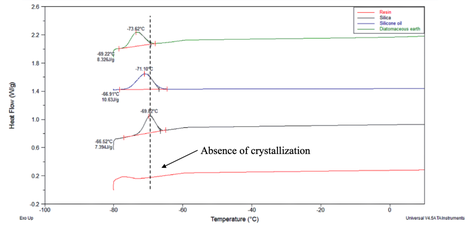
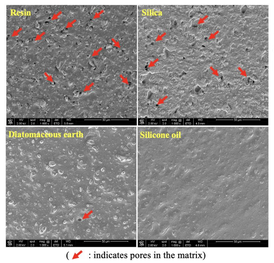


Fig. 3. Effect of additives on polymer crystallization determined *via* DSC.

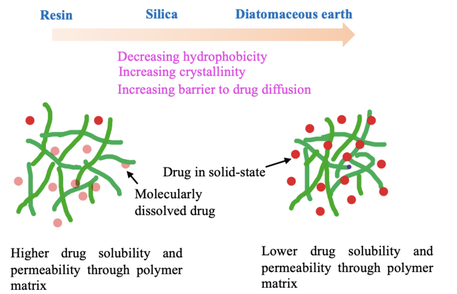


(: indicates pores in the matrix)

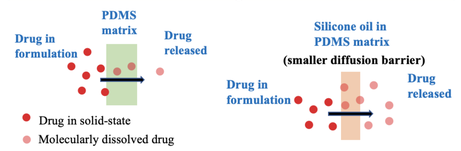
Fig. 4. Microstructure evaluation using SEM (1000X magnification).

Differences observed:
a. Porosity
b. Surface morphology

Physicochemical characteristics of excipients dictating drug release



Excipients providing a low-viscosity matrix facilitate faster drug release



Lubricants may influence release only when added in high concentrations (during manufacturing)

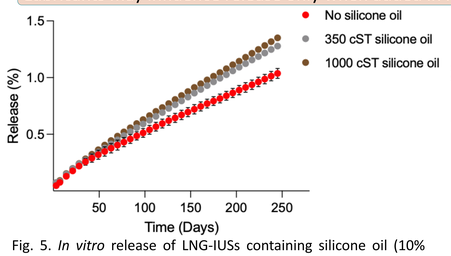


Fig. 5. *In vitro* release of LNG-IUSs containing silicone oil (10% w/w) with different viscosities (n=3 ± SD).

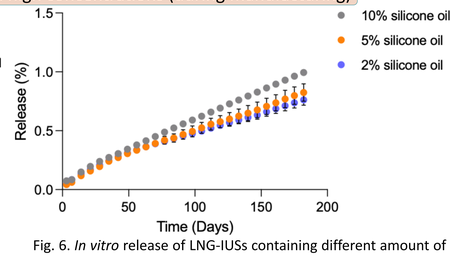
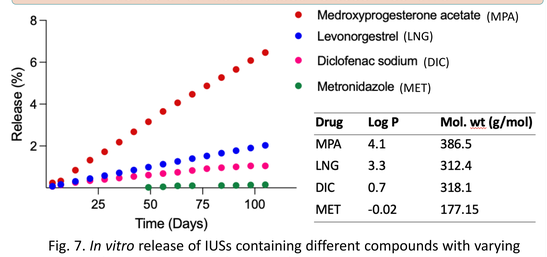


Fig. 6. *In vitro* release of LNG-IUSs containing different amount of silicone oil (350cST) (n=3 ± SD).

Evidence of diffusion-based release mechanism



Drug	Log P	Mol. wt (g/mol)
MPA	4.1	386.5
LNG	3.3	312.4
DIC	0.7	318.1
MET	-0.02	177.15

Fig. 7. *In vitro* release of IUSs containing different compounds with varying physicochemical properties (n=3 ± SD).

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

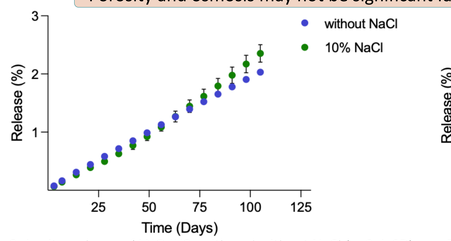


Fig. 8. *In vitro* release of LNG-IUSs with and without NaCl (n=3 ± SD).

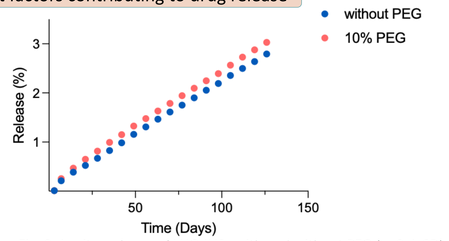
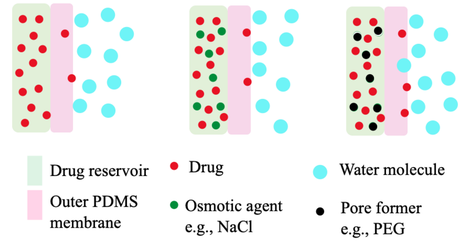


Fig. 9. *In vitro* release of LNG-IUSs with and without PEG (n=3 ± SD).



CONCLUSIONS

1. Excipients affect the hydrophobicity, crystallinity and viscosity of the matrix which subsequently influences drug release.
2. The presence of osmotic agents and pore formers in the reservoir did not drastically increase the release rate highlighting that solvent penetration is limited by the presence of the outer polymer membrane. Thus, the outer polymer membrane may be the rate-controlling component in IUSs.
3. High drug release rates of compounds with a large log P (lipophilicity) substantiates that drug release occurs by drug solubilization in the hydrophobic polymer matrix and subsequent diffusion through the outer polymer membrane.
4. Overall, this research highlights the significance and role of excipients in tailoring drug release from long-acting IUSs and provides improved understanding of release mechanisms which can help guide formulation development.

FUNDING

Funding for this project was made possible by a U.S. Food and Drug Administration grant (1U01FD005443-01). This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.