Understanding Release Mechanism and Development of Accelerated Release Tests for Long-term Intrauterine Systems

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PURPOSE

The complex product design and the long in vivo application duration present unique challenges for developing generic levonorgestrel (LNG) intrauterine systems (IUSs). To this end, FDA has published a draft product-specific guidance (PSG) on LNG-IUS recommending a combination of in vitro, in vivo/ex vivo studies referencing the brand-name LNG-IUS, Mirena[1]. Although the PSG-recommended short-term (1-year) in vivo study design significantly reduces the burden on the clinical evaluation side, recommended long term (5 years) in vitro drug release testing can be challenging. Therefore, understanding the formulation design and drug release mechanism is critical for developing an accelerated in vitro drug release testing (IVRT) method without changing the drug release mechanism.

OBJECTIVES

- The short-term goal of this current study is to explore potential accelerated IVRT methods for LNG-IUSs by better understanding the drug release mechanism.
- The long-term goal is to facilitate development of generic LNG-IUSs by providing science-based recommendations on IVRT for bioequivalence purpose.

METHODS

Real-time in vitro release testing for the commercial LNG-IUS (Skyla) was performed at 37±5°C and 100 rpm in 0.9% NaCl release media. Possible solvents for accelerated drug release studies were selected based on Hanson Solubility Parameter (HSP) analysis. HSP approach was utilized to explain LNG-IUS accelerated release data from literature[2]. Water permeability of the polydimethylsiloxane (PDMS) membrane was investigated. Disc Shaped Drug Reservoir-Membrane (DR-M) system that mimic the drug release mechanism of IUS was fabricated by compression molding. The drug release rates of fabricated DR-M systems in selected solvents were investigated using vertical diffusion cells and fiber optic-based UV-spectroscopy. The impact of drug release on the microstructure of Skyla IUS was investigated using artificial intelligence (AI) assisted surface scanning electron microscopy (SEM) and Focused ion beam scanning electron microscopy (FIB-SEM).

RESULTS

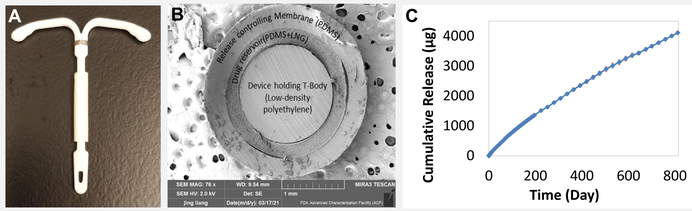

Figure 1. A. Skyla LNG-IUS. B. Cross-section of the Skyla LNG-IUS. C. In-vitro real-time drug release profile of Skyla LNG-IUS.

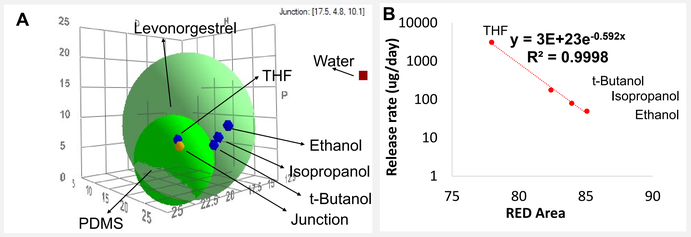

Figure 2. A. Overlay of HSP solubility spheres for Levonorgestrel and PDMS showing selected solvents. B. RED area vs. accelerated release rate from Bao et al., 2019 showing exponential increase of release rate with decreasing RED area (R^2 = 0.9998).

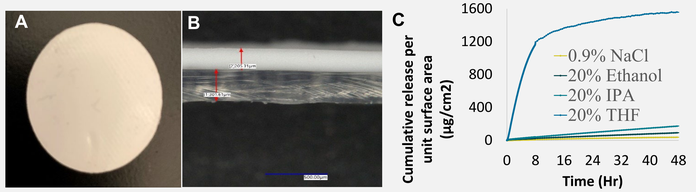

Figure 2. A. Drug Reservoir-Membrane (DR-M) system. B. Cross section of DR-M system. C. Drug release in different solvents form DR-M system

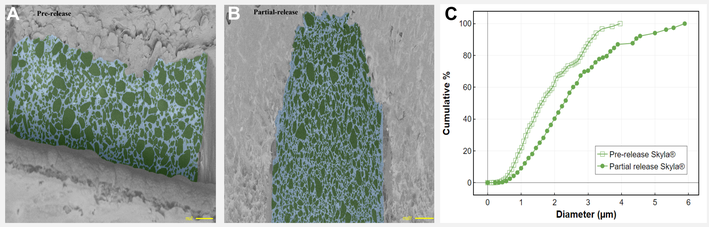

Figure 3. Similar drug concentrations in A. Pre-release, and B. Partial release of Skyla IUS samples as revealed by AI segmentation. C. Comparable LNG size distributions between pre-release and partial release samples.

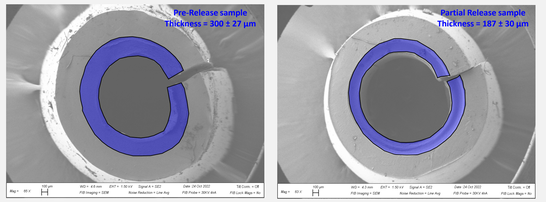

Figure 4. Impact of Drug Release on IUS Drug Reservoir. 25% of drug release caused a 40% reduction in the IUS drug reservoir volume.

- Drug release from the IUS was found to be biphasic (**Figure 1C**). Initial first order release indicated release from the saturated membrane while beginning of zero order release indicated establishment of steady state.
- PDMS membrane was found to be impermeable to aqueous solvents, suggesting partitioning as the main mechanism of drug release.
- Accelerated Drug release rates were found to correlate well with the release trend predicted by HSP analysis (**Figure 2A and 3C**).
- The faster drug release rate in THF may be attributed to a change in the release mechanism from partitioning to solvent mediated diffusion as PDMS is permeable to THF (**Figure 3C**).
- The drug release rates were directly correlated with Relative Energy Difference Area (RED-Area) as was the case with previously published release data[2] (**Figure 2B**).
- The particle size distribution of drug in pre-release and partial release Skyla IUS samples was found to be similar (**Figure 3**) indicating that the release medium did not come in contact with drug in the inner reservoir due to the impermeable PDMS membrane.
- The AI-assisted microstructural analysis of Skyla IUS samples revealed a significant decrease in the volume of inner drug reservoir possibly due to the pressure exerted on the inner drug reservoir by the outer elastic membrane (**Figure 4**).

CONCLUSIONS

- Membrane-mediated drug partitioning appears to be the main mechanism of drug release from the IUS due to the impermeability of PDMS membrane to water.
- The experimentally determined accelerated drug release rates in selected solvents followed the same order as predicted by HSP analysis.
- HSP values of drug, polymer, and the solvent may be used to predict the release behavior of drug from the polymer and may help in developing accelerated IVRT.
- Work is in progress to understand the implications of drug release on microstructure changes in the LNG-IUS to elucidate drug release mechanism.

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DISCLAIMER

The views expressed in this poster do not reflect the official policies of the U.S. FDA or HHS; nor does any mention of trade names, commercial practices, or organization imply endorsement by the U.S. Government.

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