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Understanding the Drug Release Mechanism of Long-term Intrauterine Systems

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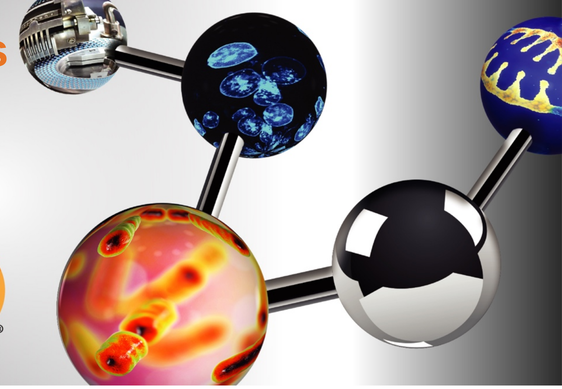


PURPOSE

Levonorgestrel (LNG) intrauterine systems (IUSs) are an effective and reversible long-term contraception method. There are four different brand-name LNG-IUSs available in the U.S. market without any generic competition. All the IUSs consist of a T-shaped polyethylene frame, a silicone (polydimethylsiloxane, PDMS)-based drug reservoir, and a PDMS-based drug release controlling membrane (Figures 1A and 1B). The long in vivo application duration (e.g., 3–6 years) and complex product design present unique challenges to the development of generics. To date, FDA has published a product-specific guidance (PSG) that outlines FDA's recommended studies to develop a generic IUS 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, the recommended long-term (5-year) in vitro drug release testing can still be cumbersome. In this regard, mechanistic understanding of formulation design and performance of LNG-IUS through developing novel accelerated in vitro drug release testing is critical. In most cases, the selection of the test conditions and release media for accelerated release study is done empirically on a trial-and-error basis. For a more rational approach to identify appropriate accelerated release conditions, we propose to explore the use of Hansen Solubility Parameters (HSP), which reflect thermodynamics of materials, as a guiding factor. This approach also provides a more fundamental understanding of the drug release mechanism of LNG-IUS.

METHODS

Real-time in vitro release testing for the commercial LNG-IUS (Skyla®) was performed using a temperature-controlled incubating orbital shaker at 37±5 ºC and 100 rpm in 0.9% NaCl release media. LNG concentration in the release media was determined using a validated HPLC method. Solubility study of LNG and PDMS in different solvents was done to determine the HSP values for LNG and PDMS respectively. HSPiP software package (Steven Abbott TCNF Ltd, Ipswich, UK) was used to determine the solubility ranking of different solvents for both LNG and PDMS ((2, 3). HSP approach was used to explain LNG-IUS accelerated release data from literature (4). Water permeability of the PDMS membrane was determined by examining the permeation of Methylene Blue aqueous solution through the PDMS membrane using Hanson Vision® Microette™ automated diffusion test system. Several short-term release studies were conducted to determine the time required for the drug to saturate the PDMS membrane. IUS samples were placed in 0.9% NaCl as release media at 37 ± 5 ºC and 100 rpm for 5 hours to monitor initial release rates. IUSs were then dried at room temperature for different intervals (1 to 30 days) before subsequent release testing.

RESULTS

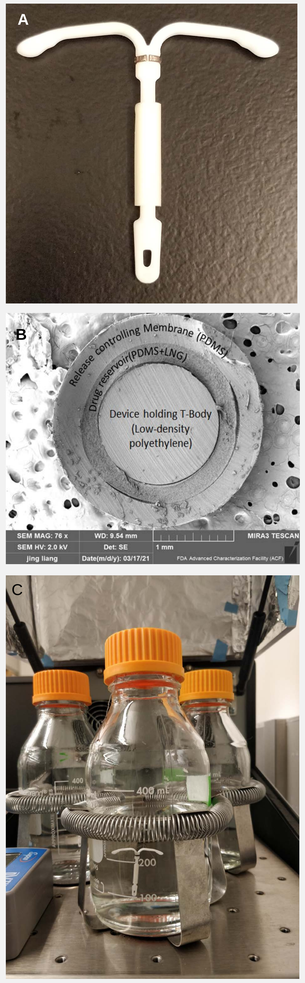
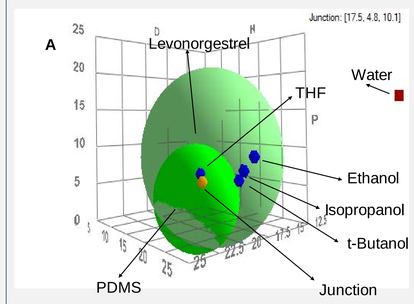
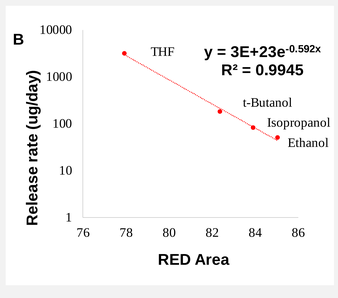


Figure 1. A. *Skyla LNG-IUS.* ***B.*** *Cross-section of the Skyla LNG-IUS.* ***C.*** *Real-time Release Study Setup*

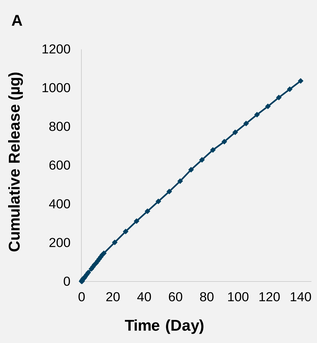


Overlay of HSP solubility spheres for Levonorgestrel and PDMS

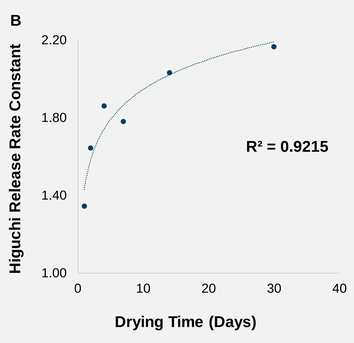


Relative Energy Difference (RED) area vs accelerated release rate

Figure 2. A. *Overlay of HSP solubility spheres for Levonorgestrel and PDMS with associated solvents used by Bao et al., 2019. solubility sphere of PDMS has significant overlap with the solubility sphere of LNG.* ***B.*** *RED area vs. accelerated release rate from Bao et al., 2019 showing exponential increase of release rate with decreasing RED area (R^2 = 0.9945).*



Real- Time Release



Drug Saturation Study

Figure 3. A. *In-vitro real-time drug release profile of LNG-IUS (Skyla®).* ***B.*** *Relationship of Higuchi release rate to LNG-IUS (Skyla®) drying time shows the time for drug saturation is between 7 to 14 days.*

- Solubility sphere of PDMS has significant overlap with the solubility sphere of LNG, indicating that the drug is highly soluble in the polymer (Figure 2A).
- Water permeability testing of the PDMS membranes demonstrates the impermeability of the PDMS membranes to highly polar (lyophobic) molecules.
- Drug saturation in the membrane takes between 7 to 14 days (Figure 3).
- Processing of existing release data from Bao et. al., 2019 showed a direct correlation between drug release rates and Relative Energy Difference Area (RED-Area), a term coined to describe the area covered by the drug, polymer, and solvent in 3D Hansen space (Figure 2B).

CONCLUSIONS

- The drug release mechanism of LNG-IUSs in an aqueous environment appears to be solely mediated by the partitioning of the drug from reservoir to membrane then to the release media.
- Utilization of HSP space may provide predictive power for selecting accelerated release media and enable a deeper understanding of the release mechanism for polymeric membrane-based drug delivery systems.

ACKNOWLEDGMENT

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DISCLAIMER

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

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