Accelerated Drug Release Method for Long-Acting Levonorgestrel Intrauterine Systems

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Quanying Bao[1], Yuan Zou[2], Yan Wang[2], Darby Kozak[2], Stephanie Choi[2], Diane J. Burgess[1]

[1] University of Connecticut, School of Pharmacy, Storrs, CT 06269, USA

[2] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA

CONTACT INFORMATION: d.burgess@uconn.edu; quanying.bao@uconn.edu

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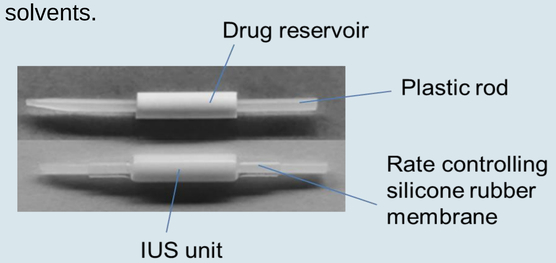
PURPOSE

- The research and development of long-acting (5 years) levonorgestrel intrauterine systems (IUS) is challenging due to the extremely long duration of drug release. The marketed product (Mirena®) is a locally acting slow release (average daily release of 20 µg) hormonal intrauterine device for long term contraception. Accordingly, it is important to develop reliable accelerated drug release testing methods to screen the *in vitro* performance of these formulations during the early development phase.
- Accelerated release testing methods can include elevation of release temperature as well as addition of surfactants or organic solvents. Ideally the accelerated method should expedite the evaluation process of the long-acting IUS without changing the underlying mechanism of release.

METHODS

- Levonorgestrel IUS drug reservoirs with 50% drug loading were prepared by mixing with an uncrosslinked, liquid, silicon polymer (liquid silicone rubber, Nusil®) that is then cured at 80°C for 20 hours to form the 50% silicone rubber reservoir.
- The drug reservoir was cut into 100 mg units and a rate controlling silicone rubber elastomer membrane was then applied by first swelling the membrane in hexane and then pulling it over the drug reservoir.
- Drug release was tested in real-time at 37°C using 0.9% NaCl as the media. Accelerated drug release testing was performed at 45°C in pH 7.4 PBS with 0.25% SDS and 20% alcohol (ethanol, isopropanol or tert-butanol).
- Due to the length of the studies, a water bath shaker with a rotation speed of 100 rpm was used for both real-time and accelerated release testing. An effort was made to correlate the drug release rate to the swelling ratios of the crosslinked silicone rubber in the different organic solvents.



RESULTS

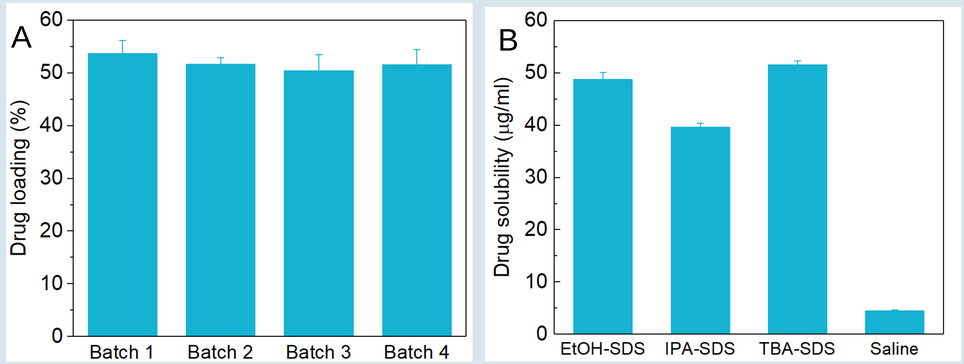


Figure 1. **A)** Drug loading and content uniformity of the prepared levonorgestrel IUS (four batches, sampling from three different regions of the IUS; THF was used to extract the drug and diluted using mobile phase); **B)** equilibrium solubility of levonorgestrel in different release media. (EtOH-SDS, IPA-SDS and TBA-SDS: abbreviations represent 20% (v/v) of ethanol, isopropanol or tert-butanol, respectively in pH7.4 PBS containing 0.25% (w/v) SDS.

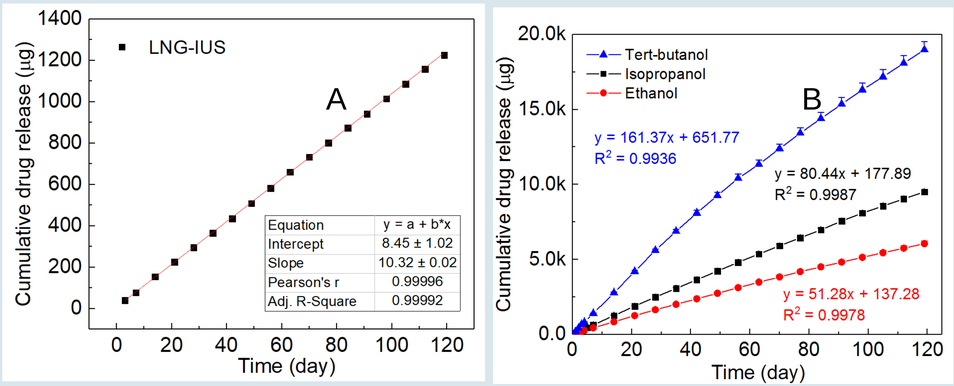


Figure 2. **A**) Real-time release profile of levonorgestrel IUS (LNG-IUS) in normal saline at 37°C; and **B**) Accelerated drug release profiles of prepared levonorgestrel IUS in pH 7.4 PBS and 20% (v/v) of one of the organic solvents (ethanol, isopropanol and tert-butanol) with 0.25% (w/v) SDS added to this hydroalcoholic media.

[1] Lee, Jessamine Ng, Cheolmin Park, and George M. Whitesides. Solvent compatibility of poly (dimethylsiloxane)-based microfluidic devices. Analytical chemistry 75.23 (2003): 6544-6554.

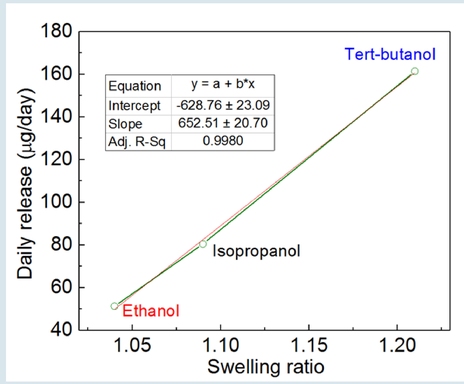


Figure 3. Linear regression plot of the accelerated daily release against the swelling ratios of silicone polymer in different organic solvents [1].

CONCLUSIONS

- Addition of organic solvents can accelerate the drug release rate of long-acting IUS to a certain extent.
- A strong correlation was revealed between the accelerated release rates and the swelling ratios of the crosslinked silicon rubber in the organic solvents. Drug release was controlled by the swellability of the silicon matrix in the solvents.

ACKNOWLEDGEMENTS

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