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In Vitro Release Testing Methods for Long-Acting Intrauterine Systems

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PURPOSE

- The development and testing of long-acting (*e.g.*, 3-5 years) levonorgestrel (LNG) intrauterine systems (IUSs) like MIRENA® is challenging due to their complex formulation and extremely long duration of drug release.
- To achieve the long duration of drug release of the LNG-IUS, a large amount of LNG (up to 52 mg in MIRENA®) is required to be incorporated in the drug reservoir. Consequently, dose dumping or unanticipated changes in the *in vivo* release characteristics of the LNG-IUS may lead to adverse effects or altered ~~product safety and~~ efficacy.
- Therefore, to ensure product quality and equivalence, it is crucial to establish a reproducible physicochemical testing method as well as a robust *in vitro* release testing

MATERIALS AND METHODS

Materials

Levonorgestrel with a particle size of 16 µm was purchased from Tecoland Corporation (Irvine, CA, USA). Liquid silicone rubber (MED-4840 Part A and Part B) was purchased from NuSil™ (Carpinteria, CA, USA). Sodium chloride and sodium dodecyl sulfate (SDS) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Unless otherwise specified, all materials were of analytical grade.

Methods

- The LNG-IUSs were prepared using the twin-syringe model method described previously **(Figure 1)**[1]. Polydimethylsiloxane (PDMS)-based cylindrical LNG-IUS drug reservoirs with 50% w/w LNG were prepared using a mold and were cured at 80°C for 20 hours. The drug reservoir was cut into 100 mg per unit and a rate controlling silicone rubber elastomer membrane was applied by first swelling the membrane in hexane, and then pulling it over the drug reservoir.

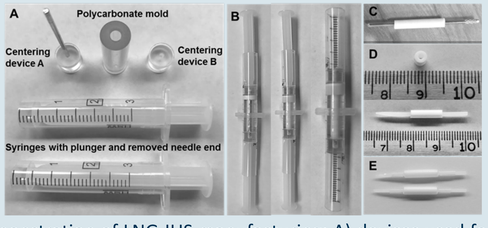

Figure 1. Pictorial demonstration of LNG-IUS manufacturing: A) devices used for preparation of IUS drug reservoirs; B) the processes of extrusion of PDMS polymer and LNG mixture to form the drug reservoirs; C) the resultant LNG drug reservoir with steel rod; D) 100 mg standard LNG reservoir with plastic rod; and E) LNG-IUS (with release controlling membrane)[1].

- Real-time drug release was tested at 37°C using 300 ml of 0.9% w/v NaCl and 0.25% w/v SDS in pH 7.4 PBS as the media. The *in vitro* release test was performed using either a **water bath shaker** with a rotation speed of 100 rpm or an **USP apparatus 2** (Xtend, Sotax) with an agitation speed of 100 rpm (**Figure 2**).
- The sampling plan was as follows: 1 mL samples were withdrawn on Days 3 and 7, and replenished with fresh media. Following the Day 7 sampling, all the media in the bottles were drained and replenished with fresh media. Thereafter samples were withdrawn weekly and all the media in the bottles was drained and replenished with fresh media following sampling.

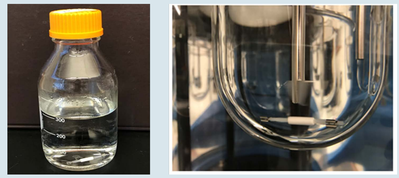

Figure 2. Pictorial demonstration of *in vitro* drug release from LNG-IUSs using water bath shaker and USP apparatus 2 methods.

RESULTS

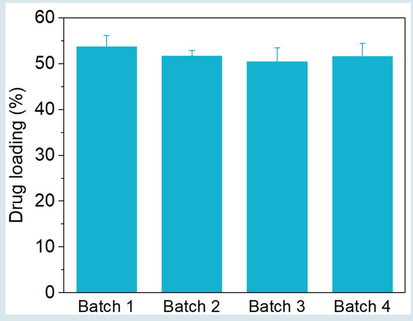

Figure 3. Drug loading and content uniformity of the prepared levonorgestrel IUS (four batches, sampling from three different regions of the IUS; THF was used to extract the drug and diluted using mobile phase).

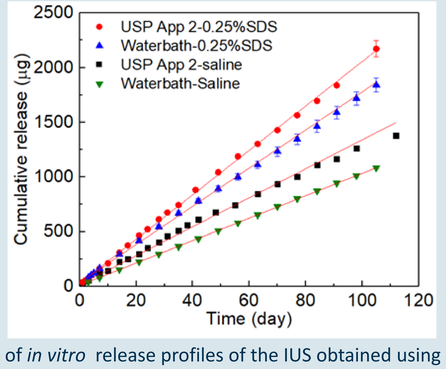

Figure 4. Linear regression of *in vitro* release profiles of the IUS obtained using USP apparatus 2 and water bath shaker methods in different release media at 37°C (average values ± standard error, n=3).

Table 1. Zero-order model fitting of the drug release profiles of IUS-1 using different release methods and release media.

	Intercept	Intercept	Slope	Slope	Statistics
	Value	Standard Error	Value	Standard Error	Adj. R-Square
USP App2-0.25%SDS	26.27	5.46	20.30	0.16	0.9988
Water bath-0.25%SDS	35.43	2.57	17.44	0.16	0.9986
USP App2-Saline	16.02	1.74	13.24	0.16	0.9970
Water bath-Saline	9.33	0.84	10.25	0.03	0.9999

CONCLUSIONS

- Real time drug release testing is still on going. The current available drug release profiles obtained from both water bath shaker and USP apparatus 2 showed zero-order release kinetics. The two methods are comparable in terms of the reproducibility of the release data.
- The use of SDS can increase the daily drug release to the same extent using both release testing methods.
- However, the set-up of USP apparatus 2 had issues with media evaporation and mechanical issues that may need to be addressed for the *in vitro* release testing of the long-acting LNG-IUS.

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REFERENCE

1. Bao, Q., Gu, B., Price, C.F., Zou, Y., Wang, Y., Choi, S., Kozak, D. and Burgess, D.J., 2018. Manufacturing and characterization of long-Acting levonorgestrel intrauterine systems. International journal of pharmaceutics, 550(1-2), pp.447-454.

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