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The Effect of Crosslinking Reagent Ratio of a 5-Year Contraceptive Implant on Drug Release

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PURPOSE

Levonorgestrel intrauterine systems (IUS) are highly effective and reversible contraceptives that deliver small amounts of levonorgestrel locally from a drug reservoir through a release-controlling membrane over a period of several years. In order to ensure the safety and efficacy of these drug products, it is critical to identify and evaluate manufacturing processes that may affect drug release, despite Q1 (qualitative) and Q2 (quantitative) sameness. In this study, the crosslinking density of the elastomer in the drug reservoir was investigated to determine the effect on drug release. Manufactured drug reservoirs were prepared with three different crosslinking reagent ratios and the drug release rates were evaluated.

METHOD

1. Preparation of drug reservoirs

Drug reservoirs containing levonorgestrel (LNG) (50%, w/w) were prepared by mixing PDMS (polydimethylsiloxane) base solution and curing agent (Silastic® MDX4-4210, vinyl-terminated, Dow Corning) at three different ratios (10:1, 6:1, and 4:1, w/w). These samples were first degassed for 1 hour under vacuum at room temperature, and then cured at 80°C for 18 hours. A representative drug reservoir is shown below.

1. Characterization of drug reservoirs

- *Solid-state NMR analysis*: The prepared PDMS drug reservoirs were analyzed using ^{29}Si solid-state NMR (Bruker Avance III 400 MHz) at 10 kHz.
- *Drug loading*: Tetrahydrofuran (THF) was used to extract LNG from the prepared drug reservoirs. Briefly, approximately 5 mg of drug reservoir was immersed in 10-mL of THF using 25 mL volumetric flasks and then sonicated in a bath sonicator for approximately 1 hour until the reservoirs became fully swollen and transparent. Additional THF was added into the flasks to reach a total of 25 mL followed by vigorous mixing to obtain a homogeneous LNG solution. 100 µL of filtered LNG solution was then diluted to 1 mL using 95% methanol for HPLC analysis following sample vortexing.

***3. In vitro* release testing**

5 mg pieces of the manufactured drug reservoirs (without the release-controlling membrane) were incubated in glass bottles containing release media (0.25% SDS in PBS) under sink conditions. The glass bottles were incubated at 37°C in a shaker bath and the media was sampled and changed twice a week. Levonorgestrel content was determined *via* HPLC.

RESULTS

1. ^{29}Si Solid-State NMR

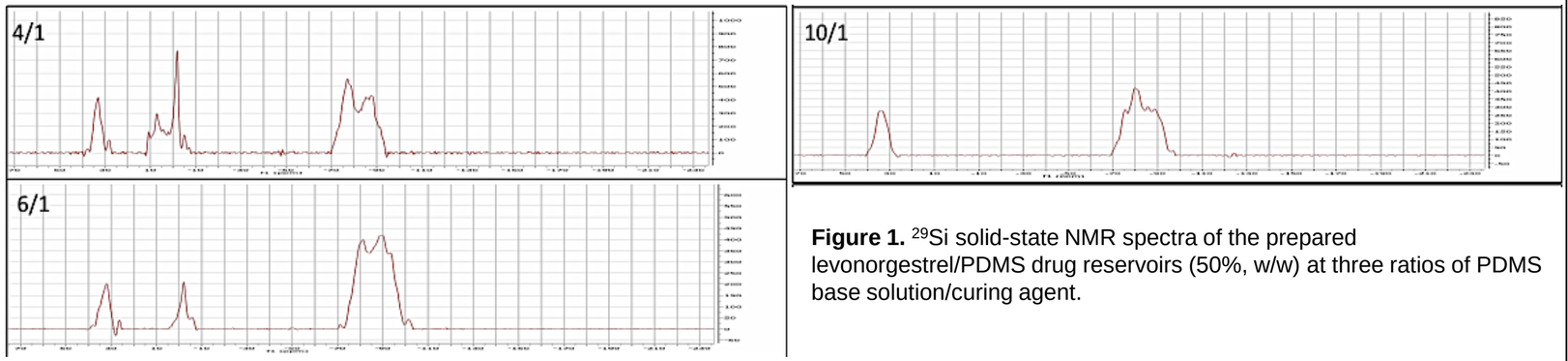

Figure 1. ^{29}Si solid-state NMR spectra of the prepared levonorgestrel/PDMS drug reservoirs (50%, w/w) at three ratios of PDMS base solution/curing agent.

The NMR spectra reveals differences between the structures of the manufactured drug reservoirs, as evidenced by the different ppm values and different peak shapes. For example, when comparing the manufactured drug reservoirs, all three NMR spectra show broad peaks around 30 ppm and 80 ppm. However, only the 4:1 and 6:1 formulations show peaks around 0 ppm, and these peak shapes differ between the two formulations.

***2. In vitro* release profiles**

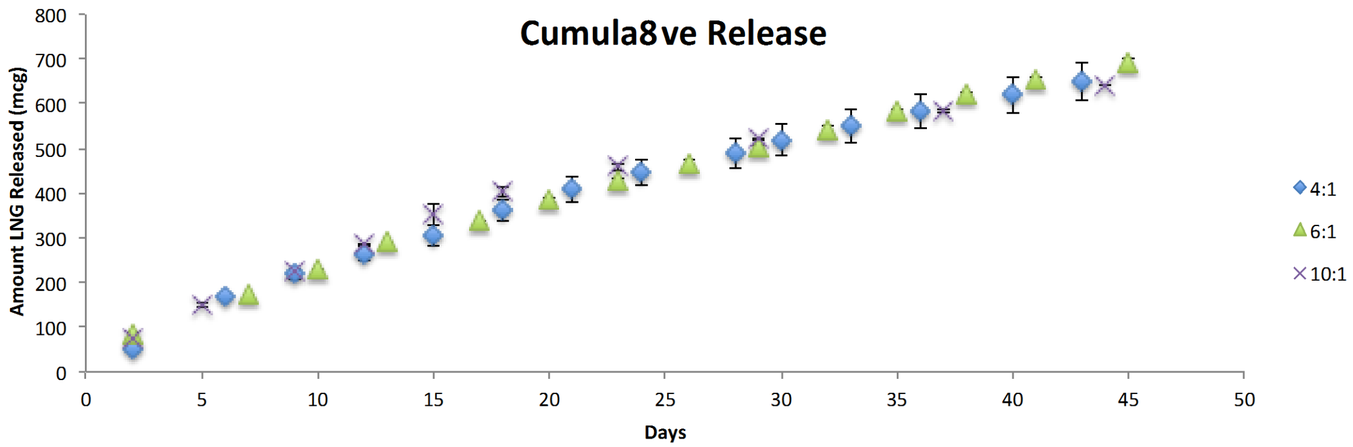

Figure 2. Cumulative release of levonorgestrel from manufactured PDMS drug reservoirs of three different formulations (4:1, 6:1, and 10:1 base solution/curing agent, w/w).

CONCLUSIONS

Differences in the cross-linking reagent ratio of PDMS drug reservoirs (resulting from varied concentrations of the curing agent) can be characterized *via* solid-state NMR but do not result in different drug release profiles when tested for a period of 30 days. Therefore, structural differences in the components of drug reservoirs do not appear to be a critical manufacturing parameter of long acting intrauterine hormone devices during the initial 45 day release period. Additional work is warranted to determine the effect of crosslinking on long-term drug release.

FUNDING/DISCLAIMER

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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.