Impact of polymer crosslinking on the properties and performance of levonorgestrel intrauterine systems

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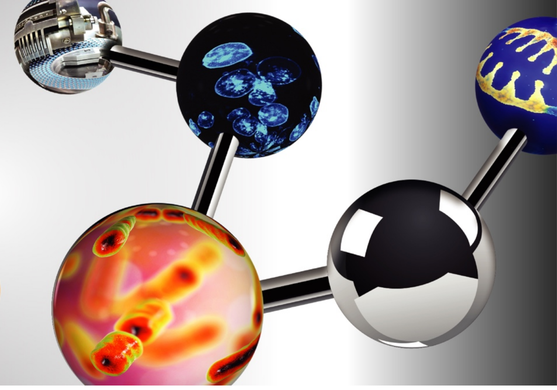
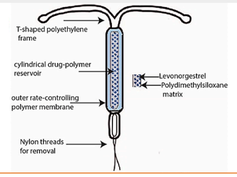


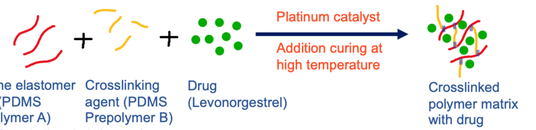
PURPOSE



Levonorgestrel intrauterine systems (LNG-IUSs) such as Mirena® are long-acting complex products designed to provide drug release for contraception over a period of 3-6 years.

High drug loading to sustain extended drug release

Unintended consequences associated with the possible premature release of large quantities of drug



[Text] The ratio of the PDMS elastomer base and the crosslinking agent used significantly impacts the degree of crosslinking achieved in these products, which may influence drug release.

[Text] Accordingly, it is critical to understand the physicochemical properties and the drug release characteristics of LNG-IUSs with different degrees of crosslinking prepared with various ratios of PDMS elastomer base and crosslinking agent.

METHODS

LNG-IUS drug reservoirs with 50% w/w LNG were cured at 80°C for 20 hours. Five different formulations were prepared using different ratios of the PDMS prepolymers A and B (MED-4840 Nusil®). Prepolymer A contains the PDMS elastomer base along with a catalyst, and prepolymer B contains the crosslinking agent. The degree of crosslinking in the formulations was determined by a solvent swelling method using tetrahydrofuran and hexane (Fig. 1).

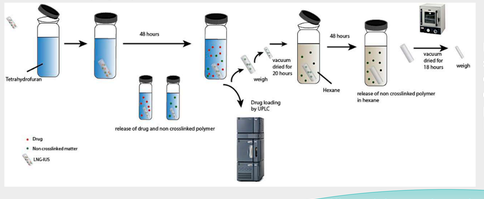


Fig.1. Demonstration of the solvent swelling and extraction method used to determine the degree of polymer crosslinking in the LNG-IUSs

Characterization: Differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA), mechanical strength by TA.XT Plus texture analyzer, Morphology using Scanning electron microscopy (SEM), Porosity by Mercury Intrusion Porosimetry (MIP)

In vitro drug release: Accelerated *in vitro* drug release testing was performed (media: 45% v/v tert-butanol in PBS at 65°C) using a water shaker bath at 100 rpm. Real time *in vitro* drug release testing was carried out in saline at 37°C using a water shaker bath at 100 rpm.

RESULTS

The degree of crosslinking increased initially as prepolymer B (crosslinking agent) was increased until an optimum ratio of 1:1 was reached. Further increase in the molar ratio of prepolymer B/A resulted in a lower degree of crosslinking which could be due to the insufficient amount of catalyst required for crosslinking.

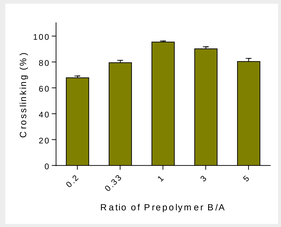


Fig.2. The effect of prepolymer ratio (B/A) on the degree of crosslinking (%) (mean ± SD, n=3)

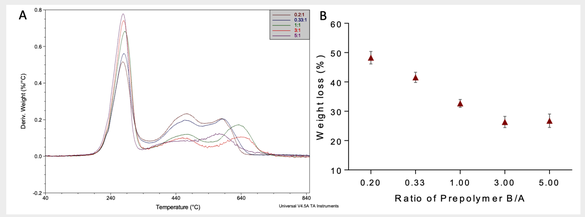
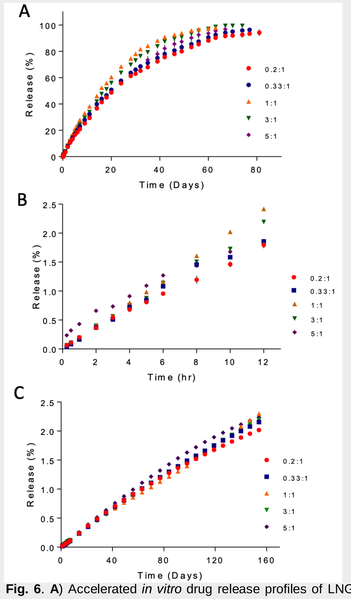


Fig.4.A) Derivative weight (%/ °C) vs temperature (°C) of the LNG-IUSs prepared using different ratios of prepolymers A and B
B) The effect of prepolymer ratio (B/A) on the weight loss (%) of LNG-IUSs using TGA (mean ± SD, n=3)



The formulations with a higher crosslinking had faster drug release under the accelerated conditions. All the formulations followed first order release kinetics. An initial burst release was observed for the two formulations with the lowest degrees of crosslinking.

As the degree of crosslinking increased, the formulations had a higher swelling ratios. Higher degrees of crosslinking led to a highly branched network structure with pockets which caused higher swelling. This was confirmed by the porous structures observed in SEM as well as by the mercury intrusion porosimeter data.

Fig. 6. **A**) Accelerated *in vitro* drug release profiles of LNG-IUSs with different prepolymer ratios in 45% v/v tert-butanol in PBS at 65°C (mean ± SD, n=3);
B) Zoomed-in view of the accelerated *in vitro* drug release profiles of LNG-IUSs (mean ± SD, n=3)
C) Real time *in vitro* drug release profiles of LNG-IUSs with different prepolymer ratios in 0.9% w/v saline at 37°C (mean ± SD, n=3, the error bars are so small that they are barely visible)

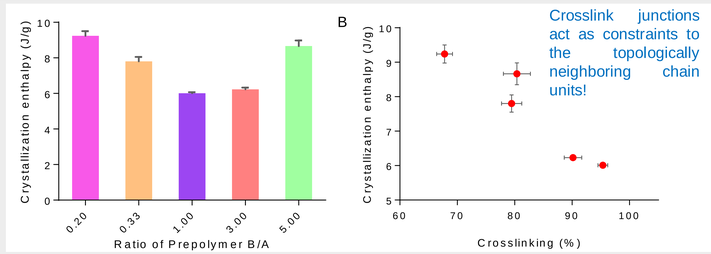


Fig.3.A) Differences in the crystallization enthalpy (J/g) of PDMS (by DSC) with changes in prepolymer ratio (B/A) in LNG-IUSs (mean ± SD, n=3)
B) Impact of the degree of crosslinking on the polymer crystallization enthalpy in LNG-IUSs (mean ± SD, n=3)

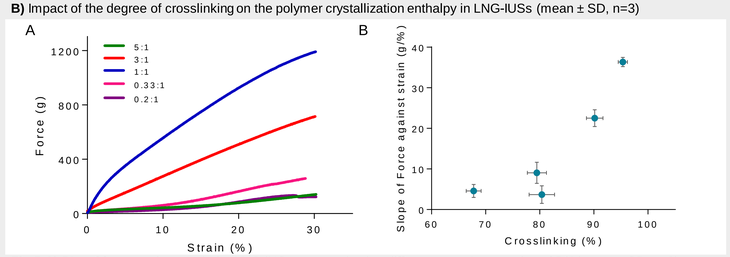


Fig.5.A) Plot of force against strain for LNG-IUSs prepared using different prepolymer ratios of B/A(mean ± SD, n=3)
B) Impact of the degree of crosslinking on the mechanical strength of LNG-IUSs (mean ± SD, n=3)

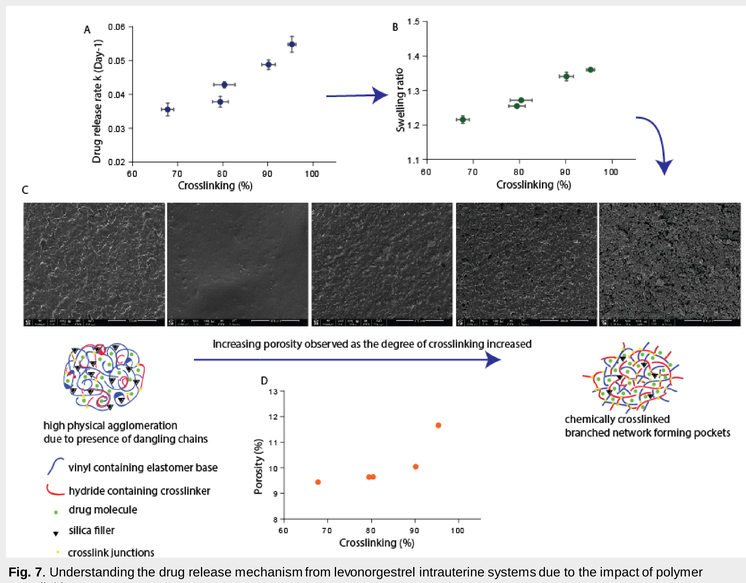


Fig. 7. Understanding the drug release mechanism from levonorgestrel intrauterine systems due to the impact of polymer crosslinking
A) The effect of degree of crosslinking (%) on the first order release rate constant (mean ± SD, n=3);
B) The effect of degree of crosslinking (%) on the swelling ratio of the formulations (mean ± SD, n=3);
C) SEM images of LNG-IUS drug reservoirs at 500X resolution;
D) The effect of degree of crosslinking (%) on the porosity of the formulations (mean ± SD, n=3).

CONCLUSIONS

- The ratio of prepolymers used in the formulation of LNG-IUSs significantly affects the degree of crosslinking which in turn affects the physicochemical properties and drug release.
- Formation of a crosslinked PDMS network leads to a decrease in the crystallinity in LNG-IUSs which may contribute to faster drug release from LNG-IUSs with a higher degree of crosslinking.
- The mechanical strength of LNG-IUSs can be controlled by varying the degree of crosslinking. This is essential during the manufacturing and administration of LNG-IUSs.
- An investigation of the physicochemical properties revealed that the observed differences in the drug release rates could be attributed to the differences in the porosity of the drug-polymer reservoir which ultimately influenced polymer swelling and diffusion-controlled drug release.
- Controlling the degree of crosslinking of LNG-IUSs can be used to tune the drug release kinetics of these long-acting formulations.

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