Injectable in situ Forming Depot Systems for Long Acting Contraception
Dileep R. Janagam1, Linfeng Wu1, Kamaljit Chaudhry1, Timothy D. Mandrell2, James R. Johnson1, Tao L. Lowe1
Departments of Pharmaceutical Sciences1 and Comparative Medicine2, University of Tennessee Health Science Center, Memphis, TN

Statement of Purpose: Birth control is still a major concern worldwide. The currently available contraceptive injectables are for 1-3 months and these need frequent clinic visits which could result in discontinuation and prolonged return to fertility due to users’ difficulty in complying with the multiple-injection schedule. Although an extensive research has been made to develop long acting injectable hormonal contraceptives, still there is an unmet need for injectable contraceptives which can provide contraception for more than three months after single shot and offer a greater flexibility to women. The purpose of this study is to develop polymeric based injectable in situ forming depot system containing levonorgestrel (LNG) for contraceptive effect for six months or longer after single injection that help to reduce unintended pregnancies with high patient compliance and low cost.

Methods: In situ forming depot formulations (F-55, F-64, and F-96) were prepared using a combination of poly (lactide-co-glycolide) and polylactic acid and a mixture of solvents containing N-methyl-2-pyrrolidone and benzyl benzoate or triethyl citrate. The syringeability of the formulations through 18-22G needle was evaluated. Viscosity of the final in situ depot forming polymeric solution formulation was evaluated using rheometer AR G2 at room temperature. The in vitro release studies of LNG from the depots were performed at 37°C in PBS sink conditions. In vitro LNG release content was quantified using HPLC-UV analysis. The depots formed in vitro were also observed for gel integrity and morphological changes with time. The formulation was subcutaneously injected into female SD rats (40mg/kg dose), blood collected as a function of time for four months. Plasma samples were analyzed for LNG concentration using UFLC/MS/MS.

Results: Manual syringeability test showed that the formulations F-55 and F-96 can go through 22G needle while F-64 can go thorough 21G needle. Depots formed in vitro by formulations F-55 and F-96 started disintegrating by 3 and 4 months, respectively, while the formulation F-64 remained intact and fine up to seven months. In vitro release data show that prototype formulations can continuously release LNG for more than four months. In vivo data from Figure 1 show that the formulations can continuously release LNG in vivo that can achieve plasma LNG levels within a range of 0.5-4 ng/mL for more than six months after the sub-Q injection in rats. Other formulations F-55 and F-96 can continuously release LNG in vivo robustly for 3-5 months and even extended till seven months in some rats.

Conclusions: The prototype formulations can be injected through 21/22G needle, and can constantly release LNG in vivo to achieve target plasma LNG levels for six months or longer. The data showed that the prototype formulations have a great potential for sustained release of LNG for longer-acting contraception.

Figure 1: Plasma concentration of LNG as a function of time after Sub-Q injection of the formulations in female SD rats.