Injectable In Situ Forming Depot Systems for Long-Acting Contraception

University of Tennessee

Purpose

Birth control is still a major concern worldwide and injectable contraceptives have been increasingly used for preventing unintended pregnancies as they can be administered by patients themselves, and do not require surgical implantation and removal. Currently, over 40 million women worldwide use injectable contraceptives. However, the currently commercially available injectable contraceptives are only effective for 1–3 months and require patients to return to their provider 4–12 times per year. The frequent clinic visits could result in discontinuation due to users’ difficulty in complying with the multiple injection schedule. Therefore, there is unmet need to develop injectables capable of providing more than 3-month contraception to offer greater compliance and flexibility to women. The purpose of this study is to develop injectable polymeric in situ forming depot system containing levonorgestrel (LNG) for contraceptive effect for six months or longer after single shot that help to reduce unintended pregnancies with high patient compliance and low cost.

Methods

In situ forming depot formulations were prepared using a blend of polymers containing poly (lactide-co-glycolide) and polylactic acid, and a mixture of solvents containing N-methyl-2-pyrrolidone and benzyl benzoate or triethyl citrate. The injectability through 21-23 gauge needles and the viscosity of the formulations were measured by using manual and injection force testing device and ARG-2 rheometer, respectively. The in vitro release studies of LNG from the depots were performed in PBS (pH 7.4) sink conditions at 37°C. The 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. Each formulation was subcutaneously injected into female Sprague-Dawley rats (40mg/kg), and then blood was collected from the rats at selected time points for 7 months. LNG was extracted from the plasma samples and analyzed using UFLC/MS/MS to obtain LNG concentration. The body weights of the rats were measured and vaginal smears were obtained when the blood samples were collected. The vaginal smears were stained with DIFF stain kit for microscopic vaginal cytology study to check the effect of contraceptive treatment on reproductive/estrus cycle of the female rats at various time intervals. Further mating studies were conducted to evaluate if the pregnancy is returned after the treatment period.

Results

Manual injectability test showed that the formulations can go through 21-23G needle. Injection force measurements were proportional to the viscosity of the formulations. Formulations with viscosity around 0.6 P.s have shown to pass easily through 23G needle while those with 1.7 P.s pass through 21G needle. The depots formed in vitro remained intact for up to 3-7 months depending on the composition of the formulation. In vitro release kinetics fitted to the Korsmeyer-Peppas model show that the drug release from the depot followed anomalous transport, both diffusion and erosion. Depending on the intrinsic viscosity of the polymer used, the formulations were able to release LNG in vivo that can achieve plasma LNG levels within a range of 0.5-4 ng/mL till seven months. In the rats treated with LNG containing formulations, body weight increased with time compared to that of control. Vaginal cytology study results showed that all of these cells are either from early diestrus, diestrus or proestrus stages in all the formulations and none of them show estrus stage. After the end of the treatment, rapid and predictable return of fertility was observed in rats.

Conclusion

The prototype formulations can pass through thin size needle and showed promising LNG release in vivo to achieve target plasma LNG levels for six months or longer and showed contraceptive effect in rats. The data showed that the prototype formulations have a great potential for developing future robust long-acting contraceptive products.