An Accelerated Release Study to Evaluate Long-acting Levonorgestrel Contraception Dosage Forms

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Statement of Purpose: Levonorgestrel (LNG) release from biodegradable polymeric gels for long term contraception span from weeks, to months depending upon the polymer concentration, drug loading, molecular weight and formulation morphology. The long-term *in vivo* release study in animal models is essential to evaluate the real release profiles while an accelerated short-term *in vitro* release approach necessitate rapid screening of polymer gel formulation. In this work, we used different conditions by varying temperature, solvents, surfactants and pH in release media to develop an accelerated method to study LNG release from the polymeric gel systems. The purpose of the accelerated method is to correlate short-term *in vitro* release with long-term *in vivo* release to screen the LNG dosage forms.

Methods: *In situ* forming depot formulation were prepared from the combination of poly(lactide-co-glycolide) and poly(lactic acid) in N-methyl-2-pyrrolindone and benzyl benzoate or triethyl citrate. The samples were injected to PTFE molds and immersed in four release conditions at 50 °C as shown in Table 1. The samples were collected at the selected time points and quantified by HPLC or LC/MS/MS analysis. The accumulated release was calculated from the analysis data. The correlation of *in vitro* release in accelerated conditions and *in vivo* release in animal experiments is being established.

Results: Previously, the LNG formulation work was focused on *in vivo* release in animal model and *in vitro* release in PBS (pH 7.4). We have demonstrated that the sustainable LNG release can maintain for 7 months depending on the composition of the formulation. In this study, we found that addition of co-solvent ethanol to the release media significantly increased LNG release from both 64 and 96 formulations as indicated in Figure 1. The initial release increased with the pH increasing from 7.4 to 9.0. However, probably due to the degradation of the polymers which generated acidic groups in the release media, the formulations in condition D with pH 9 media showed slower LNG release at the late stage of 2-week study compared to those in conditions B and C with pH 7.4. The formulation 64 showed less LNG release than the formulation 96 under the same release media.

Table 1. Release conditions for accelerated study

Conditions	PBS (mL)	Ethanol (mL)	Tween 20(g)	pH
A	400	0	0	7.40
B	300	100	0	7.40
C	300	100	2	7.40
D	300	100	2	9.00

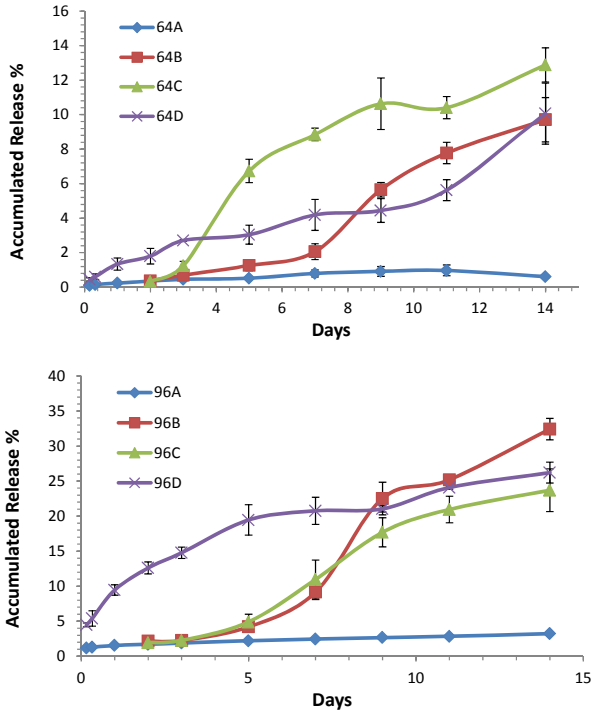

Figure 1. 64, 96 formulation samples release profiels in accelerated conditions.

Conclusions: Compared to the release in PBS (pH 7.4), the samples in accelerated conditions showed higher LNG release. The gel formulation has an effect on the *in vitro* release study to the great extent. The higher pH generated greater initial release. The *in vitro* accelerated experiments can potentially be used to predict the long term *in vivo* release.

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References

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