In Vivo Release of Celecoxib-loaded Acetyl-capped PCLA-PEG-PCLA Thermogels in Rats

P.M. van Midwoud\textsuperscript{1}, M. Sandker\textsuperscript{2}, M. van Dijk\textsuperscript{1}, L.G.J. de Leede\textsuperscript{1}, C.H.A. van de Lest\textsuperscript{3}, H. Weinans\textsuperscript{4,5}

\textsuperscript{1}InGell Labs BV, Groningen, The Netherlands; \textsuperscript{2}Department of Orthopaedics, Erasmus Medical Centre, Rotterdam, The Netherlands; \textsuperscript{3}Department of Equine Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands; \textsuperscript{4}Department of Orthopaedics and Department of Rheumatology, UMC Utrecht, Utrecht, The Netherlands; \textsuperscript{5}Department of Biomechanical Engineering, TU Delft, Delft, The Netherlands

m.vandijk@ingellpharma.com

ABSTRACT SUMMARY

InGell Gamma thermogels consist of acetyl endcapped PCLA-PEG-PCLA triblocks. These triblocks have the property of forming temperature dependent micellar aggregates and, after a temperature increase, of gellifying due to micelle aggregation or packing. This property enables drugs to be mixed in the sol state at room temperature and the solution can be injected into a target tissue, forming a gel depot \textit{in-situ} at body temperature. The goal is to provide controlled drug release. Here we demonstrate the sustained in vivo release of celecoxib, a small hydrophobic compound, injected subcutaneously in rats. A release of 8 weeks was observed with a half-life of 10.5 days. No side-effects were observed. This drug delivery system has great potential in the field of orthopedics, especially for the local treatment of osteoarthritis.

INTRODUCTION

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that is used in the treatment of e.g. osteoarthritis and rheumatoid arthritis (Figure 1) \cite{1}. It is a selective COX-2 inhibitor and causes inhibition of prostaglandin production. COX-2 is extensively expressed in cells involved in inflammation and by inhibiting COX-2 the inflammation (and pain) is reduced. Celecoxib is commercially available as Celebrex\textsuperscript{\textregistered}, which is an oral formulation taken usually once or twice daily. Concerns have risen about the systemic toxicity of celecoxib, mainly on myocardial muscles \cite{2}, and consequently there is a need for formulations reducing its toxicity. Our approach to reach this goal is to develop a novel injectable formulation containing acetyl-capped PCLA-PEG-PCLA thermogel loaded with celecoxib, to locally release celecoxib for a prolonged period. This will ideally result in therapeutically effective local concentrations with plasma concentrations below toxic level, and the patient compliance will be greatly improved.

The presented study is focusing on the pharmacokinetic profile of celecoxib in rats after subcutaneous administration of acetyl-capped PCLA-PEG-PCLA (InGell Gamma) formulations. The triblock based formulation is liquid at room temperature and turns into a gel after injection (body temperature). Rats will be dosed with two different concentrations of celecoxib formulated in two different InGell Gamma polymers. After subcutaneous administration of the formulations, blood will be withdrawn to analyze the celecoxib concentration present in the blood. This study will demonstrate the sustained release of celecoxib from InGell Gamma thermogels.
EXPERIMENTAL METHODS
Per group six rats were injected subcutaneously in the neck region with aseptically prepared PCLA-PEG-PCLA formulations. Only male rats were used in this study, the rats were 14-weeks-old and weighed 400-450 g. The Animal Ethic committee of the Erasmus Medical Center, Rotterdam, The Netherlands approved all conducted procedures.

Per rat 100 or 500 µL formulation was injected through a 25G needle and blood samples were collected at predetermined time points from the lateral tail vein. Two celecoxib doses were used in this study, a 10 mg/mL and a 50 mg/mL celecoxib concentration.

Celecoxib was extracted from the collected blood samples by liquid-liquid extraction using parecoxib as internal standard. The celecoxib concentration in the extracted samples were determined by liquid chromatography – mass spectrometry.

RESULTS AND DISCUSSION
All tested formulations resulted in prolonged release of celecoxib of at least 2 weeks. In case of the acetyl-endcapped formulation loaded with 50 mg/mL celecoxib, a release of 56 days (8 weeks) was determined (Figure 2). An initial release of 17% was observed for the first day and around 80% of the dose is released in a sustained mode over 4-8 weeks.

The half-life of the bolus injection was 5 hours, but for the thermogel formulations loaded with 10 mg/mL celecoxib the half-life increased to 7 days and for formulations containing 50 mg/mL celecoxib even to 10.5 days with 8 weeks release.

CONCLUSION
InGell Gamma polymers loaded with celecoxib showed sustained release in vivo, and have good potential as a drug delivery system for sustained delivery of celecoxib.

This drug delivery system has great potential in the field of orthopedics, especially for the local treatment of osteoarthritis.

REFERENCES

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Figure 2: Serum concentrations of celecoxib corrected for dose after subcutaneous administration of 100 µL and a 500 µL acetyl-capped polymer solution containing both 50 mg/mL celecoxib. Data presented as mean ± SD, n=6.