Biocompatible in situ gelling hydrogel formulations for intra-articular drug delivery

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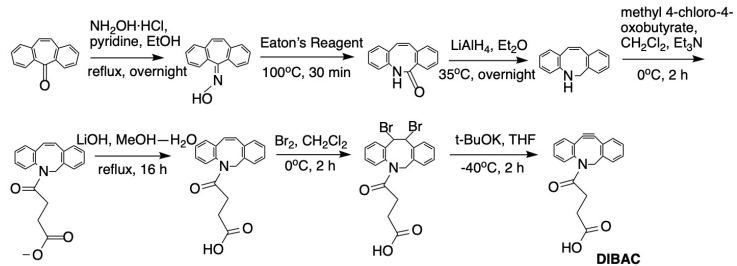
1. Introduction

- Osteoarthritis (OA) is a progressive disease impacting > 4 million Canadian adults [1]. OA results in the overall degeneration of the joint which is typically accompanied by pain and stiffness that can be debilitating [2].
- Currently there are no disease-modifying treatments available that aim to slow the progression of OA [2].
- An injectable hydrogel formulation developed in our lab using a free radical crosslinking system has shown promise for the sustained release of disease-modifying drugs in the joints.
- Alternative crosslinking mechanisms are needed, that avoid free radicals to achieve a clinically-translatable formulation.
- This study focuses on a crosslinking system that uses copper-free click chemistry [3]. The reaction is based on the strain-promoted azide-alkyne cycloaddition (SPAAC) of an azido-endcapped poly(caprolactone-*co*-lactide)-poly(ethylene glycol)-poly(caprolactone-*co*-lactide) (N_3-PCLA-PEG-PCLA-N_3) triblock copolymer and a PEG star polymer with a strained-alkyne end group, such as an azadibenzocyclooctyne (DIBAC) [3,4].

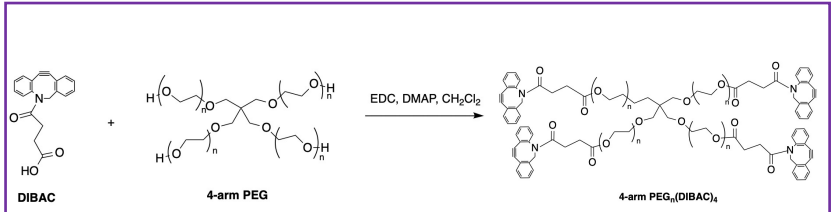
2. Purpose

This biocompatible drug delivery system will be applied to disease-modifying drugs to treat OA. The drug-loaded hydrogel will be injected directly into the targeted joint as a liquid at or below 21°C . The thermoresponsive hydrogel will gel spontaneously at 37°C under physiological conditions. The system will achieve a sustained drug release over a prolonged period.

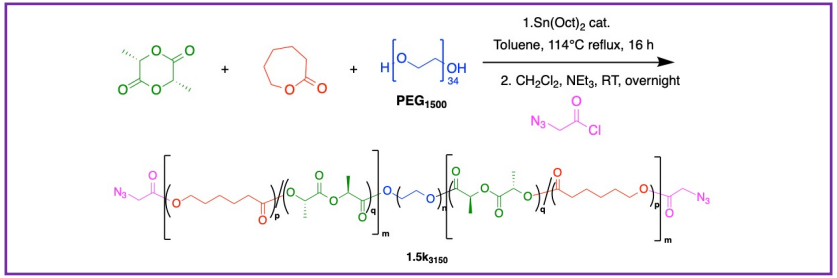
3. Synthesis of DIBAC



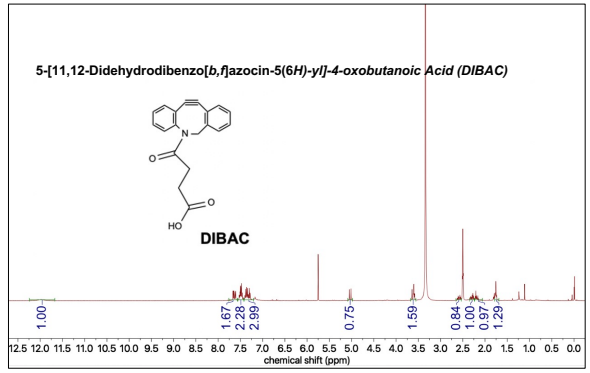
4. Synthesis of 4-arm PEG-DIBAC



5. Synthesis of azido-endcapped PCLA-PEG-PCLA



6. ^{1}H-NMR characterization of DIBAC



7. Conclusions and current work

- Precursors for hydrogel formation were successfully prepared
- Gelation tests are currently being carried out
- The hydrogels will be further characterized through mechanical tests including syneresis and degradation studies, *in vitro* release studies, and cytotoxicity tests.

8. References

[1] J. Hochman, https://arthritis.ca/about-arthritis/arthritis-types-(a-z)/types/osteoarthritis, (Accessed 08/14/2021).
[2] Holyoak, D. T.; Tian, Y. F.; van der Meulen, M. C. H.; Singh, A. *Ann Biomed Eng.* **2016**, *44*, 2062–2075.
[3] Wang, W.; Narain, R.; Zeng, H. *Front. Chem.* **2018**, *6*.
[4] Chadwick, R.C., et al. *Synthesis.* **2014**, 46, 0669-0677

9. Sources of funding

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