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Development of a Scalable Synthesis of HP-β-CD Pluronic Polyrotaxanes

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ABSTRACT

Polyrotaxanes are polymers that have macrocycles threaded onto them, analogous to beads threaded onto a string. These materials are used for a variety of different biomedical applications.[1-3] The Thompson group has been developing 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) polyrotaxanes as therapeutics for the treatment of Niemann-Pick Type C (NPC) disease. NPC is a debilitating genetic disorder where cholesterol accumulates in the lysosomes of cells.[4] Developing a scalable process is crucial for the advancement of these materials as NPC therapeutics. The goal of this project is to optimize the only protocol for the synthesis of HP-β-CD/Pluronic polyrotaxanes in order to develop a synthetic method that can be operated on the multi-gram scale to support preclinical studies.[5] Each component of the protocol was screened to determine which combination lead to the formation of polyrotaxanes with the highest yields and threading efficiencies in the shortest amount of time. Threading efficiency is a measure of how many HP-β-CD molecules are threaded onto each polymer. In addition to optimizing the current protocol, we have also explored flowing the reaction mixture through a bath sonicator and using a hydraulic press as alternative syntheses. It was found that probe sonication and bath sonication are both necessary components of the protocol. This indicates that sufficient agitation of the reaction mixture is required to promote the non-covalent threading reaction. Furthermore, bath sonication for one hour, followed by stirring for two days gave the highest threading efficiency. The results of these studies have simplified the existing protocol, but additional studies are needed to reveal whether this protocol is robust enough for efficient preparation of other HP-β-CD/Pluronic polyrotaxane derivatives.

KEYWORDS

Polyrotaxanes, Niemann-Pick Type C disease, 2-hydroxypropyl-β-cyclodextrin, Pluronic

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