Heparosan production and modification towards a bioengineered heparin

by

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ABSTRACT

Heparin is a very widely used anticoagulant drug. It is currently produced from a porcine intestinal extract. The animal-sourced heparin production has several disadvantages and imposes quality concerns on the product. This issue was brought to international attention when a heparin contamination crisis happened in 2008. To overcome the drawbacks of the current heparin production process, our laboratory proposed a new process to prepare anticoagulant heparin from non-animal-source by fermentation and chemo-enzymatic reactions. To substitute the current animal-sourced heparin in medical practices, the bioengineered heparin need to be chemically equivalent to porcine heparin and has the same biological and pharmacological properties. The cost of the bioengineered heparin preparation process also need be reduced to be comparable with the current porcine heparin. We hypothesize that by controlling and optimizing the fermentation and chemo-enzymatic reaction conditions, the bioengineered heparin product can be chemically and biologically equivalent to the porcine heparin, and its cost can be significantly reduced. In this study, the improvement in the fermentation process greatly increased the bioengineered heparin precursor yield and reduced the process cost. The chemo-enzymatic steps was controlled and optimized to yield the bioengineered heparin product that closely resembles the porcine heparin. The bioengineered heparin and its precursor were extensively characterized to compare with porcine heparin. Novel process analytical techniques were also developed to support the bioengineered heparin preparation. The fermentation step was further scaled up.