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CORE CROSSLINKING OF POLYMERIC FLOWER LIKE MICELLES USING NATIVE CHEMICAL LIGATION

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Native chemical ligation (NCL) is an attractive method to covalently cross-link polymers, because of its ability to react under physiological conditions avoiding the use of toxic reagents and catalysts, making this method very biofriendly. Since NCL is a very specific ligation between N-terminal cysteines and thioesters, side reactions with biomolecules can be ruled out and therefore NCL is expected to be highly compatible with encapsulated drugs. In this study, native chemical ligation (NCL) was used as a selective crosslinking method to form core-crosslinked thermosensitive polymeric micelles for drug delivery applications. To this end, two ABA triblock copolymers consisting of polyethylene glycol (PEG) as midblock and thermosensitive poly isopropylacrylamide (PNIPAM) outer blocks decorated with either cysteine (NIPAM-co-HPMA-Cys)-PEG-P(NIPAM-co-HPMA-Cys) (PNC) or thioester P(NIPAM-co-HPMA-ETSA)-PEG-P(NIPAM-co-HPMA-ETSA) (PNE) functionalities were synthesized by atom transfer radical polymerization (ATRP). Mixing of these polymers in aqueous solution followed by heating to 50°C resulted in the formation of thermosensitive flower-like micelles. Subsequently, native chemical ligation in the core of micelles resulted in stabilization of the micelles with an average diameter of 65 nm at 37°C. Decreasing the temperature to 10°C only affected the size of the micelles (increased to 90 nm) but hardly affected the polydispersity index (PDI) and aggregation number (N_{agg}), confirming covalent stabilization of the micelles by NCL. Notably, by simply adjusting the molar ratio between the polymers, the extra cysteine or thioester moieties could be used for conjugation of functional molecules. Furthermore, *in vitro* cell experiments demonstrated that fluorescently labeled micelles were successfully taken up by HeLa cells, while cell viability remained high even at high micelle concentrations. These results demonstrate the potential of these micelles for drug delivery applications.

Biography

Tina Vermonden obtained her PhD in Physical and Organic Chemistry from Wageningen University and Research Centre, and conducted her Post-doctoral training at Utrecht University. She is currently an Associate Professor in the Department of Pharmaceutics at Utrecht University and Coordinator of the Honours Program Pharmaceutical Sciences and is part of several large national and EU consortia. Her research is focussed on the development of biomaterials for tissue engineering and drug/protein delivery. Her group designs, synthesizes and characterizes polymers with special emphasis on cross-linking techniques to obtain advanced material properties for biomedical applications. His research interests are in the fields of Biomaterials, Hydrogels, Polymeric Micelles, Drug Delivery and Regenerative Medicine.

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