

## Hydrolyzable polyrotaxanes consisting of $\beta$ -cyclodextrins and Pluronic<sup>®</sup> for drug delivery

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### Abstract

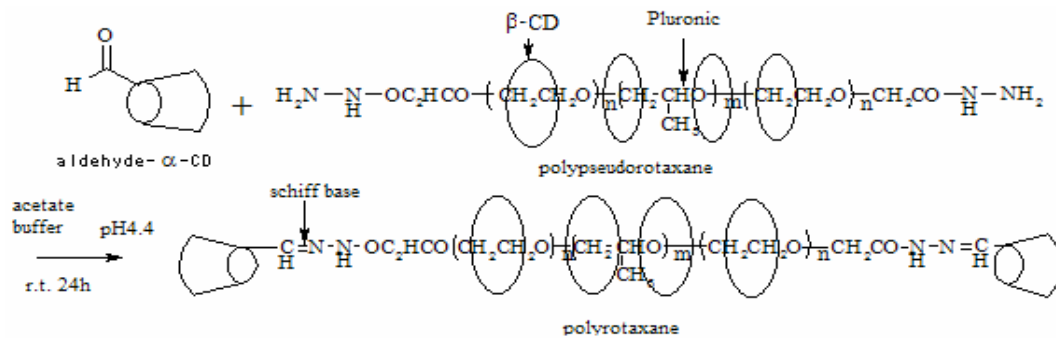
*In recent years, polyrotaxanes (PRXs) have been extensively studied as a novel supramolecular assembly that has interlocked structure between a cyclic molecule and a linear polymeric chain. Based on the interlocked structure of PRXs, one can expect excellent properties in terms of supramolecular motion of the cyclic molecules. In pharmaceutical fields, we have studied biodegradable PRXs as a drug carrier, in which many  $\alpha$ -cyclodextrins ( $\alpha$ -CDs) are threaded onto a poly (ethylene glycol) (PEG) capped with bulky blocking group via peptide linkages<sup>1</sup>. Drugs were immobilized  $\alpha$ -CDs via biodegradable spacer. When the terminals of PRX were enzymatically hydrolyzed, drug-immobilized  $\alpha$ -CDs could be released. If the immobilized drugs are incorporated in the hydrophobic cavity of CDs after the releasing, it can be great advantage in terms of drug stability and solubility. Considering the terminal hydrolysis – triggered drug incorporation into the CD cavity,  $\beta$ -CD is much preferable because the size of  $\beta$ -CDs is suitable for drug molecules. The objective of this study is to synthesize new hydrolysable PRX consisting of  $\beta$ -CDs and a triblock copolymer of PEG and poly (propylene glycol) (Pluronic<sup>®</sup>). Here, schiff base is selected as a pH-dependent hydrolysable linkage that may have a potential as pH-sensitive drug-immobilized  $\beta$ -CD release.*

*Terminal hydroxyl groups in Pluronic P105 ( $M_n = 6500$ , PPG segment  $M_n = 3250$ , PEG segment  $M_n = 975 \times 2$ ) were hydrazidated using the N-hydroxysuccinimide ester activated Pluronic and hydrazine hydrate. The hydrazidated Pluronic was added to  $\beta$ -CDs aqueous solution to obtain a pseudopolyrotaxane. The pseudopolyrotaxane was capped with mono-6-aldehyde- $\alpha$ -CDs via schiff base to obtain PRX (Scheme.1). The PRX was less soluble in water, so that carboxyethylester (CEE) groups were introduced to the threaded  $\beta$ -CDs and the terminal  $\alpha$ -CDs.*

*The CEE-PRX was characterized by <sup>1</sup>H-NMR and GPC, and the threading number of  $\beta$ -CDs and the number of CEE groups per CD molecule were calculated to be 26 and 11, respectively. The schiff base hydrolysis under acidic conditions and the release of CEE- $\beta$ -CDs from the PRX were evaluated by fluorescence intensity change of sodium 2-(p-toluidino) naphthalene-6-sulfonate (TNS), which is based on an increase in the intensity by incorporation into the hydrophobic cavity of  $\beta$ -CD (Figure.1). The fluorescence intensity at a certain time increased with decreasing pH, indicating inclusion complexation between the released  $\beta$ -CDs and TNS. At pH 7, the fluorescence intensity was less changed, indicating that the schiff base was stable at the neutral conditions.*

These results suggest that the pH-triggered  $\beta$ -CD release exposes its hydrophobic cavity in the medium, which can allow to incorporate hydrophobic compounds. Thus, the design of hydrolysable  $\beta$ -CD-based PRXs can lead to complexing a drug model with the released  $\beta$ -CDs in response to pH-dependent terminal hydrolysis.

Reference: 1) T. Ooya, N. Yui, *Crit. Rev. Ther. Drug Carrier Syst.*, 1999, 16, 289.



Scheme.1 Synthesis of polyrotaxane consisting of  $\beta$ -CD, Pluronic and  $\alpha$ -CD

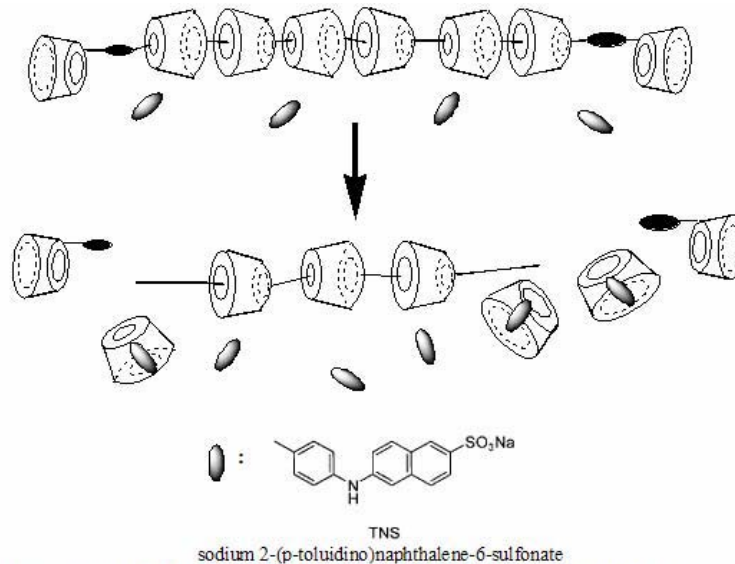


Figure.1 Release of CEE- $\beta$ -CDs from PRX via terminal hydrolysis and TNS- $\beta$ -CD inclusion complexes.