**Effect of Acrylic Acid as a pH-sensitive Moiety on Paclitaxel Release from Hydrotropic Micelles**

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**Statement of Purpose:** Paclitaxel (PTX) is one of the most effective anti-cancer agents used for chemotherapy. The major mechanism of anti-tumor activity is based on the strong binding affinity of PTX onto cellular microtubules, which disturbs the proliferation function. Because water-solubility of PTX is very low (< 1 μg/mL) [1], however, Taxol® is the only one formulation to be commercially available. Systemic administration of Taxol®, containing ethanol and Cremophor EL, frequently induces hypersensitivity in patients, which is due to the Cremophor EL rather than PTX. For this reason, the hydrotropic micelle that can provide a water-soluble form of PTX is a good alternative PTX formulation. Although hydrotropic micelles increased loading efficiency and stability of PTX [1], for a successful delivery, release control of the drug needs to be adjusted depending on the administration route. In this study, therefore, the effect of acrylic acid (AAc) as a pH-sensitive moiety on PTX release kinetic from hydrotropic micelles was evaluated.

**Methods:** Four kinds of AAc-incorporated polymers were prepared. Poly(ethylene glycol) (PEG)-*b*-poly(2-(4-vinylbenzyloxy)-*N,N*-diethylnicotinamide) (PDENA)-*b*-poly(AAc) (PAAc) was synthesized by the method of an atom transfer radical polymerization (ATRP) using bromine-containing initiators, as previously reported [2]. By the same method, PEG-*b*-PDENA was also obtained as a control polymer. To prepare PAAc-*b*-PDENA, tertiary butyl-protected AAc was used for the ATRP and deprotected in the final step. P(DENA-*co*-AAc) was prepared by the free radical polymerization using azobisisobutyronitrile (AIBN) as a initiator as well as cysteamine as a chain transfer agent. PEG-*b*-P(DENA-*co*-AAc) was synthesized by coupling reaction between P(DENA-*co*-AAc) and carboxylated MPEG. For each polymer, feed ratio of DENA to AAc was varied from 0.5 to 5 % (mol/mol). Obtained polymers were characterized by $^1$H-NMR (300 MHz) and GPC (DMF eluent).

PTX loading and micelle formation were simultaneously accomplished by dialysis (MWCO 3,500) of acetonitrile solution containing PTX and polymer. Loading content of each micelle was measured by reverse phase (RP)-HPLC with $C_{18}$ analytical column. Particle size was determined by dynamic light scattering method. PTX release experiments were conducted using dialysis membrane against 0.8 M sodium salicylate solution in water at 37 °C. Liberated PTX was determined by RP-HPLC using a PTX standard curve. Release profile dependent on pH and nanoparticle stability with time were also monitored.

**Results/Discussion:** AAc-incorporated hydrotropic polymers were synthesized by different methods in this study. Although carboxylic acids are ready to terminate the polymer propagation in ATRP, AAc oligomers with small molecular weight could be obtained from PEG-*b*-PDENA-Br macro-initiator. It was difficult, however, to control the molecular weight of PAAc. Either for random copolymerization of DENA and AAc or for polymerization of AAc with relatively high molecular weight, the ATRP method was no more available. Therefore, free radical polymerization method was used for the former and tertiary butyl-protected AAc was for the latter.

Particle size of hydrotropic micelles containing PTX ranged from 30 to 50 nm. The amount of loaded PTX depended on the pH of the dialysis medium. The lower pH could load more PTX into micelles, because AAc became hydrophilic above its pKa. For the same reason, the higher content of AAc in hydrotropic polymers led to the lower PTX loading efficiency. PTX release was also influenced by the AAc content and pH. In general, PTX release was accelerated, as the AAc content in a polymer and pH increased. As shown in Fig. 1, most of the loaded PTX was released much faster from the PEG-*b*-PDENA-*b*-PAAc triblock micelles. Since fast release of PTX is important in oral PTX delivery, the triblock micelles are expected to be useful for oral formulations.

**Conclusions:** PTX release from hydrotropic micelles could be modified by introducing AAc. It is expected that the pH-dependency of PTX release is highly useful for oral administration of the drug. Mucoadhesiveness of AAc in acidic pH may also have a positive effect on the PTX bioavailability.

**References:**

[1] Huh KM et al. J Control Release. 2005;101:59-68.
[2] Lee SC et al. Macromolecules. 2003;36:2248-2255.

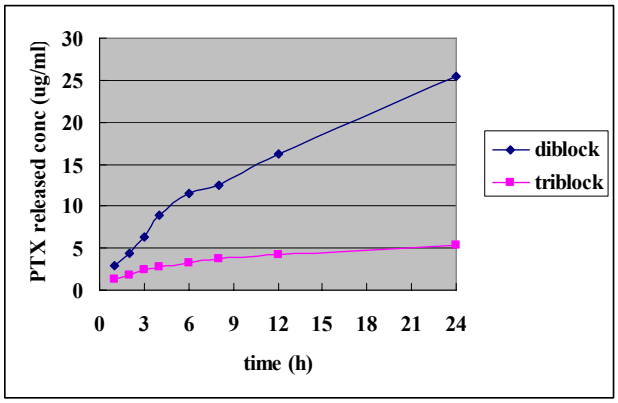


Figure 1. PTX release from hydrotropic micelles of $PEG_{5,000}$-*b*-$PDENA_{5,400}$ (diamond) and $PEG_{5,000}$-*b*-$PDENA_{5,100}$-*b*-$PAA_{1,400}$ (square) for 24 hours at 37 °C.