Chapter 12
Rational Design of Polymeric Micelle for Cancer Therapy

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ABSTRACT
Clinical application of anticancer drugs is limited by problems such as low water solubility, lack of tissue-specificity and toxicity. Formulation development represents an important approach to these problems. Among the many delivery systems studied, polymeric micelles are an attractive nano-scaled delivery system due to their simplicity, ability to solubilize water-insoluble drugs, and small size (10-100 nm) that can take advantage of enhanced permeability and retention effect to specifically accumulate in tumors. This book chapter provides a brief review of recent advancements in developing environmentally responsive micellar systems for controlled delivery of chemotherapeutic agents to tumor tissues. The emphasis is placed on the discussion of several dual functional nanomicellar systems that were recently developed in our laboratory as well as a new strategy of improving micellar formulations via incorporation of an interfacial drug-interactive motif(s).

INTRODUCTION
Cancer is a major cause of death around the world, especially in USA. The most common cancer treatments are surgery, radiation and chemotherapy, with chemotherapy being the major treatment modality. However, the chemotherapeutic agents are limited by their unsuitable properties, such as low water solubility, toxicity and drug resistance (Mishra et al., 2010; Alexis, et al., 2008; Shapria, et al., 2011). Currently, nanotechnology has been extensively studied for their potential applications in cancer diagnosis and treatment. Various nanocarriers have been developed including liposomes, micelles, dendrimers and nanocrystals.

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Most of the nanoparticles use enhanced permeability and retention (EPR) effect which is a property by which molecules of certain sizes (typically liposomes, micelles and macromolecular drugs) tend to accumulate in tumor tissue much more than they do in normal tissues (Matsumura, & Maeda 1986; Duncan, & Sat 1998). In addition, a tumor-specific ligand can be introduced onto the surface of nanoparticles to further facilitate their interaction with tumor cells following accumulation at tumor sites (Michalet, et al., 2005; van Vlerken, et al., 2007). The development of tumor-targeting nano delivery systems has revived the therapeutic uses of many potent chemotherapeutics that are too toxic to be applied in human body directly. In the past decade, polymeric micelles have been utilized as a novel promising colloidal carrier for the targeted delivery and controlled release of drugs, proteins and genes in the cancer diagnosis and therapy. Micelles have a size of 10-200 nm, a structure with the hydrophobic core for efficient loading of poorly water soluble drugs and a layer of hydrophilic shells to warrant excellent colloidal stability and more importantly intrinsic stealth effect (Davis, et al., 2008).

One major advantage of polymeric micellar systems is their simplicity. However, conventional micellar systems suffer from limited drug loading capacity and colloidal stability in the blood circulation. Accordingly, significant efforts have been devoted to resolve these problems. In addition, significant progress has been made in developing intelligent micellar systems that are stable in blood but become destabilized and release payload drug in response to “tumor-specific” microenvironment. This review summarizes recent progress in targeted delivery of chemotherapeutic agents via polymeric systems.

**Polymeric Micelles**

Most polymeric systems involve the use of polymers as the hydrophobic domain including polyesters such as poly(lactic acid) (PLA) and polyamides such as poly (L-aspartic acid) (PAPS) and poly (beta-amino ester). One critical consideration for clinical application of micellar carriers is the biocompatibility and biodegradability. Polyesters and polyamides can be hydrolyzed by enzymes in vivo and are considered biodegradable. There are several polymeric micelle systems that have been studied in clinical phase. For example, Genexol-PM is a polymeric micelle formulation of PTX that is based on monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) (Jones, et al., 1999; Kim, et al., 2004, Lee, et al., 2008). It has a mPEG molecular weight of 2000 g/mol and a PDLLA molecular weight of 1750 g/mol. In this system, the drug loading was as high as 16.7% (w/w) and the size was smaller than 50 nm. The solution can be stable for 2 months at 4 °C and 1 day at room temperature, respectively. Genexol-PM has been in market in Korea and Europe (see Figure 1).

NK-105 used poly(ethylene glycol)-poly(aspartic acid) (PEG-P(Asp)) that was modified with 4-phenyl-1-butanol to increase the hydrophobicity (Hamaguchi, et al., 2007). The micelle system could effectively load PTX via hydrophobic interaction with a drug loading of about 23% (w/w) and particle size of around 85 nm. NK105 can be readily dissolved in 5% glucose solution and is stable for more than 1 day at room temperature. NK-105 has been examined in a phase I study in patients suffering from pancreatic, bile duct, gastric, and colonic cancers. NK-105 was administered intravenously for 1 h every 3 weeks, and the recommended dose of 150 mg/m² was well-tolerated with less hypersensitivity reactions than Taxol. Currently, a phase II study in patients with advanced stomach cancer is underway.

NC-6004 is another polymeric micelle formation that is loaded with cisplatin. Cisplatin (cis-dichlorodiammineplatinum (II), CDDP) is an important anti-tumor agent and is frequently used for the treatment of many cancers (Alami, et al., 2005). Due to its water solubility, CDDP was rapidly cleared from circulation after i.v. injection and excreted through the kidney filtration within a few minutes. NC-6004
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