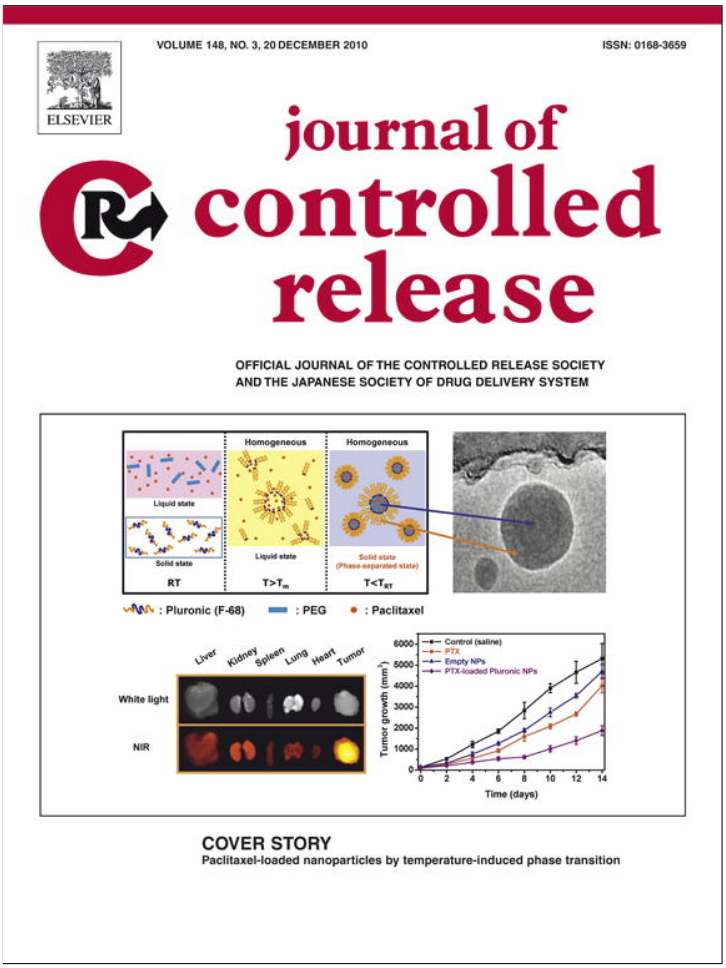

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Cover Story

Paclitaxel-loaded nanoparticles by temperature-induced phase transition

Paclitaxel (PTX) has been formulated into various delivery systems. The first formulation based on Cremophor EL® and ethanol has been used clinically despite its side effects associated with Cremophor. One of the main goals of PTX formulation is to replace undesirable excipients with more benign delivery vehicles. Thus, other formulations without using Cremophor EL have been introduced, such as those based on albumin and polymer micelles [1,2]. Cremophor EL, however, is known to be an inhibitor of P-glycoprotein (PGP), mediating multidrug resistance. Naturally, a preferable PTX formulation is expected to have increased PXT solubility as well as PGP inhibitory effect.

In this issue, Professor Yuk and his group present a new PTX formulation made of poly(ethylene oxide)–poly(propylene oxide)–poly (ethylene oxide) (PEO–PPO–PEO) triblock copolymers (commonly known as Pluronics®) and polyethylene glycol (PEG, molecular weight 400) [3]. The mixture of Pluronic F-68 and PEG, containing PTX, undergoes temperature-induced phase transition to form nanoparticles, and the process is fast, simple, continuous and solvent-free. The liquid PEG is used as a solubilizer of PTX and Pluronic F-68 is used for encapsulation of PTX. At the phase transition temperature, the polymer mixture was changed to the liquid phase, and stirring the liquid polymer mixture formed emulsions composed of PEG containing PTX and liquidized Pluronic F-68. Pluronic F-68 encapsulated PTX-containing PEG to form Pluronic nanoparticles when the solution was cooled to 0 °C. The spherical shape of the PTX-loaded nanoparticles was confirmed with electron microscopy. The cryogenic transmittance electron microscopic images revealed the two phases (a dark core area and a white shell area) in the nanoparticles indicating the formation of a core/shell structure. The PTX-loaded Pluronic nanoparticles resulted in enhanced anti-tumor efficacy when tested in SCC-7 tumor-bearing mice as compared with the control Cremophor EL formulation. The time-dependent excretion profile, in vivo biodistribution, and circulation time using non-invasive live animal imaging technology showed extended retention of the Pluronic nanoparticles in the blood stream. It appears that the PTX-loaded Pluronic nanoparticles are very efficient for cancer therapy.

The Pluronic–PEG combination formulation provides several distinct advantages in PTX formulation. The formulation can be prepared without using undesirable excipients, such as Cremophor EL and toxic organic solvents. The temperature in the process is increased to 120 °C which is far below the PTX melting temperature of >210 °C. Pluronic copolymers are also known to reduce multidrug resistance. The nanoparticulate nature of the Pluronic formulation allows taking advantage of the enhance permeability and retention (EPR) effect. The Pluronic nanoparticle formulation was successfully used for PTX, and thus, the same formulation is expected to be used for other poorly soluble drugs. While each poorly soluble drug is different in its physicochemical properties, and thus, the loading and release properties from the nanoparticles, the Pluronic formulation provides a good starting point for various poorly soluble drugs.

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