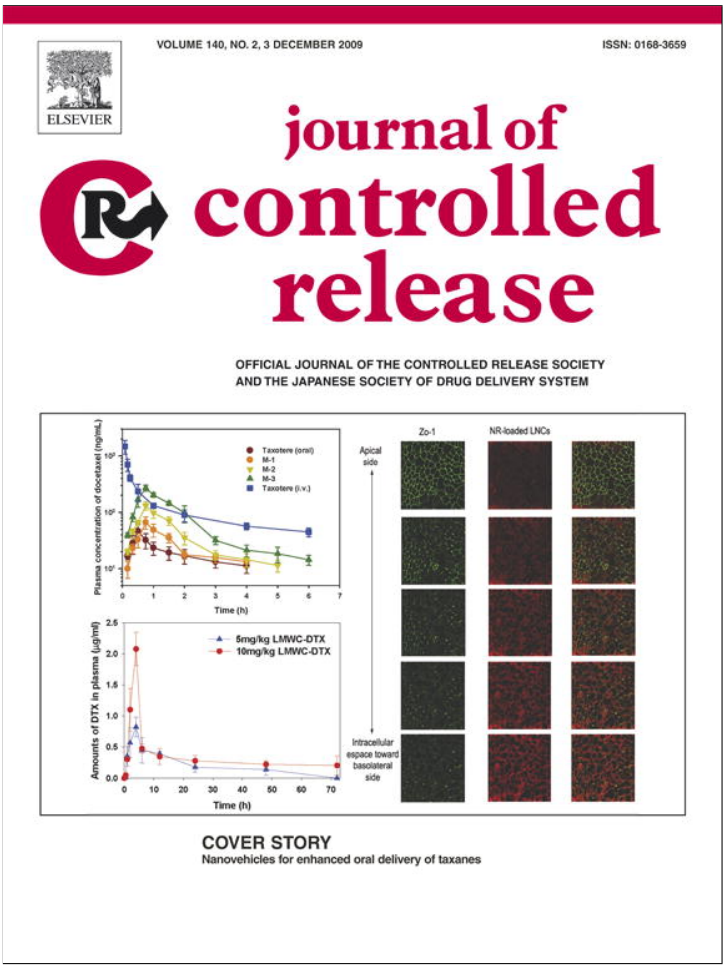

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Cover Story

Nanovehicles for enhanced oral delivery of taxanes

Each issue of this journal contains a dozen or so articles with a variety of research topics in the controlled drug delivery field. It is common to see one or two articles dealing with delivery of anti-cancer agents or drug targeting to solid tumors. In this issue, however, we have five papers all dealing with delivery of anti-cancer agents, such as docetaxel (DTX), paclitaxel (PTX), and tocotrienol. Two articles describe tumor-targeted delivery of PTX in RGD-grafted nanoparticles [1] and tocotrienol in transferrin-bearing vesicles [2]. A large number of papers published in this journal in the past have dealt with targeted delivery of anti-tumor agents following i.v. administration. Not many articles, however, have described delivery of anti-tumor agents by oral administration. In this issue, two articles happen to describe enhanced delivery of DTX using microemulsion [3] and low molecular weight chitosan (LMWC) [4]. Another factor that makes this issue especially interesting is that the above two articles are nicely supplemented by a paper describing the mechanisms of improved transport of PTX through human epithelial cells [5].

Oral delivery of taxanes, especially DTX and PTX, has been attempted, but the bioavailability after oral administration has been poor. This, however, can be changed by using new delivery systems. The paper by Professor Dae-Duk Kim et al. [3] clearly shows that their novel DTX-loaded microemulsions significantly improve the solubility of DTX (to about 30 mg/mL) and also dramatically inhibit the P-glycoprotein (PGP) efflux effect *in vitro*. The two properties result in the plasma concentration of DTX as high as 300 ng/mL after oral administration in rats. The peak plasma concentration is several times higher than that achieved by oral delivery of Taxotere, a DTX formulation developed for i.v. administration.

The level of DTX plasma concentration was even higher when LMWC-grafted DTX (LMWC-DTX) was administered to nude mice. At the oral dose of 5 mg/kg and 10 mg/kg the peak plasma concentrations are 0.8 μg/ml and 2.1 μg/ml, respectively. It is remarkable that such high plasma concentrations can be achieved after oral administration. What is most remarkable is the observation that oral administration (p.o.) of LMWC-DTX resulted in higher bioavailability than that obtained by the i.v. injected DTX at the same dose. This result could be explained by the observation that DTX was released from LMWC-DTX (p.o.) in a sustained manner for up to 72 h, whereas DTX was undetectable 6 h after delivery of free DTX by i.v. administration. Thus, the relative bioavailability of the conjugate calculated from the area under the curve can be higher than that of i.v. administered DTX. Even with the higher bioavailability, the *in vivo* anti-tumor effect of LMWC-DTX (p.o.) was comparable to that of DTX (i.v.), suggesting that the concentrations of free DTX at the tumor site are similar between the two groups.

It is highly interesting to know the mechanisms of enhanced bioavailability after oral administration. In case of the microemulsion formulations, the authors ascribed the increase in bioavailability to the improved solubility, inhibition of PGP, and increased permeability [3]. For the LMWC formulation, the dramatically enhanced bioavailability was attributed to increased water solubility (>200 times), prolonged retention of the conjugate in the GI tract due to the mucoadhesive property of LMWC, and an ability to bypass the PGP-mediated efflux. The significant increase in solubility alone may not be enough to explain the result, unless it is accompanied with enhanced permeability. The article by Dr. Lagarce et al. describes improved PTX transport through the intestinal epithelial cells by active endocytic processes, especially via caveolae- and clathrin-mediated endocytosis [5]. This work investigates the different pathways used by PTX-loaded lipid nanocapsules (PTX-LNCs) to cross a Caco-2 cell layer, an *in vitro* model of intestinal barrier. Firstly, it demonstrates that encapsulation of PTX in LNCs was able to increase absorption and consequently explained the enhancement of PTX bioavailability after oral administration observed in their previous study using PTX-LNCs in rats [6]. In their present work [5], the intracellular uptake of nanocapsules was observed by flow cytometry and confocal microscopy as well as the presence of nano-objects on the basolateral side of the monolayer cell model when LNCs were applied on the apical side. In addition, the different transport studies of nanocapsules in the presence of inhibitor of endocytosis mechanism reveal internalization via receptor mediated endocytosis and also by passive transport.

Currently, it is still not completely understood what properties of nanocarriers are mainly responsible for caveolae- and clathrin-mediated endocytosis. Nevertheless, transport by caveolae-mediated endocytosis is interesting because of the effective escape of the particles from endosomal structure after uptake by this pathway and consequently, the possibility of obtaining intact nanocarriers in the blood stream. A better understanding of the intracellular trafficking process and, more importantly, the integrity of carriers after intestinal transport is critical for developing highly efficient vehicle for oral administration. Thus, developing effective oral taxane formulations requires gastrointestinal stability and intracellular uptake by intestinal cells. Both DTX-loaded microemulsions and LMWC-DTX appear to meet such requirements. The three articles regarding oral administration of DTX and PTX in this issue promise a bright future for successful development of oral formulations not only for taxanes but also for many other poorly soluble drugs.

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