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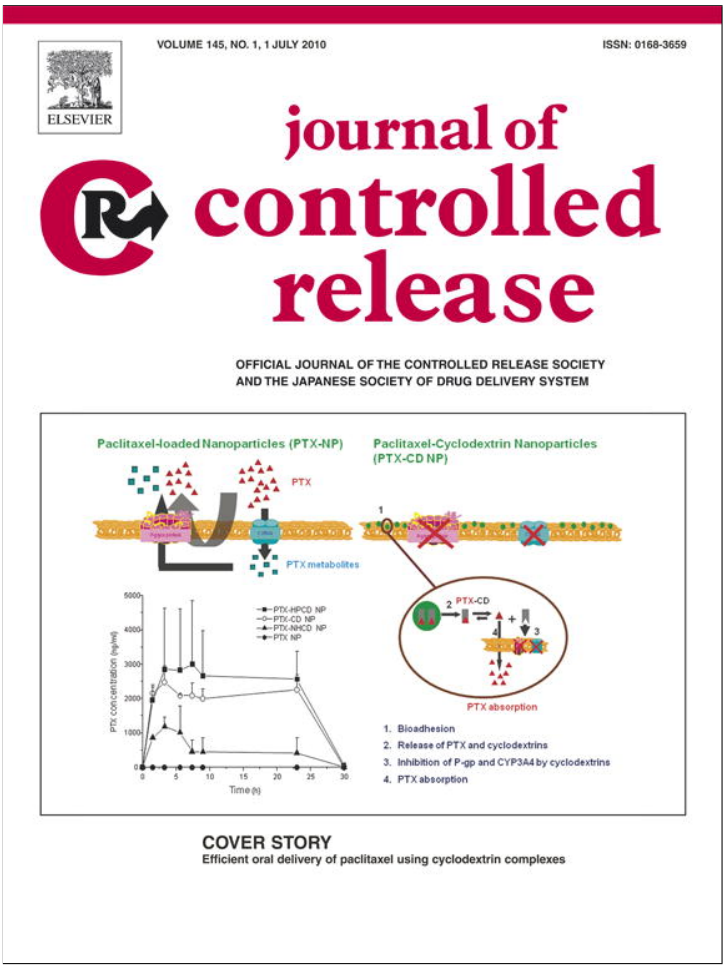

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Cover Story

Efficient oral delivery of paclitaxel using cyclodextrin complexes

Oral administration of the drugs that belong to the Class IV of the Biopharmaceutical Classification System still represents a major challenge. In general, these drugs display a poor aqueous solubility and specific permeability characteristics. In fact, most of these compounds are substrates for the biological transporters (including P-glycoprotein, or PGP) and for metabolism via cytochrome P450 enzymes, resulting in a significant pre-systemic metabolism. Consequently, the unfavorable physicochemical properties of the drug in tandem with the adverse physiological environment of the gastrointestinal tract constitute major challenges for successful oral delivery. Various anticancer drugs suffer from these drawbacks and limit the possibilities to develop oral formulations and treatments. Despite these difficulties, the development of oral formulations for antineoplastics is always very attractive for a number of reasons. First of all, oral delivery is the most convenient mode of drug administration for all patients. Oral delivery also improves patients' compliance and comfort as well as the development of chronic treatment schedules which would decrease the cost of the therapy [1]. In fact, oral delivery of cytotoxic agents would eliminate or minimize the need for hospitalization, medical and nursing assistance, and infusion equipment.

Paclitaxel (PTX) is a potent anticancer agent approved for the treatment of a large number of solid tumors. However, its oral administration is severely hampered due to its low aqueous solubility, P-glycoprotein efflux and first pass metabolism by cytochrome P450 located in the gut and the liver (CYP2C8 and CYP3A4). As a result, the oral bioavailability of PTX with conventional formulations is very low. To overcome these drawbacks various approaches have been explored, such as increasing the solubility or co-administering a PGP inhibitor. In an article in this issue, Professor Irache and his coworkers approached the problem with a new idea of combining bioadhesive nanoparticles and "soft" inhibitors of biological transporters and cytochrome P450 [2].

The new nanoparticles were obtained by using poly(methylvinyl ether-co-maleic anhydride) [(Gantrez AN or poly(anhydride)] and cyclodextrins. Poly(anhydride) nanoparticles have already demonstrated their excellent property of bioadhesive interactions with the mucus layer of the gastrointestinal tract. More importantly, their surface can be easily modified by simple incubation with different excipients or ligands to modify their distribution within the gut and/or their bioadhesive potential [3]. Cyclodextrins have been used for encapsulation of lipophilic drugs, and they have also demonstrated a certain ability to inhibit both PGP and cytochrome P450 localized on the surface of enterocytes [4]. To exploit the useful properties of both poly(anhydride) and cyclodextrins, PTX was loaded into poly(anhydride) nanoparticles after complexing with cyclodextrins. In the study, the PTX-loaded nanoparticles were orally administered in rats, and the PTX plasma levels were characterized by a plateau close to the C_{max} spanning from T_{max} till 24 h post-administration. These sustained levels of PTX were found to be significantly higher than the reported value of cytotoxic activity. Interestingly, the relative oral bioavailability of PTX was calculated to be close to 80%, which is remarkable for oral formulations.

The authors hypothesized that bioadhesive nanoparticles would transport PTX-cyclodextrin complexes up to the surface of the mucosa where these carriers would remain immobilized in intimate contact with the cell membrane. Then, the nanoparticles would progressively degrade to release their content (i.e., PTX-cyclodextrin complexes). In the membrane environment, the complexes would dissociate and, the free PTX would be rapidly absorbed whereas the cyclodextrin molecules would interact with lipidic components of the membrane disturbing the activity of PGP and cytochrome P450. It appears that modulating PGP and cytochrome P-450 simultaneously time is necessary for efficient drug absorption. This hypothesis was supported by the observation that PTX metabolites were not detected in plasma during the first 24 hours after the oral administration of these nanoparticles.

The nanoparticle carriers developed by Professor Irache and his group are certainly of great interest to the drug delivery scientists, as the approach allow implementation of new strategies permitting the oral administration of Class IV drugs. In fact, other recent studies have also clearly shown that proper formulations, such as lipid nanocarriers and chitosan-conjugated nanoparticles, allow effective oral delivery of PTX [5] and docetaxel [6,7]. Although further studies are necessary, it is clear that effective oral delivery of poorly soluble drugs is highly feasible. Our continued progress in oral formulation development is expected to produce clinically useful oral delivery systems in the near future.

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