Development of Ionic-Liquid Mediated Novel Drug Delivery System for Cancer Treatment

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論　文　内　容　の　要　旨

In the past several years, ILs have been at the cutting edge of the most promising research and technology in the scientific field. The applications of ILs not only found to be covered the classical areas of knowledge but also expended as an important candidates to solve critical problems such as clean and efficient energy. In particular. ILs were found to play a special role in the pharmaceutical industry as clean and multifunctional solvents for a variety of applications. This neoteric class of solvents, ILs, generally presents interesting properties, namely, negligible vapor pressure at relatively ambient conditions, high thermal, chemical, and electrochemical stability, and broadly tunable properties with regard to polarity, hydrophobicity, and solvent miscibility. These properties result from a matchless combination of molecular characteristics of their constitutive ions. Moreover, many types of ILs can be regarded as nanosegregated fluids with polar networks permeated by apolar domains, which enables the understanding of their peculiar solvent behavior at a molecular level and the numerous applications to solve classical problems addressing today's societal challenges. One of the major challenge of the pharmaceutical research is the increasing number of active pharmaceutical ingredients (APIs) possessing limited aqueous solubility in biopharmaceuticals classification system class II drugs. The challenging aspects of new formulations of such drug molecules are associated with their slow dissolution in biological fluids, and thus insufficient and inconsistent systemic exposure and consequent suboptimal clinical efficacy. ILs have been considered as solvents and/or materials in the field of pharmaceuticals with the possibility of improved performance such as improved solubility, stability and drug delivery. In fact, due to

their tailor-made properties, ILs can dissolve complex molecules including biologically active compounds and it is highly desirable for ILs to be potential solvents for overcoming the problems concomitant with pharmaceutical industries.

At first**,** we preliminary reported an IL-based paclitaxel (PTX) formulation that composed PTX/cholinium amino acid ILs/ethanol/tween-80/water. A significant enhancement in the solubility of PTX was observed with considerable correlation with the density and viscosity of the ILs, and with the side chain of the amino acids used as anions in the ILs. Moreover, the formulations were stable for up to 3 months. The driving force for the stability of the formulation was hypothesized to be the involvement of different types of interactions between the IL and PTX. In vitro cytotoxicity and anti-tumor activity of the IL-based formulations were evaluated on HeLa cells. The IL vehicles without PTX were found to be less cytotoxic than cremophor EL-based formulation (Taxol), while both the IL-based PTX formulation and Taxol exhibited similar antitumor activity. Finally, in vitro hypersensitivity reactions were evaluated on THP-1 cells and found to be significantly lower with the IL-based formulation than Taxol. This study demonstrated that specially designed ILs could provide a potentially safer alternative to Cremophor EL as an effective PTX formulation for cancer treatment giving fewer hypersensitivity reactions.

Then**,** as a follow-up to previous study, further investigation of the IL-based PTX formulation was reported where in vivo biocompatibility, pharmacokinetics, antitumor activity, and hypersensitivity were evaluated using mouse model with Taxol as a reference. In this study, the stability of the IL-PTX formulation was monitored by quantitative HPLC analysis, which showed that IL-PTX was more stable at 4 °C than at room temperature. The in vivo study showed that the IL-PTX formulation could be used in a therapeutic application as a biocompatible component of a drug delivery system. To assess the in-vivo biocompatibility, IL or IL-mediated formulations were administered intravenously by maintaining physiological buffered conditions (neutral pH and isotonic salt concentration). From in vivo pharmacokinetics data, the IL-PTX formulation was found to have a similar systemic circulation time and slower elimination rate compared to Taxol. Furthermore, in vivo antitumor and hypersensitivity

experiments in C57BL/6 mice revealed that IL-PTX had similar antitumor activity to Taxol, but a significantly smaller hypersensitivity effect compared with Taxol. Therefore, the IL-mediated formulation has potential to be an effective and safe drug delivery system for PTX.

Finally**,** we reported a one-step emulsification and rapid freeze-drying process to develop a curcumin–ionic liquid (CCM–IL) complex that could be readily dispersed in water with a significantly enhanced solubility and stability (half-life) compared to free CCM. For this study, the IL consisted of choline as cation and oleic acid as anion used as a surfactant. Both the cation (choline) and anion (oleic acid) of the IL are widely accepted as biocompatible. Furthermore, oleic acid has been reported to have many interesting biological functions including anti-inflammatory, anti-carcinogenic, anti-oxidative, and immune system activation properties. The developed CCM-IL complex could be readily dispersed in water with a significantly enhanced solubility of ~8 mg/mL and half-life ($t_{1/2}$) of ~260 min compared with free CCM (solubility ~30 nM and $t_{1/2}$ ~20 min). Comparison with a similar complex encapsulated using oleic acid sodium salt (Ole-Na), led to the conclusion that both the cation and anion of the IL have significant contributory roles in the solubilization and stabilization of CCM in the complex. Furthermore, release studies in three different physiological fluids showed bi-phasic profiles with an initial burst release of CCM over a few hours, followed by slow sustained release up to 24 h. Finally, the anticancer activity of the CCM-IL complex was found to be significantly higher when used to treat cancer cells (HepG2) compared with normal cells (fibroblast). The emulsification and freeze-drying process using an IL consisting of a long chain carbon backbone, as a surfactant, may provide an alternative way of enhancing the solubility of poorly water-soluble compounds. Therefore, combining the therapeutic effects of the surfactant and drug considered as a novel approach for the preparation of surfactant–drug complexes.