Development of Lipid-based Biocompatible Ionic Liquids to Enhance Transdermal Drug Delivery Systems for Cancer Treatment.

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（がん治療のための経皮ドラッグデリバリーシステムを増強する生体適合性イオン液体の開発）

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論　文　内　容　の　要　旨

In the past several years, ionic liquids (ILs) have been at the cutting edge of the most promising research and technology in the scientific field. The applications of ILs have been discovered to not only cover traditional areas of knowledge, but also to be an important candidate for solving critical problems such as clean and efficient energy. Specifically, ILs have been 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 nano-segregated 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 challenges of pharmaceutical research is the increasing number of active pharmaceutical ingredients (APIs) possessing limited aqueous solubility in biopharmaceutical 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 the pharmaceutical industry.

In **chapter 2**, we synthesized a series of lipid-based biocompatible ILs (LBILs), which contained a long chain phosphatidyl choline derivative as a cation (1,2-dimyristoyl-snglycero -3-ethyl-phosphatidylcholine; EDMPC) and a series of long chain fatty acids (linoleic acids; $C_{18:2}$, oleic acids; $C_{18:1}$, and stearic acids; $C_{18:0}$) as its structural counter anion. Physiochemical properties of synthesized ILs were characterized by thin layer chromatography (TLC), proton nuclear magnetic resonance (^{1}H NMR), Fourier transform infrared (FTIR), elementary analysis (EA), Karl-fisher moisture analyzer, TOA pH meter, and mass spectrometry (MS). Thermal properties were confirmed by dynamic scanning calorimetry (DSC) and temperature-dependent optical polar microscopy (OPM). Solubility and particle size in different polar and nonpolar solvents was investigated by UV-visible spectrophotometric analysis and dynamic light scattering (DLS), respectively. Finally, the biocompatibility of LBILs was confirmed in the human artificial LabCyte EPI-Model cell line by MTT assay methodology.

In **chapter 3**, we developed the LBILs mediated nanodispersion (ILs in oil nanodispersion; IL/O-NDs) formulations containing leuprolide acetate peptide as a model peptide drug and Span-20 at a specific ratio as a cosurfactant to increase the stability of drug-ILs formulations. The physiochemical properties of IL/O-NDs were characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM)confocal laser scanning microscopy (CLSM), and the high-pressure liquid chromatography (HPLC) system. We observed the in-vitro transdermal drug delivery using Franz-cell and quantified by HPLA. Moreover, we investigated the pharmacokinetic effect on BALB/C mice blood in-vivo using ELISA enzyme linked immunosorbent assay (ELISA) methodology. We also observed the mechanisms of transdermal drug delivery into the SC layer by FTIR analysis. Finally, *in-vivo* and *in-vitro* biocompatibility of IL/O-NDs were observed on LabCyte EPI-Model and BALB/C mice skin histopathology, respectively. LBILs act as a promising biocompatible carrier to increase the stability of nano-drug formulation and enhance the transdermal delivery of a peptide drug, leuprolide acetate.

In **chapter 4**, we developed a LBIL; [EDMPC][Lin]mediated protein antigenic drug in oil phase nano particles (LPNPs) formulations. LPNPs contain a bulky antigenic protein, ova albumin from chicken egg white (OVA) with a molecular weight of 42.7 kDa as a model anticancer drug and Tween-80 is used as a co-surfactant to increase the stability of LPNPs. The formulations were characterized by DLS and CLSM, and in-vivo and in-vitro biocompatibility was confirmed by the human artificial 3D reconstructed Lab-Cyte Epi-Model cell and the mice's skin H & S staining histopathological observation. In vitro skin permeation of protein via the LPNPs system was investigated by the Franz cell system. CLSM and FTIR analysis were performed to investigate the mechanism of intercellular routes of drug permeation via the SC layer of the skin. The effect of LPNPs against tumor growth and development was confirmed on C57/BL6N by inoculation of tumor OVA responsible cancerous cells, EG7OVA for the tumor development. The anti-cancerous antigen uptake of skin dendritic cells (DCs) and other antigen presenting cells (APCs) by flow cytometric and CLSM analysis also revealed the cancer immune response of LPNPs. Finally, we observed $CD8^+$ T-cell inflammation in the tumor microenvironment. We found that LPNPs have an excellent anti-cancerous immune therapeutic effect compared with conventional chemical permeation enhancers and aqueous injection formulations. The effective application of LBIL-mediated LPNPs has indicated that LBIL will be a potential candidate for the platform of a nano-drug delivery system for cancer treatment.