Development of Biocompatible Ionic Liquid Mediated Transdermal Delivery Systems for Sparingly Soluble Drugs

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論　文　内　容　の　要　旨

New breakthroughs for the therapeutic delivery methods are happening faster than ever. Although various pragmatic methods for delivering the drug have been implemented, transdermal drug delivery systems (TDDSs)-a systemic distribution of drug molecules through the skin, have appealed much attention in research today because of their numerous prospective including improved patient compliance, avoidance of first-pass metabolism, and reduced undesirable adverse effects over others conventional delivery systems. However, the prevalent uses of TDDSs is restricted for a few drugs only due to the impermeable nature of stratum corneum (SC), so more attention has been focused on the permeation enhancer containing vesicles to overcome these limitations. Moreover, the pharmaceutical companies have faced many difficulties for TDDSs of sparingly soluble drugs, especially that are insoluble in water and other conventional solvents.

ILs have played a significant role throughout the world of research and technology over the past couple of years. They have been used not only in the classical arenas of science, but also in the widespread branch of engineering to the solve critical emissions problems and lack of productive resources. As a modern contemporary class of solvents, ILs usually exhibit fascinating properties in terms of polarity, hydrophobicity, and solvent miscibility, including negligible vapor pressure under

relatively ambient conditions, high thermal, chemical, and electrical stability. Considering these outstanding features, ILs are expected to be the highly promising alternative to typical organic solvents. In fact, because of their tunable features, ILs might be used for dissolving macromolecules like protein, nucleotides as well as amino acids derivatives. The tunable properties of ILs allow for the possibilities of synthesizing novel medicine of expected specification.

Despite of various advantages, the use of ILs are limited because of their high toxicity, and low biocompatibility and degradability. In fact, most of the previous studies imidazolium, pyridinium, and quinolinium cations based-ILs were never gone in clinical applications because of high toxicity and low biocompatibility. Therefore, finding the cutting-edge technology for resolving these obstacles, like seeking environment friendly, non-toxic, and biocompatible ILs as solvents, co-solvents, and surfactants is of the highest concern.

In **chapter 2**, we reported a potent ternary TDDSs that composed of three different biocompatible ILs, namely choline glycinate ([Ch][Gly]), choline serinate ([Ch][Ser]), and choline alaninate ([Ch][Ala]) in the presence of IPM as a lipophilic phase and EtOH as a co-solvent. The improvement of ACV permeation into and across the pig skin using this new ternary system (IL-EtOH-IPM) is supposed to be due to the combination of several factors including the excellent ACV solubility in IL, IL-EtOH and IL-EtOH-IPM systems, and the push-and-pull effect of lipophilic IPM and amphiphilic EtOH, and the system's synergistic penetration enhancing effect. In addition, *in vitro* cytotoxicity and skin irritation studies using L-929 fibroblast cells and a reconstructed human epidermis model (LabCyte EPI-MODEL), respectively, demonstrated no or less toxicity of the IL and IL-based ternary systems while *in vivo* histological study on mice skin further confirmed the biocompatibility of the IL-based ternary systems. Finally, it was concluded that biocompatible IL mediated ternary system created a new potential scope for the controlled transdermal delivery of

sparingly soluble drugs which have been facing severe problems by other conventional delivery routes.

In **chapter 3**, we reported a novel IL/O ME using biocompatible [Ch][Pro] IL and [Ch][Ole] SAIL as non-aqueous dispersed phase and surfactant, respectively, for improving transdermal delivery of sparingly soluble drug, ACV. The results of this study clearly indicated that the optimum S/Co weight ratio; i.e. 2:1 ([Ch][Ole]/Span-20), was required to formulate IL/O ME with having higher drug loading capacity, excellent physical and chemical stability, and outstanding permeation enhancing ability. This outstanding permeation of ACV into and across the YMP skin was found owing to the combination of several factors such as excellent ACV solubilizing capacity of [Ch][Pro] IL, effective lipid extraction by [Ch][Ole] from SC, and exceptional skin barrier function disrupting ability of lipophilic IPM. The latter two was confirmed by FTIR analysis. If considering the drug loading capacity and skin permeation studies, the successful formation of a ME could be attributed to the favorable interfacial properties provided by a blend of [Ch][Ole] and Span-20, compared with a blend of Tween-80 and Span-20. Finally, *in vitro* skin irritation study using reconstructed human epidermis model (LabCyte EPI-MODEL-12) confirmed that the prepared IL/O MEs were safe and non-toxic, and [Ch][Pro] IL was more safe than commercial [C1mim][DMP] IL. Therefore, MEs containing biocompatible ILs might be promising nano carrier for transdermal delivery of insoluble or sparingly soluble drugs, as well as proteins, peptides, and genetic material, through a TDDS.

In conclusion, the obtained results (**chapter 2 & 3**) recommended that choline cation-based biocompatible ILs could be potent solvents and/or surfactants to eliminate the use of traditional toxic solvents and/or surfactants for topical/ transdermal delivery of sparingly soluble drugs, since they allow an improved solubility and bioavailability or permeability of the studied IL mediated formulations.