AL07 **Design of novel drug formulation for medical needs based on physicochemical property and mathematic model**

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Drug delivery system (DDS) has been drawn attention as novel preparations enabling drugs to maximize their potential by quantitative, spatial, and temporal control of pharmacokinetics. Drug pharmacokinetics are greatly affected by interactions among drug, vehicle, and body. Mathematical model of pharmacokinetics, based on physicochemical and biological properties, is important for rational design of DDS. Novel DDS must be developed by matching the mathematical model to clinical needs. I would like to present several novel DDSs developed in my laboratory based on clinical pharmaceutical sciences.

1. Application of lipophilic prodrug to lipid dispersion system

Various prodrugs of GABA, β -blocker, and steroid have been prepared in different physicochemical properties and their pharmacokinetics (PK)/pharmacodynamics (PD) have been examined to develop the mathematical models of brain transfer, transdermal permeation, intestinal absorption, and liver transfer. These prodrugs were also applied to lipid dispersion systems (liposomes and emulsion) and their PK and efficacy were evaluated to develop the models based on the affinity of drugs and dispersion systems. In particular, the physicochemical properties of mitomycin C prodrugs were demonstrated to determine the DDS properties and PK/PD in tumor-bearing mice.

2. Topical DDS based on pharmacokinetics

Novel transdermal DDSs for clinical use have been developed by systematically examining the PK of drug based on the drug affinity to the formulation. The DDSs were designed by the concepts of thermodynamic activity, solvent parameter, and Fick's diffusion, considering the physicochemical properties of drugs, vehicle, and skin. Unique absorption promoters were also prepared by similar molecular design to transdermal prodrug.

Ophthalmic DDS for clinical use have been developed based on the PK/PD model in the eyes. The corneal permeability *in vitro* and local pharmacokinetics *in vivo* of several drugs and fluorescent dyes were analyzed mathematically to construct new ophthalmic PK model including Fick's equation. Novel ophthalmic PK/PD model including aqueous humor turn-over was also developed by measuring the intra-ocular pressure (IOP), which showed a hysteresis effect, after instillation of various concentrations of anti-glaucoma drugs.

3. Self-assembly nanoparticles from clinical use

Gene and nucleic acids are macromolecules which are degradable and have strong anionic charge. Targeting DDS for gene and nucleic acid is essential for clinical use. Novel targeting DDS have been developed as nano-particles using electrostatic interaction and hydrophobic bond. The particles were constructed with medical products, supplements, and foods. Targeting organ of particles depended on the constructed content. They were prepared easily on sterile process and stored as freeze-dry for long periods. The particles including nucleic acids vaccine showed suppressive effects on malaria and melanoma in mice. The particles of siRNA decreased the melanoma metastasis and prolonged the survival time. These particles for clinical use are expected to contribute to development of gene and nucleic acid medicines in Japan.