Title of Research:

21-3-01 Establishment of in silico model to predict skin absorption of chemical compounds with two-layered diffusion model

Principal Investigator:

Hiroaki Todo, PhD (Associate Professor, Faculty of Pharmacy and Pharmaceutical Sciences, Josai University)
1-1 Keyakidai, Sakado, Saitama 350-0295, Japan
(tel)+81-049-271-7367

Collaborators:

Kenji Sugibayashi, PhD (Josai University)
Kozo Takayama, PhD (Josai University)
Shoko Itakura, PhD (Josai University)
Kenji Mori, PhD (Josai International University, 1 Gumyo, Tougane-shi, Chiba, 283-8555, Japan)
Takeshi Oshizaka, PhD (Josai International University)
Chihiro Takei (Josai International University)
Tetsuya Watanabe (Ohu University) 31-1 Koriyama-shi, Fukushima, 963-8611, Japan
Masahiro Sugino (Ohu University)

Summary of Research:

The skin is the site of exposure to various chemicals. Therefore, the prediction of the chemical's permeability to the ski and local concentration in the skin is very important to assure ensure the safety of the chemicals. Many *in silico* models for predicting these parameters are based on the prediction of the permeability coefficient (*P*) of the exposed chemical. On the other hand, the amount of chemicals absorbed in the body after dermal exposure is calculated from the sum of the amount of the chemical permeated through the skin and the amount of chemical in the viable epidermis and dermis (VED). The amount of chemical permeated through the skin can be calculated by the *P* value. However, the amount of chemical distributed in the VED layer, which is also related to the local safety of the exposed substance, cannot be predicted.
We have already reported that two-layer diffusion model based on Fick's second law of diffusion could predict blood concentration- and skin concentration-time profiles. However, this model has the drawback that skin permeation parameters (chemical diffusivity in stratum corneum (SC) and Ved layers, chemical partitioning into SC and VED layers) must be obtained from *in vitro* skin permeation experiment.
Therefore, this year, we aimed to develop an *in silico* model by clarifying the relationship between skin permeation parameters and characteristic values of chemical substances (molecular weight, fat solubility, molecular volume, energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the molecule, etc.).
The approach with linear regression analysis, it was not possible to obtain a highly correlated relationship between skin permeation parameters and characteristic values of the chemical substance. On the other hand, the regression analysis using random forest regression analysis revealed that good correlations were obtained with all skin permeation parameters when molecular weight, lipophilicity, HOMO, and LUMO were selected. The permeability coefficients of 30 compounds were calculated based on the results using random forest regression analysis, and while two chemicals showed more than 5-fold difference in permeability coefficients, 22 chemicals showed a difference within 2-fold. In the future, we would like to evaluate the predictability of skin permeability of various compounds that listed in the EDETOX database to clarify the applicability of this method.

Timeline:

March 1st, 2021-

Topics:

Publications:

ICCA-LRI Workshop (June 20, 2022)