Proc. of the 9th Intl. Conf. of Asian Society for Precision Engg. and Nanotechnology (ASPEN 2022)
15–18 November 2022, Singapore. Edited by Nai Mui Ling Sharon and A. Senthil Kumar
doi://10.3850/978-981-18-6021-8_OR-08-0147

Prediction of Drug Permeation Through Human Skin Treated with Microneedles Using Machine Learning Methods

Yunong Yuan[1], Yiting Han[2,3], Chun Wei Yap[4], Jaspreet S. Kochhar[5], Hairui Li[6], Xiaoqiang Xiang[2,*], Lifeng Kang[1,*]

1 School of Pharmacy, Faculty of Medicine and Health, University of Sydney, NSW, 2006, Australia
2 Department of Clinical Pharmacy and Pharmacy Administration, School of Pharmacy, Fudan University, Shanghai, 201203, China
3 Harvard T.H. Chan School of Public Health, 677 Huntington Avenue Boston, MA 02115, USA
4 National Healthcare Group, 1 Fusionopolis Link, Singapore 138542, Republic of Singapore
5 Procter & Gamble, 70 Biopolis St, Singapore 138547, Republic of Singapore
6 MGI Biotechnology, 21 Biopolis Rd, Nucleos, Singapore 138670, Republic of Singapore
** Corresponding authors: xiangxq@fudan.edu.cn, lifeng.kang@sydney.edu.au*

KEYWORDS: Microneedle, Transdermal, Machine learning, XGBoost, Random Forest, Drug delivery

Microneedles are sharp protrusions, which can penetrate the stratum corneum, the utmost layer of skin preventing external substances from getting into human body. Then drugs can passively diffuse through skin and are absorbed into blood circulation. The process of measuring the amounts of drugs permeated through skin is challenging yet crucial for transdermal drug delivery. In vitro drug permeation testing is a commonly used method, but it is costly and time-consuming. To this end, the simulation method may be a better alternative to predict the drug permeation than experimental testing. For in vitro drug permeation testing, Fick's law is used find the diffusion coefficient, which is hard to determine. This paper proposes to apply machine learning methods to predict the rate of drug permeation through skin, circumventing the process of measuring diffusion coefficient with experiments. XGBoost and Random Forest methods are used and compared with conventional methods. The results showed that XGBoost was the best method to predict of drug permeation through skin. It was found that drug loading, permeation time and microneedle surface area are critical parameters in the prediction models. With the prediction models enabled by machine learning, microneedles could be tailored to deliver prescribed drug dose through skin for precision medication.

NOMENCLATURE

MN = microneedle
MW = molecular weight
RMSE = Root Mean Square Error

1. Introduction

Precision medicine is to consider individual variability in genes, environment, and lifestyle of each person for disease prevention and/or treatment. The intervention can be customized for a certain patient, with minimum medically side effects, reduced healthcare costs and optimal treatment effects.

Microneedles (MNs) are small, highly customizable, and minimally invasive devices to deliver drugs through skin. By creating multiple microscale passages through skin, they can enhance the permeation of drug molecules through skin to reach the therapeutic levels, making MNs potentially useful for precision medicine.

Previous studies have shown that mathematical modelling was useful in elucidating the mechanism of drug permeation through skin. However, the reported models for predicting drugs penetrating through the skin involved an important parameter, namely, diffusion coefficient, which varies with ambient temperature, drug concentration, water content, etc. As a result, it is difficult to measure diffusion coefficient accurately.

In this study, machine learning method is used to simulate the process of drug permeation through skin, without the need to determine diffusion coefficient experimentally.

2. Results and discussion

2.1 Overview of four simulation methods

Four simulation methods were used in this study to simulate the experimental data of various drugs, which were determined in our previous studies. As a control, Fick's law was used to fit the drug-releasing curve. A two-dimensional model representing the central cross-section of the MN and skin was applied to predict the evolution of the drug based on Fick's law and domain discretization, as shown in Figure 1 (a). Drug concentration in each element would exchange passively with their neighbor elements. Multiple linear regression is a traditional method to predict the response value for the collected variables. Random Forest and XGBoost are machine learning methods based on the decision tree, as shown in Figure 1 (c) and (d). The data were divided into the training set and test set. The training set was used to build the models in the machine learning algorithm, while the test set was used to verify the robustness and precision of the models.

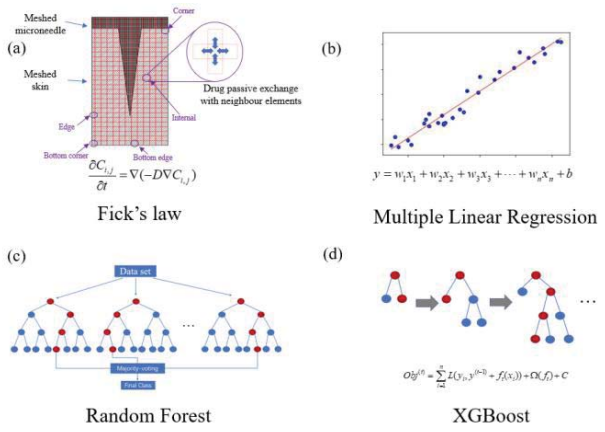

Fig. 1 Four methods were used to compare the prediction capability of the drug permeation from MN: (a) Fick's Law; (b) Multiple Linear regression; (c)Random Forest; and (d) XGBoost.

2.2 Simulation results

The RMSE and R-squared values of the four simulation methods were obtained. XGBoost method had the lowest RMSE value and highest R-squared for drug permeation amount and percentage prediction, among the four simulation methods. Between RF and Fick's Law, RF showed better performance in permeation percentage prediction, while Fick's law was better in predicting permeation amount. MLR showed the worst prediction among the four methods for both drug permeation amount and percentage.

The predicted drug permeation results were compared with the experimental data from 6 different drugs and 2 types of skin samples. The predicted results using XGBoost and RF methods matched well with experimental data. However, they had a significant deviation when the data set was relatively small for a specific drug.

Both RF and XGBoost methods showed that the surface area of the MN and permeation time were the key parameters in predicting drug permeation percentage through skin, while the drug loading in MN and permeation time were the key features in predicting drug permeation amount through skin. In RF method, the importance of MW, drug loading, MN length, skin type and MN type were below 12% in predicting drug permeation percentage. The importance of surface area, MN length and type, skin type and MW were below 7% in predicting permeation amount.

3. Conclusions

This study presented four models to compare the precision of the predicted MN drugs permeation results with experimental data. In the machine learning models, the parameters include: the skin type, type of the MN, length and surface area of the MN, drug loading in MN, drug permeation time, the MW of the drugs and the amounts of accumulated drugs in the receptor. The MN surface area and permeation time are the most important parameters in predicting drug permeation percentage through skin. Drug loading in MN and permeation time are the most important parameters in predicting drug permeation amounts through skin. Other features have limited effects on the prediction of drug permeation through skin.

Among the four models, the XGBoost showed the best prediction results with R-squared 0.98. RF method ranked in the second position in predicting drug permeation percentage, while Fick's law was in the second position in predicting drug permeation amounts. Taken together, the machine learning methods were found useful in predicting drug permeation through skin.

ACKNOWLEDGEMENT

This work was funded by the University of Sydney-Fudan University Partnership Collaboration Awards (PCA) of the year 2019. Y. Yuan is a recipient of the USYD-CSC (University of Sydney - China Scholarship Council) scholarship (No. 202008320366).

REFERENCES

1. Chen J, Bian J, Hantash BM, Albakr L, Hibbs ED, Xiang X, Xie P, Wu C, Kang L. Jul 2021. Enhanced skin retention and permeation of a novel peptide via structural modification, chemical enhancement, and microneedles. International Journal of Pharmaceutics. 606 (2021), 120868.
2. H. Kathuria, K. Kang, J. Cai, L. Kang, Rapid microneedle fabrication by heating and photolithography. International journal of pharmaceutics 575 (2020) 118992.
3. H. Li, Y.S. Low, H.P. Chong, M.T. Zin, C.Y. Lee, B. Li, M. Leolukman, L. Kang, Microneedle-Mediated Delivery of Copper Peptide Through Skin, Pharmaceutical Research 32(8) (2015) 2678-89.