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Compartmental Modeling Approach: Application on Transdermal Delivery for In Vitro Drug Permeation Mechanism Analysis

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Abstract: Compartmental modeling analysis was used to understand the transport mechanism of drugs in biological systems by computation presented as intercompartmental flows or material. This study was aimed to implement compartmental modeling analysis for in vitro permeation studies in transdermal delivery. The cumulative drug transported versus time were obtained based on the previous report and implemented the two structural different proposed models. WinSAAM software (Windows-based Simulation Analysis and Modeling-WinSAAM Project Group, University of Pennsylvania) was used to analyze data with compartmental analysis. The chosen models were selected through visual and numeric evaluation. The best model had been chosen and could figure out the drug transport kinetics in the biological system. The compartmental modeling approach was helpful used in understanding drug transport mechanisms in transdermal delivery and effectively estimate the drug transport parameter.

Keywords: WinSAAM; compartmental modeling; transdermal transport; in vitro permeation

1. INTRODUCTION

Modeling computation may support to estimate of the mathematical drug transport mechanism in transdermal delivery. The particular software is necessary to help compute and analyze those mathematical models [1]. Such studies can be carried out using an approach called compartmental modeling. Compartmental modeling is a mathematical representation of part of the body that assumes the body as a series of compartments either in series or parallel depending on material transport flow. The developed model is used to understand pharmacological or physiological kinetic characteristics [2].

In this approach, to describe the mechanism of transdermal delivery transport, a compartment-based model was developed, implementing a drug transport flow from donor phase or patch across the skin before achieving into acceptor phase or plasma [3]. A compartmental modeling approach gives the advantage that data transport analysis does not depend on whether the steady-state condition is achieved or not in the experimental process as in the diffusion lag time

method. Compartmental modeling studies had been constructed by Nugroho et al. for analyzing and describing the drug transport of the transdermal iontophoresis both in vitro [4,5] and in vivo [6] also in passive transport [7,8].

Several commercial software is used for compartmental modeling analysis, which provides the license. Such software had been reported are Winnonlin [5,6] and NONMEM [9] for data fitting. WinSAAM, a software-based Windows, is used for modeling the various biological systems based on a compartmental approach. This software was developed by Boston and coworkers at the National Institutes of Health (NIH), Washington [10]. WinSAAM is also free software, so it is very profitable for academics and researchers. This study aimed to implement compartmental modeling analysis to the data transport in transdermal delivery to understand the mechanism of drug transport using WinSAAM programs.

2. MATERIALS AND METHODS

2.1. Preparation of data

The data of in vitro permeation test from Pawestri et al. (2021) were used to implement the compartmental modeling analysis. In vitro transport data of the transdermal patch of domperidone were performed in 8 hours as the cumulative drug transported (μg/mL) versus time (hour) [11].

2.2. Modeling Analysis

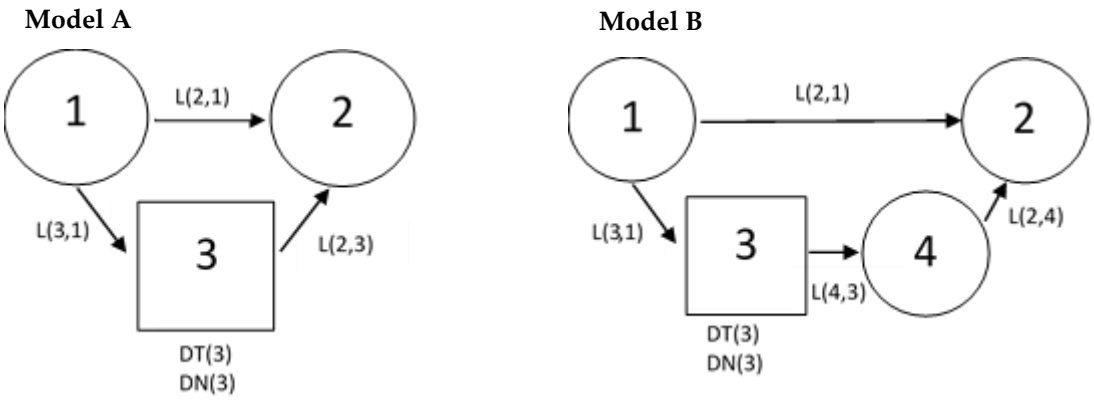

Figure 1. Schematic proposed model for transport transdermal of domperidone [8]

WinSAAM (version 3.3.0, running on Windows 10) was used to model the drug transport mechanism. The proposed models used in this study were similar to Pawestri et al.'s report (2021). Those proposed models were three- and four-compartments involving a lag compartment (depicted in Figure 1). Model A consisted of three compartments, i.e., drug in the patch, receptor medium, and lag compartment for 1, 2, and 3, respectively. Meanwhile, model B consisted of four compartments, i.e., drug in the patch, receptor medium, lag compartment (epidermis layer), and dermis layer compartment for numbers 1, 2, 3, and 4, respectively. Both models were implemented to the data transport and performed individual data fitting by a naive pooling approach to obtain visual-based evaluations of the data [5]. The notation rule in WinSAAM was used to model the data that represented the flow of mass transfer in the model and define the model parameters. Several notations were used such as 1)IC(1), i.e., initial dose amount; 2) L(y,x), i.e., coefficient of drug transport from the compartment x to the compartment y 3) DT(z), i.e., lag time in compartment z and 5) DN(z), i.e., theoretical delay number of partial elements or pseudo-compartments in a specific lag compartment z.

Those notations were listed together with the data transport, and data would be executed using the command, i.e., deck, solve, and iter. After data fitting, the visual evaluation of the model's appropriateness was observed on 1) Correlation plot of predicted and observed transport data versus time, 2) Correlation plot of predicted versus experimental transport, and 3) Correlation of residuals versus time. The further evaluation was used as the numeric evaluation, namely the Corrected Akaike's Information Criterion (AICc) [12] using R software.

3. RESULTS AND DISCUSSION

The capability of the proposed model to describe the drug transport was observed. Entering the listing code into the software and conducting data fitting could determine the parameter kinetic drug transport simply and effectively.

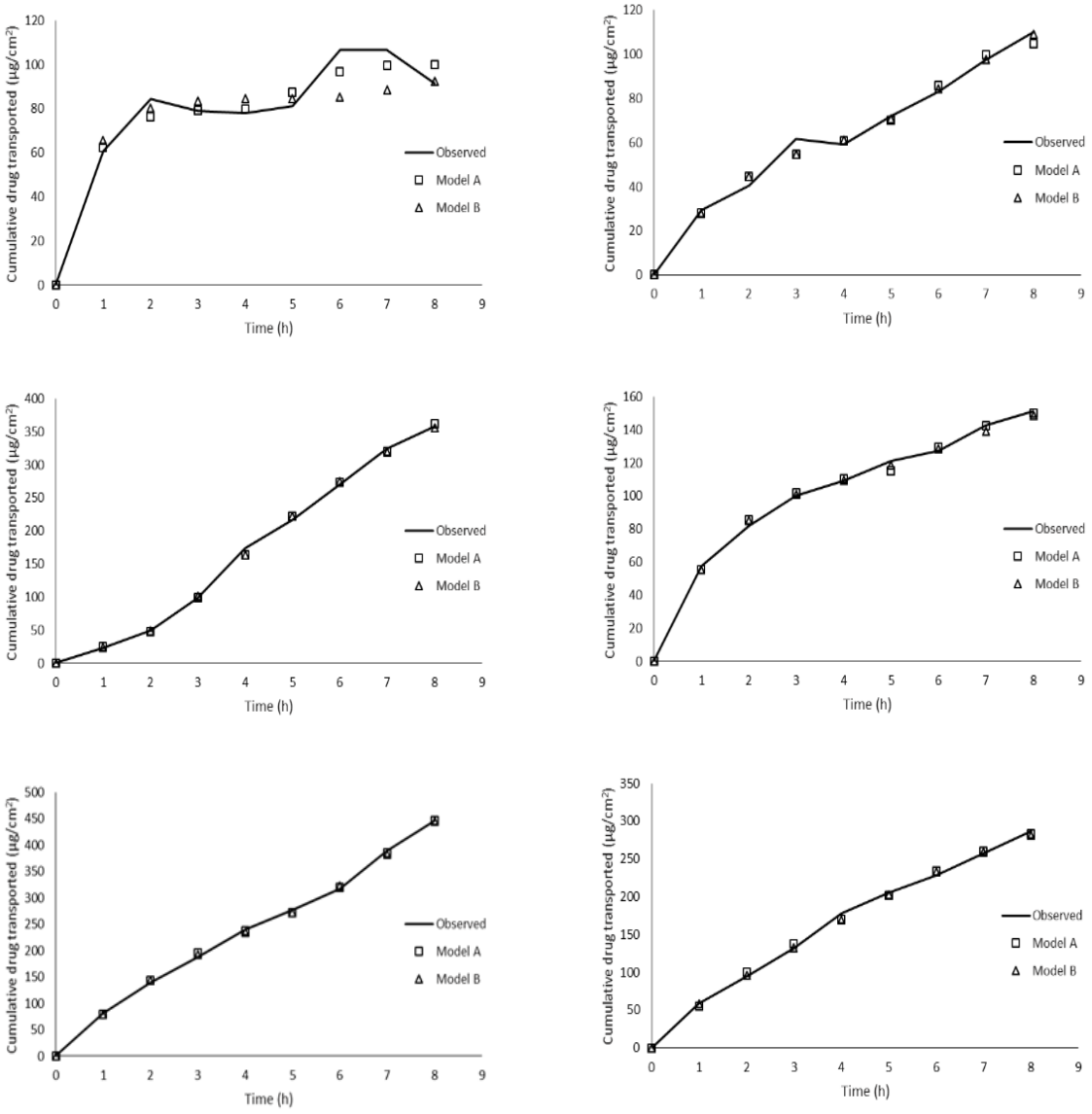

Figure 2. The fitting result of observed data applied with model A and model B

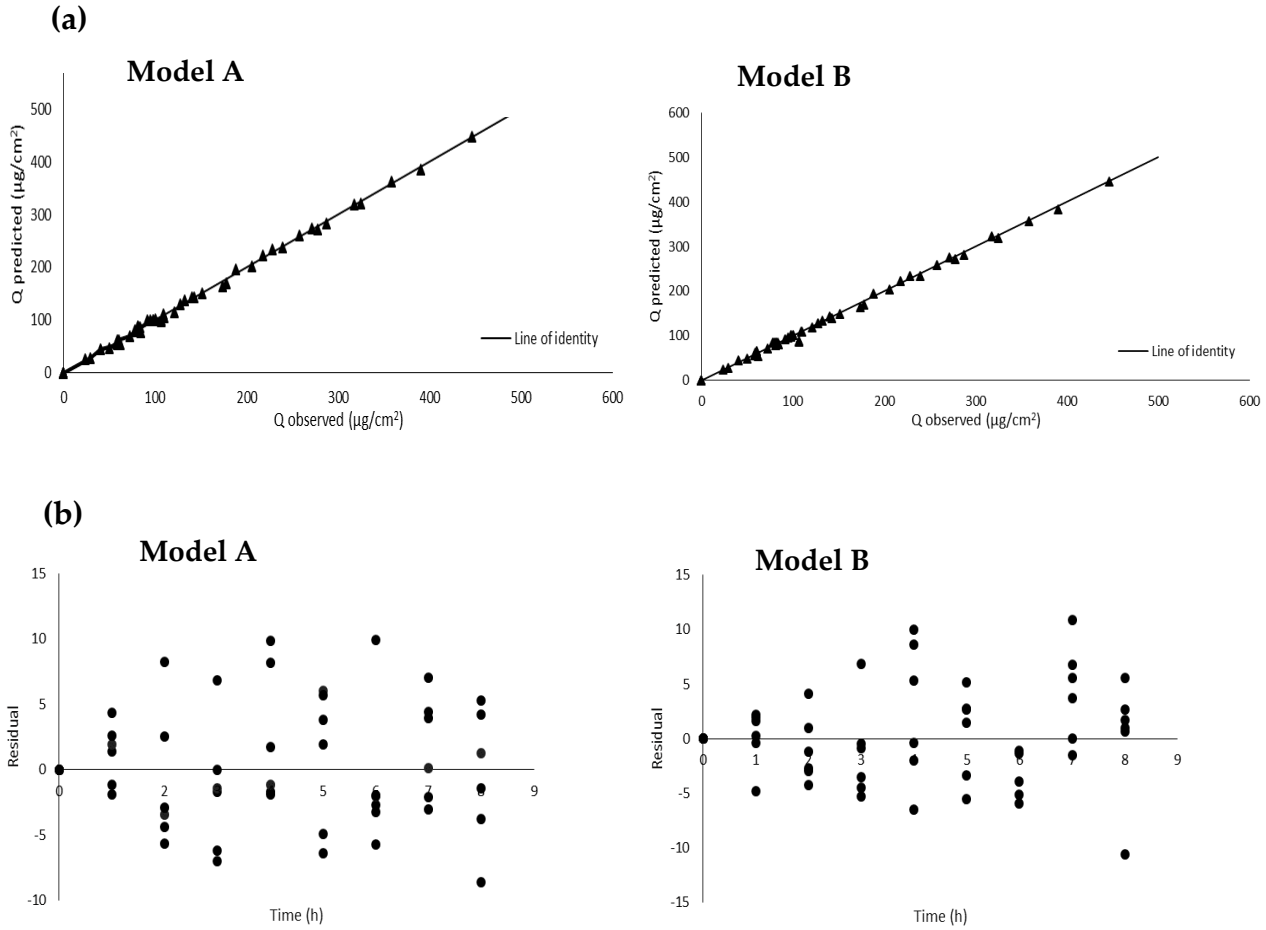

Figure 3. The correlation of Q predicted transport versus Q observed transport **(a)** and the correlation of residual versus time **(b)**.

Based on the naive pooling approach (shown in Figure 2), the predicted and observed value was very close either in Model A or B. Thus, other visual evaluations were also conducted by observing the data based on the correlation of predicted versus observed data transport and the correlation of residual versus time (presented in Figure 3). Residual values were obtained by calculating the difference between the predicted and observed values [13]. Ideally, the good-fit model showed by the residuals fluctuate in a more or less uniform band around zero lines [14,15]. It showed that the data were almost had identical situations with the fitting using models A and B.

Table 1. Table 1. AICc Parameters of proposed model A and B

Replicate	Model A	Model B
1	68.80	76.90
2	59.02	55.38
3	62.65	63.77
4	53.45	48.83*
5	59.85	62.60
6	65.50	60.54

* The lowest AICc values

Based on the visual evaluation, model B might be better fitted with observed data. It can be seen especially in the correlation of residual versus time, exhibited in Figure 3(b). The residual data on model B fluctuate more uniformly, nearly the zero line than the residual data on model A.

Therefore, further AICc evaluation was performed on the individual data-sets to ensure the best model between models A and B [7]. A lower AICc value indicates that the proposed model fits the observed data better than the other models. The lowest value of AICc of this study was Model B (presented in Table 1), so it was chosen as the best model.

Regarding the proposed model of these studies, we assumed that compartment 1 shows the drug dissolved in the patch and released either directly flows into the receptor phase (compartment 2) or lag compartment (compartment 3). Transport drug direct into compartment 2 indicates that drug hydrophobic properties easily pass through the skin barrier and move into the receptor phase. Compartment 2 was the receptor phase where the sample was analyzed and represented the amount of drug permeated. Compartment 3, involving the kinetic lag time parameter into the model, was considered the drug might need some time to enter the skin compartment [5]. Diffusion drug from the patch would face the skin barrier laid on the epidermis layer, so the drug required more time to pass those parts, considering the delaying/ lag compartment is performed. The last, compartment 4, indicates that after passing the epidermis layer, the drug diffuses into the inner layer at a particular rate constant of kinetic permeation.

Understanding drug transport through the skin in developing a transdermal drug delivery system is crucial to achieving an optimal therapeutic effect. The implication of modelling for the future development of domperidone in transdermal delivery, but not limited to other drugs, can help predict the penetration rate of drugs and the appropriate doses, exposure times or sampling intervals [16]. Furthermore, the proposed model can be developed to mathematically represent the diffusive processes in the stratum corneum as a continuous series or as a series of discrete compartments. It can be applied in the transdermal drug delivery simulation to predict the effects of dermal exposure on external elements and analyse the percutaneous kinetics of absorption and the kinematics of bio-transport phenomena [16-19].

Regarding the development of domperidone transdermal delivery, the reported research was generally formulating transdermal dosage forms such as patches, nanoemulsions, creams, and niosomes and then measuring the permeation parameters using the lag time diffusion method [20-23]. There are still no studies that have analyzed the transport of domperidone with this approach. However, this analysis is very useful, as already said above.Therefore, this study becomes interesting to carry out. Thus, based on these studies, the compartmental modelling approach could help determine the drug's flows in permeating the skin and be helpful for the future drug development of the transdermal delivery system.

4. CONCLUSION

The compartmental modeling approach helps describe the drug mechanism of in vitro transdermal transport based on the proposed models that properly fit the drug's transport data. Winsaam, as free software, has a good performance for conducting compartmental analysis effectively.

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Conflicts of interest: The authors declare no conflict of interest.

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