

In vitro Transdermal Transport of Domperidone by Compartmental Modeling Approach

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ABSTRACT

Transdermal delivery can be alternatively chosen for domperidone to improve its low oral bioavailability. The development of drugs into transdermal formulation needs information about the transport mechanism of the drug. This study aimed to develop models of domperidone transdermal transport *in vitro* based on compartmental modeling for understanding the domperidone transport mechanism. Domperidone solution (0.5g/L in a citric buffer, pH 5) was filled into the donor compartment. A comparative study was also conducted to examine the effect of different pH on domperidone transdermal transport in pH 1 (4g/L in 0.1M HCl). The shed snake-skin and cellophane membrane were pretreated for 1h with a chemical enhancer (oleic acid in propylene glycol) and assembled between the donor and the vertical diffusion cell's receptor compartment. The receptor compartment was filled in with phosphate-buffered saline at a pH of 6.8. The permeation study was performed for 8h. Samples concentration was assayed by UV-spectrophotometry. The cumulative permeation profiles of domperidone were analyzed using WinSAAM. Three and four-compartmental models were proposed with the one lag compartment. The evaluation of the appropriate number of compartments in the transport model was examined based on the visual goodness of fit (GOF) and the corrected Akaike's information criterion (AICc) values. The four-compartmental model with one lag compartment was the best model describing percutaneous domperidone transport either in pH donor of 5 or pH 1. The model indicates domperidone transport follows into two parallel routes, including a lag compartment.

Keyword: Transdermal, Domperidone, compartmental modeling, WinSAAM

INTRODUCTION

Domperidone, a dopamine antagonist, is an antiemetic and prokinetic agent with a recommended single dose of 10mg and a total daily dose of 40mg (Boyce *et al.*, 2012). The extensive first-pass metabolism in the intestine and liver results in a low domperidone's oral bioavailability (13-17%). The elimination half-life of domperidone is about 7-9h (Helmy and El Bedaiwy, 2014). An alternative formulation is via a transdermal delivery route. It can avoid the first-pass metabolism in the liver, increasing the bioavailability of drugs. It also has good acceptance for the patient (Sarath *et al.*, 2014). However, the drug must pass the barrier of the skin (i.e., stratum corneum). Chemical enhancers can

improve skin penetration of the drug. Oleic acid (OA), one of the chemical enhancers, temporarily disrupts the stratum corneum lipid, increasing the skin's fluidization and diffusivity (Haque and Talukder, 2018). Furthermore, there are reports that OA in propylene glycol (PG) can synergistically increase drug permeation. This combination has been reported to increase the transdermal transport of thymoquinone, propranolol, and alfuzosin (Haq and Michniak-Kohn, 2018; Hendriati and Nugroho, 2009; Pattnaik *et al.*, 2011).

There is no report yet about transdermal delivery of domperidone with OA in PG enhancers, as well as the concern on the transdermal domperidone transport mechanism. This

investigation is essential to study domperidone characteristics while passing across the skin layer. Compartment modeling is a mathematical model representation of parts of the body to assess pharmacological or physiological kinetic characteristics (Khanday *et al.*, 2017). This modeling approach describes transdermal transport as a drug mass transfer process from the donor compartment to the acceptor compartment via the skin as an intermediate compartment (Nugroho *et al.*, 2004). Compartmental modeling has several advantages. First, the parameter of transport can be analyzed directly from the original flux data. Second, the entire observed data can be analyzed without excluding some data points, such as the diffusion lag time method. Compartment modeling also describes the flux as a function of time to predict the steady-state flux, even though the condition has not been achieved (Nugroho *et al.*, 2004).

Several studies have been conducted to describe drug transport based on compartmental modeling. Such an approach has been applied in transdermal iontophoresis *in vitro* (Nugroho *et al.*, 2004) and *in vivo* (Nugroho *et al.*, 2005); and in passive transdermal transport *in vitro* (Nugroho *et al.*, 2014). The models can be built in by WinSAAM, free software for the biological system modeling (Stefanovski *et al.*, 2003). This study aimed to describe the transport mechanism of domperidone combined with OA in PG, based on the compartmental modeling approach. As a comparative study, we also studied the influence of extreme pH (i.e., pH 1) and enhancer concentrations on the permeation and compartment model of domperidone.

MATERIAL AND METHODS

Domperidone (Vasudha Pharma Chem Ltd., India), shed-snake skin of Albino Burmese Python species (Yogyakarta, Indonesia), cellophane membrane (Fisher Sci. Co., USA), distilled water, oleic acid, and propylene glycol (Dow Chemical Pacific, Singapore), Na₂HPO₄, KH₂PO₄, KCl, NaCl, and HCl were of analytical grade (Merck, Germany). The instrument used was UV-Vis Spectrophotometer (Genesys 10S, USA).

Shed snake-skin pretreatment

Both the shed snake-skin and cellophane membranes were cut into circular shapes 1.5 cm in diameter using scissors. They were then hydrated in phosphate-buffer saline (PBS) at a pH of 6.8

for 30 min. The cellophane was used as a supporting membrane for the shed snake-skin. The shed snake-skin was put above the cellophane membrane when assembled between the donor and the diffusion cell's receptor compartment. Oleic acid in various concentrations (1% for pH 5 and 1; 5; 10% for pH 1) in propylene glycol were prepared. A composition of 3 mL of oleic acid in propylene glycol was filled into the diffusion cell's donor compartment. The receptor compartment was filled in with PBS at a pH of 6.8. The skin pretreatment was performed for 1h.

Permeation *in vitro*

After skin pretreatment, the donor compartment was filled in with 3mL solution of domperidone (0.5 g/L in the citric buffer pH 5 and 4g/L in 0.1M HCl pH 1) while the receptor compartment was filled in with PBS at a pH of 6.8. The permeation was done for 8h. A total of 2mL samples were collected from the receptor compartment and immediately replaced with PBS at a pH of 6.8 in the same volume. Sample concentrations were determined by UV spectrophotometer at a wavelength of 285nm.

Data analysis

The cumulative permeation of domperidone was calculated. Then, the data were analyzed using WinSAAM (Windows-based Simulation Analysis and Modelling-WinSAAM Project Group, University of Pennsylvania). The evaluation of an appropriate compartmental model of transport was analyzed based on 1) the goodness of fit (GOF) analysis based on the correlation of QO (observed transport) versus QC (calculated/predicted transport) of domperidone (Nugroho *et al.*, 2014) and 2) the corrected Akaike's information criterion (AICc) (Motulsky and Christopoulos, 2003).

RESULTS AND DISCUSSION

A compartmental model of domperidone transdermal transport

The *in vitro* permeation profiles of domperidone across the shed snake-skin (Figure 1). The cumulative amount of transported domperidone was analyzed based on a similar approach reported by Nugroho *et al.* in losartan transport (Nugroho *et al.*, 2014). We proposed a three- and four-compartment model involving a lag compartment (Figure 2).

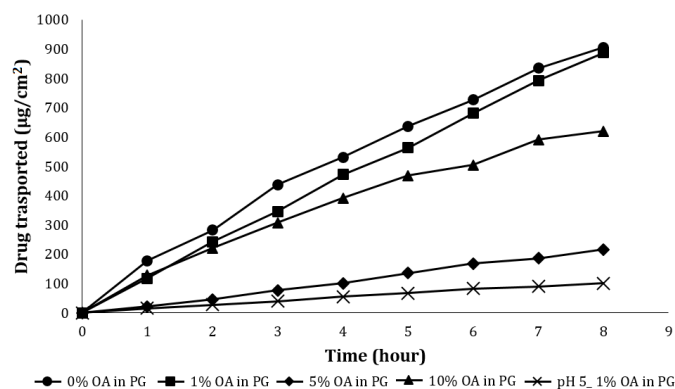


Figure 1. Permeation profiles of domperidone using 1% OA (oleic acid) in PG (propylene glycol) for pH 5 (n=3) and different concentrations of OA in PG for pH 1 (n=4).

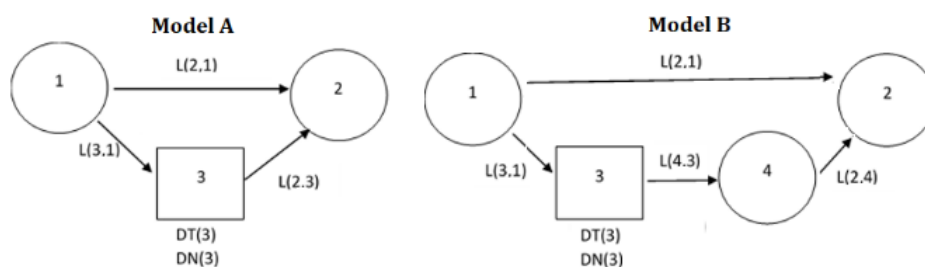


Figure 2. Schematic proposed models for transdermal transport of domperidone.

Table I. AICc Parameters of proposed model A and B

Condition	Replicate	Model A	Model B
^a 1% OA in PG	1	58.83	58.66
	2	49.20	49.31
	3	23.38	2.60*
	4	35.05	28.12*
^b OA 0% in PG (Control)	1	43.94	43.57
	2	62.86	47.91
	3	75.19	75.93
	4	55.97	52.99
^b 1% OA in PG	1	60.46	60.69
	2	33.98	14.12*
	3	48.24	49.12
	4	35.20	13.56*
^b 5% OA in PG	1	51.29	48.95
	2	38.38	45.90
	3	24.31	27.16
	4	62.17	58.24
^b 10% OA in PG	1	66.94	73.23
	2	40.57	36.72
	3	26.42	-7.98*
	4		

*The lowest AICc values among data each group ^a pH of 5 ±0.05; ^b pH of 1 ±0.05

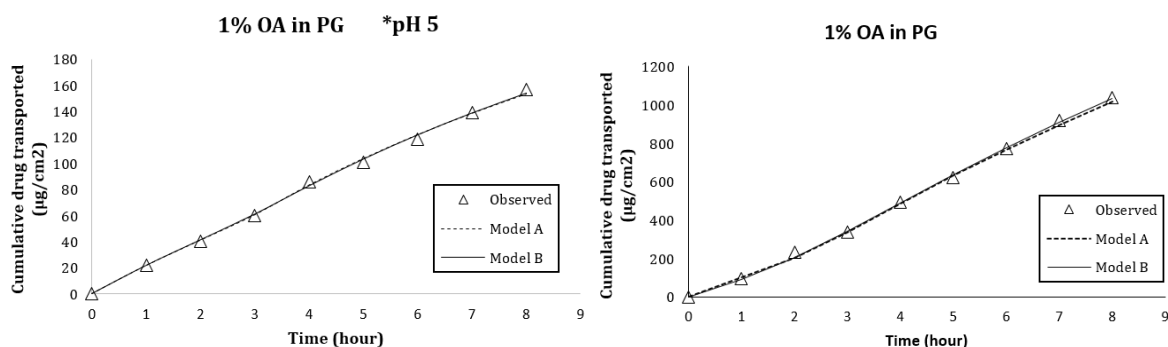


Figure 3. Typical example of fitting data of domperidone using 1% OA (oleic acid) in PG (propylene glycol) using Model A (---) and Model B (—) for pH of 5 and pH of 1.

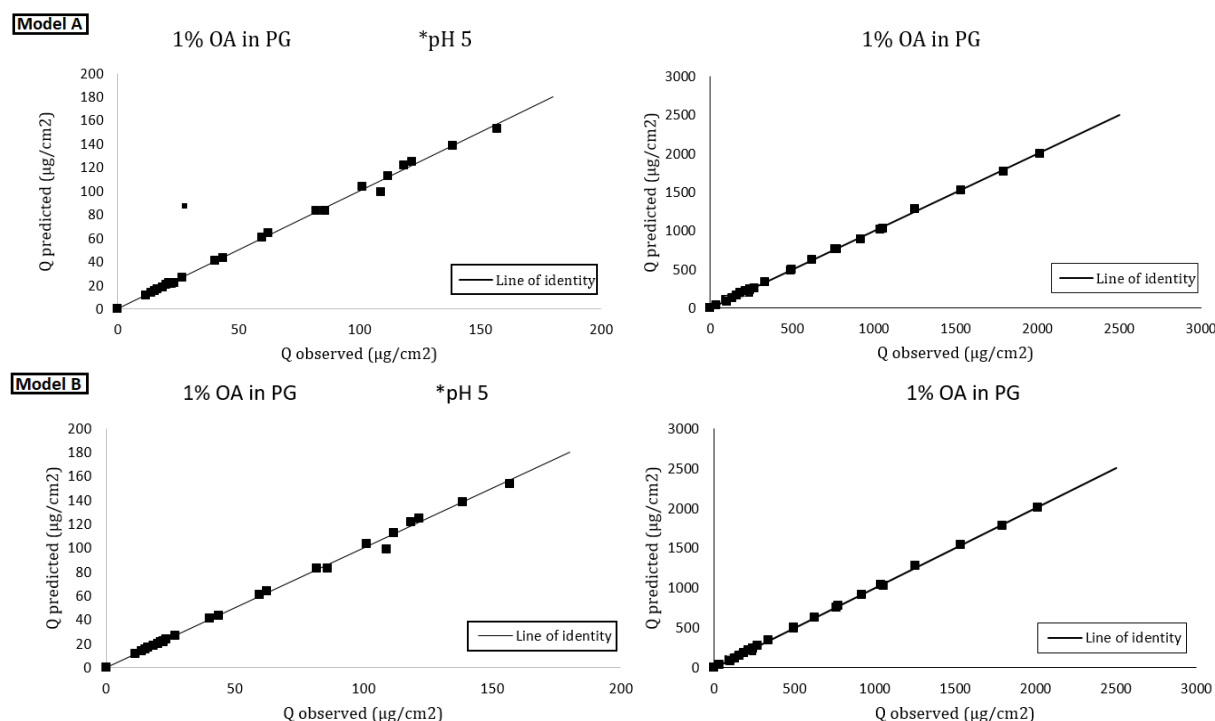


Figure 4. Goodness of fit (GOF) of transdermal transport of domperidone using 1% OA (oleic acid) in PG (propylene glycol) for pH of 5 (*) and pH of 1. The graph shown based on Q observed transport versus Q predicted transport of domperidone; OA= oleic acid, PG= propylene glycol. The data were presented from the results of three replicates (*) and four replicates experiments.

The typical examples of the analysis are presentation of model fitting (Figure 3) and based on the goodness of fit (Figure 4).

Data presentation of model fitting (Figure 3) shows model B could fit better than model A. It is also supported by GOF evaluation (Figure 4), which indicated that there was less deviation between observed and software prediction data. Further evaluation was conducted to ensure the best model.

AICc calculation was performed (Table I). The lowest AICc value is preferred because it indicates that the model fits the observed data better than the other models. AICc analysis showed that the appropriate model for domperidone transport is Model B.

Model B is a four-compartmental model involving a lag compartment. The first compartment was the drug in solution.

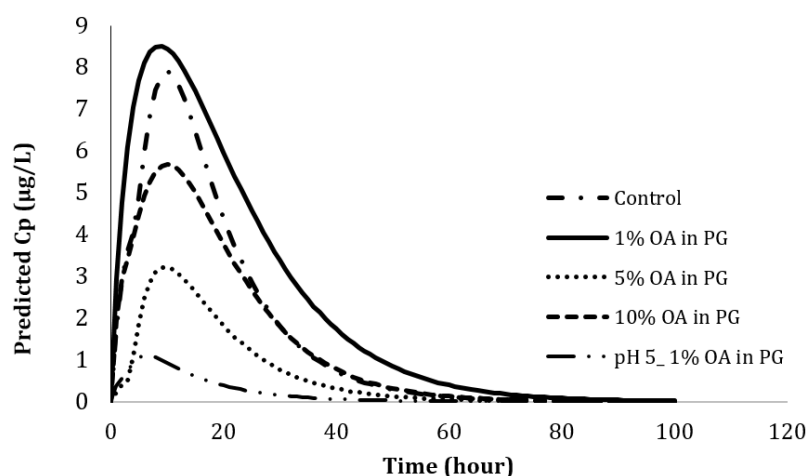


Figure 5. Predicted transport domperidone profiles in vivo by WinsAAM.

Table II. Parameters of transdermal transport *in vitro* of domperidone analyzed by WinSAAM

	^a OA 1 % in PG	^b OA 0% in PG (Control)	^b OA 1% in PG	^b OA 5% in PG	^b OA 10% in PG
L(2,1)	0.288(0.210)	0.146(0.021)	0.176(0.124)	0.047(0.015)	0.208(0.056)
L(3,1)	0.190(0.142)	0.173(0.089)	0.234(0.084)	0.207(0.104)	0.319(0.166)
L(2,4)	1.279(0.944)	0.560(0.237)	0.095(0.032)	1.401(1.301)	0.166(0.071)
DT(3)	2.178(0.108)	3.640(0.673)	1.055(0.321)	2.923(1.829)	2.525(0.577)
P(2)	173.12(78.56)	1490.13(496.52)	2118.08(1117.64)	586.62(135.83)	1263.95(780.92)

^a pH of 5 ±0.05, ^b pH of 1 ±0.05. Data represented as mean(SE);(n=3, pH of 5±0.05; n=4, pH 1±0.05).

The second was the receptor compartment. Meanwhile, the third compartment is the lag compartment, and the fourth compartment is the inner part of the skin. The compartmental scheme model indicates that the drug flows into two routes, the first is by directly flowing into the receptor phase, and the other is via transit before reaching the receptor phase.

A chemical enhancer used for these studies is oleic acid in propylene glycol. It had been reported that OA in PG could perturb stratum corneum lipids, allowing the drug molecules to pass across the upper layer of skin more easily (Haque and Talukder, 2018) and reach the receptor phase directly (compartment 2). Meanwhile, these are some explanations indicating that the lag compartment (the compartment-3) was present in the model. Based on the *Pubchem Database*, log P of domperidone is 3.9 (National Center for Biotechnology Information, 2019). Lipophilicity of domperidone could make the drug retained before passing into the receptor compartment. It may have the preference to stay longer in hydrophobic parts of the stratum corneum.

Moreover, domperidone is present in 2 forms, unionized and ionized forms. The reports said that the pH value of the skin was about 4.1-5.8 (Proksch, 2018), and pKa of domperidone was 7.9 (National Center for Biotechnology Information, 2019). Thus, based on the Handerson Hasselbach equation, the ratio of unionized domperidone to the ionized form will be approximately 1:99. In the unionized form, domperidone will be easier to permeate the skin and directly affect the receptor phase. Meanwhile, in the ionized form, as the dominant form, domperidone will be difficult to pass the skin's stratum corneum. This analysis supports explanations on the presence of the lag compartment. After passing the lag compartment, the ionized form of domperidone should be easier to diffuse into the inner skin (compartment 4), which consists of viable and hydrophilic cells.

Based on this modeling approach, parameters were obtained (Table II). The use of 1% OA in PG on pH5 resulted in the lowest domperidone transport. In contrast, the use of 1% OA in PG on pH1 provided the highest drug transport. Domperidone is a weak base drug that is

less soluble in water. The solubility of domperidone also decreases in higher pH. The transport data suggested that the donor concentration of domperidone influenced the permeation. Passive diffusion is driven by a concentration gradient (Nugroho *et al.*, 2004). As the concentration gradient across the skin increased, the percutaneous drug transport also increased. Pranitha and Lakshmi (2018) reported that pH influenced the permeation of drugs. Sildenafil citrate, another weak base drug, was reported to have a higher flux in acidic pH (1,2) than at the higher pH levels (4-8) due to the solubility level (Pranitha and Lakshmi, 2018).

The concentration of OA in PG also influenced the permeation of the domperidone solution in pH 1. The results in Table 2 indicate that OA in PG facilitated stratum corneum perturbation, resulting in a higher transport than the condition without enhancer (control formulation) (Table II). However, an increase in OA - PG concentration decreased domperidone transport even lower than the control formulation. The dominant ionized form of domperidone in this low pH could be the reason for this phenomenon. The presence of OA in PG could hinder the drug partition across the skin. Similarly, oleic acid was also reported to reduce the permeability of piroxicam in the nano-emulgel formulation (Aggarwal *et al.*, 2014).

Interestingly, domperidone permeation was appropriately described with the same compartmental model at a pH of 1 and 5, i.e. a four-compartmental model with a lag compartment. The compartmental modeling approach can simulate the steady-state concentration of the drug in plasma based on the estimated *in vitro* model transport parameters. By using the previously published pharmacokinetic data of domperidone (i.e. $V_d = 399$ L and the elimination half-life = 7.5h) (Helmy and El Bedaiwy, 2014), and the patch with a size of 2x2 cm, the concentrations of drug in plasma (Figure 5). The results indicate the presence of 1% oleic acid in propylene glycol might facilitate domperidone transport to reach a plasma concentration of approximately 8.5mg/mL.

CONCLUSION

A four-compartmental model involving a lag compartment was the suitable model for transdermal transport domperidone in pH 5 and pH 1. The maximum domperidone transport was achieved with a solution at a pH of 1 in the presence of 1% OA in PG as the chemical enhancer.

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