Supporting Information

Multiscale Modeling of Skin Electroporation

Kishore Gajula, Rakesh Gupta*, and Beena Rai

Physical Sciences Research Area

Tata Research Development and Design Centre, Tata Consultancy Services,

54 B, Hadapsar Industrial Estate, Pune – 411013, India

*Corresponding author: gupta.rakesh2@tcs.com

Phone : +91-2066086422

Number of pages: 6

Number of figures: 3

S1. Macroscopic passive diffusion model.

The macroscopic passive diffusion model was taken from our previous work.[1]. This model was used to calculate the flux and cumulative release of drug molecular under passive diffusion case. Here, at first, we showcase the utility of this model to understand the effect of SC thickness on the flux and cumulative release of the molecules through SC. The structural parameters such as number of corneocytes layers, length of corneocytes and width of corneocytes, lipid channel width and offset ratio were taken from our previous work.[1] The thickness of SC obtained using these parameters was 13.1 µm. Conjeevaram et al.[2] used a full thickness of epidermis in their experiments to study transport of fentanyl through skin epidermis. However, thickness of epidermis was not reported in the study. Sato et al.[3] reported experimentally measured thickness of SC and epidermis of human skin to be 18.2 ± 3.3 µm and 51.2 ± 12.2 µm respectively. In the present work, simulations were performed to check whether the thickness of SC is affecting the amount of fentanyl permeated through it. Simulations with 15 layers (13.1 µm), 17 layers (14.9 µm) and 25 layers (21.5 µm) were performed and cumulative release profiles for the same are shown in the Figure S1.

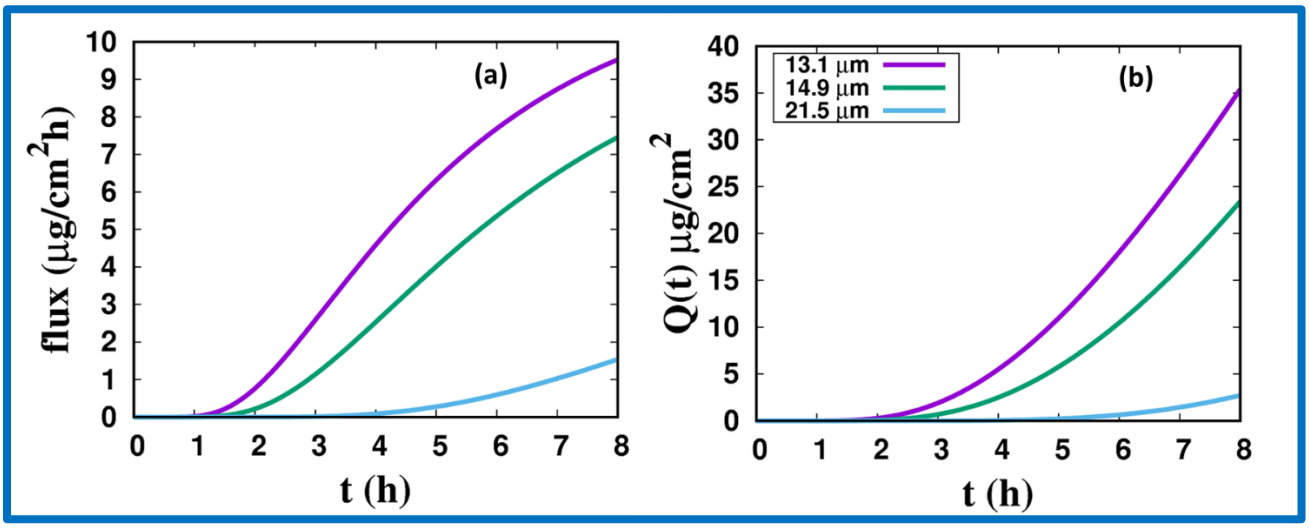

Figure S1. (a) Comparison of fentanyl flux through SC obtained using multiscale model during passive diffusion conditions for different thicknesses of SC. (b) Comparison of cumulative release of fentanyl from SC obtained using multiscale model during passive diffusion conditions for different thicknesses of SC.

It is evident from our simulations that the flux, and cumulative release of drug molecule decreased with increase in thickness of SC. This is in line with the fact that, as thickness increases fentanyl molecule had to cross more corneocyte layers before crossing the SC, experiences higher lag time and takes longer time to achieve steady state flux. Wilkinson et al.[4] reported that the percutaneous penetration of lipophilic compounds decreases with increase in thickness of skin and lag times increases with increase in skin thickness. Becker et al.[5] reported a skin electroporation model for LTR formation. Thin SC had greater LTR radius formation compared to that of thick SC for given volume. Transport through thin SC was greater than that of thick SC. Our findings from simulations were in line with the above stated experimental observations. In the subsequent simulations, SC thickness of 21.5 μm was considered to study the effect of electroporation fentanyl transport.

S2. Design of skin electroporation experiments – flux profiles for factorial simulations.

Figures S2, S3 show the fentanyl flux profiles for factorial simulations. Fentanyl flux increase with application of electric field as shown in figures S2, S3. For a given lower voltage and lower pulse duration, the magnitude of peak of flux remained low for initial pulses compared to the subsequent pulses. This effect could be because of the limited number of pores formed which requires higher pulse duration and higher voltage applied. As the pulse duration increased for a given lower voltage, magnitude of initial peak of the flux increased due to increase size of pores. For a given lower pulse duration, increase in applied voltage resulted in higher magnitude of initial peak of flux due to larger electrophoretic effect. For both higher pulse duration as well as higher pulse voltage peaks of flux remained almost equal due to larger electrophoretic effect as well as larger pore size.

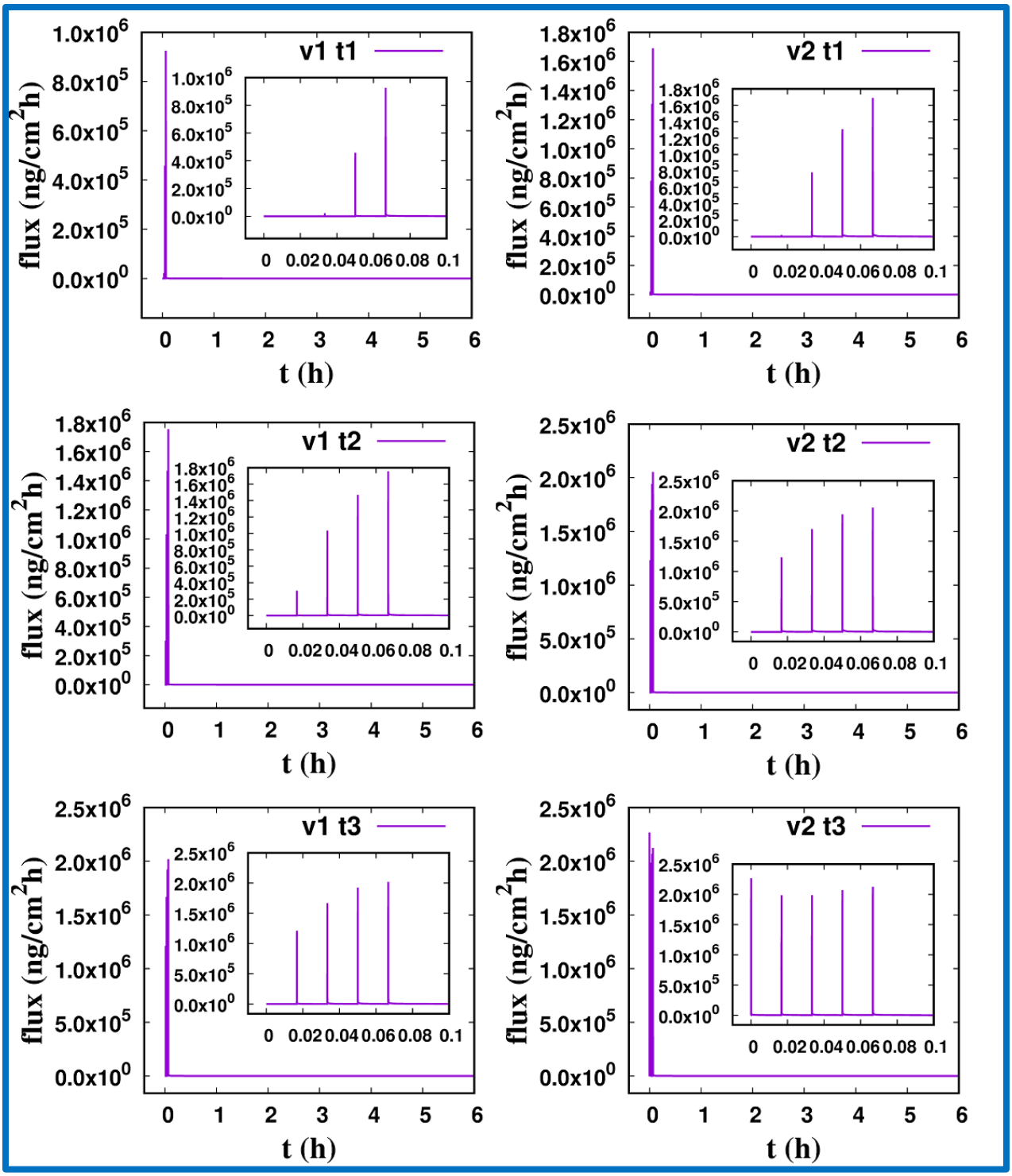

Figure S2. Flux of fentanyl (ng/cm^{2}h) at voltages of v1 (50V), v2 (100V) and pulse durations of t1 (0.133s), t2 (0.219s) and t3 (0.327s) from factorial design simulations.

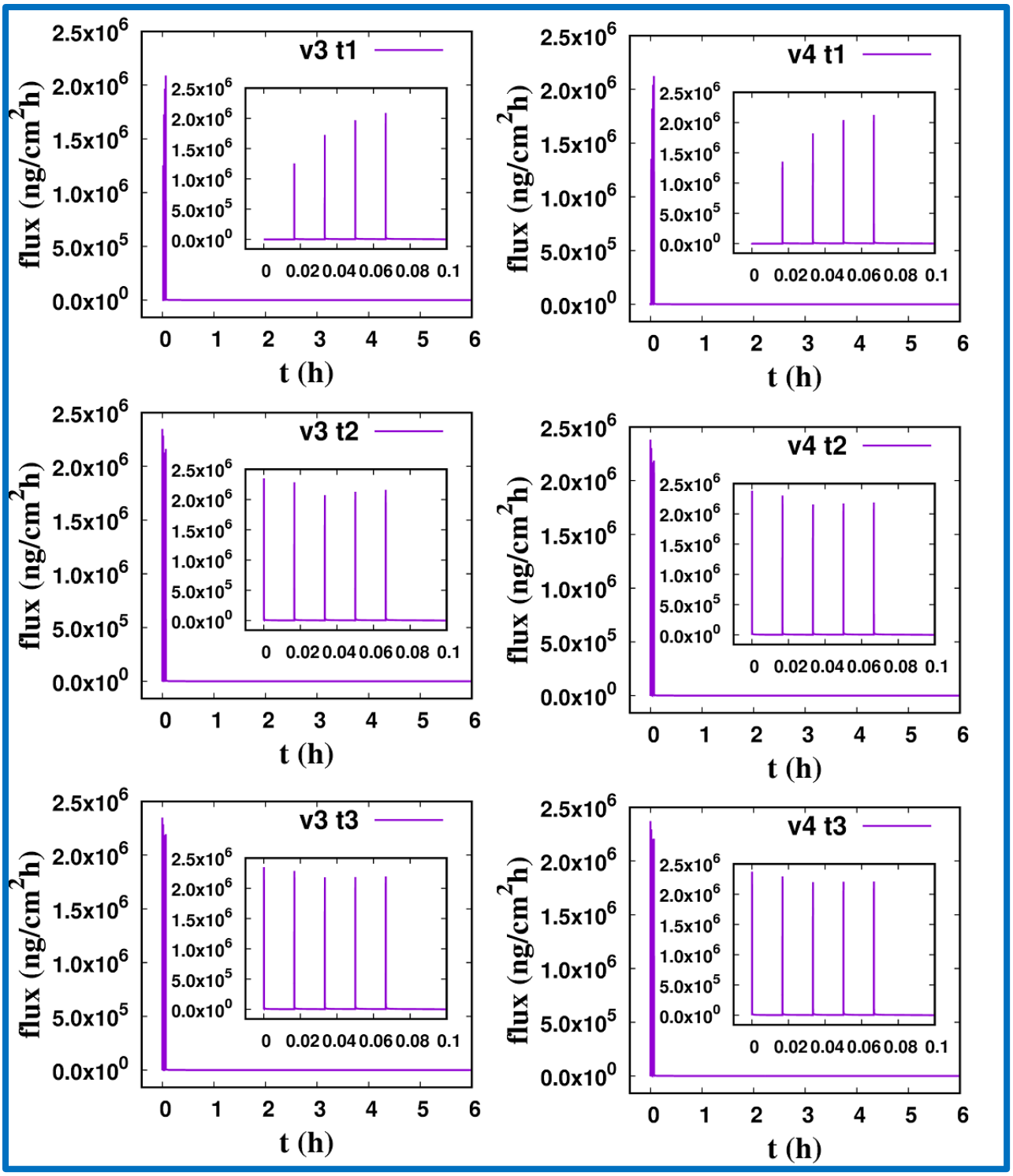

Figure S3 Flux of fentanyl (ng/cm^{2}h) at voltages of v3 (150V), v4 (250V) and pulse durations of t1 (0.133s), t2 (0.219s) and t3 (0.327s) from factorial design simulations.

References:

1. Gajula, K., Gupta, R., Sridhar, D.B. and Rai, B., 2017. In-Silico skin model: a multiscale simulation study of drug transport. Journal of chemical information and modeling, 57(8), pp.2027-2034.
2. Conjeevaram, R., Banga, A.K. and Zhang, L., 2002. Electrically modulated transdermal delivery of fentanyl. Pharmaceutical research, 19(4), pp.440-444.
3. Sato, K., Sugibayashi, K. and Morimoto, Y., 1991. Species differences in percutaneous absorption of nicorandil. Journal of pharmaceutical sciences, 80(2), pp.104-107.
4. Wilkinson, S.C., Maas, W.J., Nielsen, J.B., Greaves, L.C., van de Sandt, J.J. and Williams, F.M., 2006. Interactions of skin thickness and physicochemical properties of test compounds in percutaneous penetration studies. International archives of occupational and environmental health, 79(5), pp.405-413.
5. Becker, S., 2012. Transport modeling of skin electroporation and the thermal behavior of the stratum corneum. International Journal of Thermal Sciences, 54, pp.48-61.