Computational model for estimating the effect of heat on dermal clearance in skin transport

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Abstract

Purpose: Drug absorption from transdermal delivery systems (TDS) could be enhanced by heat in situations such as the use of TDS in conjunction with electrical or chemical heating pads and electric blankets. Heat effect on drug permeation across the stratum corneum (SC) can be studied using human skin-mounted diffusion cells by *in vitro* permeation testing (IVPT), but this method lacks the circulatory and lymphatic skin perfusion present *in vivo*. The objective of the present study was to develop a predictive skin absorption computational model that includes drug delivery from the TDS, skin permeation, and dermal clearance to quantitatively describe transdermal drug absorption under heat application and to determine the important transport parameters that could be influenced by heat during transdermal delivery. This model by itself or in conjunction with IVPT could provide the framework to help predict *in vivo* skin absorption, aid TDS development, and when applicable, provide insights into potential methods for drug delivery enhancement.

Methods: A simultaneous heat and mass skin transport computational model was developed in COMSOL, a commercially available multiphysics software package based on a finite element method of analysis. Two skin surface temperature exposures were considered: normothermic (32ºC) and elevated (42ºC). The skin model was comprised of three layers—SC, viable epidermis, and dermis, the latter of which included a blood and lymphatic dermal clearance component. The TDS layer on the SC contained nicotine as the model drug. Transport parameters for the skin layers, as well as dermal clearance, under normothermic and elevated conditions were calculated according to the microtransport analyses developed in our laboratory and values obtained from the literature. Three heat duration periods were investigated. Simulation results were compared to experimental data from separate IVPT studies under the same conditions.

Results: Simulations for skin absorption from infinite dose scenarios showed approximately a two-fold increase in steady-state flux at a skin surface temperature of 42ºC over that of 32ºC. Under normothermic conditions, absorption via blood (blood flux) accounted for approximately 75-80% of the total flux across skin for both partially- and fully-hydrated skin conditions. The remainder flux was distributed into subcutaneous tissue via the dermal lower boundary. The blood flux increased to ~95% under elevated temperature and blood flow conditions. The results from the skin transport model with TDS were similar in blood flux apportionment to the infinite dose data. Comparison of the two skin hydration state data revealed significant time reduction to achieve maximum flux under the fully-hydrated skin condition. Parametric sweeps identified two transport parameters—SC diffusivity and partitioning from TDS into the SC—that are important for skin transport under heat in the model. The model of SC transport yielded reasonable results, consistent with the trends observed in the IVPT study.

Conclusions: The simulations show that a significant portion of the total drug absorption from nicotine TDS is accounted for by the blood flux, an important aspect with respect to systemic availability. Heat increases the flux distribution shunted to blood.

Purpose

The concurrent application of heat during the administration of a transdermal drug system (TDS) can enhance the delivery of therapeutics into the skin, thereby potentially giving rise to drug dosing and toxicity issues. Insight into these complications can be gained from the characterization of the *in vivo* drug clearance mechanisms of the dermal capillary network as well as the lymphatic drainage system. An *in silico* skin absorption and heat transport model was developed to predict the absorption rates under a variety of heat exposure conditions. This all-inclusive model takes into account multiple factors, including,

a. drug delivery from TDS.
b. skin permeation.
c. dermal clearance via the circulatory and lymphatic systems.

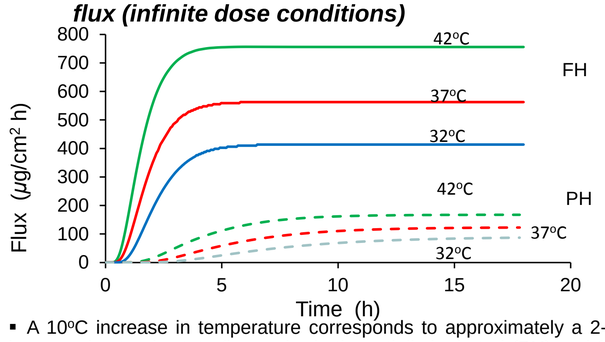
Hence, it can be useful for evaluating the effect of heat on *in vivo* TDS drug delivery.

Methodology

- Heat and mass transport was modeled using the Multiphysics finite element analysis package COMSOL.
- The geometry modeled for infinite dose drug transport consisted of the three skin layers (stratum corneum, viable epidermis, and dermis); an extension of the model with a fourth layer allowed for the representation of a TDS (finite dose). The model drug was nicotine.
- Mass (diffusivities and partition coefficients) and thermal (conductivities, heat capacities) transport parameters were calculated according to microtransport analyses developed in our lab and obtained from the literature, respectively.
- Dermal clearance (DCL) was modeled using a first-order clearance constant calculated according to a method developed in our laboratory. Skin blood flow (SBF) values for this parameter were obtained from the literature.
- Normothermic (32ºC) and elevated temperatures (42ºC) were investigated for three heat application protocols (0-24 h, 4-24 h, and 8-24 h).
- Optimized results simulated for *in vitro* conditions (no DCL, no SBF) were compared to experimental Franz diffusion cell data *in vitro*.

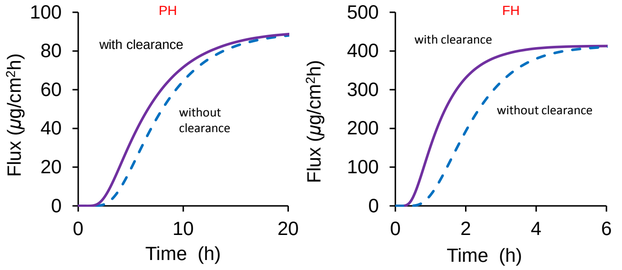
Results

(1) Effect of skin surface temperature on nicotine flux (infinite dose conditions)



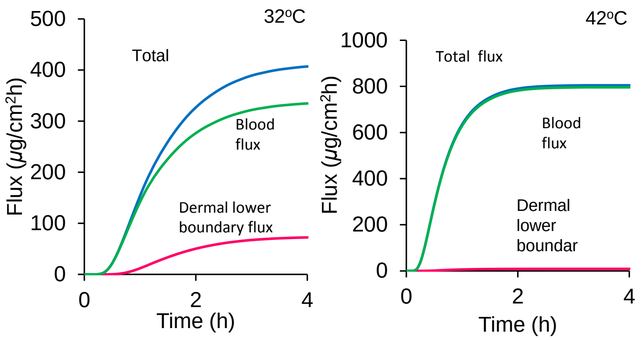
- A 10ºC increase in temperature corresponds to approximately a 2-fold increase in steady-state flux under both partially-hydrated (PH) and fully-hydrated (FH) skin conditions. This is in accord with the literature.[1,2]
- Fully-hydrated skin yields roughly a 5-6 fold increase in flux and 2-fold reduction in time to achieve steady-state compared to partially-hydrated skin.
- An inverse relationship is displayed between lag time and skin surface temperature, an effect more pronounced for partially-hydrated skin.

(2) Effect of dermal clearance on nicotine flux (infinite dose conditions, 32ºC)



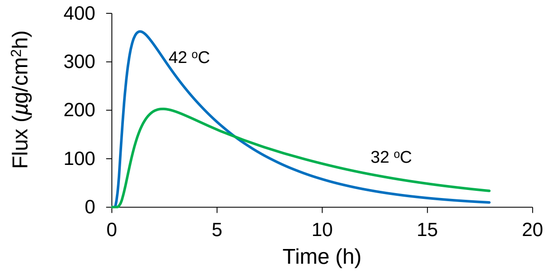
- Inclusion of a dermal clearance component leads to more rapid attainment of steady-state flux, especially for fully-hydrated skin conditions. Similar results were found for elevated temperatures. Dermal clearance directly impacts systemic availability.

(3) Apportionment of total nicotine flux into blood and dermal lower boundary fluxes as a function of skin surface temperature (infinite dose conditions, FH skin)



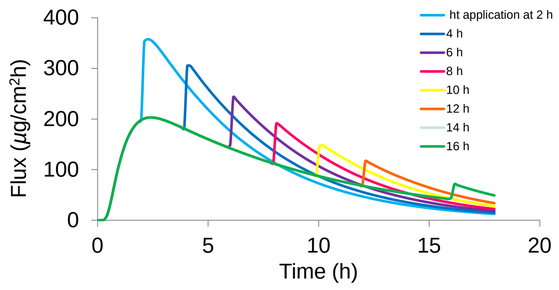
- Under fully-hydrated skin conditions and a skin surface temperature of 32ºC, the blood flux accounts for more than 75% of the total flux, resulting in rapid drug delivery into the systemic blood circulation.
- Increasing the skin surface temperature to 42ºC increases the blood apportionment to ~95%.
- Changes in skin blood flow have less of an effect on blood flux contributions at elevated temperatures, indicating the efficiency of the blood circulation in removing the drug from the dermis.

(4) Effect of temperature on blood flux for nicotine TDS (finite dose conditions, FH skin)



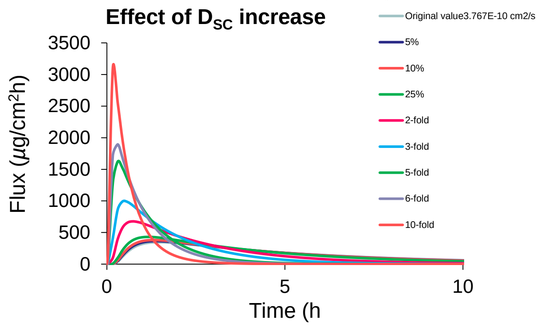
- Increasing the skin surface temperature from 32ºC to 42ºC shifts the attainment of peak flux from a TDS to earlier times.

(5) Nicotine TDS flux under varying heat application times

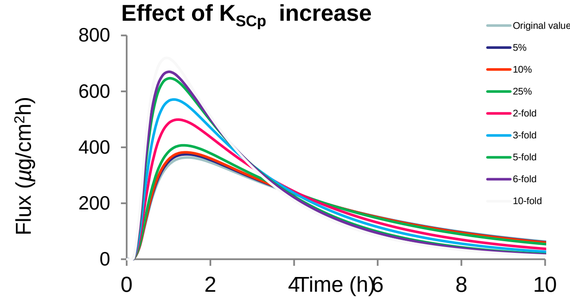


- Nicotine TDS peak flux occurs with earlier heat application times.

(6) Parameter sensitivity analyses with respect to nicotine TDS flux (42ºC)

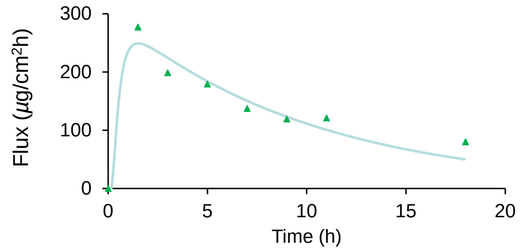


Effect of K_{SCp} increase



- Parametric sweeps indicated that two of the seven parameters investigated (D_p, K_{SCp}, D_{SC}, K_{VESC}, D_{VE}, K_{DEVE}, D_{DE}) had the most impact on nicotine flux.
- D_{SC} plays a major role in maximum nicotine flux values attained and the time to achieve maximum flux.
- K_{SCp} plays a significant role in the maximum nicotine flux attained.

(7) Simulated nicotine TDS flux using optimized D_{SC} and K_{SCp} values in comparison to in vitro data (42ºC heat application 0-24 h, FH)



- The model adequately predicts nicotine TDS flux under 42ºC heat application in comparison to *in vitro* Franz diffusion cell data.

Conclusions

- The blood flux accounts for a significant portion of the total flux, a phenomena that is exacerbated by the application of heat. A transient increase in blood flux can translate into a transient increase in systemic availability.
- This model, used alone or with *in vitro* data, provides guidance on the effect of heat on nicotine absorption *in vivo*. Other potential uses include aiding in TDS development and identifying possible methods for drug delivery enhancement.

Acknowledgements

Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD004942. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organizations imply endorsement by the United States Government..

References

1. Akomeah et al., Eur J Pharm Sci 21:337-345 (2004).
2. Peck et al., J Pharm Sci 84: 975-982 (1995).