Transdermal delivery with microneedle patches using *in silico* modelling

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Background

- Existing antiretroviral therapy (ART) is characterised by life-long daily administration
- Long-acting (LA) strategies could limit the problems associated with pill fatigue and sub-optimal adherence
- Antiretrovirals are currently developed for intramuscular injectable LA formulations
- Transdermal delivery through microneedle array patches represent an alternative strategy for LA administration

Microneedle array patches (MAPs)

- Consist of micron-sized needle arrays of varying sizes capable of disrupting stratum corneum
- Capable of local and systemic delivery, blood-free with painless application
- Provide patient friendly, low cost and minimally invasive route for drug delivery
- Deliver intact nanoformulations that form a depot in the upper skin layers
- Drug release from this nanoparticulate formulation is the rate limiting step to regulate pharmacokinetics
- Pharmacokinetics in humans was assessed using a physiologically based pharmacokinetic (PBPK) model

Hydrogel MAPs

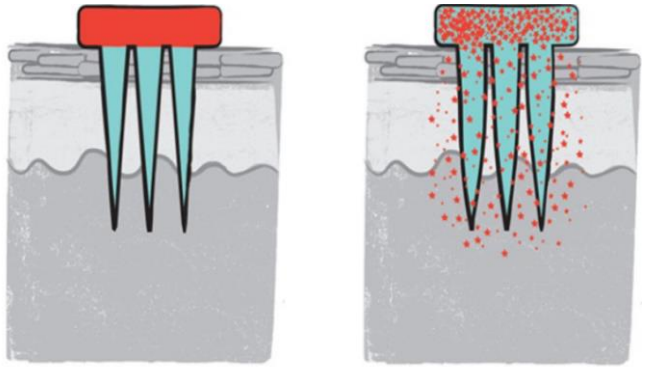


Fig. 1 *Fig. 2*

Dissolving MAPs

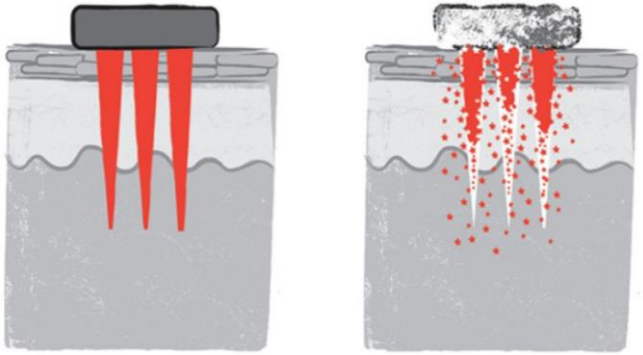


Fig. 1 *Fig. 2*

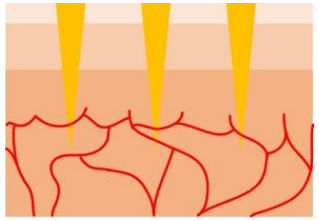
Image: PATH

PATH - http://www.path.org/publications/files/VAC_hiv_prep_poster.pdf

PBPK modelling

- Mathematical description of absorption, distribution, metabolism and elimination processes defining pharmacokinetics
- Integrates *in vitro* data to simulate drug distribution in virtual population

Transdermal release rate

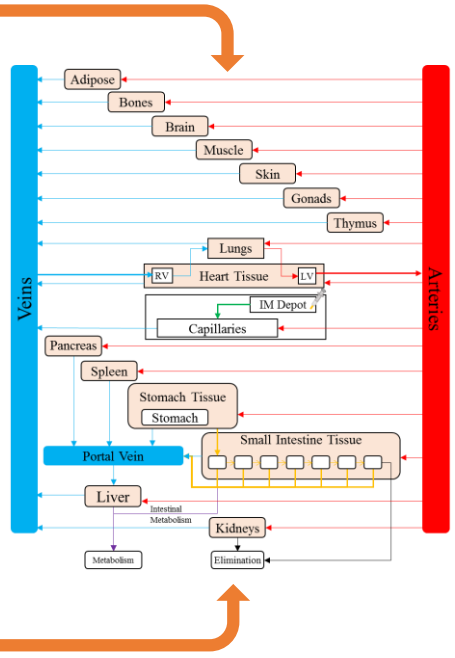


Metabolic clearance

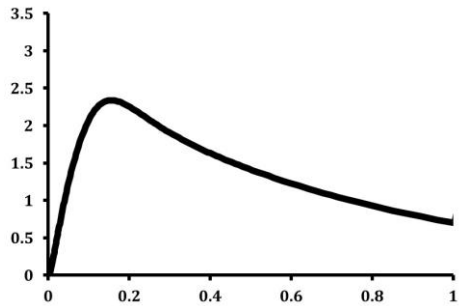
Volume of distribution

$$V_{ss} = (\Sigma V_t^* P_{t:p}) + (V_e^* E{:}P) + V_p$$

$$P_{t:p\ nonadipose} = \frac{[P_{o:w} \times (V_{nlt} + 0.3 \times V_{pht})] + [1 \times (V_{wt} + 0.7 \times V_{pht})]}{[P_{o:w} \times (V_{nlp} + 0.3 \times V_{php})] + [1 \times (V_{wp} + 0.7 \times V_{php})]} \times \frac{fu_p}{fu_t}$$

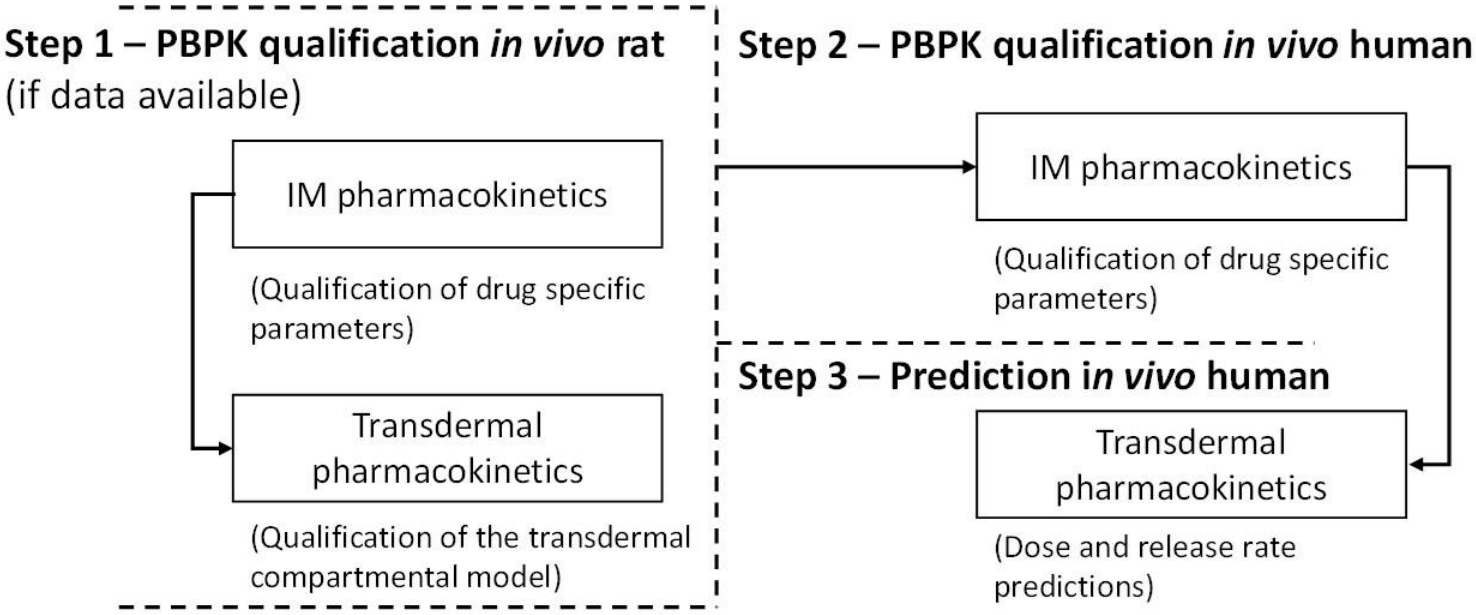


Pharmacokinetics



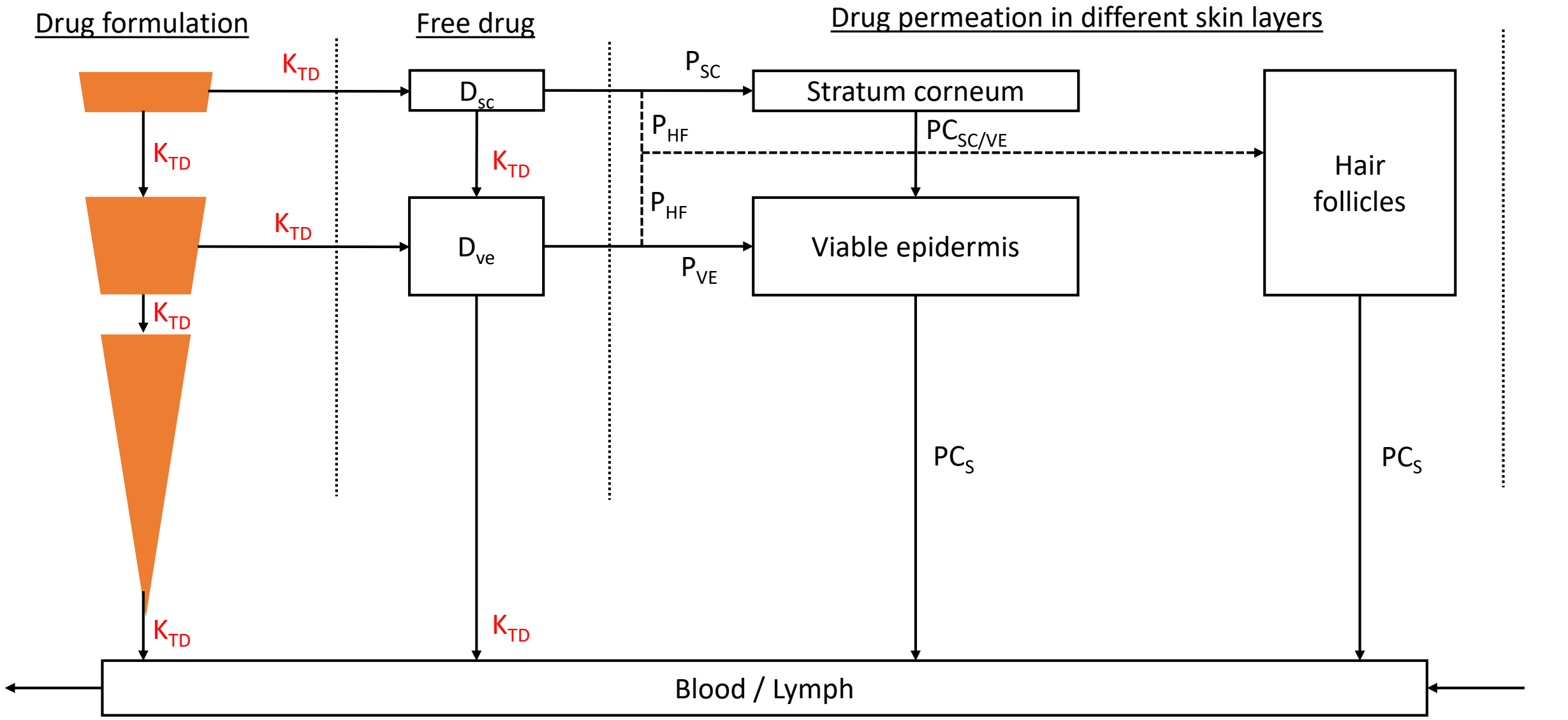
Aims

- Design a transdermal PBPK model to simulate pharmacokinetics of a model drug resulting from administration through microneedles



- Predict pharmacokinetics of a model drug across a range of dose and release rate in humans to identify optimal formulation characteristics

Transdermal model



P – permeability , PC – partition coefficient

PBPK model qualification for IM and transdermal formulations in rats *in vivo*

Rat *in vivo*

Route and dose	Observed			Simulated			% difference* simulated vs. observed		
	C_{max}	AUC	C_{min}	C_{max}	AUC	C_{min}	C_{max}	AUC	C_{min}
Intramuscular (5 mg/kg, single injection)[1]	71	3840	-	55.9 ± 6.43	5.67 ± 1.25	-	**-21.3**	**47.6**	**-**
Intramuscular (20 mg/kg, single injection)[1]	158	15300	-	222 ± 25.5	22.4 ± 4.64	-	**40.5**	**46.3**	**-**
Transdermal †(120 mg, microneedle patch)[2]	416	-	26.5	481 ± 42.9	286 ± 28.1	38.7 ± 4.45	**24.5**	**-**	**46.0**

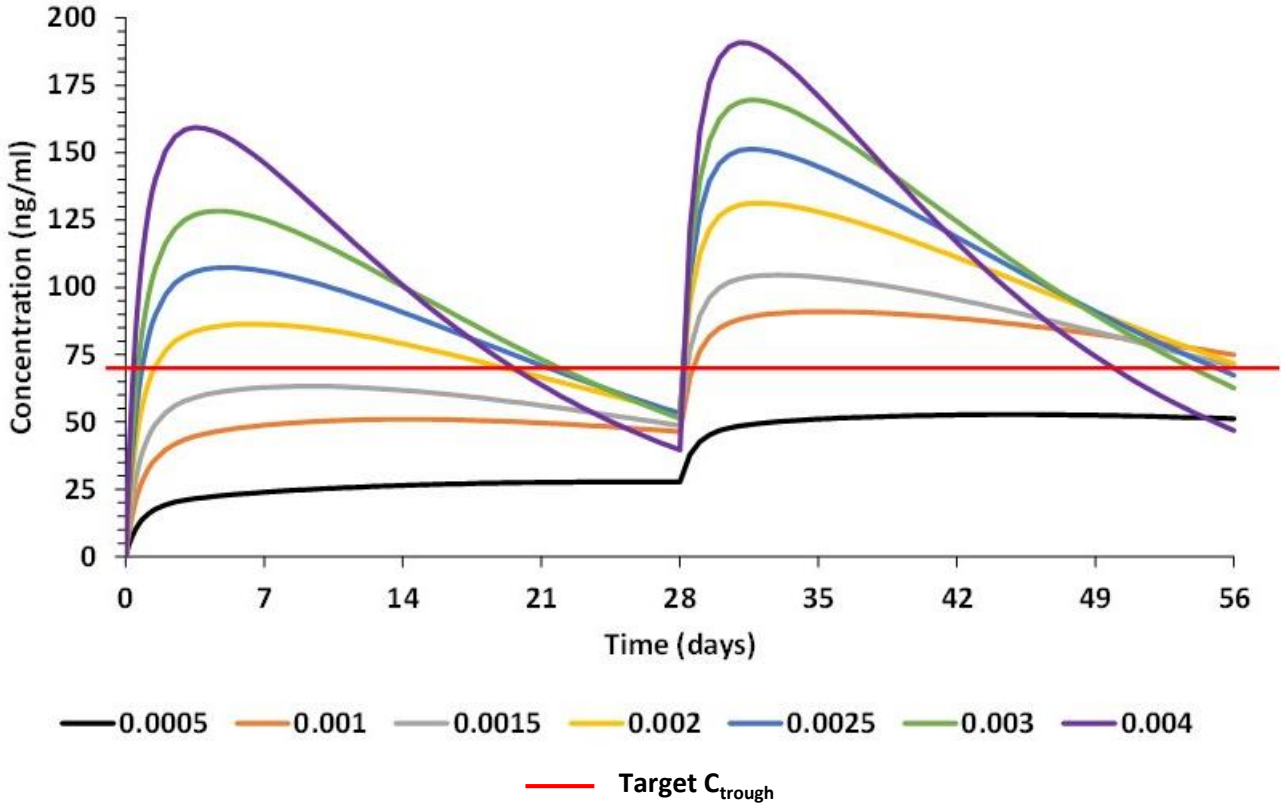
Values are represented as arithmetic mean ± standard deviation where ever applicable, AUC – area under the concentration-time curve, C_{max} – maximum plasma concentration, C_{trough} – trough plasma concentration; C_{max} and C_{trough} are expressed as ng/ml and AUC is expressed as µg × h/ml;* PBPK model is assumed to be qualified if % difference is less than 50, † Only 57.45 % of the total administered drug was assumed to be delivered using microneedle[3]

[1] van 't Klooster G, Pharmacokinetics and Disposition of Rilpivirine (TMC278) Nanosuspension as a Long-Acting Injectable Antiretroviral Formulation. 2010
[2] Darin Zehrung, Development of microarray patches for transdermal and vaginal delivery of long-acting HIV pre-exposure prophylaxis, 2016
[3] Garland MJ et al. Influence of skin model on in vitro performance of drug-loaded soluble microneedle arrays. International Journal of Pharmaceutics. 2012;434(1):80-9.

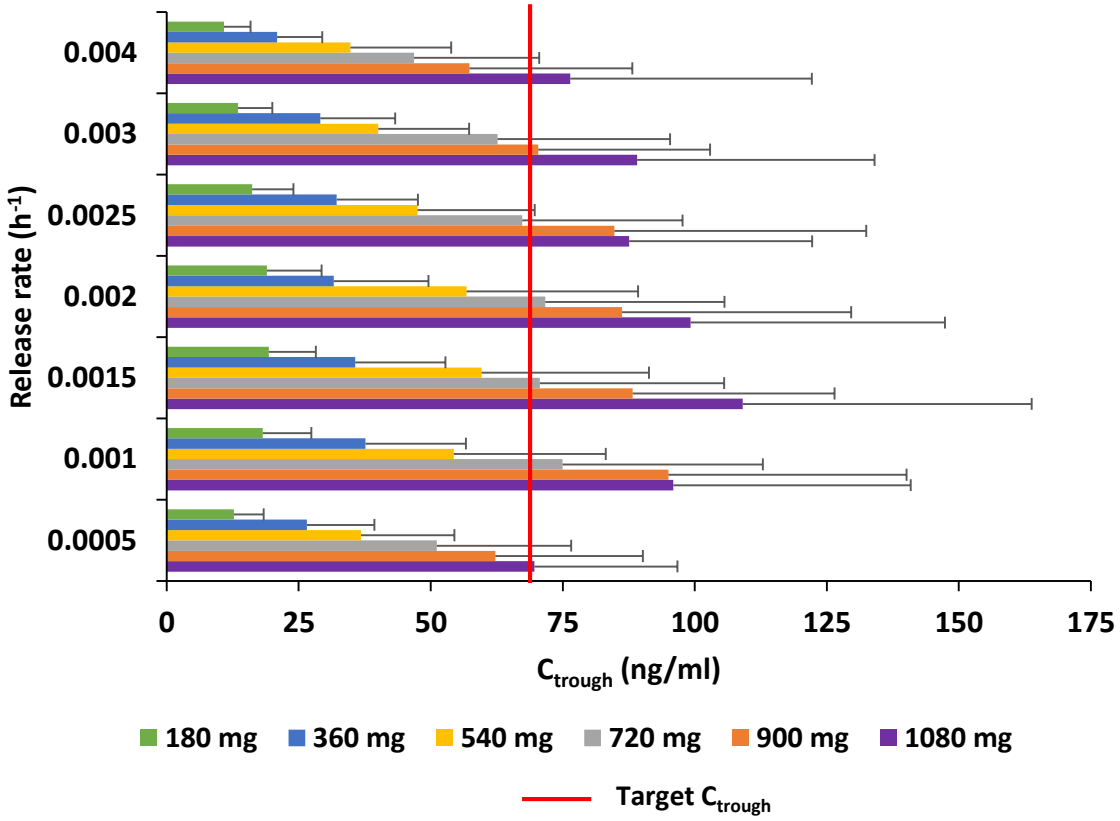
Transdermal release predictions – plasma concentrations

- C_{trough} increases up to a certain release rate and then decreases
- C_{trough} was proportional to the increase in administered transdermal dose

720 mg 4-weekly dose vs. various release rates (h^{-1})



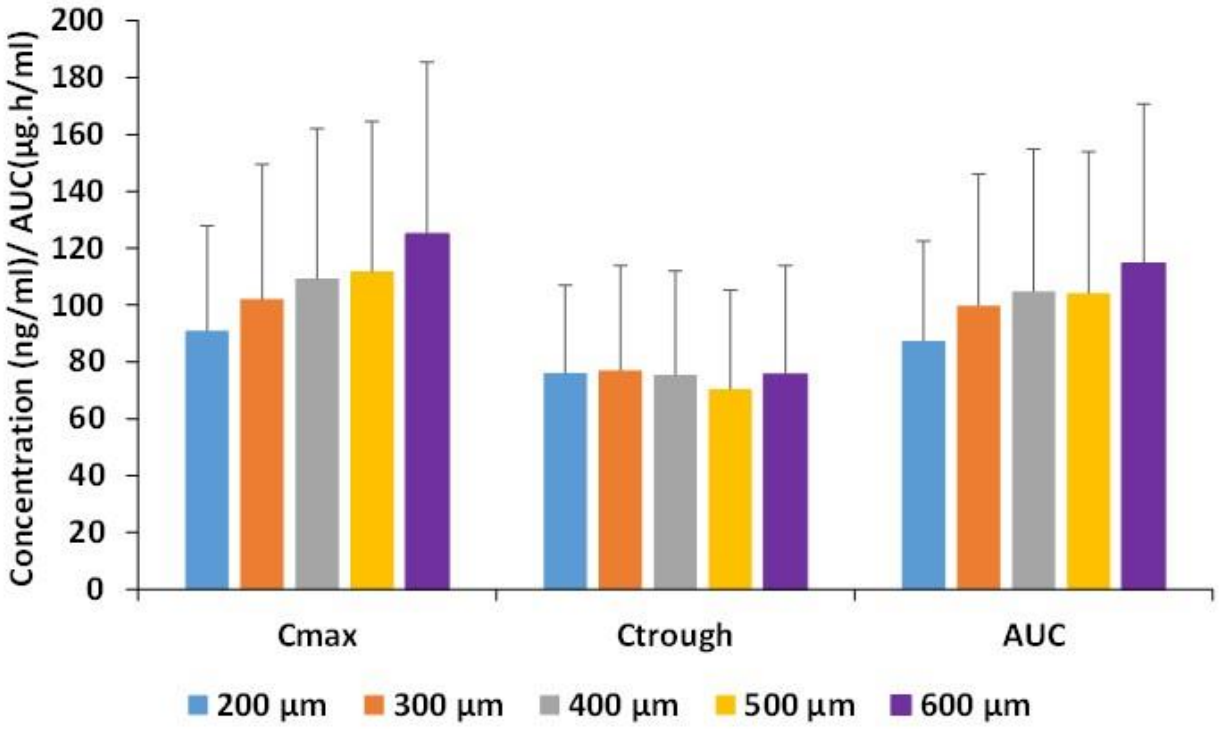
C_{trough} at the end of two 4-weekly doses



Transdermal predictions – C_{trough} vs. penetration depth, pore radius

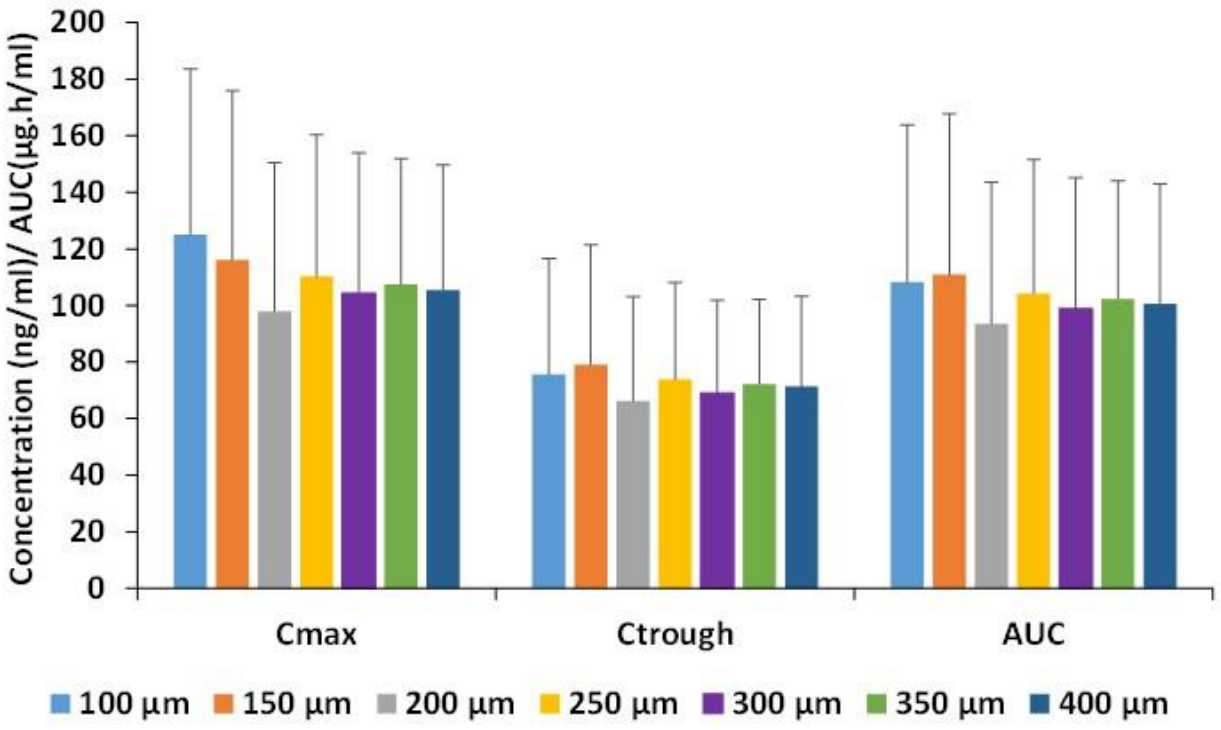
- Constant dose – 720 mg, constant release rate – 0.0015 h^{-1}
- No significant difference observed in C_{trough} ($P > 0.05$)

Pharmacokinetic summary at various needle lengths



Constant pore size – 224 µm[1]

Pharmacokinetic summary at various pore radii



Constant needle length – 429.66 µm[1]

[1] Garland MJ et al. Influence of skin model on in vitro performance of drug-loaded soluble microneedle arrays. International Journal of Pharmaceutics. 2012;434(1):80-9.

Limitations

- Immune response at the site of administration could alter the release rate
- Evaluation of long-term drug and excipients stability at the administration site is pivotal
- Modelled formulation release rate cannot be directly extrapolated to release rate *in vivo*
- Further qualification against transdermal PK from human data would improve the confidence of the PBPK model

Summary

- Transdermal delivery represents an attractive, minimally invasive and effective route for long-acting ART administration
- Design of the transdermal PBPK model was successfully qualified against observed data in rats
- Dose and release rate was optimised for a model drug for a monthly transdermal MAPs
- Transdermal PBPK model is a platform to rationalise selection of drug candidates for LA therapy using MAPs

Acknowledgements

- **Marco Siccardi**
- **Prof. Andrew Owen**
- **Prof. Ryan F. Donnelly**
- Prof. Charles Flexner
- Prof. David Back
- Prof. Saye Khoo
- Prof. Steve Rannard
- Paul Curley
- James Hobson
- Adeniyi Olagunju
- Lee Tatham
- José Moltó
- Catia Marzolini
- Neill Liptrott
- Adny Henrique Silva
- Christopher David
- Darren Michael Moss
- Owain Roberts
- Christina Chan
- Louise Tidbury
- Justin Chiong
- Rohan Gurjar
- Ana Jiminez-Valverde
- Megan Neary
- Rana Abutaima
- Gini Joshua
- Hannah Kinvig
- Helen Box
- Colleagues in the department of Molecular and Clinical Pharmacology

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