Physiologically Based Pharmacokinetic Modelling of Cabotegravir Microarray Patches in Rats and Humans

Hannah Kinvig [1,2], Rajith K.R. Rajoli [1,2], Henry Pertinez [1,2], Lalitkumar K. Vora [3], Fabiana Volpe-Zanutto [3], Ryan F. Donnelly [3], Steve Rannard [2,4], Charles Flexner [5], Marco Siccardi [1], Andrew Owen [1,2,*]

[1]Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool L7 3NY, UK

[2]Centre of Excellence in Long-Acting Therapeutics (CELT), University of Liverpool, Liverpool L7 3NY, UK

[3]School of Pharmacy, Queen's University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, UK.

[4]Department of Chemistry, University of Liverpool, Liverpool L7 3NY, UK

[5]Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA.

*Correspondence: aowen@liverpool.ac.uk; Tel.: +44-(0)-151-794-8211

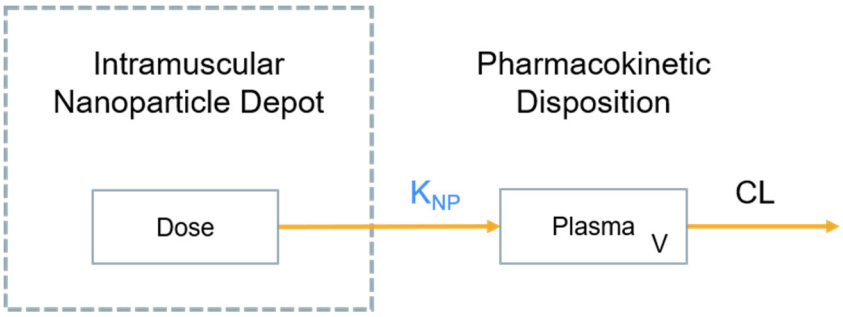

Figure S1. Schematic representation of the one-compartment empirical model describing the pharmacokinetic disposition of nanoformulated cabotegravir after intramuscular administration. Parameters highlighted in blue were implemented into the PBPK model. K_{NP}, V and CL represent the nanoparticle release rate, plasma compartment volume and clearance, respectively.

Equation S1. One-compartment empirical model.

$$\frac{dDose}{dt} = - K_{NP} \times Dose \quad (1)$$

$$\frac{dPlasma}{dt} = K_{NP} \times Dose/V - CL \times Plasma \quad (2)$$

Where K_{NP}, V and CL are the nanoparticle release rate, plasma compartment volume and clearance, respectively.

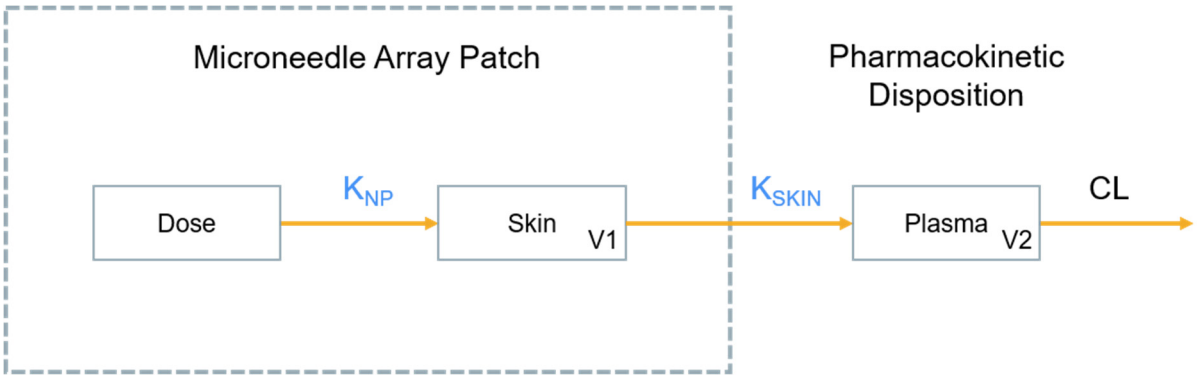

Figure S2. Schematic representation of the two-compartment empirical model describing the pharmacokinetic disposition of nanoformulated cabotegravir after microneedle array patch administration. Parameters highlighted in blue were implemented into the PBPK model. K_{NP}, K_{SKIN}, V1, V2 and CL represent the nanoparticle release rate, rate of drug movement in the skin, skin compartment volume, plasma compartment volume and clearance, respectively.

Equation S2. Two-compartment empirical model.

$$\frac{dDose}{dt} = - K_{NP} \times Dose \quad (3)$$

$$\frac{dSkin}{dt} = K_{NP} \times Dose/V1 - K_{SKIN} \times Skin/V1 \quad (4)$$

$$\frac{dPlasma}{dt} = K_{SKIN} \times Skin/V1 - CL \times Plasma/V2 \quad (5)$$

Where K_{NP}, V1, V2 and CL are the nanoparticle release rate, skin compartment volume, plasma compartment volume and clearance, respectively.

Table S1. MAP intradermal PBPK model parameters.

Equation	Description
Skin Characteristics	
$V_{SC} = V_{tBP,SC} - V_{tMN,SC}$	Volume of skin in the stratum corneum within the boundaries of the MAP
$V_{VE} = V_{tBP,VE} - V_{tMN,VE}$	Volume of skin in the viable epidermis within the boundaries of the MAP
$V_{DE} = V_{tBP,DE} - V_{tMN,DE}$	Volume of skin in the dermis within the boundaries of the MAP
$V_{BP,SC} = BP_W \times BP_L \times T_{SC}$	Volume of the stratum corneum within the boundaries of one MAP baseplate
$V_{BP,VE} = BP_W \times BP_L \times T_{VE}$	Volume of the viable epidermis within the boundaries of one MAP baseplate
$V_{BP,DE} = BP_W \times BP_L \times T_{DE}$	Volume of the viable epidermis within the boundaries of one MAP baseplate
$V_{tBP,SC} = V_{BP,SC} \times BP_t$	Volume of stratum corneum within the boundaries of total MAP baseplates
$V_{tBP,VE} = V_{BP,VE} \times BP_t$	Volume of viable epidermis within the boundaries of total MAP baseplates
$V_{tBP,DE} = V_{BP,DE} \times BP_t$	Volume of dermis within the boundaries of total MAP baseplates
T_{SC} = 17 μM (human), T_{SC} = 18 μM (rat)	Thickness of the *stratum corneum* [1]
T_{VE} = 47 μM (human), T_{SC} = 32 μM (rat)	Thickness of the viable epidermis [1]
T_{DE} = 2906 μM (human), T_{SC} = 2040 μM (rat)	Thickness of the dermis [1]
MAP Characteristics	
$BP_{MN} = 256$	Number of microneedles per 16 ×16 baseplate [2]
$BP_t = Dose/BP_{LOADING}$	Number of baseplates in MAP, based on dose

$BP_L = 0.7$ cm	Baseplate length [2]
$BP_W = 0.7$ cm	Baseplate width [2]
$MN_H = 600/10000$	Microneedle height (cm) [2]
$MN_W = 300/10000$	Microneedle width (cm) [2]
$MN_L = 300/10000$	Microneedle length (cm) [2]
$MN_{H,SC} = T_{SC}$	Height of a microneedle in the *stratum corneum*
$MN_{H,VE} = T_{VE}$	Height of a microneedle in the viable epidermis
$MN_{H,DE} = MN_H - T_{SC} - T_{VE}$	Height of a microneedle in the dermis, based on the remaining microneedle height after *stratum corneum* and viable epidermis penetration
$MN_{W,DE} = MN_W \times MN_{H,DE}/MN_H$	Width of a microneedle in the dermis, based on the fraction of microneedle height
$MN_{L,DE} = MN_L \times MN_{H,DE}/MN_H$	Length of a microneedle in the dermis, based on the fraction of microneedle height
$MN_{H,VEDE} = MN_{H,VE} + MN_{H,DE}$	Height of a microneedle in the viable epidermis and dermis
$MN_{W,VEDE} = MN_W \times (MN_{H,DE} + MN_{H,VE})/MN_H$	Width of a microneedle in the viable epidermis and dermis, based on the fraction of microneedle height
$MN_{L,VEDE} = MN_L \times (MN_{H,DE} + MN_{H,VE})/MN_H$	Length of a microneedle in the viable epidermis and dermis, based on the fraction of microneedle height
$V_{MN} = (MN_H \times MN_W \times MN_L)/3$	Volume of one microneedle
$V_{MN,SC} = V_{MN} - V_{MN,VEDE}$	Volume of one microneedle in the *stratum corneum*
$V_{tMN,SC} = V_{MN,SC} \times BP_{MN} \times BP_t$	Volume of total microneedles in the *stratum corneum*
$V_{MN,VE} = V_{MN,VEDE} - V_{MN,DE}$	Volume of one microneedle in the viable epidermis
$V_{tMN,VE} = V_{MN,DE} \times BP_{MN} \times BP_t$	Volume of total microneedles in the viable epidermis
$V_{MN,DE} = (MN_{H,DE} \times MN_{W,DE} \times MN_{L,DE})/3$	Volume of one microneedle in the dermis

$V_{tMN,DE} = V_{MN,DE} \times BP_{MN} \times BP_t$	Volume of total microneedles in the dermis
$V_{MN,VEDE} = (MN_{H,VEDE} \times MN_{W,VEDE} \times MN_{L,VEDE})/3$	Volume of one microneedle in the viable epidermis and dermis
$SA_{MN} = MN_H \times MN_W + MN_L\sqrt{(MN_W/2)^2 + MN_H^2} + MN_W\sqrt{(MN_L/2)^2 + MN_H^2}$	Surface area of one microneedle
$SA_{MN,SC} = SA_{MN} - SA_{MN,VEDE}$	Surface area of one microneedle in the *stratum corneum*
$SA_{tMN,SC} = SA_{MN,SC} \times BP_{MN} \times BP_t$	Surface area of total microneedles in the *stratum corneum*
$SA_{MN,VE} = SA_{MN,VEDE} - SA_{MN,DE}$	Surface area of one microneedle in the viable epidermis
$SA_{tMN,VE} = SA_{MN,VE} \times BP_{MN} \times BP_t$	Surface area of total microneedles in the viable epidermis
$SA_{MN,DE} = MN_{H,DE} \times MN_{W,DE} + MN_{L,DE}\sqrt{(MN_{W,DE}/2)^2 + MN_{H,DE}^2} + MN_{W,DE}\sqrt{(MN_{L,DE}/2)^2 + MN_{H,DE}^2}$	Surface area of one microneedle in the dermis
$SA_{tMN,DE} = SA_{MN,DE} \times BP_{MN} \times BP_t$	Surface area of total microneedles in the dermis
$SA_{MN,VEDE} = MN_{H,VEDE} \times MN_{W,VEDE} + MN_{L,VEDE}\sqrt{(MN_{W,VEDE}/2)^2 + MN_{H,VEDE}^2} + MN_{W,VEDE}\sqrt{(MN_{L,VEDE}/2)^2 + MN_{H,VEDE}^2}$	Surface area of one microneedle in the viable epidermis and dermis
Dermis Blood Flow	
$Q_{DE} = V_{tBP,DE} \times (Q_{DERMIS} \times 60 \times 60/1000)$	Blood flow rate in the dermis within the boundary of total MAP baseplates
$Q_{DERMIS} = 0.0022$ cm^3 blood/s/cm^3 skin	Blood flow rate in the dermis [3]
Microneedle characteristics based on a right rectangular pyramid shape, as previously described [2]. References presented in square brackets in the description column, where applicable. V - volume, t - total, BP - baseplate, MN - microneedle, SC - *stratum corneum,* VE - viable epidermis, DE - dermis, VEDE - viable epidermis and dermis, W - width, L - length, H - height, T - thickness, SA - surface area, Q – blood flow rate.	

References

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