Online Supplement:

Dual physiologically-based pharmacokinetic model of liposomal and non-liposomal amphotericin B disposition

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The equations were used to describe the dual PBPK model structure for amphotericin B disposition following IV administration of AmBisome® are shown below. Physiological parameters for mice, rats, and humans and pharmacokinetic parameters for distribution of nonliposomal amphotericin B are shown in Tables S1 and S3.

Nonliposomal compartments:

Plasma (pl):

$$V_{pl}\frac{dC_{pl}}{dt} = Q_{co}\left(\frac{C_{lu}}{Kp_{lu}} - C_{pl}\right) + rel\left(C_{pl}^{LIP}V_{pl} + C_{li,vas}^{LIP}V_{li,vas} + C_{gi,vas}^{LIP}V_{gi,vas} + C_{lu,vas}^{LIP}V_{lu,vas} + C_{ht,vas}^{LIP}V_{ht,vas}\right) \quad \text{(S.1)}$$

Gastrointestinal tract (gi):

$$V_{gi}\frac{dC_{gi}}{dt} = Q_{gi}\left(C_{pl} - \frac{C_{gi}}{Kp_{gi}}\right) + relC_{gi,exv}^{LIP}V_{gi,exv} \quad \text{(S.2)}$$

Heart (ht):

$$V_{ht}\frac{dC_{ht}}{dt} = Q_{ht}\left(C_{pl} - \frac{C_{ht}}{Kp_{ht}}\right) + relC_{ht,exv}^{LIP}V_{ht,exv} \quad \text{(S.3)}$$

Spleen (sp):

$$V_{sp,vas}\frac{dC_{sp,vas}}{dt} = Q_{sp}\left(C_{pl} - C_{sp,vas}\right) - PS_{sp}\left(f_u^{pl}C_{sp,vas} - f_u^{sp}C_{sp,exv}\right) + relC_{sp.vas}^{LIP}V_{sp,vas} \quad \text{(S.4)}$$

$$V_{sp,exv}\frac{dC_{sp,exv}}{dt} = PS_{sp}\left(f_u^{pl}C_{sp,vas} - f_u^{sp}C_{sp,exv}\right) - Ka_{sp}f_u^{sp}C_{sp,exv}V_{sp,exv} + Kd_{sp}A_{sp,deep} + relC_{sp.exv}^{LIP}V_{sp,exv} \quad \text{(S.5)}$$

$$\frac{dA_{sp,deep}}{dt} = Ka_{sp} f_u^{sp} C_{sp,exv} V_{sp,exv} - Kd_{sp} A_{sp,deep} \tag{S.6}$$

Liver (li):

$$\begin{aligned} V_{li} \frac{dC_{li}}{dt} &= Q_{ha} C_{pl} + Q_{sp} C_{sp,vas} + Q_{gi} \frac{C_{gi}}{Kp_{gi}} - Q_{li} \frac{C_{li}}{Kp_{li}} \\ &\quad - Cl_{li} f_u^{pl} \frac{C_{li}}{Kp_{li}} + relC_{li,exv}^{LIP} V_{li,exv} \end{aligned} \tag{S.7}$$

Kidney (kd):

$$\begin{aligned} V_{kd,vas} \frac{dC_{kd,vas}}{dt} &= Q_{kd} \left(C_{pl} - C_{kd,vas} \right) - PS_{kd} \left(f_u^{pl} C_{kd,vas} - f_u^{kd} C_{kd,exv} \right) \\ &\quad - Cl_{kd} f_u^{pl} C_{kd,vas} + relC_{kd,vas}^{LIP} V_{kd,vas} \end{aligned} \tag{S.8}$$

$$\begin{aligned} V_{kd,exv} \frac{dC_{kd,exv}}{dt} &= PS_{kd} \left(f_u^{pl} C_{kd,vas} - f_u^{kd} C_{kd,exv} \right) - Ka_{kd} f_u^{kd} C_{kd,exv} V_{kd,exv} \\ &\quad + Kd_{kd} A_{kd,deep} + relC_{kd,exv}^{LIP} V_{kd,exv} \end{aligned} \tag{S.9}$$

$$\frac{dA_{kd,deep}}{dt} = Ka_{kd} f_u^{kd} C_{kd,exv} V_{kd,exv} - Kd_{kd} A_{kd,deep} \tag{S.10}$$

Lung (lu):

$$\begin{aligned} V_{lu} \frac{dC_{lu}}{dt} &= Q_{li} \frac{C_{li}}{Kp_{li}} + Q_{hr} \frac{C_{hr}}{Kp_{hr}} + Q_{kd} C_{kd,vas} + Q_{rm} C_{rm,vas} \\ &\quad - Q_{co} \frac{C_{lu}}{Kp_{lu}} + relC_{lu,exv}^{LIP} V_{lu,exv} \end{aligned} \tag{S.11}$$

Remainder (rm):

$$\begin{aligned} V_{rm,vas} \frac{dC_{rm,vas}}{dt} &= Q_{rm} \left(C_{pl} - C_{rm,vas} \right) - PS_{rm} \left(f_u^{pl} C_{rm,vas} - f_u^{rm} C_{rm,exv} \right) \\ &\quad + relC_{rm,vas}^{LIP} V_{rm,vas} \end{aligned} \tag{S.12}$$

$$V_{rm,exv}\frac{dC_{rm,exv}}{dt} = PS_{rm}\left(f_u^{pl}C_{rm,vas} - f_u^{rm}C_{rm,exv}\right) - Cl_{rm}f_u^{rm}C_{rm,exv} + relC_{rm,exv}^{LIP}V_{rm,exv} \quad (13)$$

Liposomal compartments:

Plasma:

$$V_{pl}\frac{dC_{pl}^{LIP}}{dt} = Q_{co}\left(C_{lu,vas}^{LIP} - C_{pl}^{LIP}\right) - relC_{pl}^{LIP}V_{pl} \quad (14)$$

GI tract:

$$V_{gi,vas}\frac{dC_{gi,vas}^{LIP}}{dt} = Q_{gi}\left(C_{pl}^{LIP} - C_{gi,vas}^{LIP}\right) - Up_{gi}C_{gi,vas}^{LIP} - relC_{gi,vas}^{LIP}V_{gi,vas} \quad (15)$$

$$V_{gi,exv}\frac{dC_{gi,exv}^{LIP}}{dt} = Up_{gi}C_{gi,vas}^{LIP} - relC_{gi,exv}^{LIP}V_{gi,exv} \quad (16)$$

Heart:

$$V_{ht,vas}\frac{dC_{ht,vas}^{LIP}}{dt} = Q_{ht}\left(C_{pl}^{LIP} - C_{ht,vas}^{LIP}\right) - Up_{ht}C_{ht,vas}^{LIP} - relC_{ht,vas}^{LIP}V_{ht,vas} \quad (17)$$

$$V_{ht,exv}\frac{dC_{ht,exv}^{LIP}}{dt} = Up_{ht}C_{ht,vas}^{LIP} - relC_{ht,exv}^{LIP}V_{ht,exv} \quad (18)$$

Spleen:

$$V_{sp,vas}\frac{dC_{sp,vas}^{LIP}}{dt} = Q_{sp}\left(C_{pl}^{LIP} - C_{sp,vas}^{LIP}\right) - Up_{sp}\left(1 - \frac{C_{sp,exv}^{LIP}}{C_{sp}^{MAX}}\right)C_{sp,vas}^{LIP} - relC_{sp,vas}^{LIP}V_{sp,vas} \quad (19)$$

$$V_{sp,exv}\frac{dC^{LIP}_{sp,exv}}{dt} = Up_{sp}\left(1-\frac{C^{LIP}_{sp,exv}}{C^{MAX}_{sp}}\right)C^{LIP}_{sp,vas} - relC^{LIP}_{sp,exv}V_{sp,exv} \tag{20}$$

Liver:

$$\begin{aligned} V_{li,vas}\frac{dC^{LIP}_{li,vas}}{dt} &= Q_{ha}C^{LIP}_{pl} + Q_{sp}C^{LIP}_{sp,vas} + Q_{gi}C^{LIP}_{gi,vas} - Q_{li}C^{LIP}_{li,vas} \\ &\quad -Up_{li}\left(1-\frac{C^{LIP}_{li,exv}}{C^{MAX}_{li}}\right)C^{LIP}_{li,vas} - relC^{LIP}_{li,vas}V_{li,vas} \end{aligned} \tag{S.21}$$

$$V_{li,exv}\frac{dC^{LIP}_{li,exv}}{dt} = Up_{li}\left(1-\frac{C^{LIP}_{li,exv}}{C^{MAX}_{li}}\right)C^{LIP}_{li,vas} - relC^{LIP}_{li,exv}V_{li,exv} \tag{S.22}$$

Kidneys:

$$V_{kd,vas}\frac{dC^{LIP}_{kd,vas}}{dt} = Q_{kd}\left(C^{LIP}_{pl} - C^{LIP}_{kd,vas}\right) - Up_{kd}C^{LIP}_{kd,vas} - relC^{LIP}_{kd,vas}V_{kd,vas} \tag{S.23}$$

$$V_{kd,exv}\frac{dC^{LIP}_{kd,exv}}{dt} = Up_{kd}C^{LIP}_{kd,vas} - relC^{LIP}_{kd,exv}V_{kd,exv} \tag{S.24}$$

Lungs:

$$\begin{aligned} V_{lu,vas}\frac{dC^{LIP}_{lu,vas}}{dt} &= Q_{li}C^{LIP}_{li,vas} + Q_{hr}C^{LIP}_{hr,vas} + Q_{kd}C^{LIP}_{kd,vas} + Q_{rm}C^{LIP}_{rm,vas} \\ &\quad -Q_{co}C^{LIP}_{lu,vas} - Up_{lu}C^{LIP}_{lu,vas} - relC^{LIP}_{lu,vas}V_{lu,vas} \end{aligned} \tag{S.25}$$

$$V_{lu,exv}\frac{dC^{LIP}_{lu,exv}}{dt} = Up_{lu}C^{LIP}_{lu,vas} - relC^{LIP}_{lu,exv}V_{lu,exv} \tag{S.26}$$

Remainder:

$$V_{rm,vas}\frac{dC^{LIP}_{rm,vas}}{dt} = Q_{rm}\left(C^{LIP}_{pl} - C^{LIP}_{rm,vas}\right) - Up_{rm}C^{LIP}_{rm,vas} - relC^{LIP}_{rm,vas}V_{rm,vas} \tag{S.27}$$

$$V_{rm,exv}\frac{dC^{LIP}_{rm,exv}}{dt} = Up_{rm}C^{LIP}_{rm,vas} - relC^{LIP}_{rm,exv}V_{rm,exv} \quad \text{(S.28)}$$

where tissues are defined using corresponding subscripts, *vas* and *exv* – represent vascular and extravascular subcompartments; *LIP* – liposomal compartments, *C* – concentration in the compartment, *A* – amount in the compartment, *V* – volume of the compartment, *Q* – plasma flow to the tissue, f_u – fraction unbound, *Kp* – tissue partition coefficient, *PS* - permeability-surface area term, *Cl* – clearance, *Up* – liposome uptake clearance, C^{MAX} – maximal liposomal AmB concentration in tissue; *rel* – release rate, Ka and Kd – first-order association and dissociation rates constants for nonliposomal AmB partition into deep tissue subcompartment (*deep*).

The initial conditions for equations S.1-S.28 were all set to zero.

Table S1. Physiological parameters for mouse, rat, and human.

Tissue	Plasma flow, % of cardiac output			Tissue volume, % of body weight			Fraction of the vascular space, %		
	Mouse	Rat	Human	Mouse	Rat	Human	Mouse	Rat	Human
Liver	16.1	18.3	22.7	5.49	3.66	2.57	31	21	11
Kidneys	9.1	14.1	17.5	1.67	0.73	0.44	24	16	36
Spleen	1.125 [c]	1.0 [c]	1.38 [c]	0.35	0.2	0.26	17	22	22 [e]
GI tract	12.87 [d]	14.3 [c]	16.7 [d]	4.22	2.7	1.71	19 [e]	19 [f]	19 [e]
Heart	6.6	4.9	4.0	0.5	0.33	0.47	26 [e]	26	26 [e]
Lungs	100	100	100	0.73	0.5	0.76	50	36	36 e
Muscle	- [a]	- [a]	- [a]	- [a]	- [a]	- [a]	4 [b]	4 [b]	1 [b]

Data extracted from (1), except as noted.
[a] – not used in the model;
[b] – value used for the remainder compartment;
[c] – mean value from (2) and (3);
[d] – calculated as portal hepatic flow – spleen flow;
[e] – data unavailable, the value for rat was used in the model;
[f] – data from (4).

Table S2. Pharmacokinetic parameters for liposomal and nonliposomal AmB estimated using compartmental model (Figure S1) during initial analysis of the release rate.

	Parameter	Units	Human		Rat	
			Estimate	%CV	Estimate	%CV
Nonliposomal	Vc	L/kg	$4.47 \cdot 10^{-1}$	4	$8.52 \cdot 10^{-1}$	21
	k_{12}	h^{-1}	$7.28 \cdot 10^{-2}$	8	$4.92 \cdot 10^{-1}$	20
	k_{21}	h^{-1}	$2.76 \cdot 10^{-2}$	14	$1.53 \cdot 10^{-1}$	34
	k_{el}	h^{-1}	$3.32 \cdot 10^{-2}$	8	$1.60 \cdot 10^{-1}$	25
Liposomal	L_Vc	L/kg	$8.85 \cdot 10^{-2}$	7	$7.07 \cdot 10^{-2}$	27
	L_k_{12}	h^{-1}	$3.78 \cdot 10^{-2}$	8	$3.53 \cdot 10^{-1}$	82
	L_k_{21}	h^{-1}	$8.50 \cdot 10^{-3}$	17	$2.75 \cdot 10^{-1}$	74
	L_k_{el}	h^{-1}	$7.98 \cdot 10^{-2}$	6	$8.65 \cdot 10^{-2}$	39
	$k_{release}$	h^{-1}	$3.53 \cdot 10^{-3}$	11	$3.50 \cdot 10^{-3}$	22
	FR	%	8.16	6	1.83	15

Table S3. Pharmacokinetic parameters for nonliposomal amphotericin B in rats (5)

Parameter	Units	Value
Kp_{gi}		10.7
Kp_{lu}		34.3
Kp_{hr}		2.0
Kp_{li}		33.0
Cl_{li}	L/h	$6.00 \cdot 10^{-2}$
f_u^{kd}		$7.26 \cdot 10^{-3}$
PS_{kd}	L/h	$7.50 \cdot 10^{-2}$
Ka_{kd}	h^{-1}	$2.58 \cdot 10^{-1}$
Kd_{kd}	h^{-1}	$1.29 \cdot 10^{-3}$
Cl_{kd}		$1.00 \cdot 10^{-1}$
f_u^{sp}		$1.71 \cdot 10^{-3}$
PS_{sp}	L/h	$5.98 \cdot 10^{-1}$
Ka_{sp}	h^{-1}	$9.05 \cdot 10^{-1}$
Kd_{sp}	h^{-1}	$4.56 \cdot 10^{-3}$
f_u^{rm}		$1.6 \cdot 10^{-2}$
PS_{rm}	L/h	$5.47 \cdot 10^{-1}$
Cl_{rm}	L/h	$1.58 \cdot 10^{-1}$

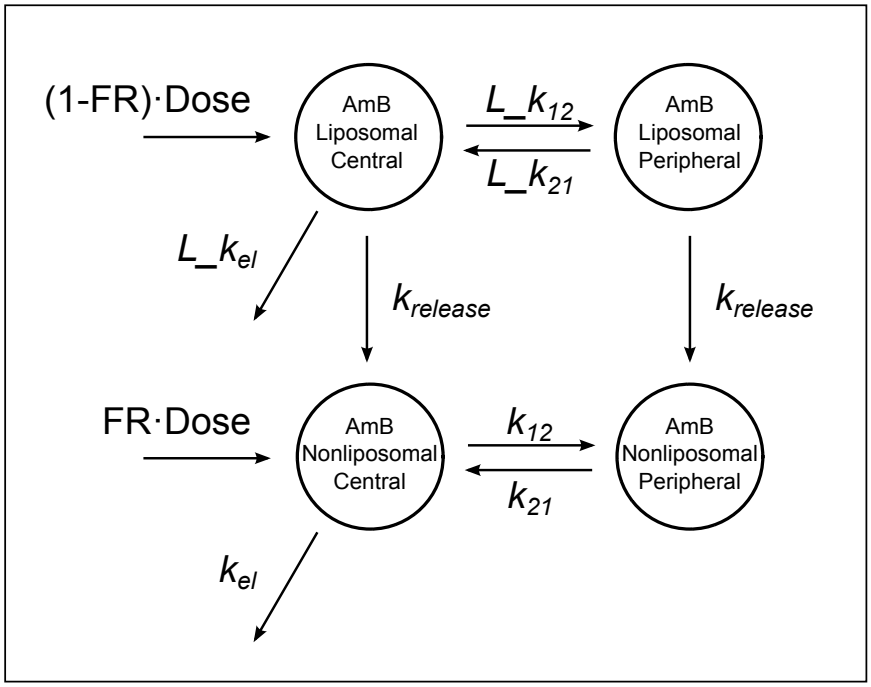

Figure S1. Pharmacokinetic model used for evaluation of release kinetics of AmB from liposomal formulation and for estimation of pharmacokinetic parameters for liposomal and nonliposomal AmB (Table S2).

References

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