

Table S1 Calibration curves for DTX in rat tissues.

Tissues	Slope ($\times 10^{-4}$)	Intercept ($\times 10^{-3}$)	<i>r</i>	Linear ranges (ng · g ⁻¹)
Lung	3.22	1.15	0.992	12.5–5.00E03
Brain	5.27	15.3	0.994	12.5–5.00E03
Heart	5.16	6.93	0.998	12.5–5.00E03
Spleen	4.20	3.02	0.993	12.5–5.00E03
Liver	5.07	9.16	0.999	12.5–5.00E03
Intestine	4.77	17.0	0.997	12.5–5.00E03
Kidney	5.57	15.5	0.996	12.5–5.00E03
Muscle	5.06	11.4	0.996	12.5–5.00E03

Table S2 Summary of the covariate model-building steps.

Effect of covariates	Parameter variation	
	Δ OFV	Δ IIV (%)
Forward selection		
dosage form on $K_{t, pl}$	-17.9	-52.7
dosage form on $K_{t, lu}$	-12.1	-39.7
dosage form on $K_{t, br}$	-11.2	-37.4
dosage form on $K_{t, sp}$	-24.0	-63.1
dosage form on $K_{t, li}$	-18.1	-52.9
dosage form on $K_{t, gu}$	-4.72	-17.9
dosage form on $K_{t, ki}$	-39.5	-80.7
dosage form on $K_{t, mu}$	-7.94	-28.2
dosage form on $K_{t, re}$	-27.6	-68.3

sex on $K_{t, lu}$	-5.12	-19.2
sex on $K_{t, he}$	-9.60	-33.0
sex on CL_{li}	-6.58	-24.0
sex on $K_{t, gu}$	-3.87	-14.9
sex on CL_{gu}	-25.9	-66.1
sex on $K_{t, re}$	-4.77	-18.0

Full-covariate model

dosage form on $K_{t, pl}$	-17.9	-52.7
dosage form and sex on $K_{t, lu}$	-17.7	-52.1
dosage form on $K_{t, br}$	-11.2	-37.4
sex on $K_{t, he}$	-9.60	-33.0
dosage form on $K_{t, sp}$	-24.0	-63.1
dosage form on $K_{t, li}$	-18.1	-52.9
sex on CL_{li}	-6.58	-24.0
dosage form and sex on $K_{t, gu}$	-8.56	-30.0

sex on CL_{gu}	-25.9	-66.1
dosage form on $K_{t, ki}$	-39.5	-80.7
dosage form on $K_{t, mu}$	-7.94	-28.2
dosage form and sex on $K_{t, re}$	-33.3	-75.0

Final model

dosage form on $K_{t, pl}$	-17.9	-52.7
dosage form on $K_{t, lu}$	-12.1	-39.7
dosage form on $K_{t, br}$	-11.2	-37.4
sex on $K_{t, he}$	-9.60	-33.0
dosage form on $K_{t, sp}$	-24.0	-63.1
dosage form on $K_{t, li}$	-18.1	-52.9
sex on CL_{gu}	-25.9	-66.1
dosage form on $K_{t, ki}$	-39.5	-80.7
dosage form on $K_{t, mu}$	-7.94	-28.2

dosage form on $K_{t, re}$

-27.6

-68.3

CL_{gu} : intestinal clearance; CL_{li} : hepatic clearance; $K_{t, br}$: partition coefficient for brain; $K_{t, gu}$: partition coefficient for gut; $K_{t, he}$: partition coefficient for heart; $K_{t, ki}$: partition coefficient for kidney; $K_{t, li}$: partition coefficient for liver; $K_{t, lu}$: partition coefficient for lung; $K_{t, mu}$: partition coefficient for muscle; $K_{t, re}$: partition coefficient for the remainder compartment; $K_{t, sp}$: partition coefficient for spleen; $K_{t, pl}$: blood-to-plasma partition coefficient. ΔIIV represents the variation of inter-individual variability. ΔOFV represents the variation of objective function value.

Figure S1.

Effects of dosage form and sex on DTX PBPK parameters. CL_{gu} : gut clearance; F: female; INJ: simple DTX injection; $K_{\text{t, br}}$: partition coefficient for brain; $K_{\text{t, he}}$: partition coefficient for heart; $K_{\text{t, ki}}$: partition coefficient for kidney; $K_{\text{t, li}}$: partition coefficient for liver; $K_{\text{t, lu}}$: partition coefficient for lung; $K_{\text{t, mu}}$: partition coefficient for muscle; $K_{\text{t, re}}$: partition coefficient for the remainder compartment; $K_{\text{t, sp}}$: partition coefficient for spleen; $K_{\text{t, pl}}$: blood-to-plasma partition coefficient; FA: FA-PEG-PCHL-modified liposomes; M: male. The *boxes* represent the 25th, 50th and 75th percentiles; the *whiskers* represent the lowest datum still within 1.5 interquartile ranges (IQRs) of the lower quartile, and the highest datum still within 1.5 IQRs of the upper quartile range; the *solid circles* represents outliers. ETA represents the relative errors based on the typical values of PBPK parameters.

