Table

Table S1 Summary of dosage regimens and population characteristics from studies in literature

No.	Ref	Subject	Ethnicity	Age (years)	Bioavailability	Weight (kg)	N	Dosage regimen	Sampling time	Validated results
1	(DR et al., 1991)	Healthy volunteers	White	51-82	60	65.9-94.2	5	Oral 6mg/kg Hydroxychloroquine sulfate	0、1、2、4、6、8、12 and 24 h	Figure 3 A and B; Figure 4 A and B
2	(SE et al., 1989)	Healthy volunteers	White	19-27	60	55-68	5	Oral 155mg	0, 0.75, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 13, 24, 32, 48, 72, 96, 120, 168 h	Figure 3 C
								IV 155mg	0、0.25、0.5 (end of infusion)、 0.75、1、1.25、1.5、 2、2.5、3.5、4.5、6.5、8.5、13、24、32、48、72、96、120、168 h	Figure 3 D
3	(J et al., 1995)	Healthy volunteers	White	20-36	NA	72-88	24	Oral 200mg Hydroxychloroquine sulfate	0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120 h and 7, 11,	Figure 3 E

									14, 18, 21, 25, 28, 32, 35, 42, 49, 56, 63, 70, 77, 84 and 91 days.	
4	(AJ et al., 1994)	Rheumatoid arthritis patients	White	34-66	78	60-86	9	Oral 155mg	1, 2, 3, 4, 6, 8, 24, and 32 h	Figure 3 F
								IV 155mg	0.5, 0.75, 1, 2, 3, 4, 6, 8, 24, and 32 h	Figure 3 G
5	(YM et al., 2012)	Healthy volunteers	Chinese	20.1-30.0	NA	51.0-74.8	27	Oral Generic 200mg Hydroxychloroquine sulfate	0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 h post-dose	Figure 3 H
				20.1-27.9	66	51.9-71.5	27	Oral branded 200mg Hydroxychloroquine sulfate		
6	(H et al., 2018)	SLE	White		100	NA	6	Oral 200mg BID for 6 months	0、1、2、4、6、8 and 12h	Figure 3 I
7	(HW et al., 2015)	Healthy volunteers	Chinese	21-29	NA	54-75	20	Oral Test formation	0-72h	Figure 3 J
							20	Oral 200mg Hydroxychloroquine	Before dosing (baseline), 1, 2, 3, 4, 5, 7, 9, 12, 24,	Figure 3 K

								sulfate	48 h (day 3), 72 h (day 4), 120 h (day 6), day 10, day 20, day 40, and day 60 after administration.	
8	(SE et al., 1988)	Healthy volunteers	White	19-27	60	55-68	5	1-4 patients：IV 155mg QD 310mg QD 1 patient：IV 150mg QD	0 (blank), 0.25, 0.5 (end of infusion)0.75, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 13, 24, 32, 48, 72, 96, 120, 168 h, then once a week thereafter until the limit of sensitivity of the assay was reached (5 months following the 155 mg dose, 6 months or more following the 310 mg dose).	Figure 3 L and M; Figure 4 C and D
9	(GM et al., 1987)	PLE	White	Mean:42	50	Mean: 42	13	Oral 400 mg QD at first month 200 mg QD at second month	Every month	Figure 3 N; Figure 4 E

10	(SB et al., 1988)	Healthy volunteers	White	NA	NA	84.88	2	Oral 310 mg QD 4 weeks	0,4,8,24,72,128 h	Figure 3 O and P
11	(T et al., 2002)	Rheumatoid arthritis patients	White	>18	NA	NA	NA	Oral 400 mg QD 6 weeks 800 mg QD 6 weeks 1200 mg QD 6 weeks	1-6,8,10,16,20 and 24 weeks	Figure 3 Q, R and S; Figure 4 F, G and H

Table S2 Dosage regimens and sampling time of validated data from COVID-19 patients

ID	Gender	Age	Disease degree	Administration time		Dosage (mg)	Sampling time (Day)
				Day	time		
Obs A	Male	45	Mild	1	16:00	600	
					22:00	600	
				2	16:00	200	
				3	8:00	200	3
					16:00	200	
				4	8:00	200	4
					16:00	200	
				5	8:00	200	5
					16:00	200	
							7
Obs B	Male	68	Mild	1	16:00	600	
					22:00	600	
				2	18:40	200	
				3	8:30	200	5
							20
Obs C	Male	45	Severe	1	16:00	600	
					22:00	600	
				2	16:00	200	
				3	8:00	200	3
							17
Obs D	Male	60	Severe	1	16:00	600	
					22:00	600	
				2	18:40	200	
				3	8:30	200	
							7
							8
							11
Obs E	Female	37	Mild	1	16:00	600	
					22:00	600	
				2	18:40	200	
				3	8:30	200	
							16

Table S3 Parameters in HCQ PBPK model

Parameter	**Input Value**	**Source**
Hydroxychloroquine (HCQ)		
Physicochemical properties		
Molecular weight (g/mol)	335.87	
Log *P*	3.84	(KP et al., 2018)
Compound type	Diprotic base	
pKa	9.67, 8.27	(KP et al., 2018)
Blood-to-plasma partition ratio	7.20	(SE et al., 1988)
Hematocrit	45.0	
Fraction unbound in plasma	0.48	(AJ et al., 1993)
Absorption		
Absorption model	ADAM	
fa	0.896	Predicted
ka (1/h)	0.798	Predicted
fu (Gut)	1.00	User
Permeability Assay	Caco-2	
Apical pH : Basolateral pH	7.4 : 7.4	
Activity		
Caco-2(10^{-6}cm/s) (HCQ)	3.68	Measured
Caco-2(10^{-6}cm/s) (Cimetidine)	0.92	Measured
Caco-2(10^{-6}cm/s) (Metoprolol)	23.51	Measured
DLM Model Options	Particle Population Balance Model	
Solid State Specific Parameters	Solid state 1	
Particle size distribution		
Monodispersed Radius (μm)	10	
Density (g/mL)	1.2	
Particle population balance model options (Simulation Parameters)		
Number of Particle Size Bins (Simulation)	30	
Radius Bounds (Simulation) (μm)		
Minimum	0.1	
Maximum	11	
Step Type	Uniform step-size	
Aqueous Phase Solubility		
Intrinsic Solubility (S_o) (mg/mL)	0.034	Predicted
Distribution		
Distribution model	Full PBPK model	
Vss (L/kg)	255.10	Predicted
Prediction Method	Method 2	
Tissue : Plasma Partition Coefficients (Species defined in Simcyp Animal Simulator, Sim-Rat)		
Adipose	75.74	Predicted

Bone	128.00	Predicted
Brain	79.49	Predicted
Gut	535.07	Predicted
Heart	577.98	Predicted
Kidney	467.85	Predicted
Liver	957.03	Predicted
Muscle	470.57	Predicted
Skin	248.55	Predicted
Spleen	530.05	Predicted
Pancreas	317.11	Predicted
Kp scalar	2.20	Fitted according to the concentration-time profile of validated data
Elimination		
Clearance type	Enzyme kinetics	
Intrinsic clearance of CYP 2C8 (μL/min/pmol)	0.089	Measured
Fraction of unbound drug in the invitro microsomal incubation (fu mic)	0.5	Fitted, according to the contribution of renal clearance
rCYP system	E.Coli	
ISEF	3.63	Default value in Simcyp
% fm	37.28%	Predicted results
Intrinsic clearance of CYP 2D6 (μL/min/pmol)	0.211	Measured
fu mic	0.5	Fitted, according to the contribution of renal clearance
rCYP system	E.Coli	
ISEF	2.49	Default value in Simcyp
% fm	19.33%	Predicted results
Intrinsic clearance of CYP 3A4 (μL/min/pmol)	0.0197	Measured
fu mic	0.5	Fitted, according to the contribution of renal clearance
rCYP system	E.Coli	
ISEF	1.14	Default value in Simcyp
% fm	16.71%	Predicted results
Typical renal clearance (L/h)	12.7	(SE et al., 1989)
% fm	26.68%	Predicted results

Interaction		
OATP1A2 Ki (OATP1A2) (μM)	8.27	(C et al., 2016)
Transporter (Permeability Ltd. Organs)		
Caco-2(10^{-6}cm/s) (HCQ)*	3.68	Measured
Fu mass	0.001	predicted
Basolateral Uptake $Cl_{int,T}$	0.2	Fitted according to Kp in monkey and plasma exposure of HCQ in human
Basolateral Efflux $Cl_{int,T}$	0.5	Fitted according to Kp in monkey and plasma exposure of HCQ in human
Desethylhydroxychloroquine (DHCQ)		
Physicochemical properties		
Molecular weight (g/mol)	307.825	
Log *P*	3.432	Predicted by ADMET Predictor
Compound type	Diprotic Base	Predicted by ADMET Predictor
pKa 1	9.45	Predicted by ADMET Predictor
pKa 2	7.15	Predicted by ADMET Predictor
Blood-to-plasma partition ratio	1.715	Predicted with prediction toolbox in Simcyp software
Hematocrit		
Fraction unbound in plasma	0.51	(AJ et al., 1993)
Distribution		
Distribution model	Full PBPK model	
Vss (L/kg)	14.13	Predicted
Kp scalar	1	
Elimination		
Clearance type	Enzyme kinetics	
Additional clearance of HLM (μL/min/ mg protein)	22	Fitted with concentration-time profile of DHCQ(GM et al., 1987)

Typical renal clearance (L/h)	2.862	(DR et al., 1991)

* Alternatively, the predicted value of 2.62×10^{-6} cm/s based on equation ($\text{Calu}-3\ P_{app}[10^{-7}\ cm/s] = 0.5881 \times Caco-2\ P_{app}[10^{-7}\ cm/s] + 4.5594; r^2 = 0.76$) can be used under Calu-3 P_{app} input in permeability limited lung model.

Table S4 Summary of PK parameters used in Figure 6

Observed AUC (h·ng/mL)	Predicted AUC (h·ng/mL)	AUC Ratio (Predicted/ Observed)	Observed C_{max} (ng/mL)	Predicted C_{max} (ng/mL)	C_{max} Ratio (Predicted/ Observed)	References
7719	7563	0.98	215	170	0.79	(SE et al., 1989)
8320	6057	0.73	1792	1290	0.72	(SE et al., 1989)
5069	6888	1.36	115	156	1.35	(J et al., 1995)
2227	3532	1.59	128	172	1.34	(AJ et al., 1994)
5083	4094	0.81	1516	1319	0.87	(AJ et al., 1994)
1605	2498	1.56	174	196	1.13	(YM et al., 2012)
609	697	1.15	34	27	0.80	(HW et al., 2015)
20939	17905	0.86	1708	1330	0.78	(SE et al., 1988)
43808	34464	0.79	488	404	0.83	(SE et al., 1988)
7584	14159	1.87	247	294	1.19	(SB et al., 1988)
18334	29836	1.63	429	406	0.95	(SB et al., 1988)
7359	14159	1.92	259	294	1.13	(SB et al., 1988)
19775	29836	1.51	313	406	1.30	(SB et al., 1988)

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