

Supplementary material

Swine as the animal model for testing new formulations of anti-inflammatory drugs: Carprofen Pharmacokinetics and Bioavailability of the intra-muscular route

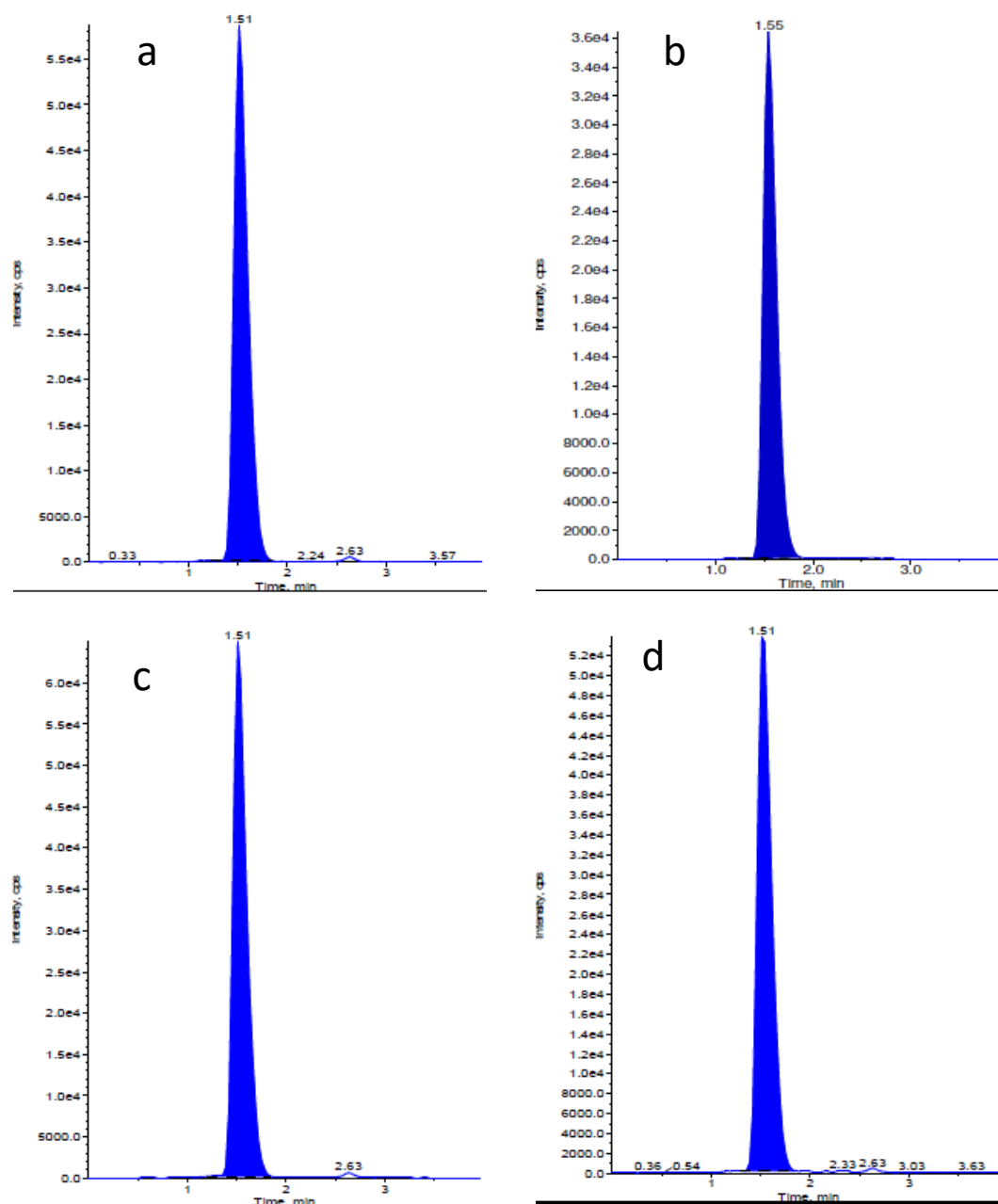


Figure S1. Ionograms of blank samples with internal standard (IS, Carprofen-d3). (a) blank sample ionogram of swine 1; (b) blank sample ionogram of swine 2; (c) blank sample ionogram of swine 3 and (d) blank sample ionogram of swine 4.

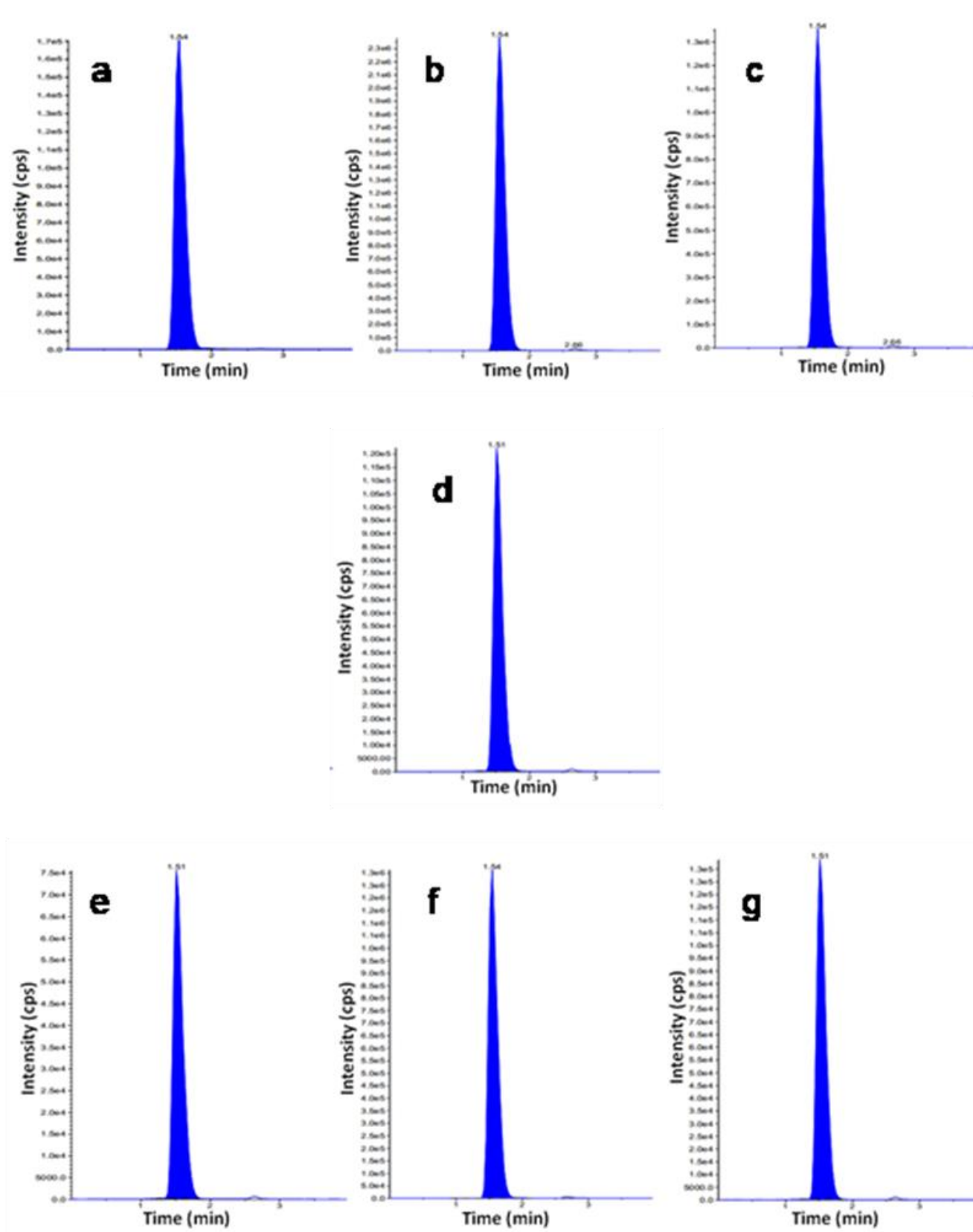


Figure S2. Ionograms of CP at different plasma samples times of swine number 1; (a) standard curve at 750 ng/mL; (b) intravenous levels at 5 min; (c) intravenous levels at 6 h; (d) intravenous levels at 24 h; (e) intramuscular levels at 5 min; (f) intramuscular levels at 6 h, and (g) intramuscular levels at 24 h.

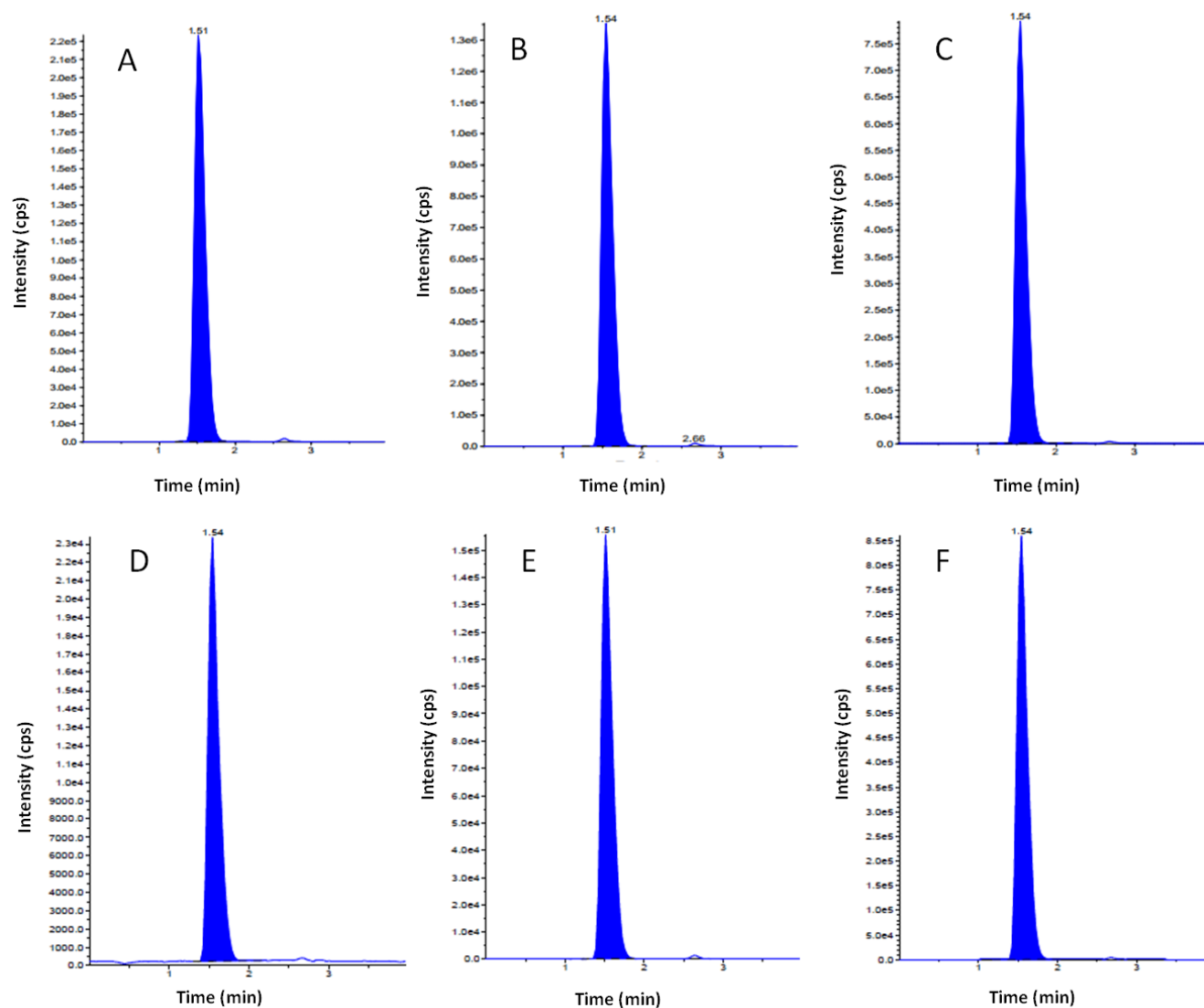


Figure S3: Ionograms of CP at different plasma samples times of swine number 2. A: IV levels at 5 min; B: IV levels at 6h; C: IV levels at 24h; D: IM levels at 5 min; E: IM levels at 6h and F: IM levels at 24h.

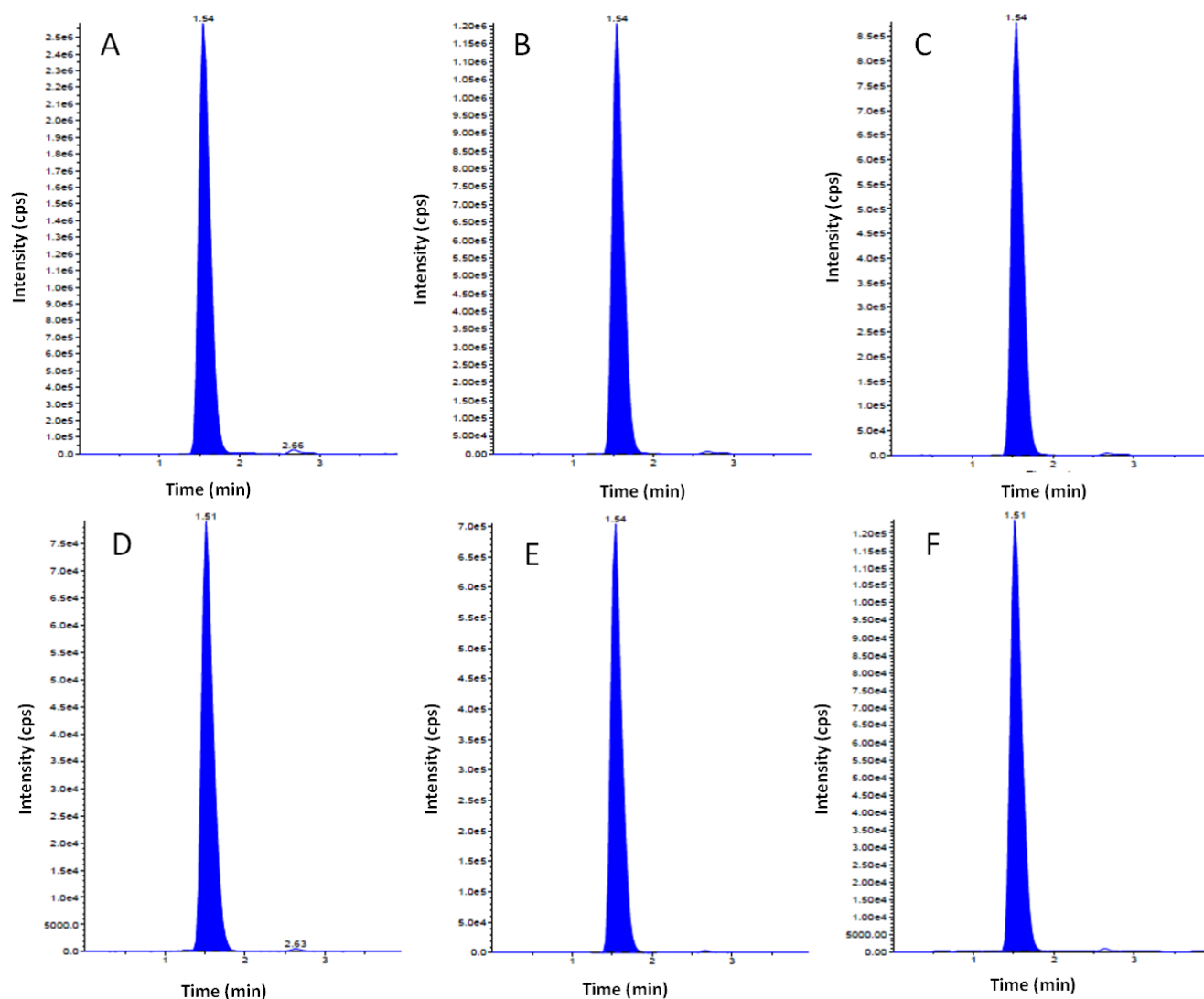


Figure S4: Ionograms of CP at different plasma samples times of swine number 3. A: IV levels at 5 min; B: IV levels at 6h; C: IV levels at 24h; D: IM levels at 5 min; E: IM levels at 6h and F: IM levels at 24h.

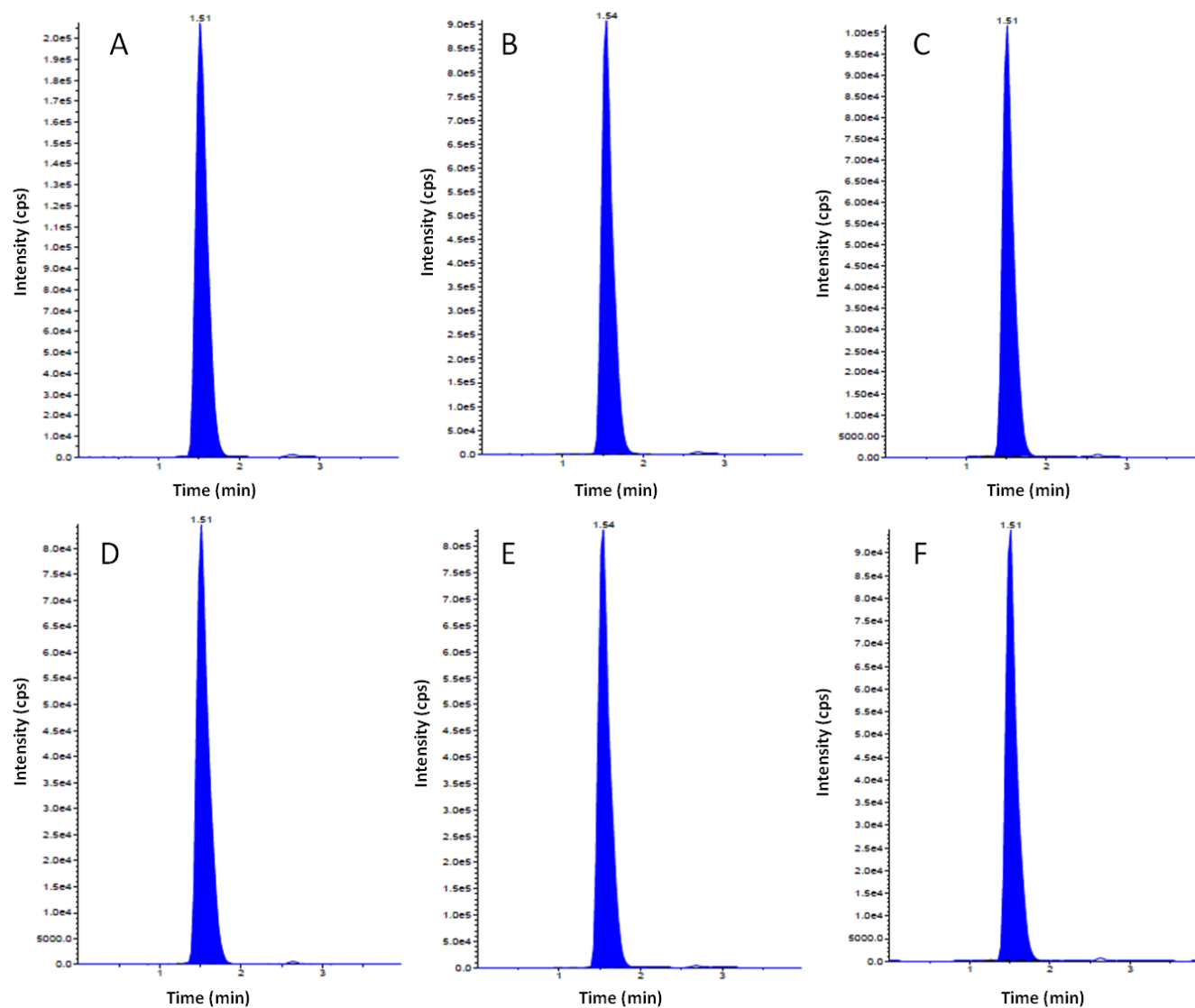


Figure S5: Ionograms of CP at different plasma samples times of swine number 4. A: IV levels at 5 min; B: IV levels at 6h; C: IV levels at 24h; D: IM levels at 5 min; E: IM levels at 6h and F: IM levels at 24h.

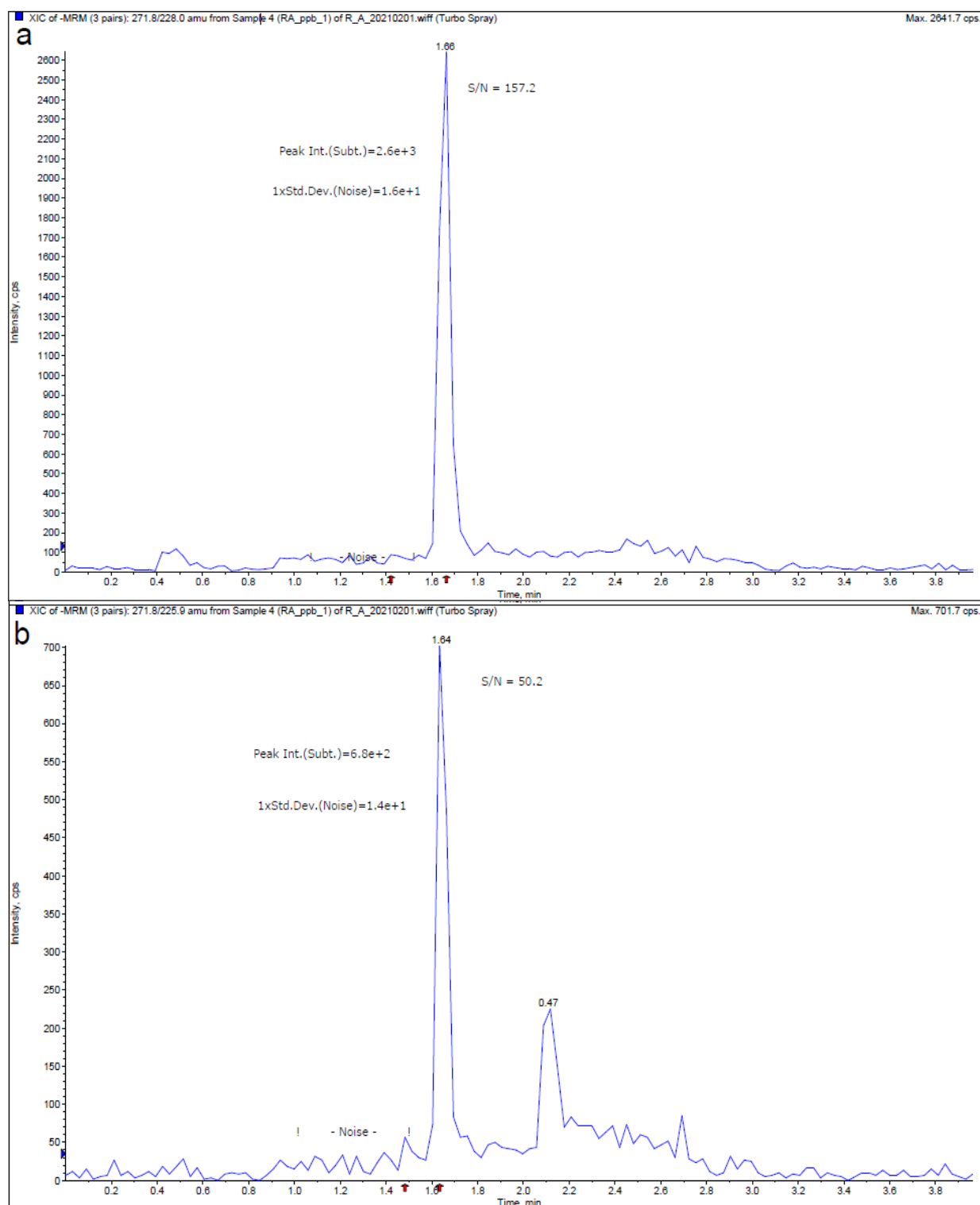


Figure S6: Ionograms of Limit of Detection (LOD) and Limit of Quantification (LOQ) for: (a) transition T1, and (b) transition T2.

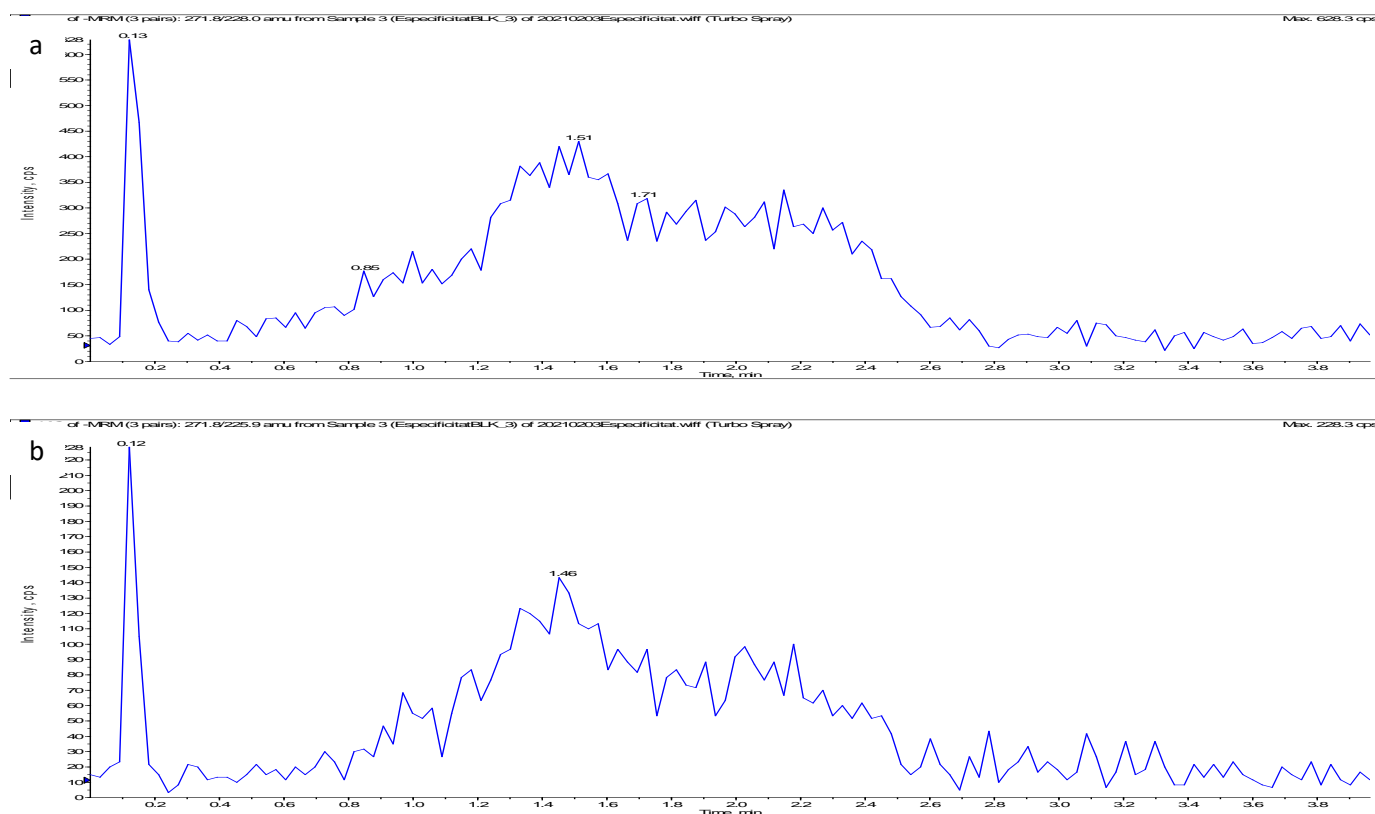


Figure S7: Ionograms of determination of Specificity with blank samples of plasma without IS for: (a) transition T1 and (b) transition T2.

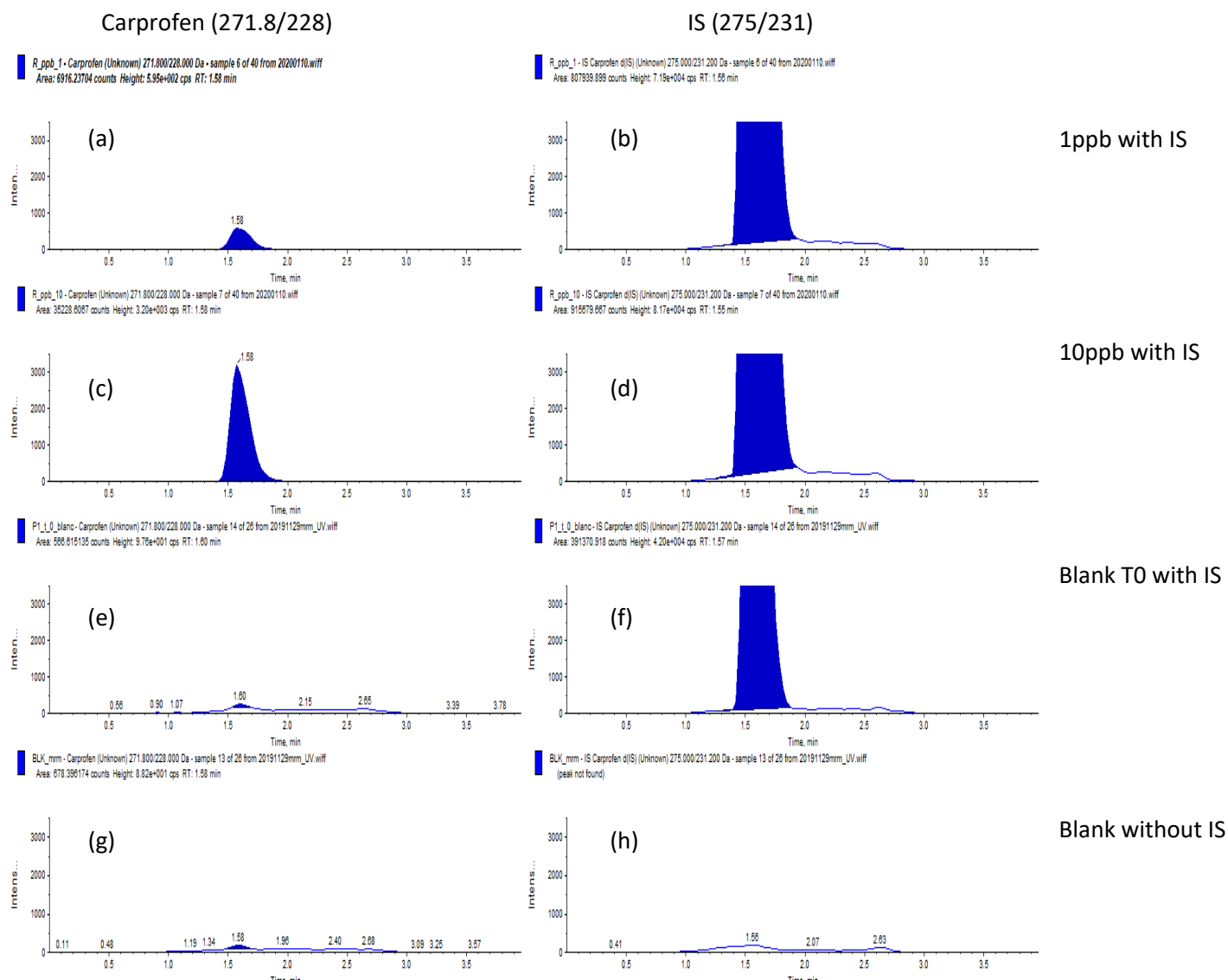


Figure S8: Ionograms of Std (1 ppb and 10 ppb with IS 100 ppb), and samples with (100 ppb) and without IS: (a) Std 1ppb: Carprofen, (b) Std 1 ppb: IS (c) Std 10 ppb: Carprofen, (d) Std 10 ppb: IS, (e) Blank sample T0 with IS (100 ppb): carprofen, (f): Blank sample T0 with IS (100 ppb): IS, (g) Blank sample without IS: carprofen (h) Blank Sample without IS: IS signal.

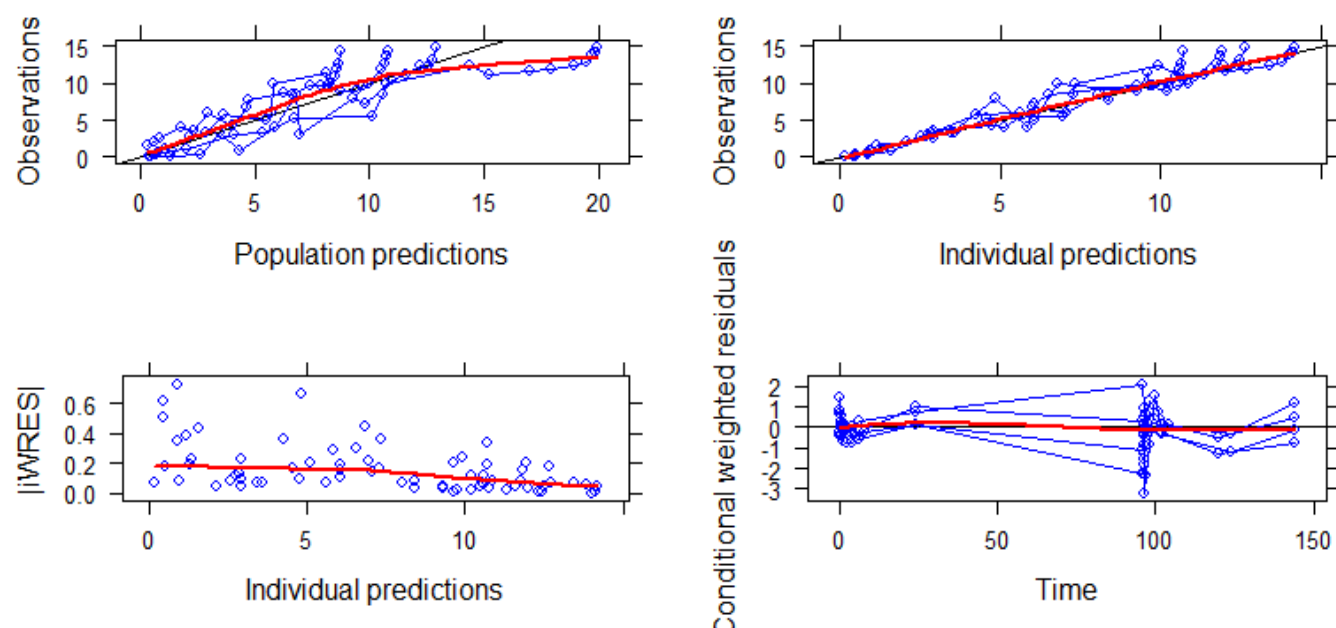


Figure S9. Goodness-of-fit plots for the final population pharmacokinetic model. Observed concentrations versus Population predicted and individual predicted concentrations. Individual weighted residuals (IWRES) vs individual predicted concentrations; Conditional weighted residuals (CWRES) vs time. Blackline: identity line; Red line: Smooth line indicating the general data trend. Concentrations expressed as $\mu\text{g/mL}$, Time given in hours.

Table S1: CP Pharmacokinetic parameter values in different animal species. Statistical comparison of the CP pharmacokinetic parameters ($HL\beta$, AUC, V_{dss} , Cl and MRT) of swine versus different studied species such as: dogs (4 mg/kg IV Rimadyl®) [29], horses (4mg/kg IV Rimadyl®) [19], cats (4 mg/kg IV Zenecarp®) [30], rabbits (2 mg/kg IV Rimadyl®) [24], sheep (4 mg/kg IV racemic CP) [23], humans (100 mg IV Imadyl®) [27], and the present study in swine (4 mg/kg IV Rimadyl®) expressed as mean \pm SD, except for dogs and swine (mean and coefficient variation, given in parenthesis, when available).

Parameters	Dog (n=6)	Horse (n=6)	Cat (n=5)	Rabbit (n=6)	Sheep (n=8)	Human (n=6)	Swine (n=4)
Co ($\mu\text{g/mL}$)	58.11 (100.70)	36.16 \pm 3.88	179.80 \pm 263.10	20.70 \pm 2.05	39.61 \pm 5.60	ND	-
A ($\mu\text{g/mL}$)	47.68 (13.39)	28.38 \pm 3.26	146.00 \pm 239.00	14.36 \pm 2.72	ND	ND	-
B ($\mu\text{g/mL}$)	10.43 (87.31)	7.78 \pm 0.61	33.80 \pm 24.10	6.10 \pm 2.08	ND	ND	-
α (h^{-1})	0.43 (25.13)	2.01 \pm 0.66	2.94 \pm 3.90	1.94 \pm 0.66	1.69 \pm 0.33	ND	-
β (h^{-1})	0.08 (17.15)	0.06 \pm 0.01	0.05 \pm 0.02	0.23 \pm 0.05	0.03 \pm 0.01	ND	-
$t_{1/2\alpha}$ (h)	1.63 (25.13)	0.39 \pm 0.13	ND	0.36 \pm harmonic	0.43 \pm 0.09	1.80 \pm 0.50	-
$t_{1/2\beta}$ (h)	9.10 (17.15)	11.35 \pm 2.21 *	20.00 \pm 16.60	3.06 \pm harmonic	24.17 \pm 5.98	9.91 \pm 0.79 *	36.34 (21.68) ^{\$}
AUC ($\mu\text{g} \cdot \text{h/mL}$)	268.94 (26.00)***	138.1 \pm 17.89 ***	636.00 \pm 237.00	37.82 \pm 9.64 ***	531.80 \pm 120.70	ND	-
K_{10} (h^{-1})	0.23 (26.61)	0.22 \pm 0.04	0.34 \pm 0.53	0.55 \pm 0.21	0.08 \pm 0.04	ND	-
K_{12} (h^{-1})	0.11 (61.30)	1.27 \pm 0.49	2.10 \pm 3.3	0.81 \pm 0.34	0.97 \pm 0.24	ND	-
K_{21} (h^{-1})	0.14 (43.31)	0.59 \pm 0.20	0.55 \pm 0.55	0.81 \pm 0.16	0.68 \pm 0.06	ND	-
Vc (L/kg)	0.07 (0.06)	0.14 \pm 0.02	0.05 \pm 0.03	0.10 \pm 0.01	0.10 \pm 0.00	0.045 \pm 0.01	0.23 (25.60) ^{&}
Vss (L/kg)	0.12 (0.01) ***	0.43 \pm 0.05 *	0.14 \pm 0.05 ***	0.09 \pm 0.02 ***	0.13 \pm 0.19 *	0.22 \pm 0.06 **	0.31 ^{&}
CL (mL/kg/h)	14.87 (26.03)	29.00 \pm 4.90 ***	7.10 \pm 2.81	27.92 \pm 7.07 ***	4.00 \pm 1.22 *	31.11 \pm 6.00 ***	8.17 (20.75) ^{&}
MRT (h)	8.02 (23.28) **	15.10 \pm 3.43 ***	23.60 \pm 16.2 *	3.45 \pm 0.5 ***	33.89 \pm 8.38 **	7.07 \pm 9.17 ***	-

* P-Value <0.05; **P-Value <0.01 and ***P-Value <0.001; ND: Not determined; \$: estimated from the non-compartmental approach; &: estimated from the population pharmacokinetic approach

Co: Initial concentration after iv bolus administration; A and B, α , β : Ordinate intercept terms and rate constants of the distribution and elimination phases, respectively; AUC: area under the curve of plasma concentrations vs time; K_{10} , elimination rate constant from the central compartment; K_{12} and K_{21} : distribution rate constants from and to the central compartment, respectively; Vc: central compartment distribution volume; Vss: steady-state distribution volume; CL: plasma clearance; MRT: mean residence time.