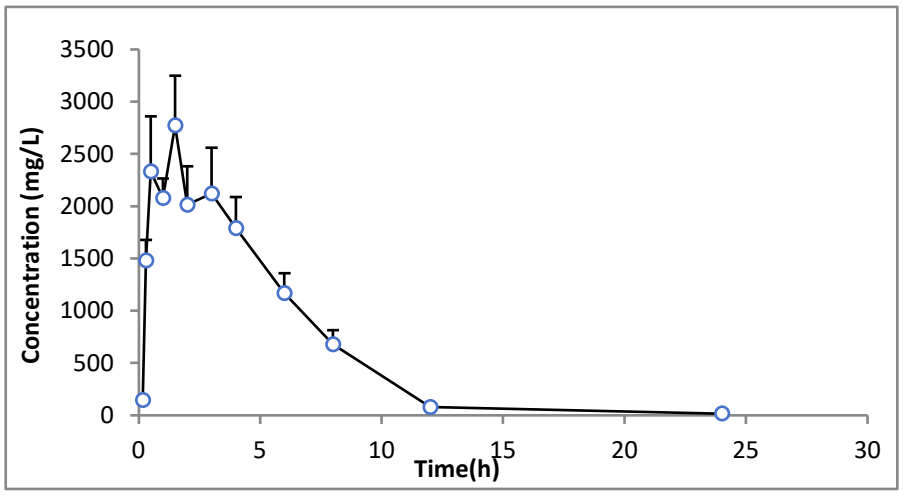
Supplementary Figures

(a)



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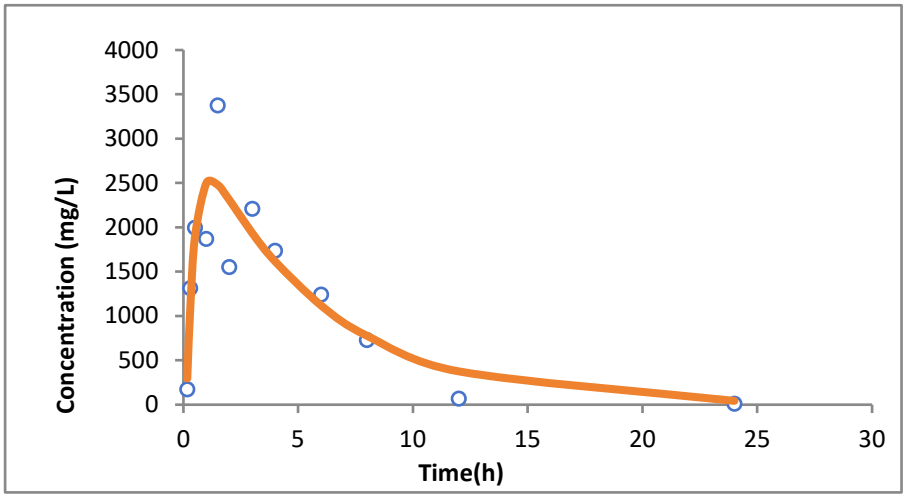

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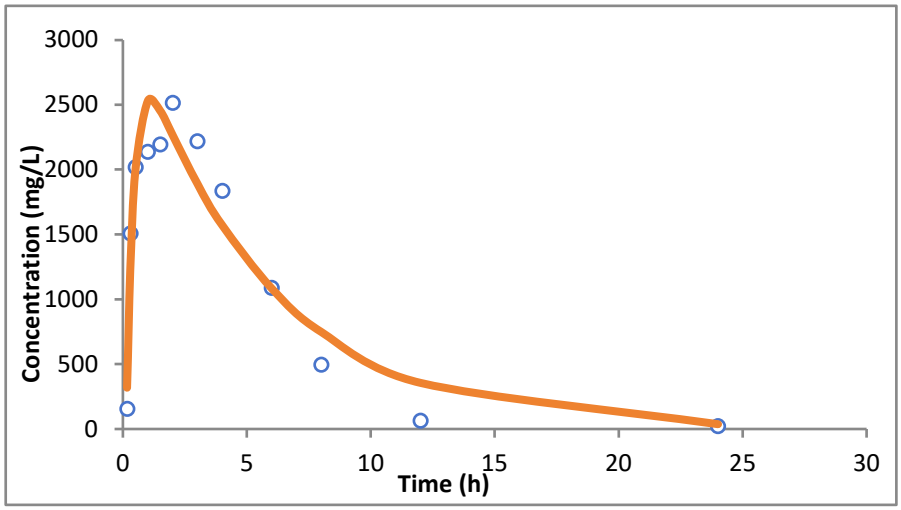

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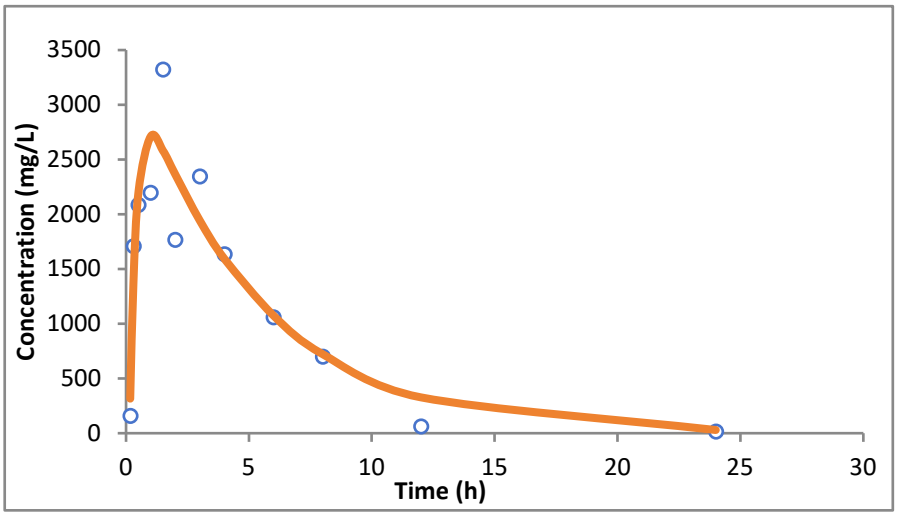
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5
10
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20
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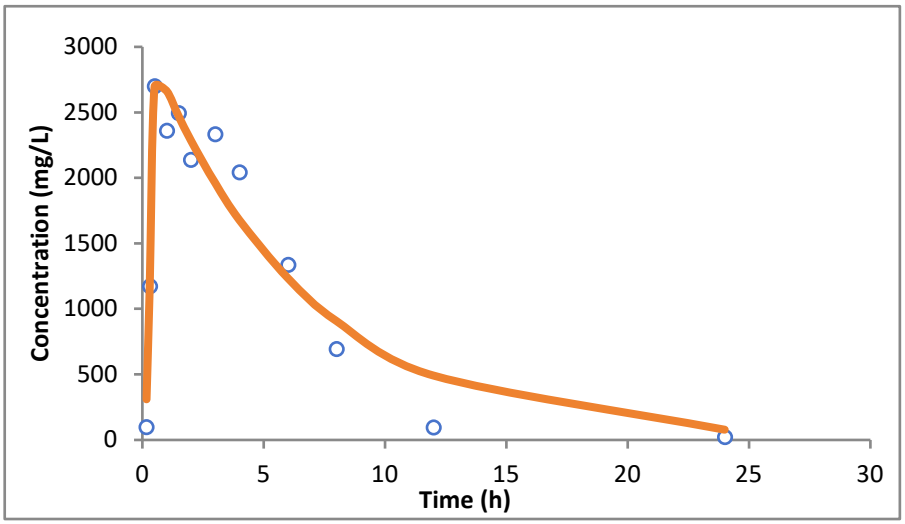
Time (h)

(e)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Time (h)

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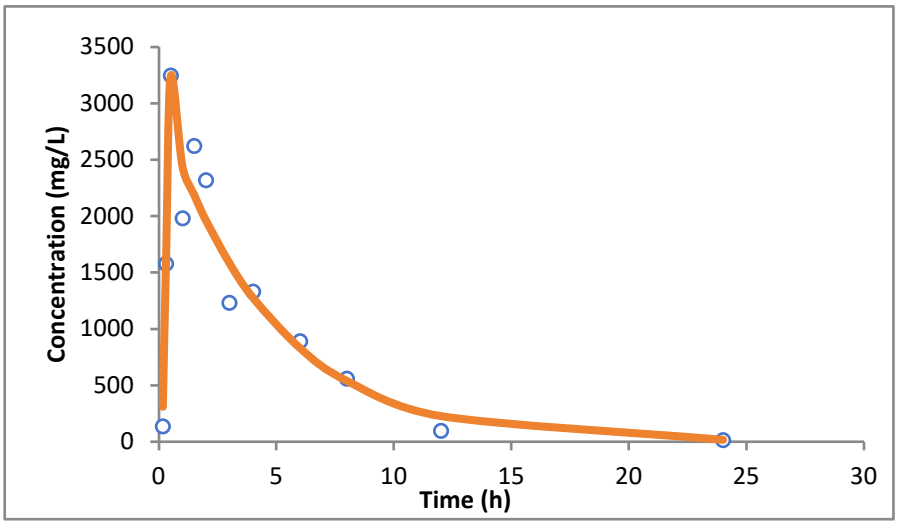
Concentration (mg/L)
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2500
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Time (h)

(g)

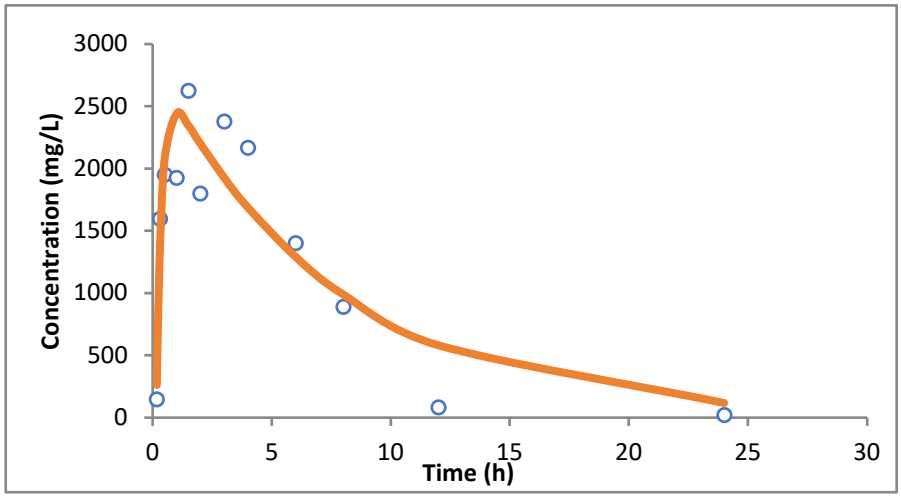
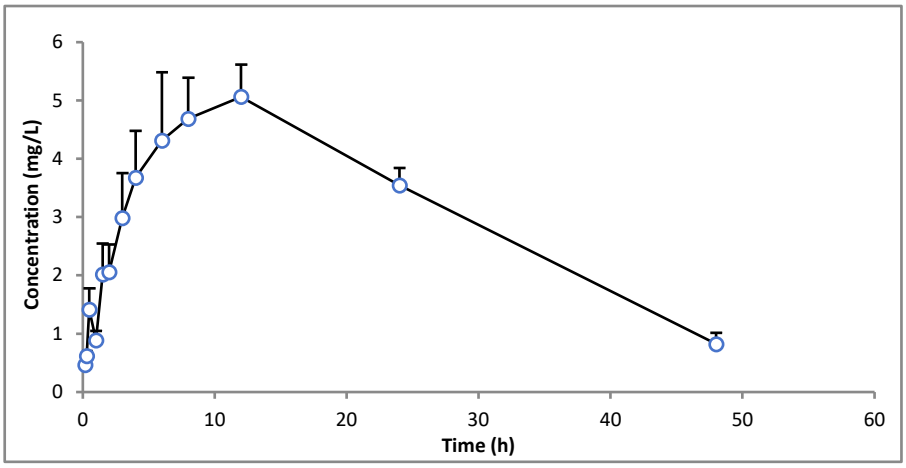


Fig. S1: Results from batch analysis of doxofylline pharmacokinetic data. (a) Average C-t curve; (b) C-t of No.1 rat; (c) C-t of No.2 rat; (d) C-t of No.3 rat; (e) C-t of No.4 rat; (f) C-t of No.5 rat; (g) C-t of No.6 rat. Note: C-t (Concentration-time curve).

Supplementary Figures

(a)



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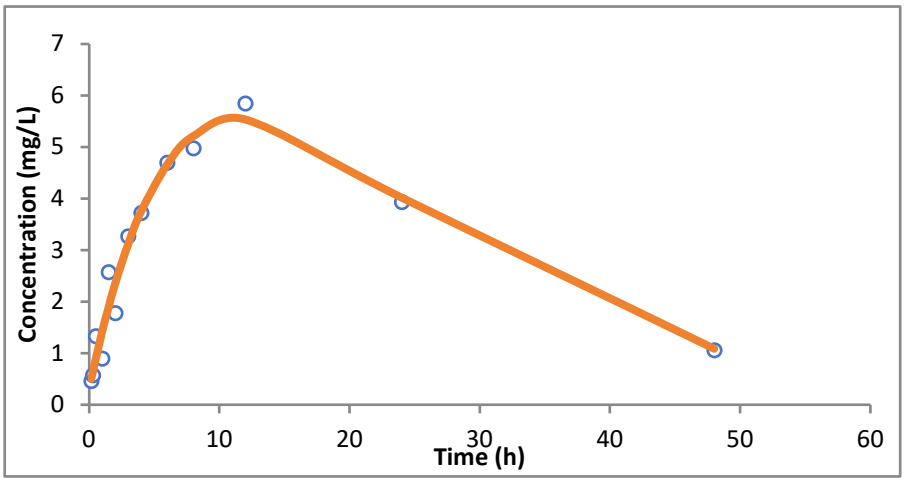

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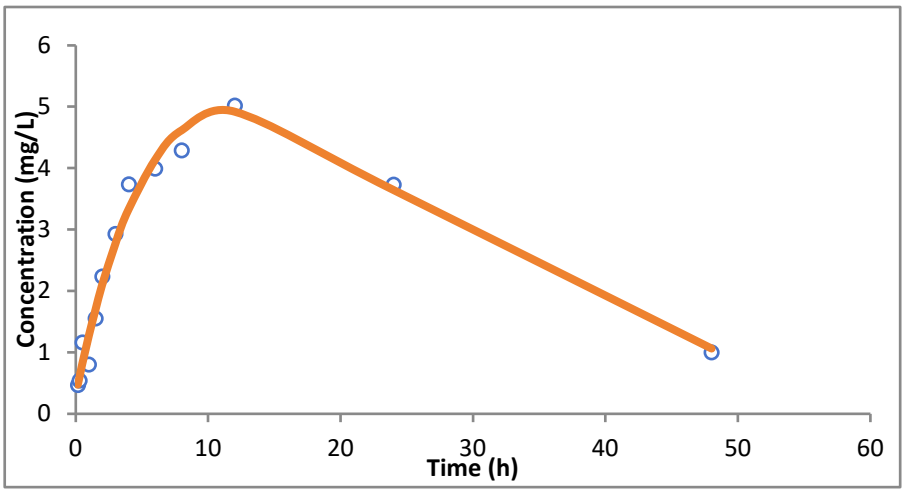

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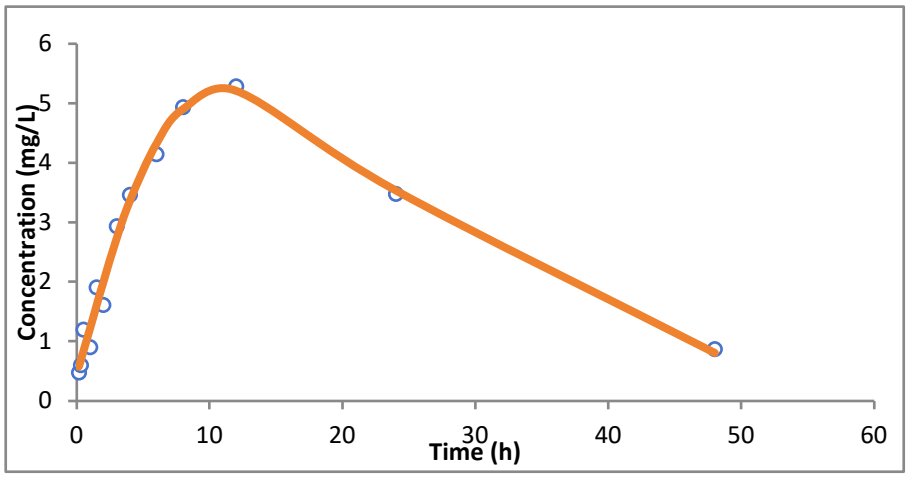
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Time (h)
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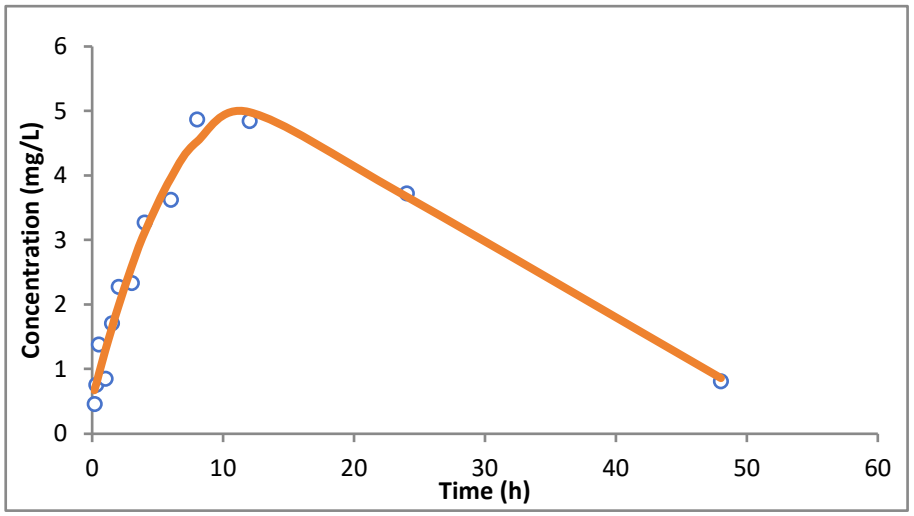
1
2
3
4
5
6
0
10
20
30
40
50
60

(e)


Concentration (mg/L)
Time (h)
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1
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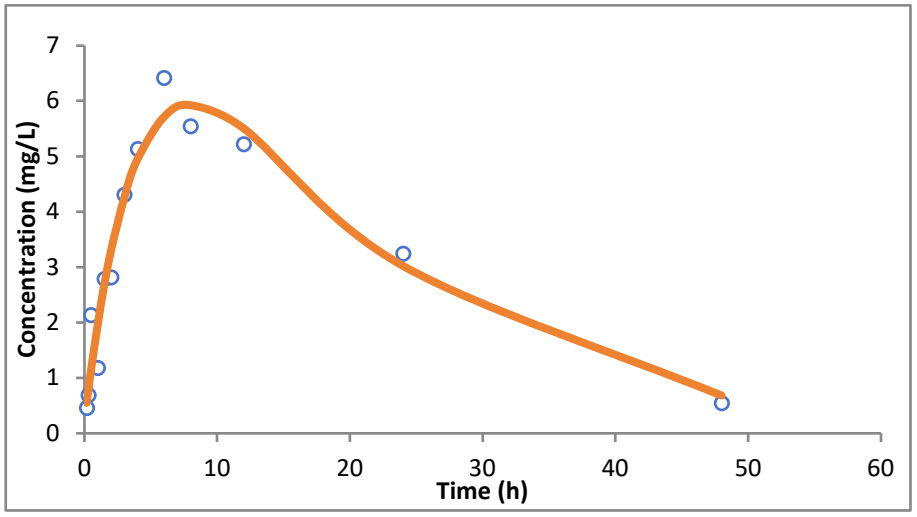
(f)


Concentration (mg/L)
Time (h)
0
1
2
3
4
5
6
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10
20
30
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50
60

(g)

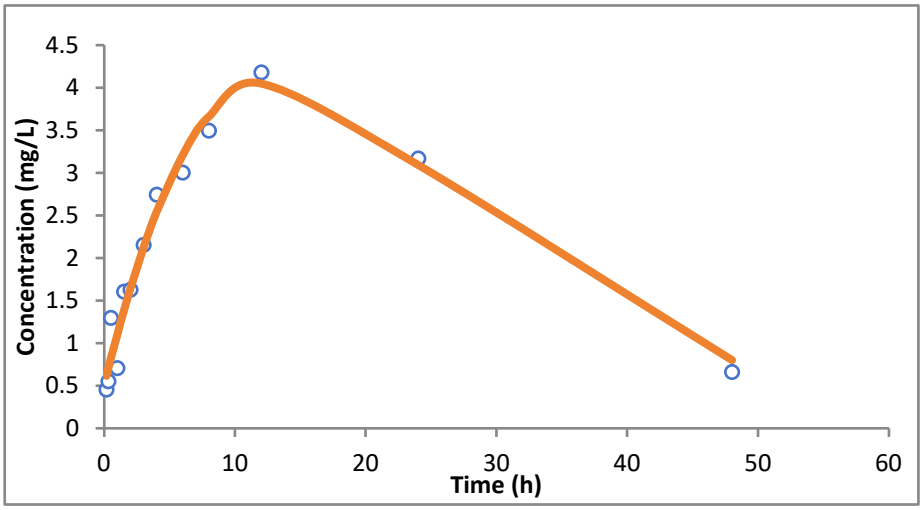

Fig. S2: Results from batch analysis of theophylline pharmacokinetic data. (a) Average C-t curve; (b) C-t of No.1 rat; (c) C-t of No.2 rat; (d) C-t of No.3 rat; (e) C-t of No.4 rat; (f) C-t of No.5 rat; (g) C-t of No.6 rat. Note: C-t (Concentration-time curve).

Supplementary Tables:
Results from Batch Analysis of Doxofylline Pharmacokinetic Data

Table S1.1: Calculation Settings.

Settings	Options	Settings	Options
File Name	Doxofylline	Drug Dose	80
Route of Administration	Non-venous	Dose Unit	mg/kg
Dosing Frequency	Single-dose administration	Concentration Unit	mg/L
Study Subjects	Rat	Time Unit	h
Number of Compartments and Weight	Custom	Limit of Detection	2

Table S1.2: Statistical Moment Parameters.

Parameters	Unit	No1	No2	No3	No4	No5	No6	Mean	SD
AUC(0-t)	mg/L*h	14881.339	14301.403	14764.638	16212.302	13007.063	16427.928	14932.446	1265.748
AUC(0-∞)	mg/L*h	14932.388	14402.208	14833.245	16306.76	13063.794	16503.854	15007.042	1273.384
AUMC(0-t)		64408.441	58767.509	61555.181	70811.845	54165.291	74561.765	64045.005	7591.896
AUMC(0-∞)		65837.183	61659.893	63493.971	73488.141	55769.049	76694.816	66157.176	7747.499
MRT(0-t)	h	4.328	4.109	4.169	4.368	4.164	4.539	4.28	0.163
MRT(0-∞)	h	4.409	4.281	4.281	4.507	4.269	4.647	4.399	0.154
VRT(0-t)	h^2	9.971	10.938	10.42	11.288	12.19	10.392	10.867	0.795
VRT(0-∞)	h^2	11.894	15.183	13.135	14.649	14.729	12.97	13.76	1.285
t1/2z	h	2.738	3.164	2.983	3.036	2.964	2.869	2.959	0.145
Tmax	h	1.5	2	1.5	0.5	0.5	1.5	1.25	0.612
CLz/F	L/h/kg	0.005	0.006	0.005	0.005	0.006	0.005	0.005	0.001
Vz/F	L/kg	0.021	0.025	0.023	0.021	0.026	0.02	0.023	0.002
Zeta		0.253	0.219	0.232	0.228	0.234	0.242	0.235	0.012
Zeta Regression End Point		134	145	145	145	134	134	--	--
Cz (Regression Value at Terminal Point)	mg/L	12.921	22.077	15.937	21.564	13.265	18.339	17.351	3.984
Cmax	mg/L	3380.174139	2513.270353	3325.067804	2699.16263	3245.970957	2622.885608	2964.422	393.124

Table S1.3: Observed Concentration-Time Data.

t	No1	No2	No3	No4	No5	No6	Mean	SD
0.1667	175.944661	155.0220684	161.7332435	98.25112637	134.7598937	144.9834247	145.116	26.938
0.3	1315.878821	1507.847896	1711.290714	1172.045395	1578.636965	1594.284788	1479.997	199.416
0.5	1997.79771	2018.79811	2087.61351	2699.16263	3245.97095	1949.42511	2333.12	526.50

	9	1	3		7	3	8	1
1	1871.605782	2137.736539	2199.862886	2359.418198	1981.277126	1925.632322	2079.255	185.89
1.5	3380.174139	2192.89021	3325.067804	2493.441445	2621.953553	2622.885608	2772.735	476.124
2	1554.576783	2513.270353	1769.875133	2136.945079	2318.186209	1797.687779	2015.09	367.251
3	2211.302979	2217.93516	2348.524188	2333.872934	1230.344882	2376.825084	2119.801	441.211
4	1738.938937	1834.644048	1636.53515	2042.392992	1329.790138	2167.075814	1791.563	298.603
6	1243.302226	1088.245177	1060.054547	1335.145135	890.6706868	1399.049798	1169.411	190.738
8	732.6739139	495.7470979	701.1412543	694.3340556	560.3694019	887.5207312	678.631	137.653
12	70.32697801	62.91412192	64.03688697	93.55701069	97.543537	79.71115811	78.015	14.888
24	12.93820701	22.17508192	15.91198975	21.52789054	13.26175745	18.30880425	17.354	3.998

Table S1.4: Measured ln c-t data.

t	No1	No2	No3	No4	No5	No6	Mean	SD
0.1667	5.17	5.044	5.086	4.588	4.903	4.977	4.961	0.204
0.3	7.182	7.318	7.445	7.067	7.364	7.374	7.292	0.141
0.5	7.6	7.61	7.644	7.901	8.085	7.575	7.736	0.209
1	7.535	7.668	7.696	7.766	7.591	7.563	7.637	0.088
1.5	8.126	7.693	8.109	7.821	7.872	7.872	7.916	0.17
2	7.349	7.829	7.479	7.667	7.749	7.494	7.595	0.183
3	7.701	7.704	7.762	7.755	7.115	7.774	7.635	0.257
4	7.461	7.515	7.4	7.622	7.193	7.681	7.479	0.174
6	7.126	6.992	6.966	7.197	6.792	7.244	7.053	0.168
8	6.597	6.206	6.553	6.543	6.329	6.788	6.503	0.206
12	4.253	4.142	4.159	4.539	4.58	4.378	4.342	0.189
24	2.56	3.099	2.767	3.069	2.585	2.907	2.831	0.233

Supplementary Tables:

Results from Batch Analysis of Theophylline Pharmacokinetic Data

Table S2.1: Calculation Settings.

Settings	Options	Settings	Options
File Name	Theophylline	Drug Dose	80
Route of Administration	Non-venous	Dose Unit	mg/kg
Dosing Frequency	Single-dose administration	Concentration Unit	mg/L
Study Subjects	Rat	Time Unit	h
Number of Compartments and Weight	Custom	Limit of Detection	0.1

Table S2.2: Statistical Moment Parameters.

Parameters	Unit	No1	No2	No3	No4	No5	No6	Mean	SD
AUC(0-t)	mg/L*h	166.943	151.981	149.644	148.368	153.372	124.19	149.083	13.902
AUC(0-∞)	mg/L*h	195.403	180.892	167.228	165.938	162.717	141.446	168.937	18.164
AUMC(0-t)		3077.564	2853.145	2710.636	2735.33	2480.979	2298.911	2692.761	274.189
AUMC(0-∞)		5204.394	5068.979	3851.589	3943.469	3090.109	3567.729	4121.045	842.063
MRT(0-t)	h	18.435	18.773	18.114	18.436	16.176	18.511	18.074	0.953
MRT(0-∞)	h	26.634	28.022	23.032	23.765	18.991	25.223	24.278	3.17
VRT(0-t)	h^2	127.244	129.339	122.728	118.313	106.719	115.938	120.047	8.281
VRT(0-∞)	h^2	611.301	694.674	371.9	398.47	247.288	511.324	472.493	165.2
t1/2z	h	18.691	20.032	13.511	14.844	11.874	17.975	16.155	3.219
Tmax	h	12	12	12	8	6	12	10.333	2.658
CLz/F	L/h/kg	0.409	0.442	0.478	0.482	0.492	0.566	0.478	0.053
Vz/F	L/kg	11.042	12.784	9.327	10.327	8.424	14.671	11.096	2.302
Zeta		0.037	0.035	0.051	0.047	0.058	0.039	0.045	0.009
Zeta Regression End Point		145	145	123	134	145	145	--	--
Cz (Regression Value at Terminal Point)	mg/L	1.055	1	0.902	0.82	0.545	0.665	0.831	0.197
Cmax	mg/L	5.842302368	5.016251365	5.281971228	4.871102706	6.418503253	4.178671833	5.268	0.782

Table S2.3: Observed Concentration-Time Data.

t	No1	No2	No3	No4	No5	No6	Mean	SD
0.1666	0.45947210	0.46831517	0.47246745	0.46303444	0.46048351	0.45461280	0.463	0.006

7	4		8	9	4	8		
0.3	0.570686478	0.538836862	0.596892145	0.757762354	0.694390829	0.551514284	0.618	0.088
0.5	1.329243813	1.159708173	1.194477653	1.384905862	2.13936309	1.295112739	1.417	0.364
1	0.895254059	0.798994445	0.900168194	0.855272746	1.184555975	0.704798458	0.89	0.162
1.5	2.568188056	1.550677728	1.906249479	1.710033417	2.789254321	1.604198477	2.021	0.528
2	1.77288657	2.233404494	1.607021488	2.274398791	2.821641533	1.626612344	2.056	0.476
3	3.266155859	2.92623272	2.930902127	2.335237714	4.30718773	2.155460471	2.987	0.767
4	3.715375994	3.733419375	3.460059869	3.273945939	5.137572109	2.745079822	3.678	0.802
6	4.69548449	3.992547431	4.143422589	3.627889805	6.418503253	3.004973358	4.314	1.174
8	4.9745847	4.289452524	4.932148071	4.871102706	5.548127807	3.495538493	4.685	0.707
12	5.842302368	5.016251365	5.281971228	4.845622121	5.225446244	4.178671833	5.065	0.55
24	3.929927857	3.727460347	3.476812325	3.726065068	3.249285731	3.170231398	3.547	0.299
48	1.05180802	0.99675489	0.867009485	0.812476537	0.545804702	0.661577126	0.823	0.194

Table S2.4: Measured ln c-t data.

t	No1	No2	No3	No4	No5	No6	Mean	SD
0.16667	0.459472104	0.468315177	0.472467458	0.463034449	0.460483514	0.454612808	0.463	0.006
0.3	0.570686478	0.538836862	0.596892145	0.757762354	0.694390829	0.551514284	0.618	0.088
0.5	1.329243813	1.159708173	1.194477653	1.384905862	2.139363099	1.295112739	1.417	0.364
1	0.895254059	0.798994445	0.900168194	0.855272746	1.184555975	0.704798458	0.89	0.162
1.5	2.568188056	1.550677728	1.906249479	1.710033417	2.789254321	1.604198477	2.021	0.528
2	1.772886577	2.233404494	1.607021488	2.274398791	2.821641533	1.626612344	2.056	0.476
3	3.266155859	2.926232722	2.930902127	2.335237714	4.307187733	2.155460471	2.987	0.767
4	3.715375994	3.733419375	3.460059869	3.273945939	5.137572109	2.745079822	3.678	0.802

6	4.69548449	3.992547431	4.143422589	3.627889805	6.418503253	3.004973358	4.314	1.174
8	4.9745847	4.289452524	4.932148071	4.871102706	5.548127807	3.495538493	4.685	0.707
12	5.842302368	5.016251365	5.281971228	4.845622121	5.225446244	4.178671833	5.065	0.55
24	3.929927857	3.727460347	3.476812325	3.726065068	3.249285731	3.170231398	3.547	0.299
48	1.05180802	0.99675489	0.867009485	0.812476537	0.545804702	0.661577126	0.823	0.194

NOTE: Please save this file locally before filling in the table, DO NOT work on the file within your internet browser as changes will not be saved. Adobe Acrobat Reader (available free here) is recommended for completion.

The ARRIVE guidelines 2.0: author checklist

The ARRIVE Essential 10

These items are the basic minimum to include in a manuscript. Without this information, readers and reviewers cannot assess the reliability of the findings.

Item		Recommendation	Section/line number, or reason for not reporting
Study design	1	For each experiment, provide brief details of study design including: a. The groups being compared, including control groups. If no control group has been used, the rationale should be stated. b. The experimental unit (e.g. a single animal, litter, or cage of animals).	Animal experiment.P1 Cage of animals, 6 rats per group.
Sample size	2	a. Specify the exact number of experimental units allocated to each group, and the total number in each experiment. Also indicate the total number of animals used. b. Explain how the sample size was decided. Provide details of any *a priori* sample size calculation, if done.	12 rats.P3 Animal experiment.P3
Inclusion and exclusion criteria	3	a. Describe any criteria used for including and excluding animals (or experimental units) during the experiment, and data points during the analysis. Specify if these criteria were established *a priori.* If no criteria were set, state this explicitly. b. For each experimental group, report any animals, experimental units or data points not included in the analysis and explain why. If there were no exclusions, state so. c. For each analysis, report the exact value of *n* in each experimental group.	Animal experiment The 48-hour doxofylline concentration monitoring time point. The number of samples tested in the LC-MS/MS condition optimization experiment was n = 3.P2
Randomisation	4	a. State whether randomisation was used to allocate experimental units to control and treatment groups. If done, provide the method used to generate the randomisation sequence. b. Describe the strategy used to minimise potential confounders such as the order of treatments and measurements, or animal/cage location. If confounders were not controlled, state this explicitly.	Generate a random sequence and divide 12 numbered animals into two groups of six. The order in which animals are selected for blood collection at each time point is randomly determined rather than based on a fixed sequence of cage numbers or groups.
Blinding	5	Describe who was aware of the group allocation at the different stages of the experiment (during the allocation, the conduct of the experiment, the outcome assessment, and the data analysis).	The randomization planners and drug preparers have been fully informed.
Outcome measures	6	a. Clearly define all outcome measures assessed (e.g. cell death, molecular markers, or behavioural changes). b. For hypothesis-testing studies, specify the primary outcome measure, i.e. the outcome measure that was used to determine the sample size.	After plasma collection. Table 3:AUC and Cmax are two key parameters.P7-8.
Statistical methods	7	a. Provide details of the statistical methods used for each analysis, including software used. b. Describe any methods used to assess whether the data met the assumptions of the statistical approach, and what was done if the assumptions were not met.	Section: Pharmacokinetic and statistical evaluation. P3-4. The pharmacokinetic experiment requires that the data meet three core assumptions: independence, normality, and homogeneity of variance.
Experimental animals	8	a. Provide species-appropriate details of the animals used, including species, strain and substrain, sex, age or developmental stage, and, if relevant, weight. b. Provide further relevant information on the provenance of animals, health/immune status, genetic modification status, genotype, and any previous procedures.	Section: Animal experiment, 1st paragraph.P3. Sprague-Dawley rats, health.P3.
Experimental procedures	9	For each experimental group, including controls, describe the procedures in enough detail to allow others to replicate them, including: a. What was done, how it was done and what was used. b. When and how often. c. Where (including detail of any acclimatisation periods). d. Why (provide rationale for procedures).	Animal experiment, 2nd paragraph. P3. The experiment began on June 1st,2025. School of pharmacy, Yantai university. Investigate the influence of EVO on the PKs of DFL and TPL to provide valuable evidence for clinical decision-making.
Results	10	For each experiment conducted, including independent replications, report: a. Summary/descriptive statistics for each experimental group, with a measure of variability where applicable (e.g. mean and SD, or median and range). b. If applicable, the effect size with a confidence interval.	Table 1-3. The pharmacokinetic parameters do not follow a normal distribution or have unequal variances.

The Recommended Set

These items complement the Essential 10 and add important context to the study. Reporting the items in both sets represents best practice.

Item		Recommendation	Section/line number, or reason for not reporting
Abstract	11	Provide an accurate summary of the research objectives, animal species, strain and sex, key methods, principal findings, and study conclusions.	Abstract
Background	12	a. Include sufficient scientific background to understand the rationale and context for the study, and explain the experimental approach. b. Explain how the animal species and model used address the scientific objectives and, where appropriate, the relevance to human biology.	Introduction, 1st paragraph. SD rats were selected for this experiment primarily because of their similarity to humans in terms of drug metabolism characteristics. As a widely recognized mammalian model, the CYP450 enzyme system in SD rats is highly homologous to that of hum
Objectives	13	Clearly describe the research question, research objectives and, where appropriate, specific hypotheses being tested.	Introduction,5th paragraph.
Ethical statement	14	Provide the name of the ethical review committee or equivalent that has approved the use of animals in this study, and any relevant licence or protocol numbers (if applicable). If ethical approval was not sought or granted, provide a justification.	Animal Ethics and Welfare Committee of Yantai University (No. 20250516).
Housing and husbandry	15	Provide details of housing and husbandry conditions, including any environmental enrichment.	Animal experiment, 1st paragraph.
Animal care and monitoring	16	a. Describe any interventions or steps taken in the experimental protocols to reduce pain, suffering and distress. b. Report any expected or unexpected adverse events. c. Describe the humane endpoints established for the study, the signs that were monitored and the frequency of monitoring. If the study did not have humane endpoints, state this.	dose routine. The number of blood draws per animal and the total blood volume collected were strictly controlled, not exceeding 10% of the total blood volume. At the conclusion of the experiment, the animals were euthanised with an overdose of sodium pentobarbital. Administering the drug via gastric lavage may cause gastrointestinal irritation, resulting in loose stools. Using evodiamine may also result in transient elevations in liver enzymes. No unexpected adverse events were observed in this study. The following humanitarian endpoints were established in this study: weight loss exceeding 20%, severe neurological symptoms, and respiratory distress. Vital signs were monitored daily, with more frequent monitoring during the dosing period.
Interpretation/ scientific implications	17	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including potential sources of bias, limitations of the animal model, and imprecision associated with the results.	Discussion,2-5 paragraphs. The study is preclinical in nature and does not address the underlying inflammatory mechanisms.
Generalisability/ translation	18	Comment on whether, and how, the findings of this study are likely to generalise to other species or experimental conditions, including any relevance to human biology (where appropriate).	This study has several limitations. It was based on a rodent model, limiting translational applicability to humans. The observed herb-drug interactions between EVO and DFL require further clinical validation. Additionally, as a preclinical investigation, it did not address the underlying inflammatory mechanisms.
Protocol registration	19	Provide a statement indicating whether a protocol (including the research question, key design features, and analysis plan) was prepared before the study, and if and where this protocol was registered.	A protocol containing the research question, key design features, and analysis plan was established before the study but was not publicly registered. The animal experiments were approved by the Animal Experiment Ethics Committee of Yantai University (No. 20250516), and all procedures adhered to the university's Animal Ethics and Welfare Committee standards.
Data access	20	Provide a statement describing if and where study data are available.	responding author on reasonable request.
Declaration of interests	21	a. Declare any potential conflicts of interest, including financial and non-financial. If none exist, this should be stated. b. List all funding sources (including grant identifier) and the role of the funder(s) in the design, analysis and reporting of the study.	The authors declared that they have no conflict of interest. n Health Management (2024JGYQ08) and Science and Technology Plan Project of Wenzhou (Grant No. Y2023188). The funders played no role in the study design, data analysis, interpretation, or manuscript preparation.