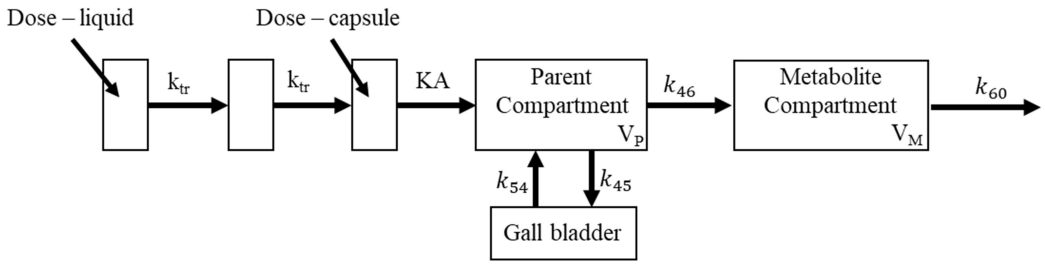

Figure 1: Structure of the 13-CRA parent-metabolite model

Visual Predictive Check

The VPC of the final model was stratified according to the formulations for 13-CRA and according to day for 4-oxo-13-CRA (Figure 2). The VPC plots show that the model is able to explain both the central tendency and variability in the PK observations for 13-CRA, for both the new liquid and reference capsule-extracted 13-CRA. The VPC also demonstrate that the model is able to adequately explain the 4-oxo-13-CRA data on day 1, however there is a slight overestimation of the 95th percentile of 4-oxo-13-CRA data. The extent of the overestimation is small and is not considered to invalidate the model. Nevertheless, caution should be used when simulating steady-state profiles for 4-oxo-13-CRA.

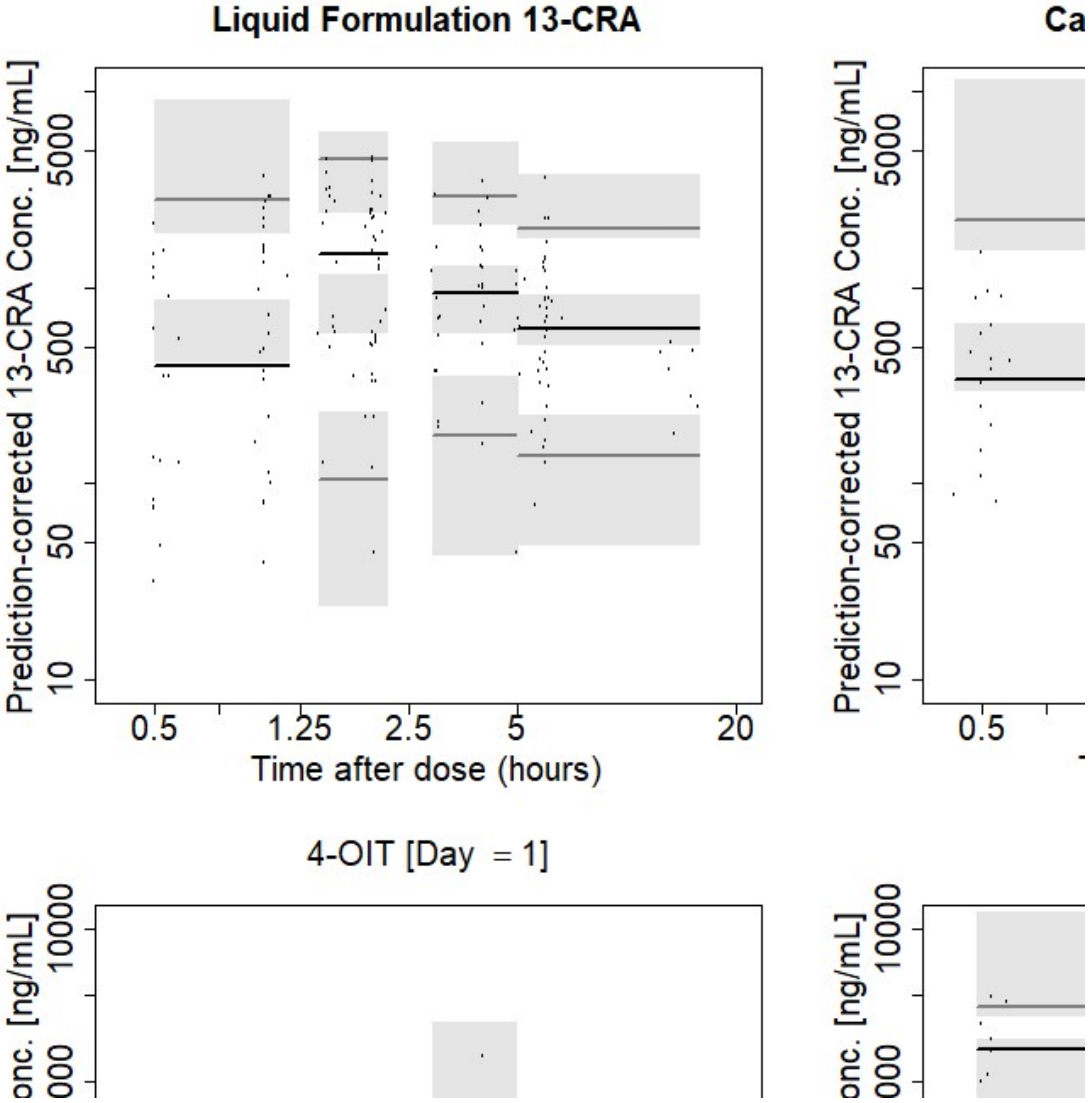

Figure 2 : VPC plots for liquid and capsule: 13-CRA (upper panel) and 4-oxo-13-CRA (lower panel). The VPC plot shows grey and black horizontal lines depicting the 5th, 50th and 95th percentiles of the prediction-corrected observed data in each bin, along with shaded regions depicting the limits of the 90% confidence intervals around the 5th, 50th and 95th percentiles of the prediction-corrected simulated data.

Table 1: Model Parameters

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
k_{tr}	h^{-1}	9.23	27.002	4.345	14.115	Transit compartment rate constant for typical patient administered liquid formulation
KA	h^{-1}	0.249	63.606	-0.061	0.559	Absorption rate constant for typical patient
$^1CL_P^{pop}$	L/h	9.74	30.294	3.957	15.523	Clearance of 13-CRA for a typical patient
$^1V_P^{pop}$	L	41.15	--	--	--	Volume of distribution of 13-CRA for a typical patient
$^1CL_M^{pop}$	L/h	2.66	56.809	-0.302	5.622	Clearance of 4-OIT for a typical patient
$^1V_M^{pop}$	L	30.3	29.658	12.686	47.914	Volume of distribution of 4-OIT for a typical patient
F1		1.65	4.204	1.514	1.786	Relative bioavailability of liquid formulation with respect to the extracted capsule
k_{45}	h^{-1}	0.1047	--	--	--	Rate constant governing simplified enterohepatic recycling model
k_{54}	h^{-1}	0.05652	--	--	--	Rate constant governing simplified enterohepatic recycling model
Random effects: Inter-individual variability (OMEGA) diagonal elements						
V_P (ω^2)	-	1.6	166.231	-3.613	6.813	Inter-individual variability on V_P
V_P $(CV)^2$	%	198.82				
V_P $(Sh)^3$	%	4.87				
CL_P (ω^2)	-	0.141	110.279	-0.164	0.446	Inter-individual variability on CL_P
CL_P $(CV)^2$	%	38.91				
CL_P $(Sh)^3$	%	5.25				
CL_M (ω^2)	-	0.392	106.415	-0.426	1.21	Inter-individual variability on CL_M
CL_M $(CV)^2$	%	69.28				
CL_M $(Sh)^3$	%	5.16				
Random effects: Inter-individual variability (OMEGA) off-diagonal elements						
V_P and CL_P (ω^2)	-	0.346	175.242	-0.842	1.534	
V_P and CL_M (ω^2)	-	0.517	189.908	-1.407	2.441	
CL_P and CL_M (ω^2)	-	0.23	103.901	-0.238	0.698	
Residual error (SIGMA)						
Err_{parent} (σ^2)	-	0.39	17.521	0.256	0.524	Variance of exponential residual error for 13-CRA.
Err_{parent} $(CV)^4$	%	69.06		54.01	82.99	
Err_{parent} (σ^2)	-	46656	19.44	17875.4226	88983.4866	Variance of additive[6] residual error for 13-CRA.
Err_{parent} $(CV)^5$	%	21.6		13.37	29.83	
$Err_{metabolite}$ at Day=1 (σ^2)	-	0.793	14.386	0.569	1.017	Variance of exponential residual error for 4-OIT on day 1
$Err_{metabolite}$ at Day=1 $(CV)^4$	%	110		87.55	132.85	
$Err_{metabolite}$ at Day=14 (σ^2)	-	0.139	21.206	0.081	0.197	Variance of exponential residual error for 4-OIT on day $\geq$ 14

$Err_{metabolite}$ at Day=14 (CV)[4]	%	38.62		29.05	46.66	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[1] Apparent PK parameter, equivalent to CL_{pop}/F and V/F, where F is the absolute bioavailability of the capsule formulation.
[2] The coefficient of variation (CV) is calculated as 100·SQRT(EXP(OMEGA^2)-1)
[3] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
[4] The coefficient of variation (CV) is calculated as 100·SQRT(EXP(OMEGA^2)-1)
[5]The coefficient of variation (CV) is calculated as 100·SQRT(SIGMA^2)/1000, which is the CV for an observation of 1000 ng/mL.
[6]This parameterization of the residual error model approximates an additive structure on the untransformed scale.

k_{tr}, transit compartment rate constant, KA, absorption rate constant; V_p and V_M volume of distribution for the central compartments of the parent (13-CRA) and the metabolite (4-OIT), respectively; k_{45} and k_{54}, are the rate constants between central and peripheral compartments for the parent; k_{46} and k_{60}, are the elimination rate constants for the parent and the metabolite; CL_P and CL_M, respectively are the clearance for the parent and the metabolite while CL_P^{pop}, CL_M^{pop}, V_P^{pop} and V_M^{pop}, respectively are the estimated clearance and volume of distribution for a typical patient.