Delineating the Complex Interplay of Enzymes and Transporters Governing the Absorption and Disposition of Atorvastatin and the Metabolites Using Physiologically Based Pharmacokinetic (PBPK) Modeling

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ABSTRACT

Atorvastatin (ATS) is widely used to treat high cholesterol and potentially lower the risk of cardiac complications. Absorption and disposition of atorvastatin and the metabolites 2-hydroxy atorvastatin (2-OH ATS), 4-hydroxy atorvastatin (4-OH ATS) and atorvastatin lactone (AL) is governed by complex interplay of multiple enzymes and transporters.

OBJECTIVES

i. To develop a mechanistic physiologically based pharmacokinetic (PBPK) model delineating the role of enzymes and transporters in the absorption and disposition of atorvastatin, using a middle-out approach by incorporating the *in vitro* and *in vivo* data representing all the key mechanisms that reproduced the observed clinical data of atorvastatin and the metabolites 2-OH ATS, 4-OH ATS and AL across the dose range of 10-80 mg.

ii. To verify the role of individual enzymes and transporters by using drug-drug interaction (DDI) studies with rifampicin, gemfibrozil and itraconazole.

iii. To verify the observed food effect.

METHODS

PBPK modeling: PBPK modeling was performed using simulation software GastroPlus Ver. 9.8.2.

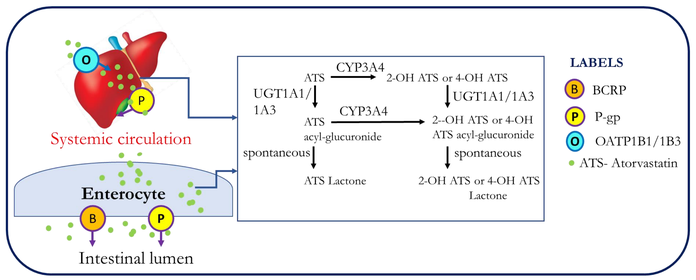

Figure 1: Schematic View of Enzymes and Transporters Involved in Absorption and Disposition of Atorvastatin in Human Body

Table 1: Input Parameters used for Atorvastatin PBPK Model Development

Parameter	Value	Reference
Molecular weight	558.64	PubChem
LogP	4.1	(Poli 2007) (Gertz et al. 2011)
Ionisation constant (pKa)	11.05 (acid); 4.46 (acid)	(Gertz et al. 2011)
Human Jejunal P_{eff} ($\times 10^{-4}$ cm/s)	3.97	(Human jejunal P_{eff} value is estimated from $P_{app(A-B)}$ data in Caco2) (Wu et al. 2000)
Blood Plasma concentration ratio ($R_{b/p}$)	0.55	(Morse et al. 2019)
Fraction unbound in plasma (F_{up}) %	2.0	CPBR-FDA-1996
Enzyme-mediated kinetics		
CYP3A4 (Formation of 2-OH AA)		
K_m (µM)	29.7	(Jacobsen et al. 2000)
V_{max} (pmol/min/pmol of isoform)	14.7	Optimized value
CYP3A4 (Formation of 4-OH AA)		
K_m (µM)	25.6	(Jacobsen et al. 2000)
V_{max} (pmol/min/pmol of isoform)	3.0	Optimized value
UGT1A1(Formation of AL)		
K_m (µM)	2	(Schirris et al. 2015)
V_{max} (pmol/sec/mg protein)	0.15	Optimized value
UGT1A3 (Formation of AL)		
K_m (µM)	4	(Schirris et al. 2015)
V_{max} (pmol/sec/mg protein)	0.3	Optimized value

Parameter	Value	Reference
Transporter-mediated kinetics		
OATP1B1(liver-basolateral)		
Km (µM)	0.77	(Karlgren et al. 2012)
Vmax (mg/s)	0.1	Optimized value
OATP1B3 (liver-basolateral)		
Km (µM)	0.73	(Karlgren et al. 2012)
Vmax (mg/s)	0.1	Optimized value
P-gp		
Km (µM)	10.7	(Deng et al. 2021)
Vmax (mg/s) (gut-apical)	0.01	Optimized value
Vmax (mg/s) (liver-apical)	0.005	Optimized value
BCRP (gut-apical)		
Km (µM)	82.4	(Deng et al. 2021)
Vmax (mg/s)	0.05	Optimized value
Renal Clearance	Fup*GFR	Assumed value (since renal elimination is <1%)
CL_{PD} (mL/min/million cells)	0.02	(Zhang 2015)

RESULTS

PBPK Model Development and Verification of Atorvastatin and Its Metabolites

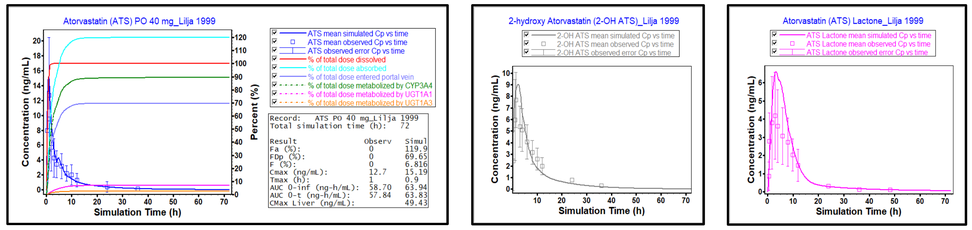

Figure 2: Cp-time Profile for a 40 mg Oral Dose of Atorvastatin in Healthy Subjects Under Fasting Conditions

Simulated blue line (—) and observed blue squares (■) of atorvastatin (A), simulated grey line (—) and observed grey squares (■) of 2-hydroxy atorvastatin (B), and simulated pink line (—) and observed pink squares (■) of atorvastatin lactone (C) (Lilja et al. 1999). The plot also displays simulated total amount of dose dissolved (red), absorbed (blue), entered portal vein (purple), metabolized by CYP3A4 (green), UGT1A1 (pink), and UGT1A3 (orange) are shown as a percent of total administered dose (A).

Model Verification: Comparison of Predicted vs. Observed PK Data of Atorvastatin and Its Metabolites

Reference	Dose (mg)	Condition	PK Parameter	Observed#	Simulated	Sim/Obs Ratio
(Lilja et al. 1999)	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	12.7 ± 7.8	15.2	**1.2**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	61.4 ± 36.2	63.9	**1.04**
(Nagard et al. 2021)	10 mg, IR tablet	Fasted	C_{max} (ng/mL)	2.0	2.01	**1.01**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	11.0	12.3	**1.12**
(Fukazawa et al. 2004)	10 mg, IR tablet	Fasted	C_{max} (ng/mL)	4.6 (3.2-6.6)	3.85	**0.84**
			$AUC_{(0\text{-}48)}$ (ng.hr/mL)	19.0 (12.6-28.6)	19.2	**1.01**
(Backman et al. 2005)	20 mg, IR tablet	Fasted	C_{max} (ng/mL)	8.2	7.05	**0.86**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	35.2	31.5	**0.89**
(McKeand et al. 2018)	20 mg, IR tablet	Fasted	C_{max} (ng/mL)	7.8 (3.7-18.9)	8.33	**1.07**
			$AUC_{(0\text{-}24)}$ (ng.hr/mL)	36 (19-96)	32.1	**0.89**
(Shin et al. 2011)	20 mg, IR tablet	Fasted	C_{max} (ng/mL)	5 (3.0-13.9)	6.7	**1.33**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	38.6 (31.9-51.6)	29.8	**0.77**
(Khalilieh et al. 2017)	20 mg, IR tablet	Fasted	C_{max} (ng/mL)	7.87	6.9	**0.88**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	39.9	30.5	**0.76**
(Dingemanse et al. 2014)	20 mg, IR tablet	Fasted	C_{max} (ng/mL)	4.2	6.43	**1.53**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	35.07	29.2	**0.83**
(Malm-Erjefalt et al. 2015)	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	12.1 (3.1–51.1)	16.9	**1.4**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	61.6(22.1–158.4)	63.2	**1.03**
(Whitfield et al. 2011)	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	16.7	17.04	**1.02**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	62.8	64.4	**1.03**
(Backman et al. 2005)	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	15.8 ± 5.4	15.1	**0.96**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	64.0 ± 21.3	64.4	**1.01**
(Bullman et al. 2011)	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	14.3	14.3	**1.0**
			$AUC_{(0\text{-}24)}$ (ng.hr/mL)	62	56.5	**0.91**
	40 mg, IR tablet	Fasted	C_{max} (ng/mL)	12.1	14.2	**1.17**
			$AUC_{(0\text{-}24)}$ (ng.hr/mL)	63.4	56.2	**0.89**
(Machado et al. 2014)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	27.1	22.1	**0.82**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	146.8	128.9	**0.88**
(Chung et al. 2006)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	29.5	35	**1.19**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	167	135.3	**0.81**
Lipitor (ANDA-Ranbaxy)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	33.2	36	**1.08**
			$AUC_{(0\text{-}96)}$ (ng.hr/mL)	131.1	139.4	**1.06**
Lipitor (ANDA-Apotex)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	35.8	36	**1.01**
			$AUC_{(0\text{-}48)}$ (ng.hr/mL)	158.5	139.2	**0.88**
Lipitor (ANDA-Sandoz)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	35.5	35	**0.99**
			$AUC_{(0\text{-}60)}$ (ng.hr/mL)	139	137.3	**0.99**

Reference	Metabolite	PK Parameter	Observed#	Simulated	Sim/Obs Ratio
(Lilja et al. 1999)	2-OH atorvastatin	C_{max} (ng/mL)	7.7 ± 2.4	9.05	**1.18**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	77.5 ± 24	70.5	**0.91**
	atorvastatin lactone	C_{max} (ng/mL)	4.2 ± 2.4	6.6	**1.57**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	53 ± 27.3	64.6	**1.22**
(Nagard et al. 2021)	2-OH atorvastatin	C_{max} (ng/mL)	1.8	2.05	**1.14**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	23.5	17.4	**0.74**
(McKeand et al. 2018)	2-OH atorvastatin	C_{max} (ng/mL)	4.0 (1.6-9.2)	5.25	**1.3**
		$AUC_{(0\text{-}24)}$ (ng.hr/mL)	39 (19-79)	38	**0.97**
(Dingemanse et al. 2014)	2-OH atorvastatin	C_{max} (ng/mL)	3.02	4.15	**1.37**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	43	33.1	**0.77**
(Whitfield et al. 2011)	2-OH atorvastatin	C_{max} (ng/mL)	12.3	9.9	**0.81**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	86.8	71.6	**0.82**
	atorvastatin lactone	C_{max} (ng/mL)	4.2	6.4	**1.52**
		$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	50.7	60.9	**1.2**
(Bullman et al. 2011)	2-OH atorvastatin	C_{max} (ng/mL)	10.3 (9-11.7)	8.6	**0.84**
		$AUC_{(0\text{-}24)}$ (ng.hr/mL)	75 (67-83.6)	62.2	**0.83**
	2-OH atorvastatin	C_{max} (ng/mL)	10.5 (9-12)	8.6	**0.82**
		$AUC_{(0\text{-}24)}$ (ng.hr/mL)	85.2 (75-97)	62.4	**0.73**
Lipitor (ANDA-Ranbaxy)	2-OH atorvastatin	C_{max} (ng/mL)	29.9	17	**0.57**
		$AUC_{(0\text{-}96)}$ (ng.hr/mL)	168.6	137.3	**0.81**
	4-OH atorvastatin	C_{max} (ng/mL)	0.93	1.7	**1.9**
		$AUC_{(0\text{-}96)}$ (ng.hr/mL)	19.2	18.1	**0.94**
Lipitor (ANDA-Apotex)	2-OH atorvastatin	C_{max} (ng/mL)	28.5	17	**0.6**
		$AUC_{(0\text{-}48)}$ (ng.hr/mL)	173.3	132.7	**0.77**
	4-OH atorvastatin	C_{max} (ng/mL)	0.98	1.69	**1.7**
		$AUC_{(0\text{-}48)}$ (ng.hr/mL)	16.7	17.5	**1.05**
Lipitor (ANDA-Sandoz)	2-OH atorvastatin	C_{max} (ng/mL)	25.3	17	**0.7**
		$AUC_{(0\text{-}60)}$ (ng.hr/mL)	150.1	133	**0.9**
	4-OH atorvastatin	C_{max} (ng/mL)	0.9	1.67	**1.9**
		$AUC_{(0\text{-}60)}$ (ng.hr/mL)	16.2	17.5	**1.1**

IR = Immediate release #Observed represent values from the average of individual values and represent mean ± SD and the range enclosed in brackets, as specified in the summary of tabulated PK parameters in the respective publications.

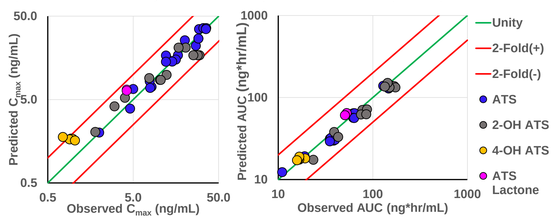

Figure 3: Observed vs Predicted Values for C_{max} and AUC of Atorvastatin and Its Metabolites

Model Verification: Food Effect

Reference	Dose (mg)	Condition	PK Parameter	Observed#	Simulated	Sim/Obs Ratio
Lipitor (ANDA-Ranbaxy)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	33.2	36	**1.08**
			$AUC_{(0\text{-}96)}$(ng.hr/mL)	131.1	139.4	**1.06**
		Fed	C_{max} (ng/mL)	29.03	27	**0.93**
			$AUC_{(0\text{-}96)}$(ng.hr/mL)	128.9	138.7	**1.08**
Lipitor (ANDA-Apotex)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	35.8	36	**1.01**
			$AUC_{(0\text{-}48)}$ (ng.hr/mL)	158.5	139.2	**0.88**
		Fed	C_{max} (ng/mL)	29.02	27	**0.92**
			$AUC_{(0\text{-}48)}$ (ng.hr/mL)	146.6	129.6	**0.88**
(Chung et al. 2006)	80 mg, IR tablet	Fasted	C_{max} (ng/mL)	29.5	35	**1.19**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	167	135.3	**0.81**
		Fed	C_{max} (ng/mL)	20.1	25.7	**1.28**
			$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	148	133.8	**0.9**

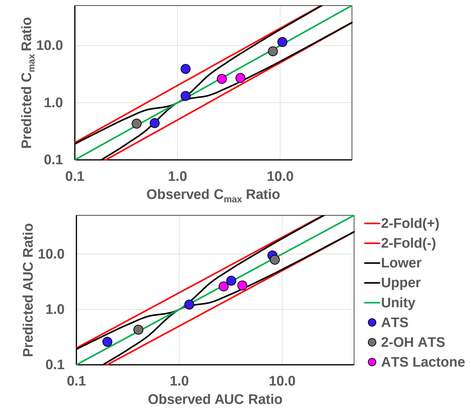

Figure 4: Observed vs Predicted DDI Ratios for C_{max} and AUC of Atorvastatin and Its Metabolites 2-OH ATS and ATS Lactone with Rifampicin, Itraconazole and Gemfibrozil

Circles represent the DDI ratios for C_{max} and $AUC_{0\text{-}t}$ respectively Blue (●) ATS, Grey (●) 2-OH ATS, and Pink (●) ATS Lactone. Red lines (—) represent 2-fold prediction error, and black lines (—) represent fold prediction error per Guest's criteria.

CONCLUSION

- Overall, our mechanistic model well captured the observed plasma profiles of 10 mg, 20 mg, 40 mg, and 80 mg doses and the predicted values for C_{max} and AUC were mostly within Bioequivalence (BE) limits (0.8 – 1.25-fold) of observed data for atorvastatin and within 2-fold for its metabolites.
- Food moderately affected the C_{max} (~10-25% reduction) by delaying the gastric emptying but had minimal effect on AUC.
- The simulated DDI ratios of C_{max} and AUCs for ATS and its metabolites with rifampicin and gemfibrozil are in excellent agreement with the observed data.
- In the DDI study with itraconazole, the simulated DDI ratio of AUC was well predicted, however for the C_{max} the simulated DDI ratio did not fall within the Guest limits.

REFERENCES

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