A Mechanistic Framework for In Vitro – In Vivo Extrapolation of Liver Membrane Transporters: Prediction of Drug-Drug Interaction between Rosuvastatin and Cyclosporine.

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Supplementary Materials 2

Simulated versus observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 10, 20, 40 and 80 mg, respectively.

Table S1 – Details of the single dose clinical studies used for Rosuvastatin performance verification

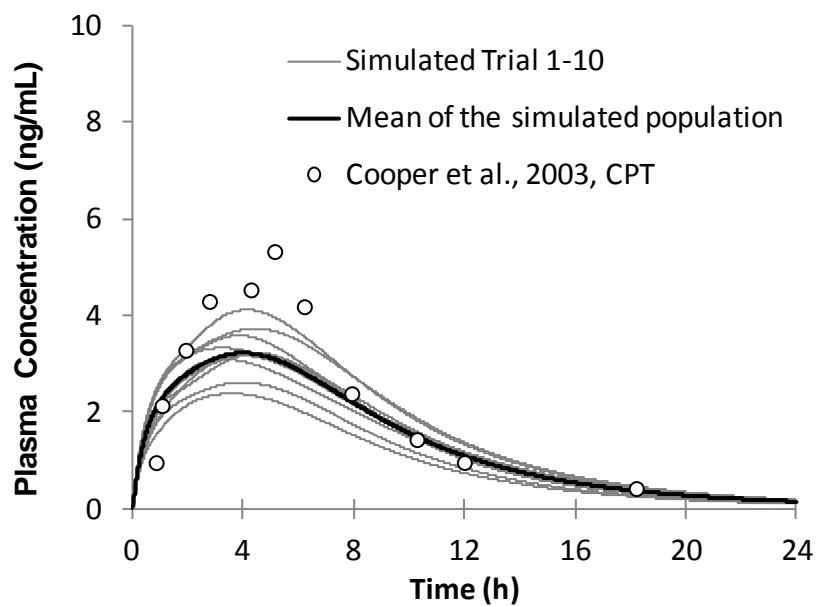| PK Study	Dose [mg]	Age range [years]	n	% female	Reference
1	10	22-42	11	0	[1]
2	10	31-60	18	0	[2]
3	20	31-60	9	0	[2]
4	40	31-60	9	0	[2]
5	40	21-51	10	0	[3]
6	40	21-39	36	13.9	[4]
7	80	22-44	11	0	[5]
8	80	25-56	14	0	[1]
9	80	29-51	14	0	[6]
10	80	31-60	18	0	[2]
11	80	35-47	20	15	[7]

Fig. S1 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 10 mg. The grey thin lines represent simulated individual trials (10) of 11 male subjects (22-42 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=110). The circles denote mean values from the clinical study by Cooper *et al.* 2003 [1].
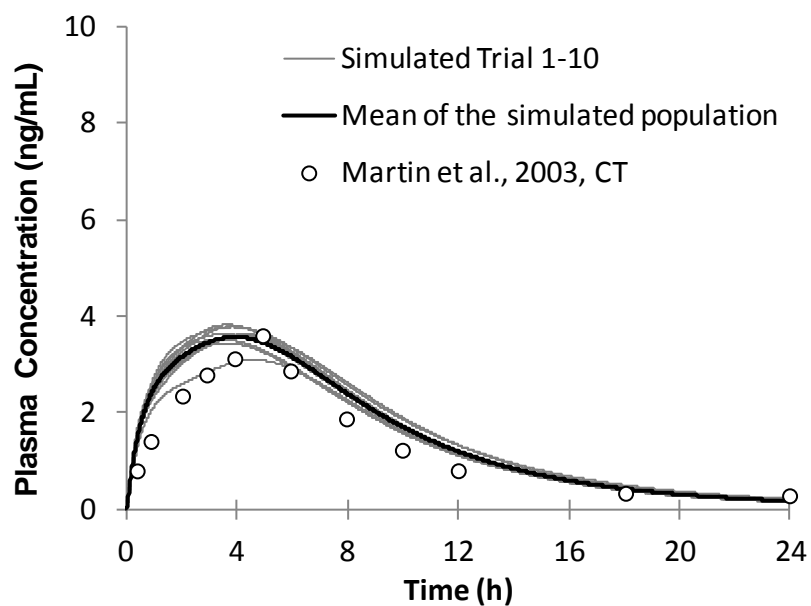
Fig. S2 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 10 mg. The grey thin lines represent simulated individual trials (10) of 18 male subjects (31-60 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=180). The circles denote mean values from the clinical study by Martin *et al*. 2003 [2].
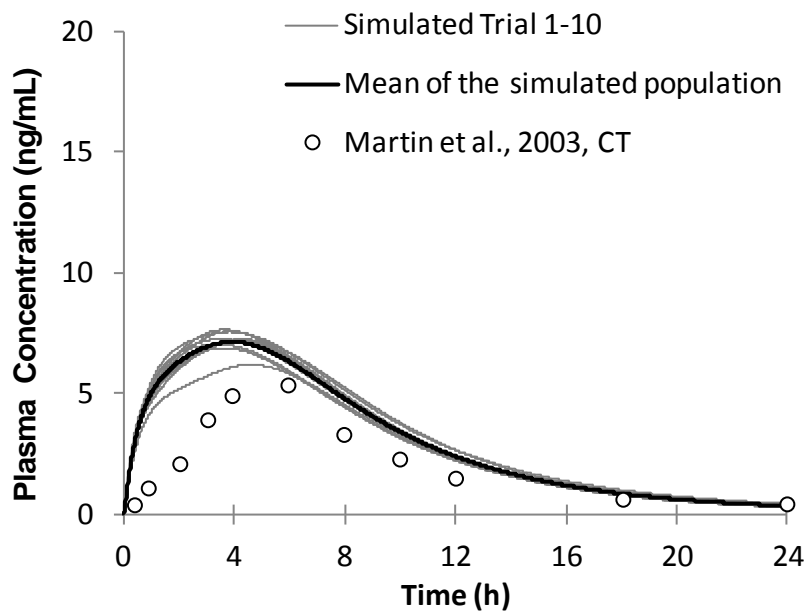
Fig. S3 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 20 mg. The grey thin lines represent simulated individual trials (10) of 9 male subjects (31-60 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=90). The circles denote mean values from the clinical study by Martin *et al*. 2003 [2].
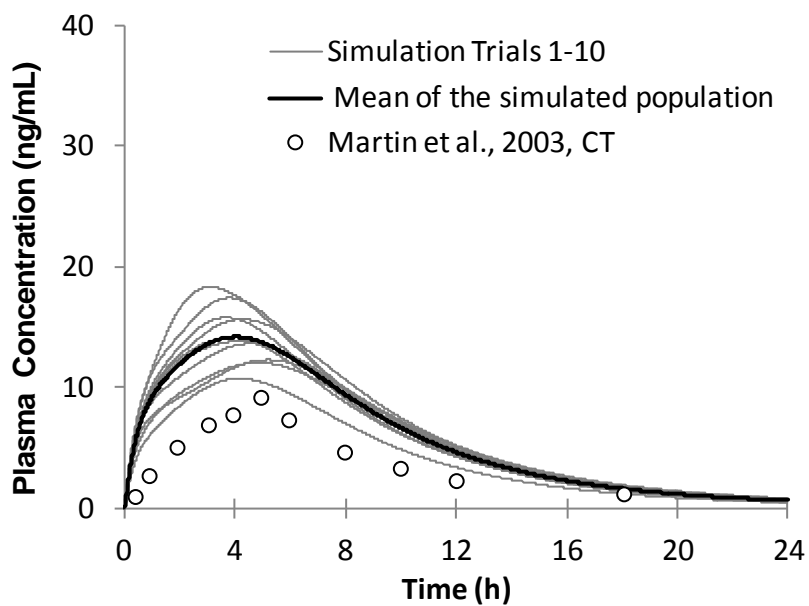
Fig. S4 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 40 mg. The grey thin lines represent simulated individual trials (10) of 9 male subjects (31-60 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=90). The circles denote mean values from the clinical study by Martin *et al.* 2003 [2].
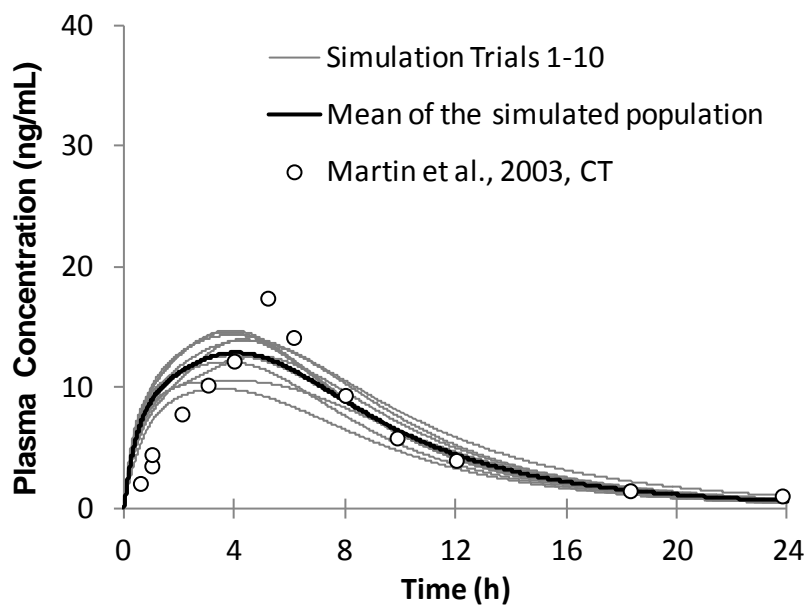
Fig. S5 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 40 mg. The grey thin lines represent simulated individual trials (10) of 10 male subjects (21-51 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=100). The circles denote mean values from the clinical study by Martin *et al*. 2003 [3].
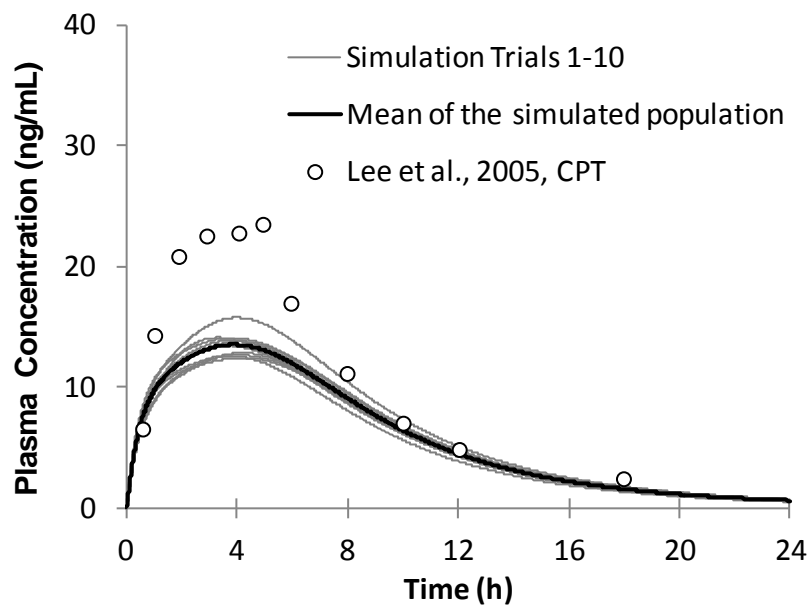
Fig. S6 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 40 mg. The grey thin lines represent simulated individual trials (10) of 36 subjects (0.139% female, 21-39 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=360). The circles denote mean values from the clinical study by Lee *et al*. 2005 [4].
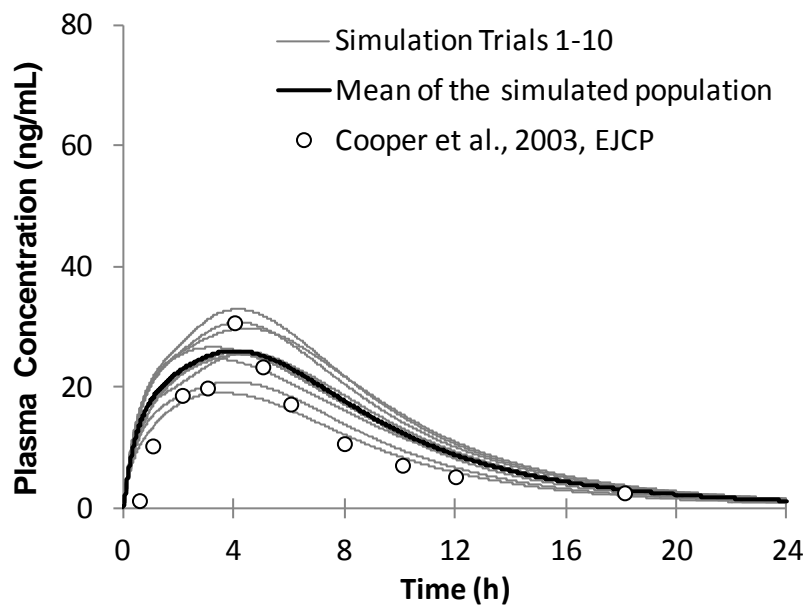
Fig. S7 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 80 mg. The grey thin lines represent simulated individual trials (10) of 11 male subjects (22-44 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=110). The circles denote mean values from the clinical study by Cooper *et al*. 2003 [5].
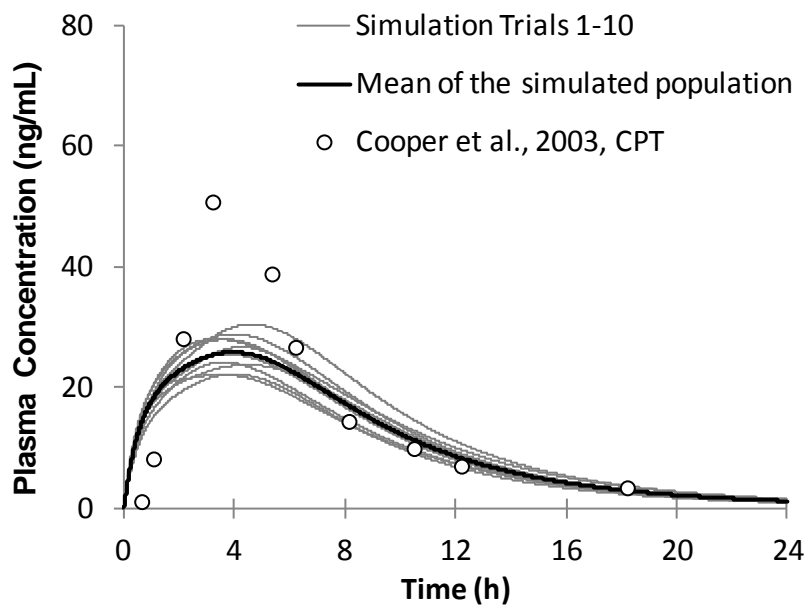
Fig. S8 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 80 mg. The grey thin lines represent simulated individual trials (10) of 14 male subjects (25-56 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=140). The circles denote mean values from the clinical study by Cooper *et al.* 2003 [1].
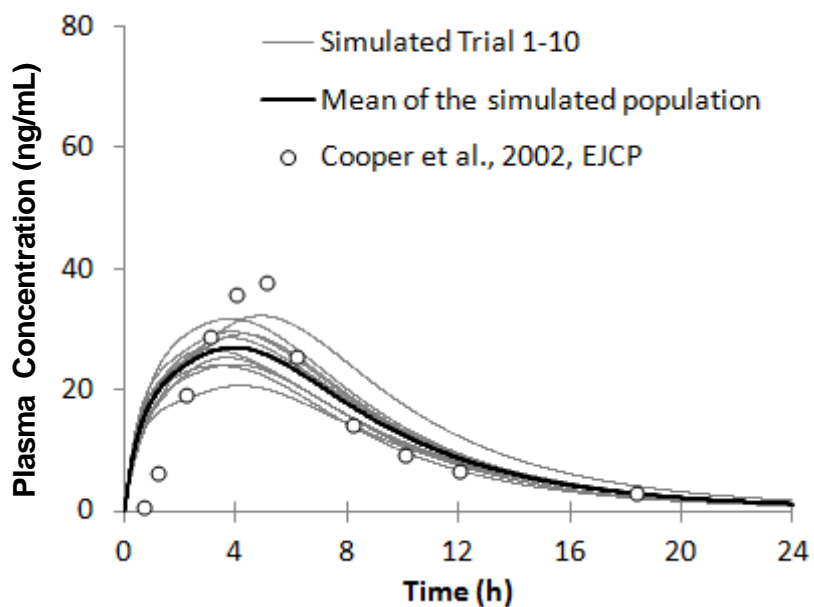
Fig. S9 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 80 mg. The grey thin lines represent simulated individual trials (10) of 14 male subjects (29-51 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=140). The circles denote mean values from the clinical study by Cooper *et al*. 2002 [6].

Fig. S10 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 80 mg. The grey thin lines represent simulated individual trials (10) of 18 male subjects (31-60 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=180). The circles denote mean values from the clinical study by Martin *et al.* 2003 [2].
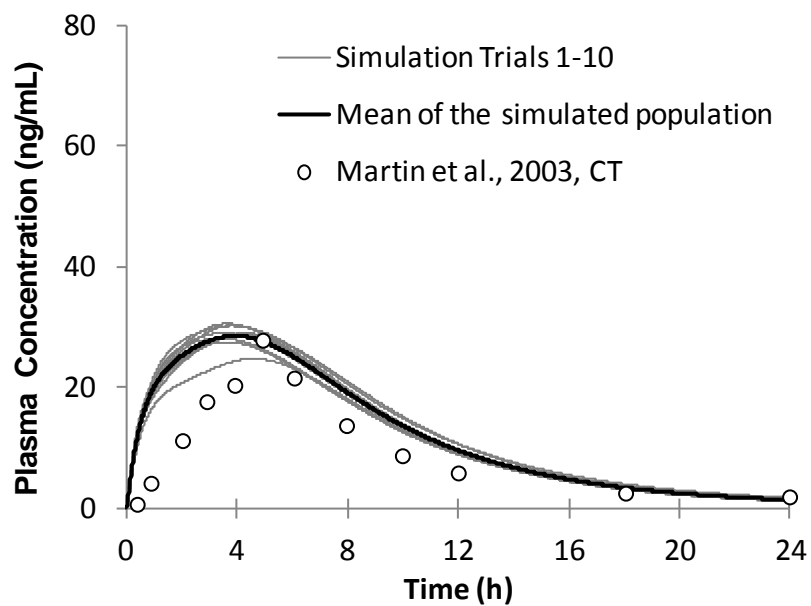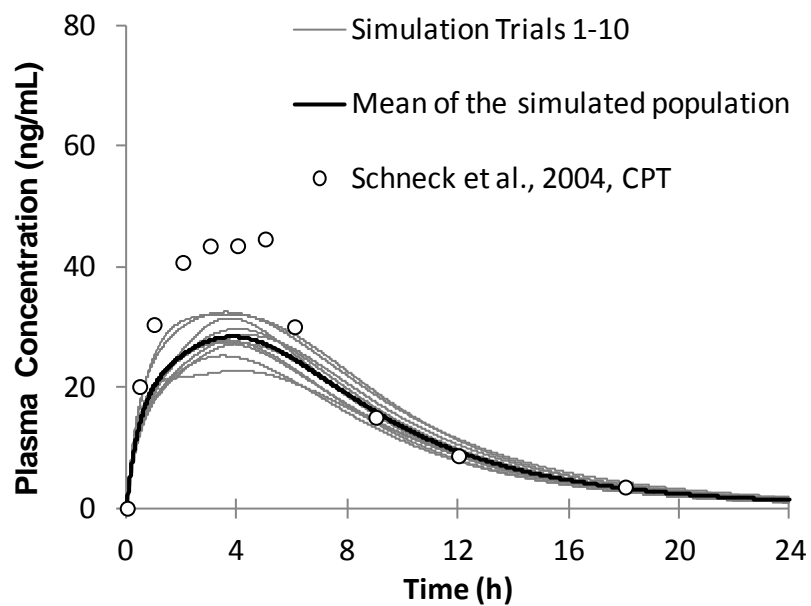
Fig. S11 - Simulated *versus* observed plasma concentration-time profiles of rosuvastatin in healthy volunteers following the oral administration of 80 mg. The grey thin lines represent simulated individual trials (10) of 20 subjects (0.15% female, 35-47 years) and the solid black line represents the simulated mean of the healthy volunteers population (n=200). The circles denote mean values from the clinical study by Schneck *et al*. 2004 [7].

References

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