

Population pharmacokinetics of S-amlodipine in healthy Korean male subjects



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BACKGROUND

Amlodipine, a third-generation dihydropyridine calcium channel blocker that has been used for hypertension and angina pectoris, is known to have large inter-individual pharmacokinetic (PK) variability.

OBJECTIVE

The aims of this study were to develop a population PK model of S-amlodipine in healthy Korean subjects and to compare estimated parameters between two amlodipine formulations.

METHODS

A randomized, open-label, two-period, crossover bioequivalence study in 30 healthy male adults was performed. All subjects were received either the test or reference formulation as a single 2.5-mg oral dose of S-amlodipine, followed by a 3-week washout period and administration of the alternate formulation. Blood samples were drawn at 0 (pre-dose), 1, 2, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, and 216 hours after dosing. Plasma S-amlodipine concentrations were analyzed using HPLC/MS/MS. A population PK analysis was conducted using NONMEM (Ver. 7.1).

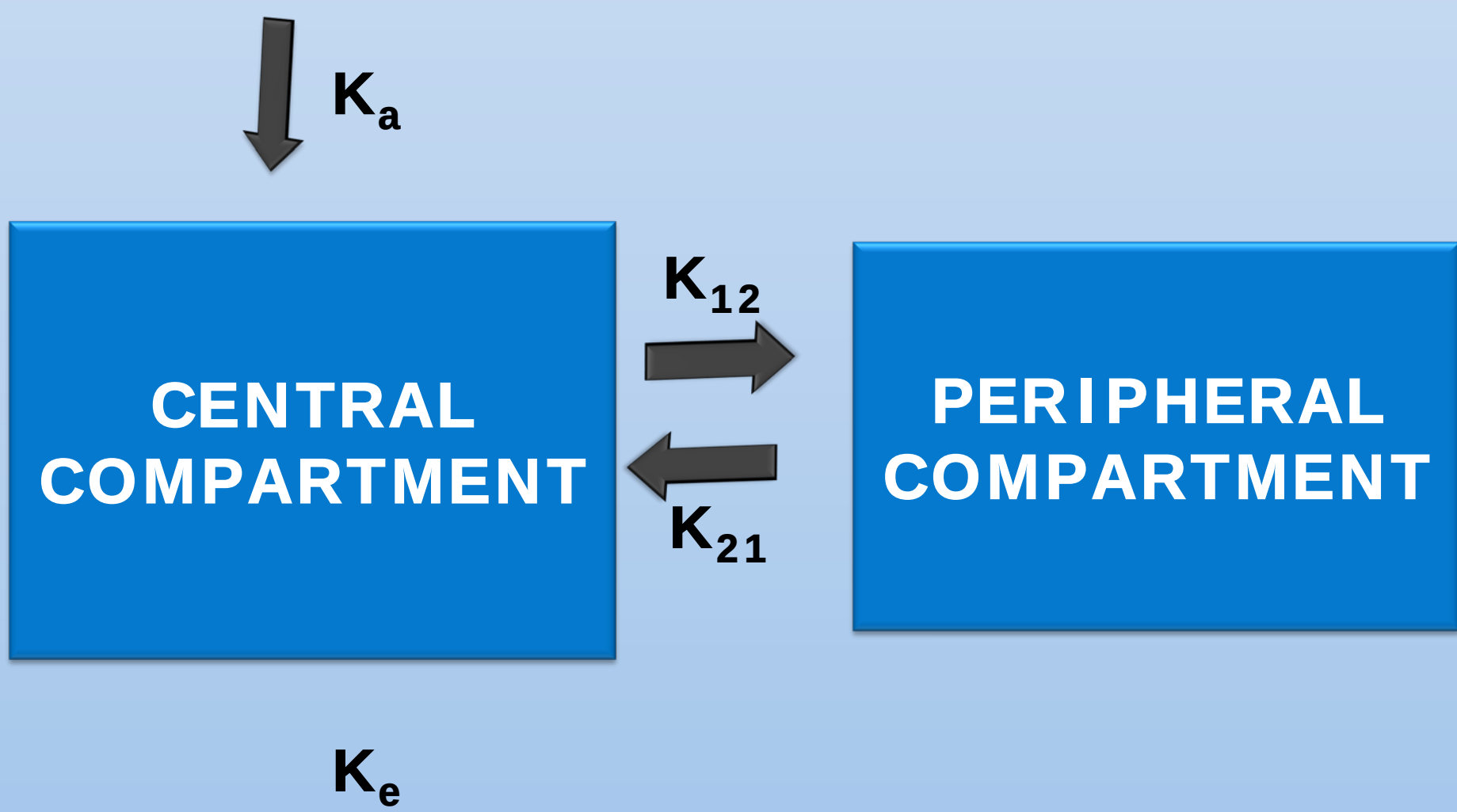
RESULTS

A 2-compartment model with zero-order absorption provided the best fit to a total of 383 concentrations from healthy subjects. Estimates of the population PK parameter were as follows; k_e , 0.019 h⁻¹; V_c , 1940 L; V_p , 515 L; Q , 102 L/h; and $D1$ (Duration of zero-order absorption), 4.99 h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model. No significant difference in the PK parameter estimates was observed between the two amlodipine formulations.

DEMOGRAPHICS

Total		
Number of subjects		30
Age (yrs) (range)	Mean±SD (Min - Max)	23.8±2.2 (19 - 28)
Height (cm) (range)	Mean±SD (Min - Max)	173.2±5.2 (164.0 - 185.4)
Weight (kg) (range)	Mean±SD (Min - Max)	67.2±8.7 (52.0 - 88.5)

PK MODEL



PARAMETER ESTIMATES

Parameter	Estimate	% RSE
K_e (h ⁻¹)	0.019	5.4
V_c / F (L)	1940	8.8
V_p / F (L)	515	12.6
Q (L/h)	102	18.1
$D1$ (h)	4.99	3.7
Interindividual variability		
ω_{Ke} (%)	14.7	53.7
ω_{Vc} (%)	43.0	30.9
Residual error		
σ_{prop}	0.36	3.3

BASIC GOODNESS-OF-FIT PLOT

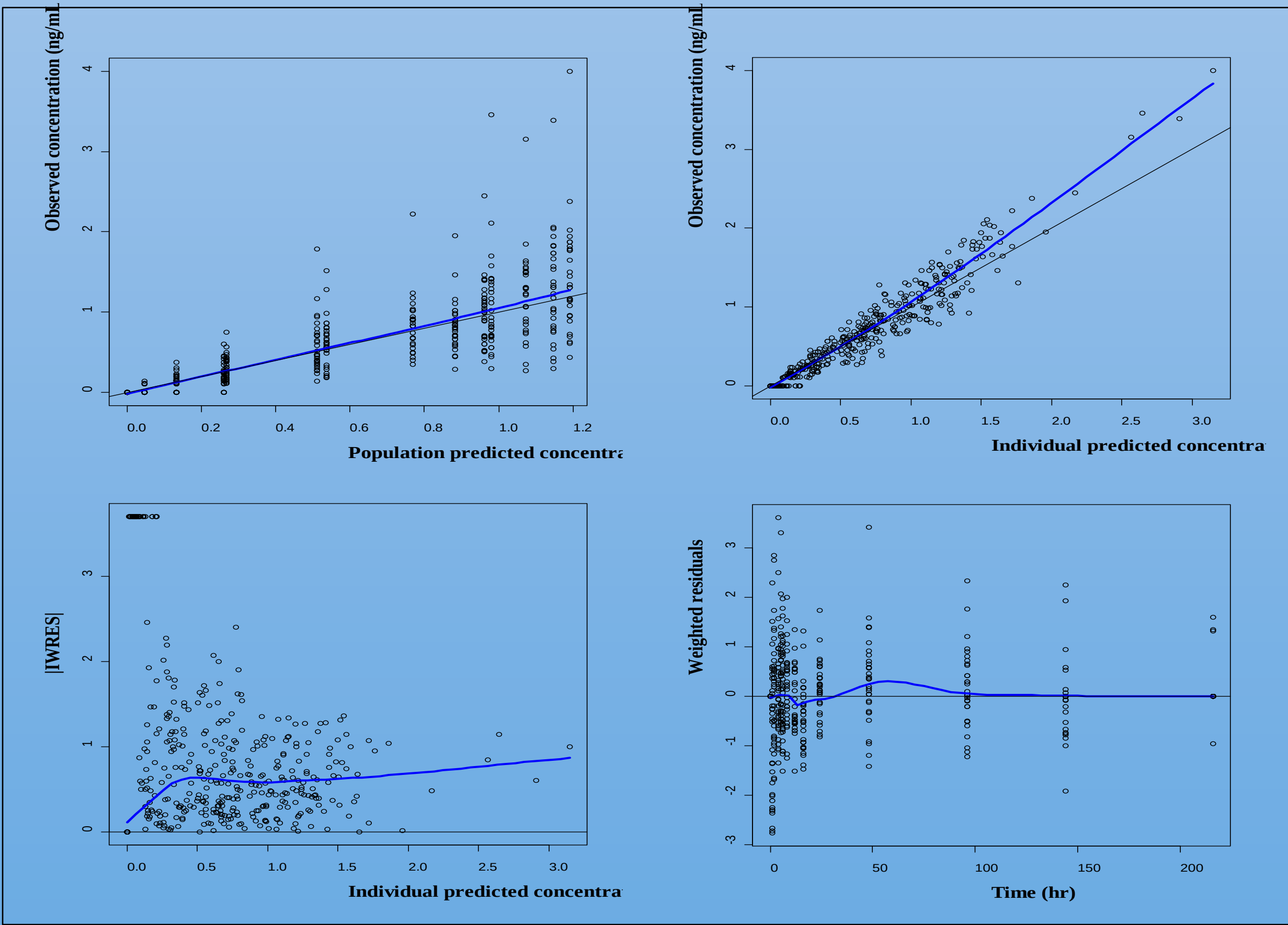


Figure 3. Scatter plots of the final population PK model (circle: observation, black line: line of identity, blue line: loess regression line)

VPC PLOT

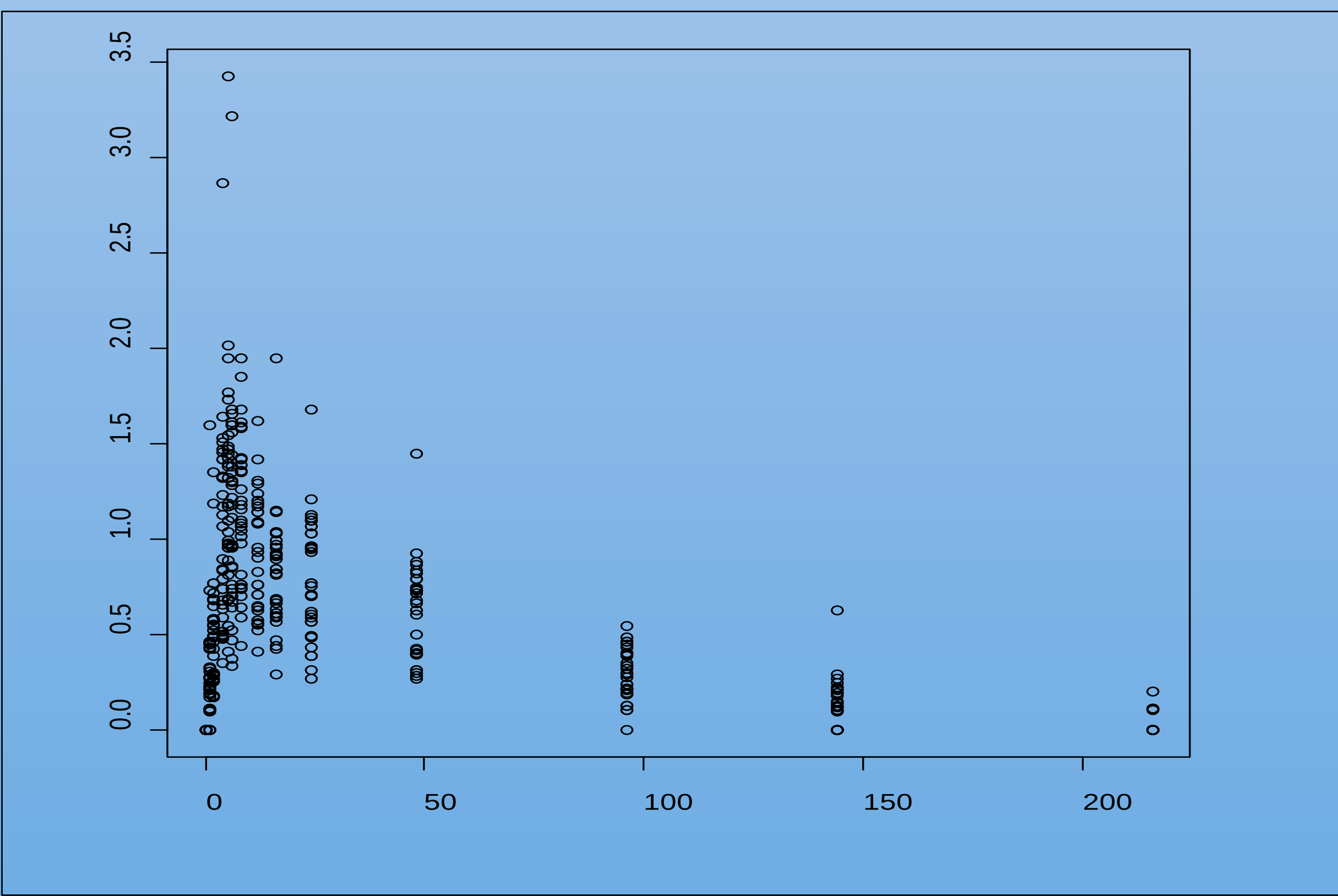


Figure 4. Results of model evaluation using simulated data. The 5th and 95th percentiles (dashed blue line) and the median value (dashed red line) from the simulated data are plotted against the observed concentration data (circle) according to time.

CONCLUSION

A population PK model was successfully developed and reasonable parameters were obtained. Both formulations were identical in the aspect of PK behavior. There were no significant covariates affecting PK parameters. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of amlodipine.

REFERENCES

- Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet 1992;22:22-31.
- Flynn JT, Nahata MC, Mahan JD Jr, and Portman RJ. Population Pharmacokinetics of Amlodipine in Hypertensive Children and Adolescents. J Clin Pharmacol 2006;46:905-916