Application of a PBPK/PD model describing the change in systolic blood pressure following administration of immediate release and controlled release nifedipine formulations.

R.H. Rose[1], N. Patel[1], L. Gaohua[1], M. Chetty[1], M. Jamei[1], A. Rostami-Hodjegan[1,2]

r.rose@simcyp.com

1-Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2-School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

Introduction

Nifedipine is a dihydropyridine calcium channel blocker commonly used in the treatment of hypertension. Both immediate release (IR) and controlled release (CR) nifedipine formulations are available. However, CR nifedipine formulations have been shown to offer a number of clinical benefits over IR nifedipine, including reduced food effects, reduced reflex sympathetic nervous system activation related to the slower release rate and reduced dosing frequency [1]. Nifedipine GITS is one such CR formulation that achieves zero order release rate sustained over 24 hours through an osmotic mechanism, allowing once daily administration [2].

PBPK models provide a mechanistic framework to integrate available physiological (system) and drug-and-formulation-specific data and can be used to predict differences, for example, in drug concentration profiles between different ethnic groups and different formulations. A mechanistic PBPK model that incorporates formulation effects for nifedipine using *in vitro* data has previously been reported [3]. However, in the clinic, it is the pharmacodynamic (PD) response to therapy that is the most relevant outcome.

A PKPD model that relates reduction in systolic blood pressure to the slow binding kinetics of nifedipine in Japanese hypertensive patients taking IR nifedipine has previously been described [4], but it is not clear whether the response profile changes with the nifedipine GITS formulation.

In this study, we aimed to integrate PBPK models developed for IR and CR nifedipine using prior physicochemical and *in vitro* data with the published PD model [4] within the Simcyp Simulator to assess the ability of the combined model to predict the plasma and PD response profiles for IR and CR nifedipine (Figure 1).
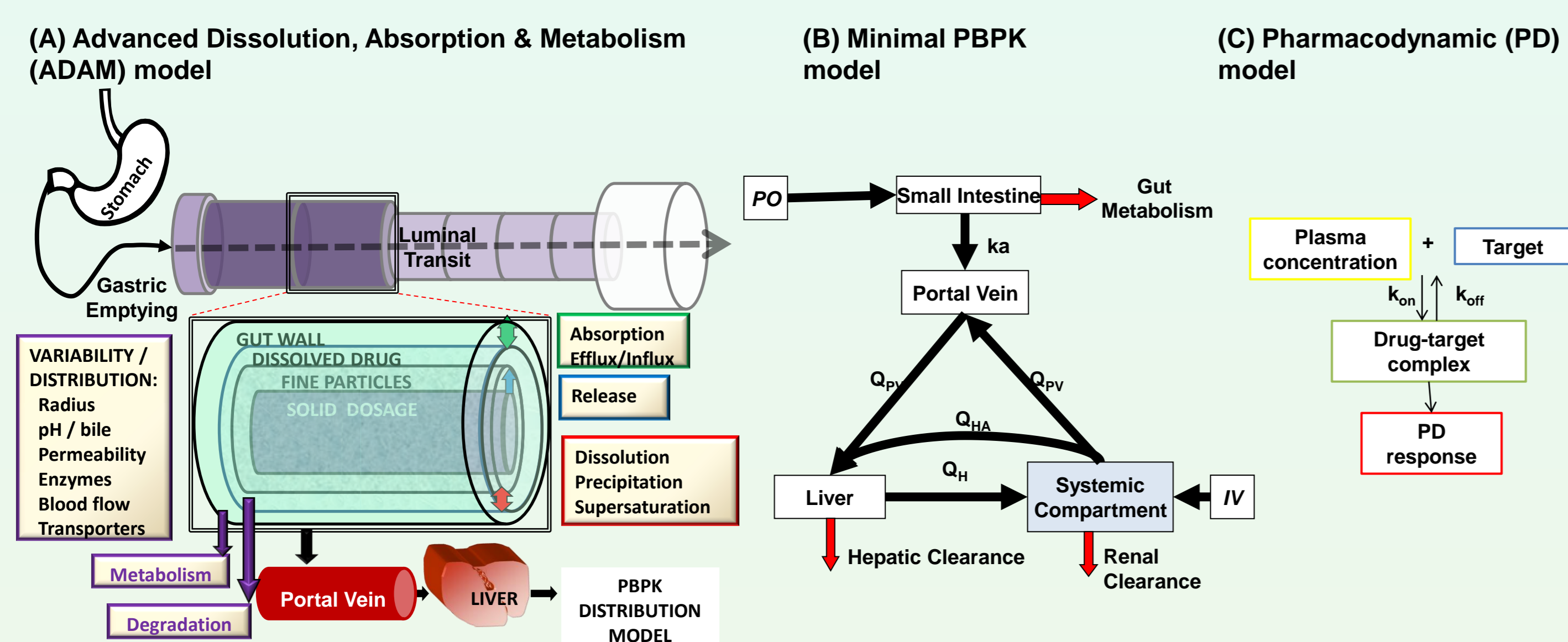
Figure 1. (A) Simcyp ADAM model; (B) Simcyp minimal PBPK model; (C) Dynamic binding PD model.

Methods

Simulations of nifedipine PK and PD were performed using the Simcyp Simulator V12 Release 1 and the Sim-Nifedipine compound file with distribution described by the minimal PBPK model and elimination described by enzyme kinetics. To simulate IR nifedipine the first order absorption was used, while for nifedipine GITS, formulation effects were described by a mechanistic absorption model (ADAM) using *in vitro* data, as previously reported [3].

The PKPD model used a dynamic binding model, as reported in [4], to describe the change in systolic blood pressure in hypertensive subjects in response to nifedipine. The PD model was assumed to be the same for IR and CR nifedipine and all study populations.

Simulated study design was matched to that reported for clinical studies, including age, proportion of females and fasted or fed state dosing. Ethnicity was also matched to the clinical study using the Sim-Japanese population to simulate the Japanese population and the Sim-NEurCaucasian population to simulate the North European Caucasian population. Each clinical study was simulated 10 times to account for statistical variability in sampling and presented displaying the mean profile for 10 trials and the overall mean (darker line) and 90% confidence interval (dashed lines) (Figures 2-4).

Results

Simulations in Simcyp recovered the observed plasma and PD profiles for IR nifedipine in Japanese hypertensive patients (Figure 2; [5,6]).

Both the magnitude and sustained plateau (>24h) of the PK and PD profiles were well captured for 60mg nifedipine GITS formulation, with mean clinical data [2] falling within the range of the mean values of simulated trials (Figure 3). However, clinical PK and PD data for a 30mg multi-dose study of nifedipine GITS were underestimated by almost 2-fold (Figure 4, Table 1).
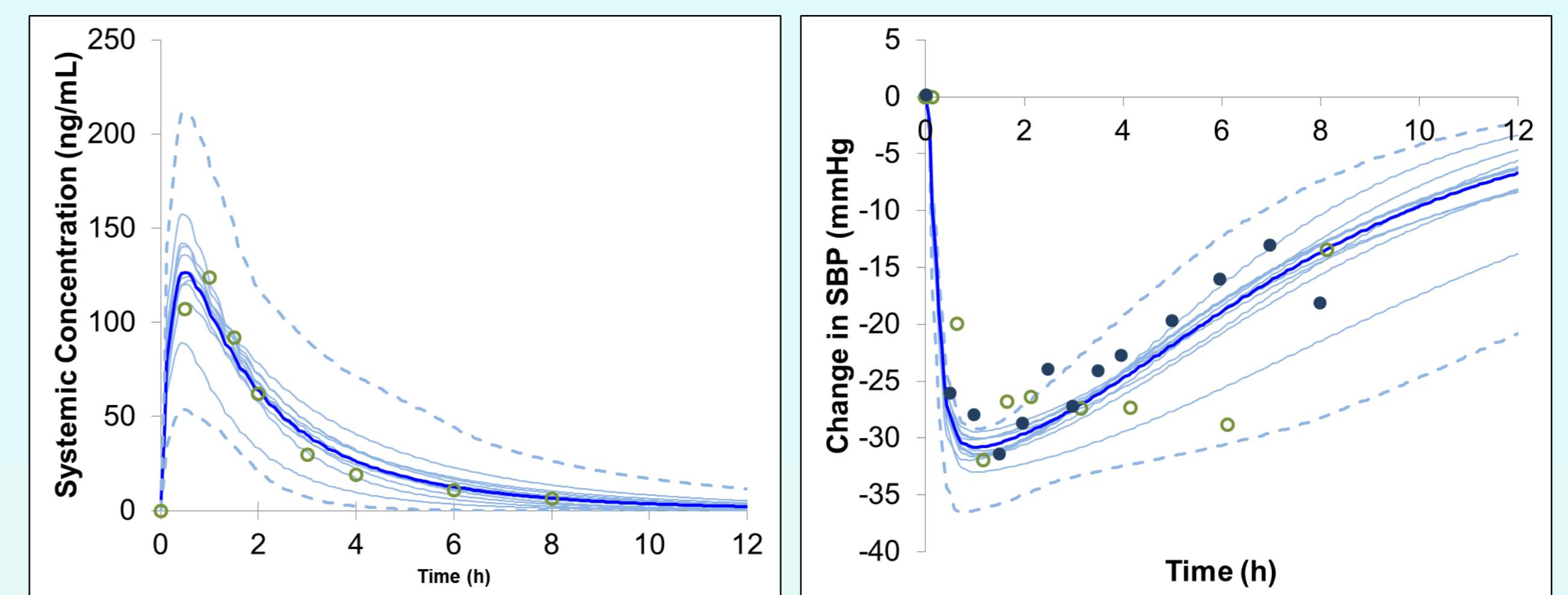
Figure 2. Predicted (lines) and observed (○ Kikuchi et al 1981 [5]; ● Takekoshi *et al.*, 1981 [6]) plasma concentration profile (left) and change in systolic blood pressure (right) after a single dose of nifedipine 10mg IR in Japanese hypertensive subjects.
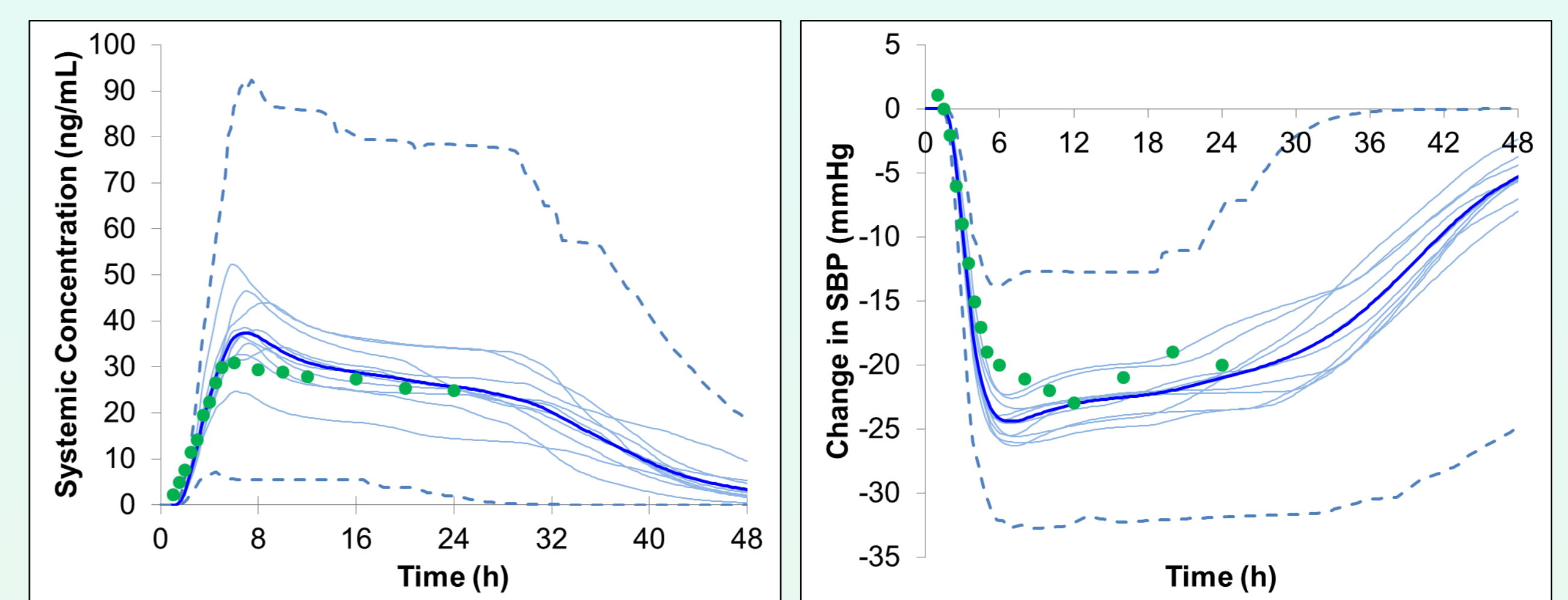
Figure 3. Predicted (lines) and observed (● Meredith and Elliott 2004 [2]) plasma concentration profile (left) and change in systolic blood pressure (right) after a single dose of nifedipine 60mg GITS in North European hypertensive subjects.

Figure 4. Predicted (lines) and observed (● Brown and Toal 2008 [1]) plasma concentration profile (top) and change in systolic blood pressure (bottom) after the initial dose and daily dosing of nifedipine 30mg GITS for 15 days in North European hypertensive subjects.
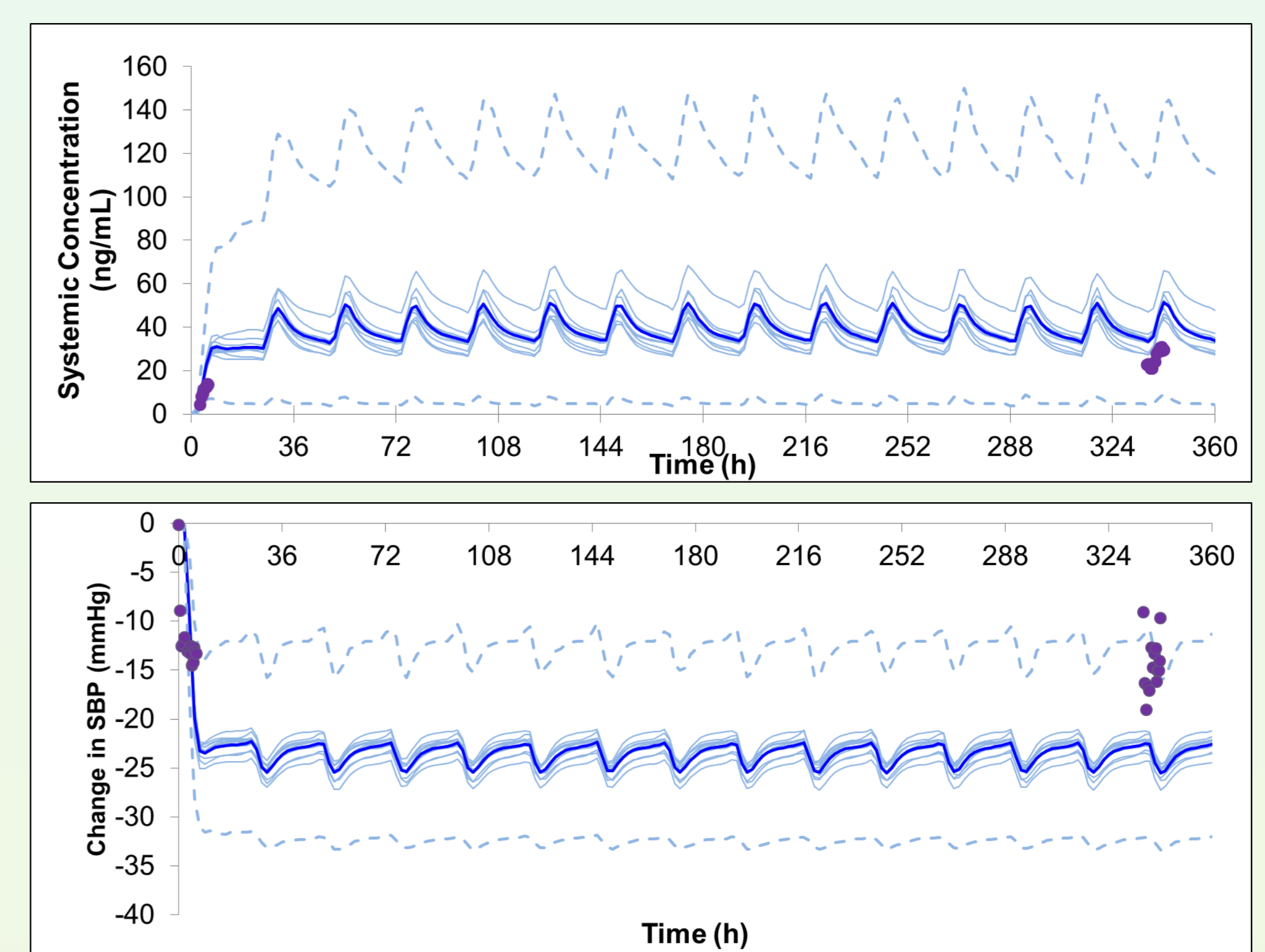
	10mg IR nifedipine		60mg nifedipine GITs		30mg nifedipine GITS 1st dose		30mg nifedipine GITS final dose	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
C_{max} (ng/ml)	127.8 ± 53.6	132.5 ± 23.7	44.3 ± 22.6	31.0	38.1 ± 31.5	16.9 ± 10.2	56.6 ± 51.1	30.7
R_{max} (mmHg)	-30.9 ± 3.6	-32.9 ± 9.9	-25.1 ± 5.5	-23.0	-24.3 ± 7.8	-13.7 ± 15.6	-26.0±5.1	-19

Table 1. Comparison of the predicted and observed [1,2,5] C_{max} and maximum reduction in systolic blood pressure (R_{max}) for the different nifedipine formulations and doses. Data are reported as the mean ± SD (where reported).

Conclusions

Integration of a PBPK model for nifedipine that accounts for formulation effects with a dynamic PKPD binding model within the Simcyp Simulator provided a good match with clinical observations. Underestimation of the response to 30mg nifedipine GITS may relate to use of the dissolution profile for 60mg nifedipine GITS in simulations due to unavailability of the dissolution profile for the 30mg dose. This may have significantly impacted on PK, and subsequently PD, predictions.

References

[1] Brown and Toal (2008) Br J Clin Pharmacol 65: 646-652; [2] Meredith and Elliott (2004) J Hypertension 22: 1641-1648; [3] Patel *et al.* (2012) 8th World Meeting on Pharmaceutics, Biopharmacuetics and Pharmaceutical Technology, Istanbul, Turkey (Poster presentation); [4] Shimada *et al.* (1996) Biol Pharm Bull 19: 430-437; [5] Kikuchi *et al.* (1982) Jpn J Clin Pharmacol Therapeut 13: 623-637; [6] Takekoshi *et al.* (1981) Jpn Circ J 45: 852-860