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Development of Physiologically Based Biopharmaceutical Model (PBBM) for Felodipine Prolonged-Release Tablet as Useful Tool for Prediction of Formulation

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Abstract

Physiologically Based Biopharmaceutical Models (PBBMs) are advanced tools that integrate physiological parameters with drug-specific properties to simulate drug behavior in vivo. In this study, we present the development of a PBBM specifically tailored for felodipine prolonged-release (PR) tablet formulations. Felodipine, a potent calcium channel blocker, is widely used for the treatment of hypertension and angina pectoris. Prolonged-release formulations aim to provide controlled drug release, ensuring sustained therapeutic effect with reduced dosing frequency and minimized adverse effects.

Our PBBM incorporates key physiological processes such as gastrointestinal transit, drug dissolution, absorption, distribution, metabolism, and elimination. Data from in vitro dissolution studies, preclinical pharmacokinetics, and clinical observations are integrated to parameterize the model accurately. Special attention is given to the physicochemical properties of felodipine and the release characteristics of the PR tablet formulation.

Validation of the PBBM is conducted against clinical pharmacokinetic data obtained from bioequivalence studies and population pharmacokinetic analyses of felodipine PR tablets. The model may demonstrate excellent predictive performance, accurately capturing plasma concentration-time profiles across different dosing regimens and patient populations.

The developed PBBM provides valuable insights into the biopharmaceutical behavior of felodipine PR tablets, facilitating rational formulation design, dosage regimen optimization, and therapeutic individualization. It serves as a powerful tool for drug developers, regulatory agencies, and clinicians to enhance the efficiency and effectiveness of drug development and clinical pharmacotherapy.

Keywords: Physiologically Based Biopharmaceutical Models, Prolonged-release, Validation,

1. Introduction

The objective of this research is to develop and validate the PBBM for felodipine PR tablet formulation. Felodipine PR tablet was used for the treatment of hypertension. The PBBM model was developed and validated successfully.

Objective

The primary objective of this work is Development of mechanistic absorption/pharmacokinetic model for felodipine PR tablet.

The secondary objective of this work is validation of developed model using the pharmacokinetic data of humans from literatures.

2. Methods

GastroPlusTM version 9.7 (Simulation Plus, Inc.) was used to build the mechanistic pharmacokinetic model for felodipine to describe the *in vivo* pharmacokinetics of this compound, across the different studies in humans[1]. The *in-silico* biopharmaceutical properties of felodipine were obtained from the literature. The experimental physicochemical data such as particle size, pH dependent solubility studies and dissolution studies were used to build the model for simulation studies.

a. Physicochemical and biopharmaceutics properties

Felodipine is chemically (4 RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine- 3,5-dicarboxylate. The molecular weight is 384.4 Da[2]. It is a neutral molecule within the physiological pH range and extremely lipophilic in nature. The partition coefficient of felodipine between toluene and water is 30000. Felodipine has low aqueous solubility of 19 mg/l at 25°C. Based on pH independent low aqueous solubility and high lipophilicity, it has been classified as BCS Class II drug[3]. The *in silico* and experimental physicochemical and biopharmaceutics properties are listed in Table 1.

Table 1; Physicochemical and biopharmaceutics properties

SN	Parameters	Values
1	Molecular weight	384.3
2	Log P	4.36 –ALOGPS 3.44 – ChemAxon 5.58[5]
3	Log D	3.4[6]
4	pKa	Strong acid: 19.46 (ChemAxon) Strong base: -6.6 (ChemAxon)
5	Protein binding	% unbound - 0.4%
6	Solubility	0.000715 mg/ml (ALOGPS) 0.009 -0.012 mg/ml (Reference)
7	Particle size (micron)	D_{10}: 4.0 µ; D_{50}: 10 µ; D_{90}: 16 µ
8	Blood to plasma ratio	0.7[6]
9	Mean precipitation time	900 s[6]
10	Drug particle density	1.2 g/ml (ADMET Predictor)
11	Diffusion co-efficient	0.75 x 10^{-5} cm^2/s (ADMET Predictor)
12	Permeability	Caco2 – 5.1 x 10^{-6} cm/s[7]

		Caco2 – 4.4 x 10^{-6} cm/s[7] Caco2 – 1.7 x 10^{-4} cm/s[6] Caco2 – 4.3 x 10^{-6} cm/s[8] Caco2 – 10.3 x 10^{-4} cm/s[9]
13	ASF model	Opt log D Model SA/V 6.1(ADMET Predictor)
14	Duodenal solubility	0.041 mg/ml (Calculated by Gastroplus)
15	First pass effect	Approximately 85%[10]
16	Enterohepatic circulation	No[10]
17	Biliary excretion	Insignificant, less than 0.1%[11]
18	PK linearity	Yes, 2.5 to 10.0 mg[10]

Table 2: Summary of pharmacokinetic studies from literature

SN	Study Objective	Subjects/ Route	Dose	Mean Age (year)	Mean Body weight (kg)	Sex	Sample size (n)	Reference
1	Pharmacokinetics of Felodipine in healthy subjects	Healthy Intravenous Infusion	1 mg	26	73	Male	10	12
2	Pharmacokinetics of Felodipine in healthy subjects	Healthy Intravenous Infusion	3 mg	26	73	Male	10	12
3	Pharmacokinetics of felodipine in healthy subjects	Healthy Oral Solution	10 mg	26	73	Male	12	13
4	Pharmacokinetics of felodipine in healthy subjects	Healthy IR Tablets	10 mg	26	73	Male	12	13
5	Pharmacokinetics of felodipine in healthy subjects	Healthy ER Tablets	10 mg	26	73	70	12	13
6	Pharmacokinetics of Felodipine in healthy subjects	Healthy Oral Solution	5 mg	26	73	Male	10	12
7	Pharmacokinetics of Felodipine in healthy subjects	Healthy Oral Solution	15 mg	26	73	Male	10	12
8	Pharmacokinetics of Felodipine in healthy subjects	Healthy Oral Solution	40 mg	26	73	Male	10	12

9	Food effect study of felodipine in healthy subjects	Healthy ER Tablets	10 mg	29	78	Male	14	14

b. Intravenous pharmacokinetic data modelling and Validation

Different mean plasma concentration over time profiles from three IV PK-data have been chosen for the optimization process. In the digitizing process, the web-browser-based digitizing software WebPlotDigitizer was used to extract numerical PK data from the plots. The demographic characteristics of the subjects such as age, body weight, sampling times and methodology have been reported in corresponding study. IV PK data were used to screen various compartmental and PBPK models using Gastroplus 9.7 software. The best-fit model was chosen and subjected to further validation and application. Table 2 summarizes the PK studies selected from literature for model building and validation. Table 3 summarizes the input parameters for PBPK model development

c. Oral Pharmacokinetic data modelling and validation

Oral PK data reported from literature were used to build PK models (reference). The similar procedure was used to extract the numerical PK data from plots. The demographic parameters such as age, sex, race and body weight were used to build the oral PK model. The distribution and elimination rate constants obtained from the validated IV PK model used as a basis to build oral PK data from literature. Opt log D Model SA/V 6.1 is used as an absorption scale factor for human fasted and fed state physiology. The advanced Compartmental Absorption Transit (ACAT) model is used for gastrointestinal PBPK and whole body PBPK and/or compartmental PK for predicting plasma drug concentration using Gastroplus 9.7 software. PBPK model is further fine-tuned to optimize the PBBM[15] with pharmaceutical characterization data such as particle size distribution of API, drug particle density and drug substance solubility and dissolution profile of dosage form. Table 1 summarizes the input parameters for PBPK model development

d. Pharmaceutical properties of felodipine prolonged release tablets

Felodipine is used in the treatment of hypertension and available 5 mg immediate release tablets (administered twice daily) and 10 mg prolonged release tablets (administered once daily). Felodipine prolonged release 10 mg tablets are designed to improve the patient acceptability and the similar safety and therapeutic efficacy[16], when compared immediate release tablets. Generic felodipine prolonged release tablet consists of a fast hydrating polymer, which facilitates rapid formation of gel. Felodipine being a low soluble drug, faster hydration of the tablet core facilitates the drug release without any lag time. Moreover, presence of lactose as a filler results in pore formation. The presence of surfactant improves the wettability of the drug and hence reduces the interfacial tension between drug particles and dissolution media. However, a polymer being a low viscosity polymer, loses its gel strength over the period of time results in surface erosion of the tablet with function of time and the tablet dimensions diminish proportionally to dissolution. Considering the nature and design of the prolonged release tablets, Controlled release undissolved particles (CRU) module was chosen in GastroPlus, the *in vivo* dissolution of the drug (released in the form) is based on particle size and physicochemical properties of the drug substances.

e. Bioequivalence studies for felodipine 2.5 mg & 10 mg prolonged release tablets

As per available literature the In-Vivo study design consists of open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study of Felodipine 10 mg Prolonged-Release Tablets with Modip® 10 mg Retardtabletten Felodipine of AstraZeneca GmbH, 22876 Wedel, Germany (Reference) in healthy, adult, male, human Subjects under fasting condition. In case of 2.5 mg strength the study design consists of open-label, balanced, randomized, single-dose, two-treatment, two-sequence, four-period, full replicate crossover bioequivalence study between test and reference product. The primary objective of this study is to investigate the bioequivalence of test and reference formulation by means of rate and extent of absorption, in healthy, adult, male human subjects under fasting condition with at least seven days' washout period between each administration. The secondary objective is to monitor the safety of the participating subjects in this study determined by means of clinical biochemistry, physical examination and adverse drug reaction and serious adverse monitoring.[13]

f. Simulation trials for felodipine 2.5 mg & 10 mg prolonged release tablets

A two-treatment, two-sequence, randomized, single-dose, crossover virtual bioequivalence trial simulation with PK endpoints in healthy subjects under fasting condition was conducted to mimic the in vivo BE study design. Groups of 76 virtual subjects (74 for virtual subjects for 2.5 mg) were generated with demographics as close as possible to those expected in the in vivo BE studies in terms of age and gender of the subjects. The oral PBBM developed in section 3.3 was used for simulation trials for felodipine 10 mg prolonged release tablets. The controlled release (CRU) was selected as a dosage form module based on the composition and design of felodipine 10 mg prolonged release dosage form. Moreover, the model consists of instant dissolution model, wherein deconvoluted *in vivo* dissolution profiles were obtained from geometric mean plasma drug concentration profiles obtained from bioequivalence studies. Felodipine prolonged release tablets consist of surfactant and hence the other parameters such as bile solubility and pH dependent solubility were obtained from literature. The developed model is validated using pharmacokinetic data obtained from the bioequivalence studies.

3. Results and discussion

a. Physicochemical and biopharmaceutics properties

Felodipine is a neutral compound with pH independent solubility because of lack of ionization across the physiological pH range of 1.2- 7.4. The experimental solubility data in table 1 is used to build the PBPK model. Felodipine, being a lipophilic molecule log P value of 5.58 based on the literature and optimization techniques. However, based on the experimental solubility data the fitted pka value of 1.0 (base) and 6.9 (acid) was used. The selection of the other physicochemical and biopharmaceutical properties such as protein binding, blood to plasma ratio, mean precipitation time and diffusion coefficient were based on either *in silico* method or experimental values obtained from literature. The duodenal solubility of 0.074 mg/ml was obtained by adjusting the solubility for bile salt effect with solubilisation ratio of 1.5 $x10^6$. The experimental particle size data listed in table 1 was used for all prolonged release dosage forms. However, the effect of nanoparticle solubility, effect of bile salts on diffusion coefficients were ignored because of the instant dissolution model. The biliary excretion of the drug is insignificant (<0.1%) and hence entero hepatic cycle mode was not used to build the model. The first pass metabolism for all oral formulations were optimized based on the literature value. The reported pharmacokinetic linearity across the dose of 2.5 mg to 10.0 mg was evaluated using intravenous pharmacokinetic data. The Opt log D Model SA/V 6.1 model was used for absorption scale factor.

b. Intravenous pharmacokinetic data modelling and validation

Intravenous pharmacokinetic data obtained from the literature was used to build the pharmacokinetic model and the developed model was further validated. Felodipine exhibits age dependent metabolism and clearance and hence the pharmacokinetic study involved in young healthy male subjects was considered for pharmacokinetic model building. The demography and dosage information are listed in table 2. The pharmacokinetic parameters obtained from the validated model are listed in table 3. The pharmacokinetic profiles of 1 mg dose and 3 mg dose were screened for various models and the best fit model and model information are listed in table 4. Figure 1 and 2 represents the single simulation outputs of intravenous pharmacokinetic data obtained from literature.

Figure 1; 1mg dose intravenous PK profile (predicted vs observed)

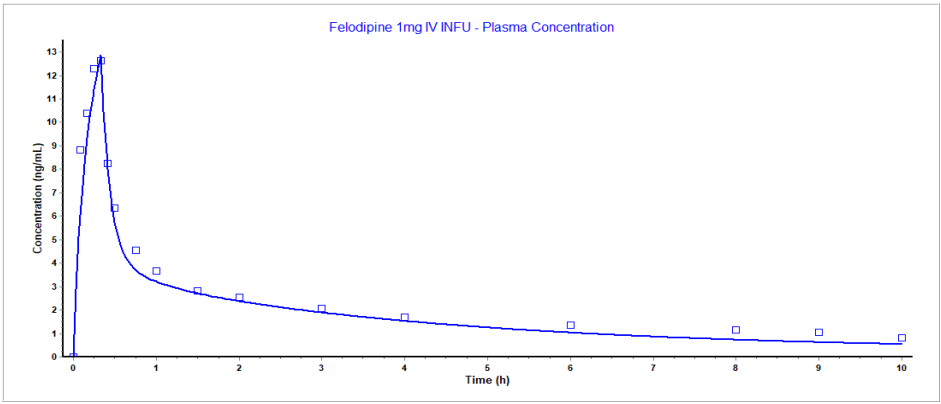


Figure 2; 3mg dose intravenous PK profile (predicted vs observed)

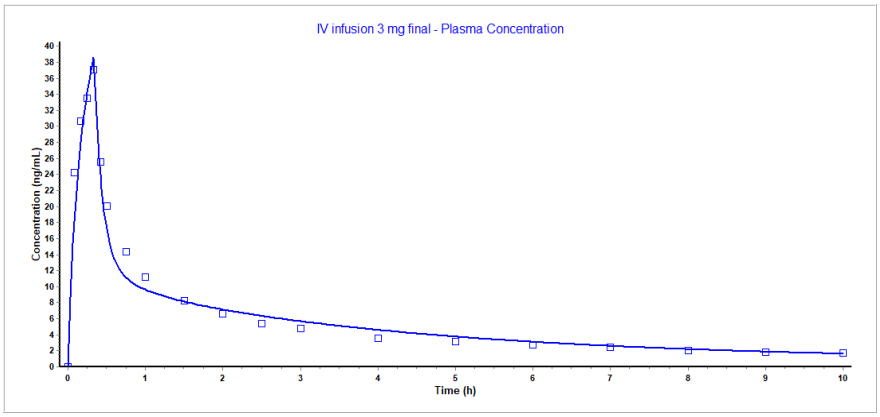


Table 3; Pharmacokinetic model parameters

PK parameters	Model output	PK parameters	Model output
Model	Compartmental	K_{12} (1/h)	0.82078
B/P ratio	0.7	K_{21} (1/h)	0.03602
Adj. Plasma % Fup	0.039	V_2 (1/kg)	9.4426
Cl; (L/h)	29.301	K_{13} (1/h)	4.433
Vc (L/kg)	0.41439	K_{31} (1/h)	1.0767
$T_{1/2}$ (h)	37.44	V_3 (1/kg)	1.8068

Table 4: Intravenous pharmacokinetic model validation

PK metrics	Dose: 1 mg;	Dose: 3 mg;

	Infusion time: 0.0833 h			Infusion time: 0.0833 h		
	Observed	**Predicted**	**% PE**	**Observed**	**Predicted**	**% PE**
Cmax (ng/ml)	12.64	12.87	-1.8	37.1	38.6	-4.0
AUC_{0-i} (ng.h/ml)	24.5	22.3	9.0	70.7	66.7	5.7
AUC_{0-t} (ng.h/ml)	21.7	18.2	16.1	54.1	54.7	-1.1

c. Oral pharmacokinetic data modelling and validation

Oral fasting pharmacokinetic data of different dosage forms such as solutions, immediate release tablets and extended-release tablets were obtained from literature. The validated pharmacokinetic model obtained from intravenous studies were used to predict the pharmacokinetic profiles of different oral formulations. Felodipine oral solution formulation consists of surfactant, which is used as a soulbilizer. The impact of soulbilizer on in vivo absorption and precipitation kinetics is unknown and similarly, the particle size of immediate release formulations was not reported in literature, hence the peak plasma drug concentration was not considered as a parameter for model validation of all oral felodipine solution and immediate release formulations. Deconvoluted in vivo release profiles were obtained for extended release formulation for prediction of pharmacokinetics of extended release dosage forms. Felodipine undergoes extensive first pass effect (approximately 85%) and hence optimized value of extent of first pass effect is used for oral pharmacokinetic model building. Figures 3-7 illustrates the pharmacokinetic profiles of oral formulation. Table 5 summarizes the validation of oral pharmacokinetic data under fasting conditions. The area under the plasma drug concentration curves of different doses of oral solution are well correlated with dose and have pharmacokinetic linearity up to 40 mg of the dose (figure 9). The prediction errors are well within the limit for single simulation and explicit the accuracy of the model.

Figure 3; Oral felodipine 5 mg solution PK profile (observed vs predicted)

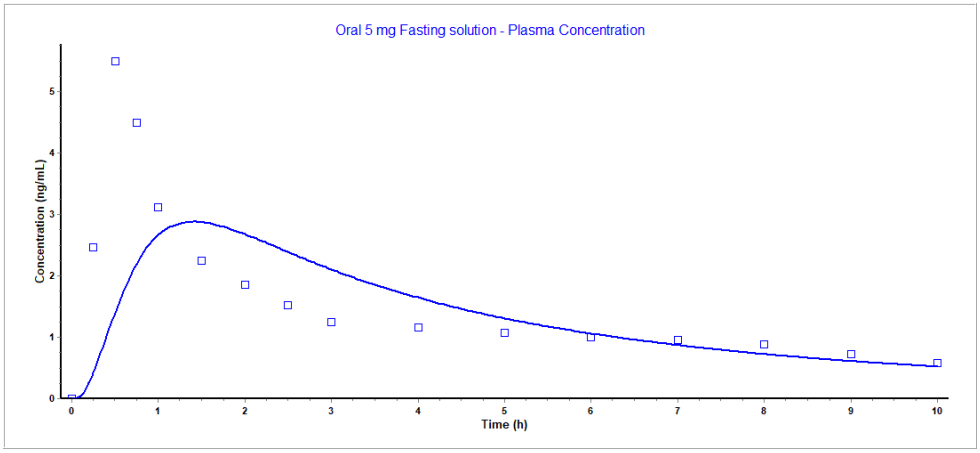


Figure 4; Oral felodipine 15 mg solution PK profile (observed vs predicted)

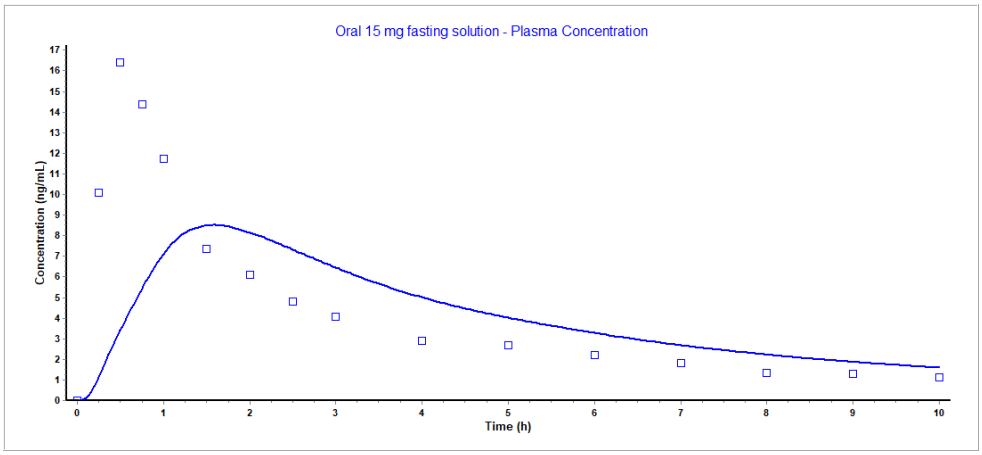


Figure 5; Oral felodipine 40 mg solution PK profile (observed vs predicted)

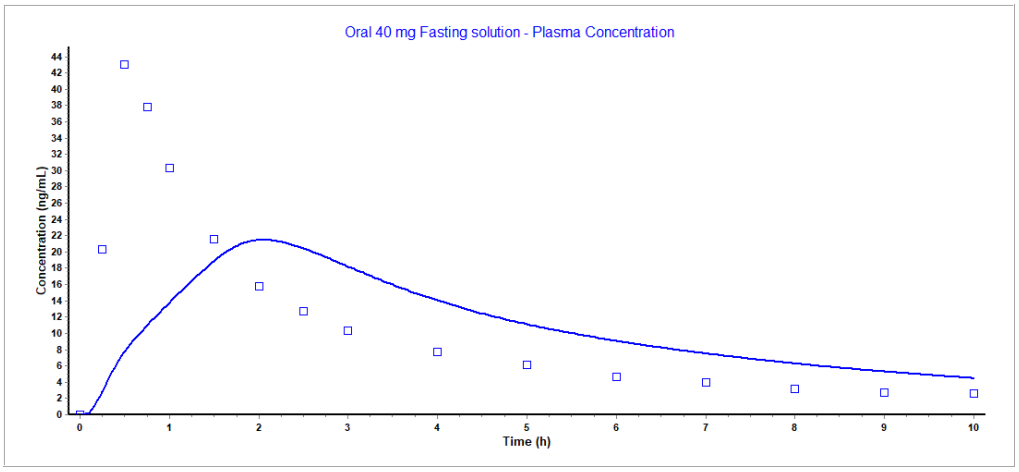


Figure 6; Oral felodipine 10 mg IR tablet PK profile (observed vs predicted)

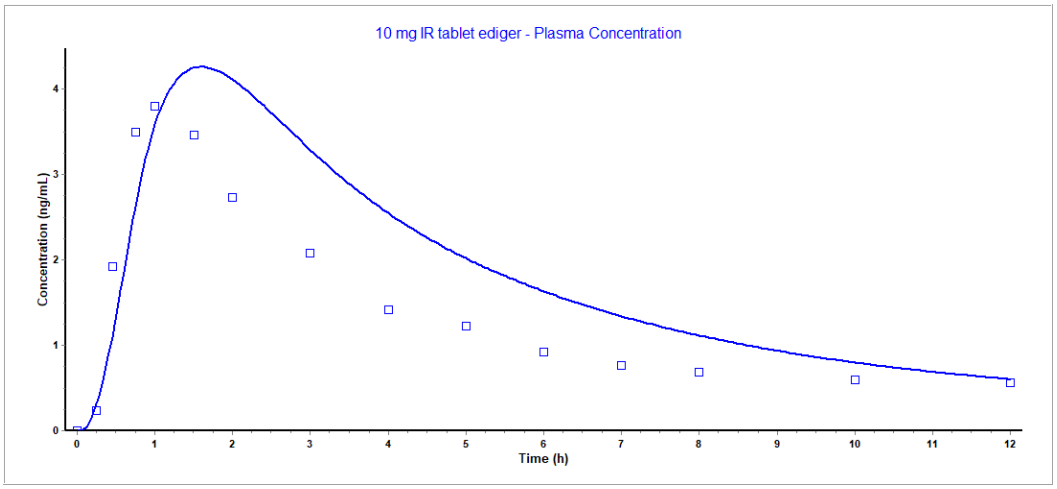


Figure 7; Oral felodipine 10 mg ER Tablet (Edger) PK profile (observed vs predicted)

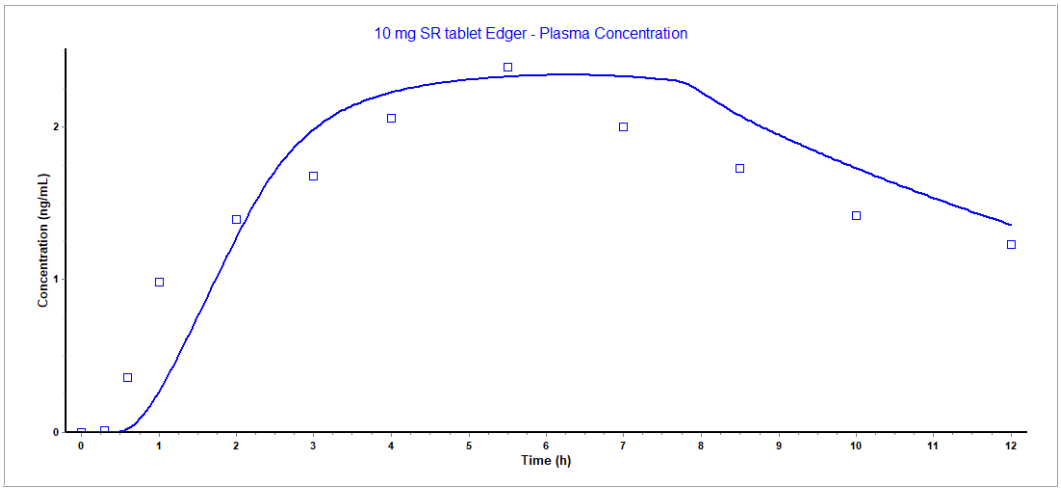


Figure 8; Oral felodipine 10 mg ER Tablet (SBOA) PK profile (observed vs predicted)

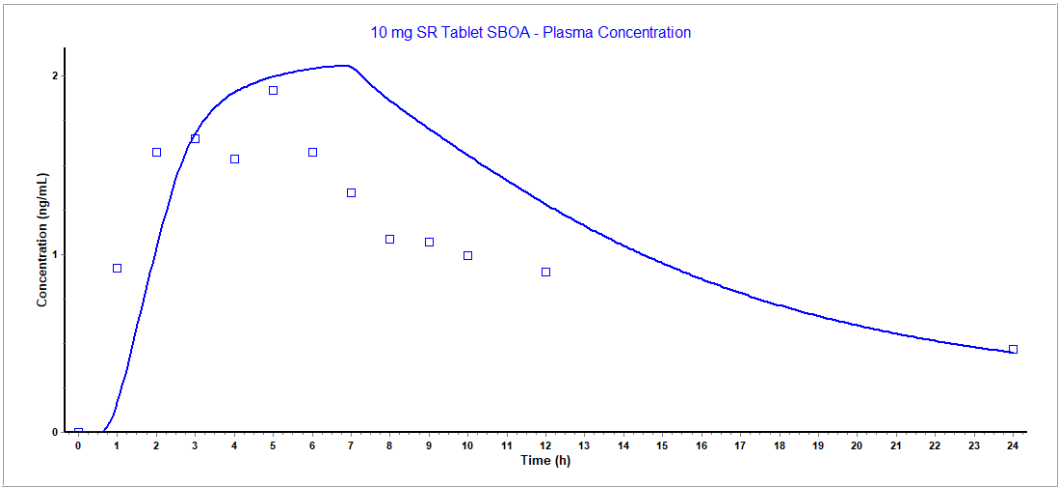


Figure 9; PK linearity of oral solution formulations

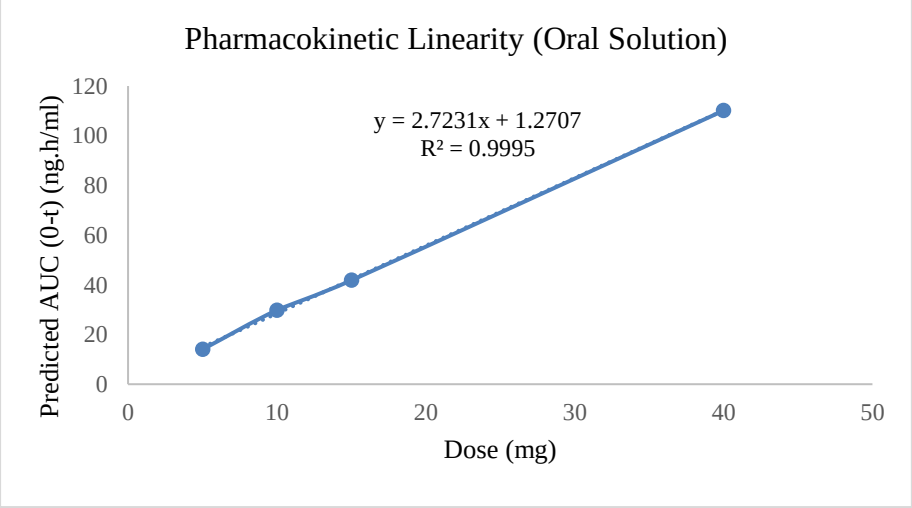


Table 5: Oral solution pharmacokinetic model validation

PK metrics	Oral Solution 5 mg	Oral Solution 15 mg	Oral Solution 40 mg	Oral Solution 10 mg

	Observed	Predicted	% PE	Observed	Predicted	% PE	Observed	Predicted	% PE	Observed	Predicted	% PE
Cmax (ng/ml)	5.5	2.9	-	16.4	8.5	-	43	21.5	-	8.8	5.7	-
AUC_{0-i} (ng.h/ml)	16.6	17.4	-4.8	48.8	52.1	-6.8	134.9	137.6	-2.0	31.7	36	-13.6
AUC_{0-t} (ng.h/ml)	14.1	14.0	0.7	39.6	41.8	-5.6	99.1	110.1	-11.1	26.4	29.8	-12.9

Table 6: Oral tablet pharmacokinetic model validation

PK metrics	Oral IR Tablet 10 mg (Edger)			Oral ER Tablet 10 mg (Edger)			Oral ER tablet 10 mg (SBOA)		
	Observed	Predicted	% PE	Observed	Predicted	% PE	Observed	Predicted	% PE
Cmax (ng/ml)	3.8	4.3	-	2.39	2.34	2.1	1.92	2.05	-6.7
AUC_{0-i} (ng.h/ml)	32.1	27	15.9	36.3	31.99	11.9	31.9	34.2	-7.2
AUC_{0-t} (ng.h/ml)	15.9	22.3	-4.0	19.36	20.8	-7.4	23.3	27.2	-16.7

d. Simulation trials for felodipine 2.5 mg and 10 mg prolonged release tablets

The simulation trials for felodipine 10 mg prolonged release was performed using validated pharmacokinetic model obtained from intravenous as well as oral formulation. The in vivo release profiles used to build the pharmacokinetics of both test and reference formulations are tabulated in table 7. Bioequivalence statistics summary data is presented in table 8. The output data of simulations trials were compared with bioequivalence study results. The parallel simulation for test and reference products were performed with a set of 76 subjects, and the prediction errors for all pharmacokinetic parameters were well within the limit (Figure 10 and 11). The results obtained from cross-over design studies between test and reference products with 76 subject data is comparable with bioequivalence results (figure 12). The prediction error of simulated pharmacokinetics parameters of both test and reference formulations are well within the limit of 10%. The % T/R ratio for Cmax, AUC0-t and AUC0-∞ are 110.8 %, 86.76 % and 87.53 %, respectively for bioequivalence study and 108.9 %, 90.1 % and 89.9 % for simulated pharmacokinetic study. The simulation study results reveal that it has predictions well well within the limit and hence could be used for virtual bioequivalence studies of felodipine 5 mg prolonged release tablets.

Table 7; *In vivo* release profile of test and reference felodipine PR Tablets

Time (h)	% *in vivo* release

	Test	Reference
0.5	9	8
1	22	21
2	44	32
4	68	62
5	74	70
8	78	86
10	-	90
12	80	92

Table 8a; Summary statistics of fasting bioequivalence of 10 mg PR tablets (n=76)

PK Metrics	Geometric LSM Reference	Geometric LSM Test	% Ratio	90% CI
Ln Cmax (ng/ml)	6.576	7.288	110.8	100.9 – 121.72
Ln AUC0-t (ng.h/ml)	93.701	81.292	86.76	81.11-92.80
Ln AUC0-∞ (ng.h/ml)	101.486	88.832	87.53	82.03-93.41

Table 8b; Summary statistics of fasting bioequivalence of 2.5 mg PR tablets (n=74)

PK Metrics	Geometric LSM Reference	Geometric LSM Test	% Ratio	90% CI
Ln Cmax (ng/ml)	1.321	1.483	112.3	103.3 – 122.12
LnAUC0-t (ng.h/ml)	19.88	18.83	105.5	97.6 – 114.06
Ln AUC0-∞ (ng.h/ml)	21.60	20.33	106.3	98.3 – 114.8

Table 9a; Comparison of geometric mean % T/R between clinical vs simulated PK (Felodipine PR Tablets 10 mg)

PK Metrics	% T/R Ratio		90% LCI		90% UCI	
	Simulated	Clinical	Simulated	Clinical	Simulated	Clinical
Ln Cmax (ng/ml)	108.9	110.8	101.2	100.9	117.17	121.72
Ln AUC0-t (ng.h/ml)	90.09	86.76	82.89	81.11	97.91	92.80
Ln AUC0-∞ (ng.h/ml)	89.91	87.53	81.97	82.03	98.61	93.41

Table 9b; Comparison of geometric mean % T/R between clinical vs simulated PK (Felodipine PR Tablets 2.5 mg)

PK Metrics	% T/R Ratio		90% LCI		90% UCI	
	Simulated	Clinical	Simulated	Clinical	Simulated	Clinical

Ln Cmax (ng/ml)	108.9	112.3	100.6	103.3	118	122.1
Ln AUC0-t (ng.h/ml)	91.9	105.5	84.5	97.6	100.1	114.1
Ln AUC0-∞ (ng.h/ml)	91.8	106.3	83.8	98.3	100.5	114.8

Figure 10; Fasting PK simulation of test felodipine 10 mg PR tablets (n=76)

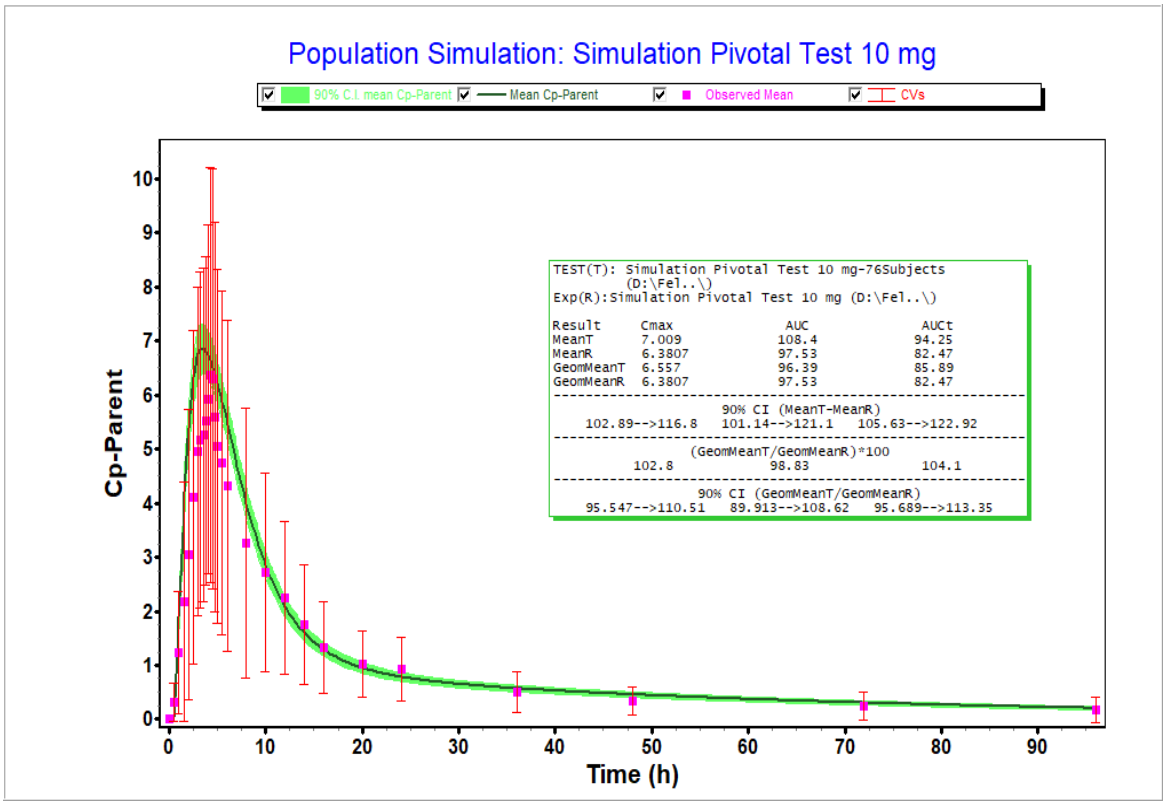


Figure 11; Fasting PK simulation of reference felodipine 10 mg PR tablets (n=76)

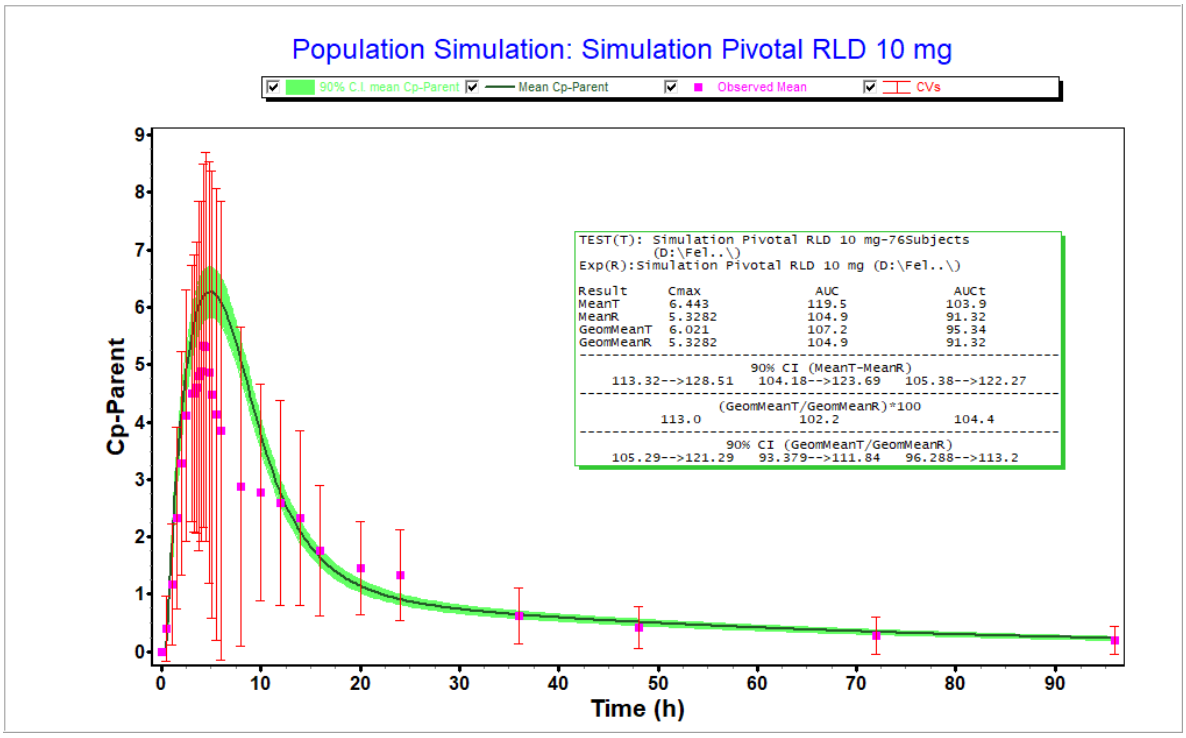
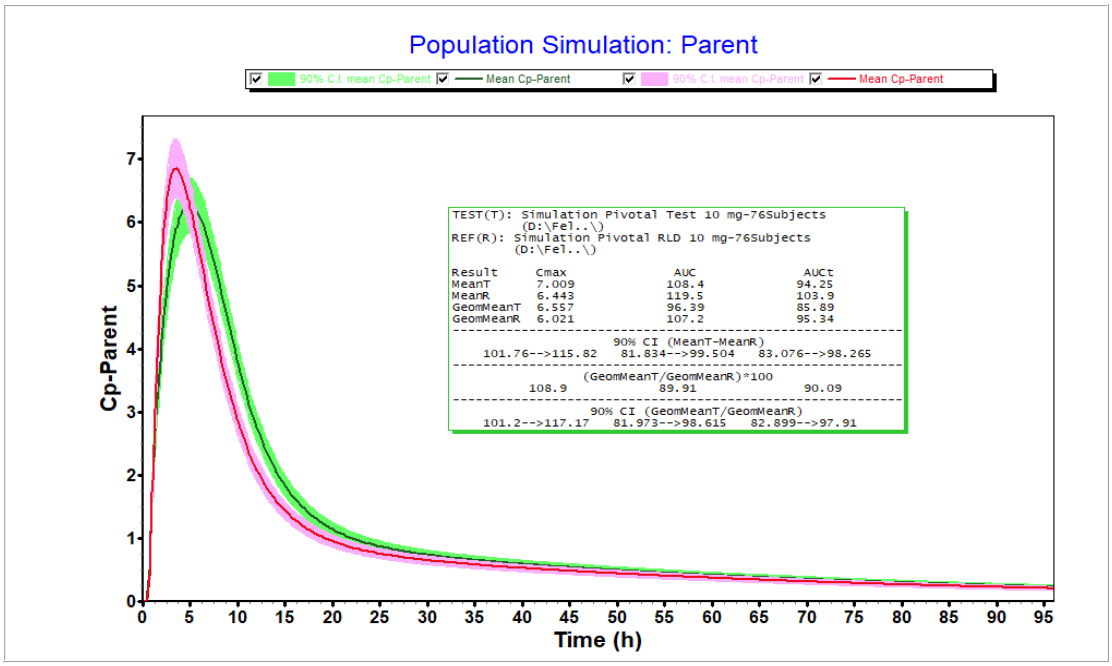


Figure 12; Fasting PK simulation of test vs reference felodipine 10 mg PR tablets (n=76)



4. Conclusion

The findings of modelling and simulation activity augments the pharmacokinetic properties such as dose linearity, high variability, higher first pass effect and solubility rate limited bioavailability. The intravenous pharmacokinetic data is used to build the pharmacokinetic model and subsequently the model

was validated with different sets of oral formulation pharmacokinetic data. The validated model may be used for simulation of bioequivalence results of felodipine 10 mg prolonged release tablets obtained from clinical studies. The prediction analysis of the model was not only considering the geometric mean values but also confidence intervals. The prediction errors are well within the limit for all pharmacokinetic parameters.

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