White Paper

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Applying GastroPlus™ for Extensions of Biowaivers for BCS Class II Compounds

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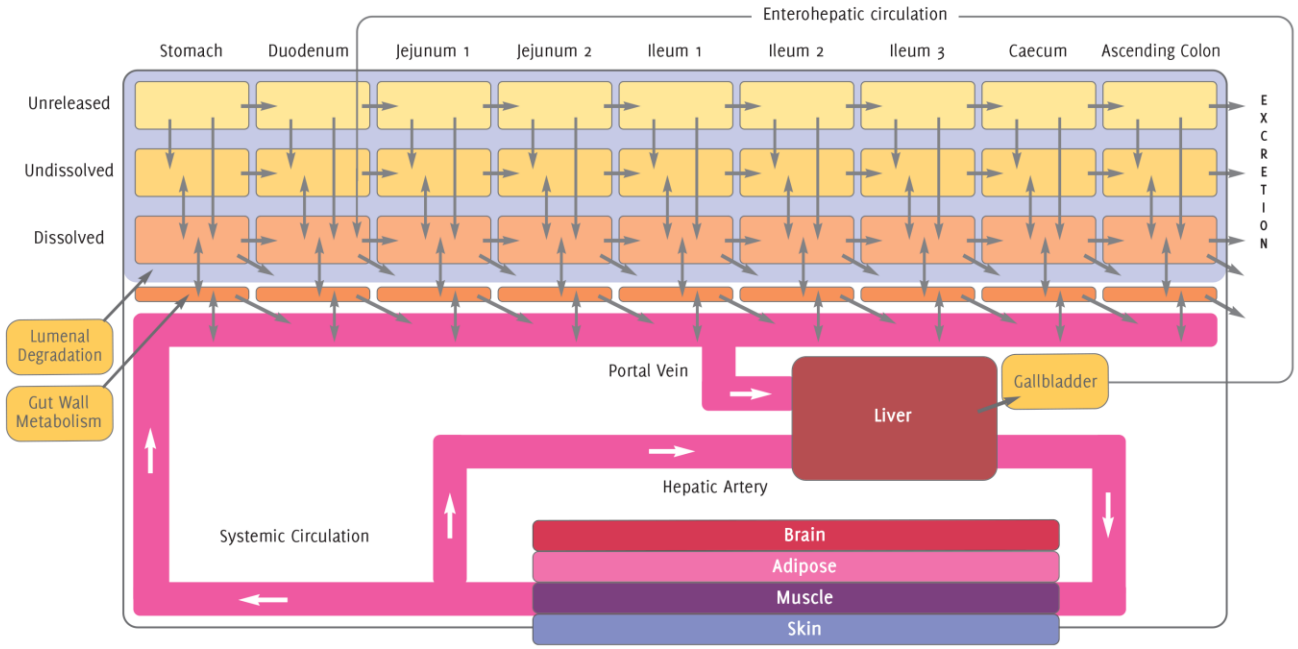
Abstract

GastroPlus™ is a mechanistically based simulation software package that predicts absorption, pharmacokinetics, and pharmacodynamics in humans and animals. GastroPlus modeling and simulation has been used to justify biowaivers for Class I, II, and III active pharmaceutical ingredients.[1-4] Simulations Plus has recently demonstrated that GastroPlus can also be applied for extensions of biowaivers for BCS Class II active pharmaceutical ingredients for which manufacturing process changes have been made. This application of GastroPlus has the potential of streamlining the introduction of reformulated drug products by eliminating bioequivalence studies, where appropriate, while still ensuring necessary drug product performance.

Technical Aspects

In many cases, there is a difference in the composition, manufacturing, formulation, or other parameters between a medicinal product that is intended for the market and the prototype batches that were used to demonstrate the efficacy and safety in clinical trials. Several pharmaceutical companies have used the advanced compartmental absorption and transit (ACAT™) model in GastroPlus to carry out physiological modeling and simulation to assess the possible effects of such changes on drug exposure. This mechanistic model incorporates many *in vivo* processes, such as dissolution, precipitation, absorption, and first-pass metabolism, and takes the complex interactions of these processes into account to provide better insight into a drug's *in vivo* behavior.

Figure 1: GastroPlus Advanced Compartmental Absorption and Transit (ACAT) model



[1] *Application of gastrointestinal simulation for extensions for biowaivers of highly permeable compounds*. Tubic-Grozdanis M, Bolger MB, and Langguth P. (2008) AAPS J. 10(1):213-26.

[2] *An investigation into the importance of "very rapid dissolution" criteria for drug bioequivalence demonstration using gastrointestinal simulation technology*. Kovacevi I, Parojci J, Tubi-Grozdanis M, Langguth P. (2009) AAPS J. 11(2):381-4.

[3] *The biowaivers extension for BCS Class III drugs: the effect of dissolution rate on the bioequivalence of BCS Class III IR drugs predicted by computer simulation*. Tsume Y, Amidon GL. (2010) Mol Pharm. 7(4):1235-43.

[4] *The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation*. Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. (2011) Int J Pharm. 418(2):151-60.

The BCS Class II drug (herein after, the "drug") discussed in this paper has low solubility and significant dissolution limitations. An in-line milling step was added to the crystallization process as part of the overall process improvement for the manufacturing of the drug's active pharmaceutical ingredient (API). This in-line milling step was added to reduce the fines in the crystallization step and to narrow the particle size distribution (particle engineered, PE). The API from the original crystallization process (non-particle engineered, NPE) was used to manufacture several Phase 1 and Phase 2 clinical supply lots. An examination of these different API lots showed that two early batches of the NPE API had a broader particle size distribution than those of the PE API lot but all other NPE API lots had a particle size distribution that was similar to that of the PE API lot. Consequently, proof had to be supplied that changes in the manufacturing process, which could affect the particle size distribution of the drug's API, did not adversely impact either its oral bioavailability or its bioequivalence. In lieu of running another clinical study to show bioequivalence between the NPE and PE lots, GastroPlus simulations were carried out to show virtual bioequivalence.

Objectives

GastroPlus, with its proprietary ACAT model, was used to carry out physiological modeling and simulation to assess the effects of changing the particle size distribution of the drug's API on its oral bioavailability and bioequivalence. The objectives of these studies, in chronological order, were the following:

- Determine the most appropriate absorption/pharmacokinetic model for the drug's API using clinical data from prior studies.
- Compare the simulated regional % absorption and gut lumen concentration-time profiles between the tablets that were manufactured from the NPE API lots and the tablets that were manufactured from the PE API lot..
- Assess the sensitivity of API particle size on drug exposure.
- Compare the predicted bioequivalence of the tablets that were manufactured from the NPE API lots and the tablets that were manufactured from the PE API lot.

The following GastroPlus features were used to achieve the objectives of these studies:

- The ADMET Predictor™ module was used to obtain *in silico* estimates of key physicochemical and biopharmaceutical properties from the drug's structure.
- The PKPlus™ module was used to fit standard compartmental pharmacokinetic parameters for one-, two-, and three-compartment PK models using intravenous and/or oral plasma concentration-time data.
- The Parameter Sensitivity Analysis mode was used to assess the sensitivity of predicted absorption and pharmacokinetic responses to the critical input parameter of particle size.
- The Population Simulator was used to assess the predicted bioequivalence between the tablets that were manufactured from the NPE API lots and the tablets that were manufactured from the PE API lot.

Methods

The physicochemical and biopharmaceutical properties for the drug were defined using a combination of *in silico* estimates from its structure (ADMET Predictor Module), default values that were defined in GastroPlus, and *in vitro* data that was measured by the drug's sponsor.

Table 1: Physicochemical and biopharmaceutical drug properties

Property	Value
logP	3.8
Diffusion coefficient	0.67 * 10^{-5} cm/s^2
pKa	None (neutral molecule)
Aqueous solubility	0.0345 mg/mL @ pH 7.5
FaSSIF solubility	0.54 mg/mL @ pH 6.5
FeSSIF solubility	5.01 mg/mL @ pH 5.0
Bile salt solubilization ratio (SR)	599,800
Human effective permeability (P_{eff})	3.66 * 10^{-4} cm/s
Drug particle density	1.2 g/mL
Mean precipitation time	900 s
Blood: plasma concentration ratio (R_{bp})	0.77
Plasma protein binding (f_{up})	2.7% unbound

All simulations for the drug were carried out with the dose administered as an immediate release (IR) tablet. The GastroPlus IR model assumes both rapid tablet disintegration and the possibility of API dissolution immediately after dosing. The actual rate of dissolution is determined from formulation properties (dose and particle size), API properties (solubility, diffusion coefficient, etc.), and physiological conditions in each ACAT compartment (pH, fluid volume, bile salt concentration, etc.). The drug's sponsor also provided complete and/or cumulative particle size distribution (PSD) data for all lots.

Because intravenous plasma concentration-time data were not available in humans at the time of these studies, the oral plasma concentration-time data from the drug sponsor's clinical trials was used to estimate the compartmental PK parameters. The sponsor's study was selected because pharmacokinetic data were available across three dose levels (50, 100, and 300 mg) in a patient population with four different NPE API lots. The PKPlus module was used to determine the initial estimates of compartmental PK parameters across all dose levels. Table 2 shows the values that were used as the PK model inputs for simulations of all dose levels.

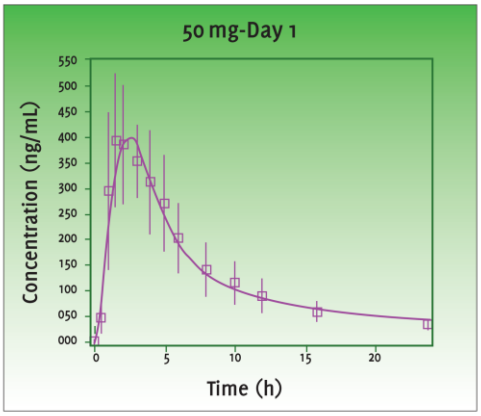
Table 2: Final optimized compartmental PK parameters

Parameter	Value
CL	0.115 L/h/kg
First pass extraction	17%
Vc	0.324 L/kg
K12	0.26 h^{-1}
K21	0.1 h^{-1}

Results

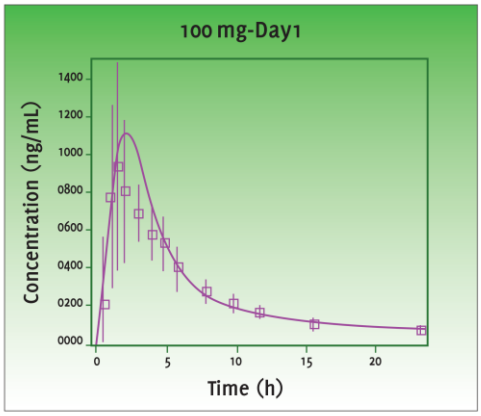
The first key step in these modeling and simulations studies was to use select physicochemical properties for the drug and formulation data to build the baseline absorption/pharmacokinetics modeling, and then validate this model against the available clinical data. Figure 2 illustrates the validation of this model, with each graph for a simulation showing the mean data and the variability around the mean in the population for a specific dose of an NPE API lot. These graphs demonstrate that the same baseline absorption model does an adequate job of predicting the observed plasma concentration-time data across the three different doses of the NPE API lots.

Figure 2: Validation of the GastroPlus model across three different doses of an NPE API lot



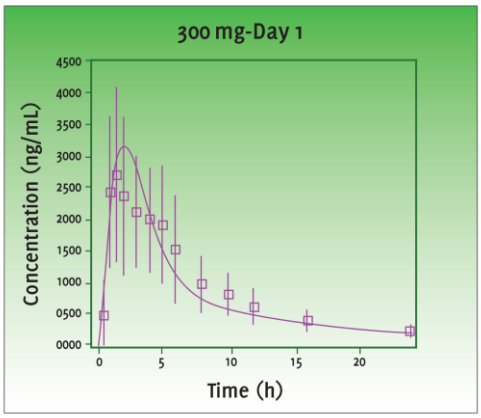
Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	85.907
FD_p (%)	0	85.907
F (%)o	0	71.303
Cmax (ng/mL):	391.2	399.12
Tmax (h):	1.5	2.56
AUC o-inf (ng-h/mL)	3563.7	3739.6
AUC o-t (ng-h/mL):	3139.1	3702
Cmax Liver (ng/mL):		531.85



Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	85.907
FD_p (%)	0	85.907
F (%)o	0	71.303
Cmax (ng/mL):	926.3	399.12
Tmax (h):	1.5	2.56
AUC o-inf (ng-h/mL)	7545.6	8462.2
AUC o-t (ng-h/mL):	6358.8	7117.3
Cmax Liver (ng/mL):		1385.9



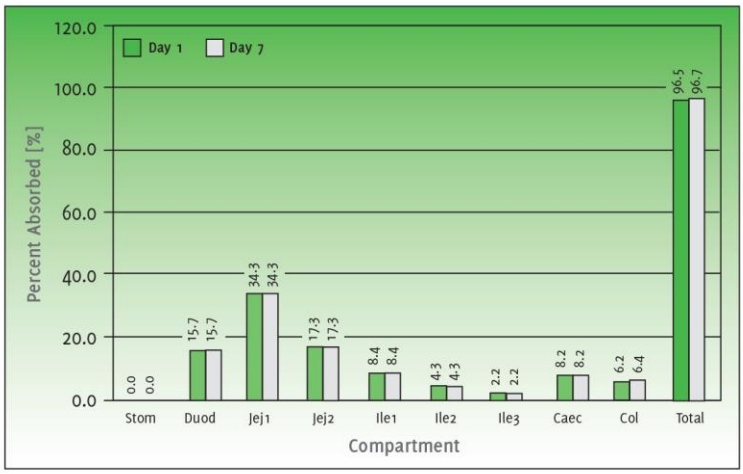
Total simulation time (h): 24

Result	Observ	Simul
Fa (%)	0	96.422
FD_p (%)	0	96.422
F (%)o	0	80.03
Cmax (ng/mL):	2768	3245.8
Tmax (h):	1.5	2.08
AUC o-inf (ng-h/mL)	26290	24970
AUC o-t (ng-h/mL):	22590	20990
Cmax Liver (ng/mL):		4079.7

Regional Absorption Comparisons

After the baseline absorption model was established, the next step was to compare the effects of particle size, doses, and possible drug accumulation (both regional absorption and gut lumen concentration) after multiple doses of the tablets that were manufactured from either the NPE API lots or the PE API lot. Figure 3 shows the results of these comparisons. No significant effect of the dose (50 mg versus 300 mg) is predicted for any of the API lots. In addition, the simulated gut lumen concentration and regional absorption are similar for Day 1 and Day 7, regardless of the dose or API lot.

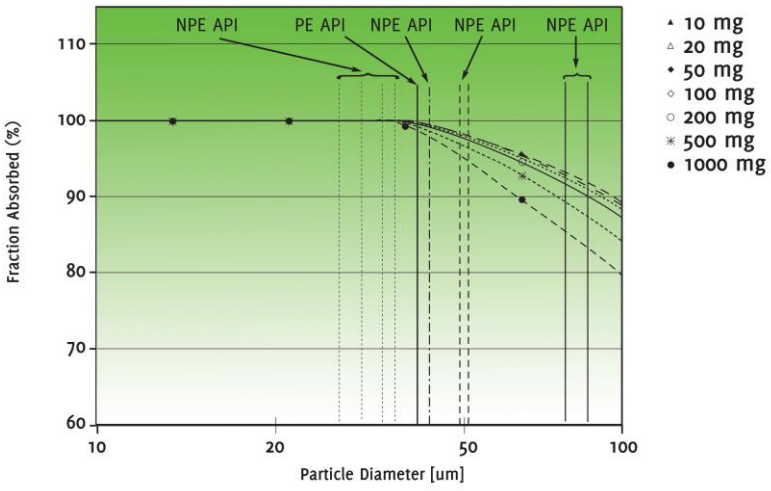
Figure 3: Regional absorption comparison, Day 1 versus Day 7



Assessment of Particle Size Changes

The Parameter Sensitivity Analysis (PSA) mode tests the sensitivity of the results to changes in single model parameters. In these studies, PSA was used to establish *particle size specifications*, which is the allowed variability in particle size before any significant changes in the predicted outcomes (for example, absorption and C_{max}) are observed. Also, because the drug is a Class II drug with known dissolution limitations, simulations were run changing both the particle size *and* the dose to determine if an increase in the dose would result in a higher or lower sensitivity to the change in particle size. Figure 4 illustrates the results of these simulations on absorption, which indicated that there would be very small changes, if any, in the Fa% until the largest particle sizes of the NPE API lots (approximately > 30 - 40 µm) were reached *and* the dose exceeded 100 mg.

Figure 4: Assessment of particle size changes



Population Simulations to Predict Virtual Bioequivalence

The Population Simulator predicts likely population distributions of PBPK/PD results over different populations. When running simulations with the Population Simulator, the values of *all* selected physiological and pharmacokinetic parameters are randomly sampled, each from their own defined distributions, for each simulation. (This is unlike the PSA, which samples only one parameter at a time while holding all other parameters constant.) This feature can be used to simulate crossover studies and evaluate whether two formulations are likely to be bioequivalent. The same simulated population of subjects with different formulations can be used in these crossover virtual trial simulations. Here, the Population Simulator was used to carry simulations for 10 different populations, each with 25 virtual subjects. A combination of default and observed variability from the analysis of individual subject data from the clinical studies of the NPE API lots was used to define the inputs for the population runs. To account for intra-subject and inter-occasion variability, a random multiplicative error term with CV = 15% was added to each of the simulated Cp-time profiles. (The intra-subject CV of 15% was selected based on the observed intra-subject CV from earlier crossover studies of the drug where the estimated intra-subject CV was ≤ 10% for AUCs and approximately 20% for C_{max}). Figure 5 shows the actual comparison of observed population PK data versus the simulation results. The dashed lines represent the 90% confidence intervals of the population simulations.

Figure 5: Comparison of observed population PK data versus simulation results

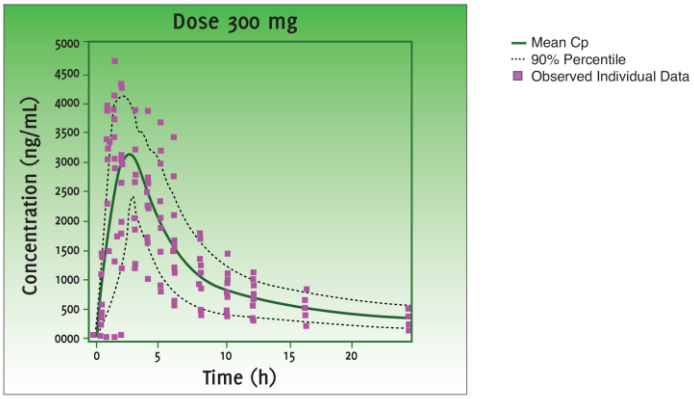


Figure 6 and Figure 7 compare the AUC and C_{max} values, respectively, for the tablets that were manufactured from the NPE API lots and the tablets that were manufactured from the PE API lot. The bioequivalence calculations, as defined by the FDA's guidance on Bioequivalence Studies, were implemented to show the similarities between AUC and C_{max} for the NPE API lots (up to 30 - 40 µm) versus the PE API lot.

Figure 6: AUC comparison for tablets manufactured from the NPE API lots and the PE API lot

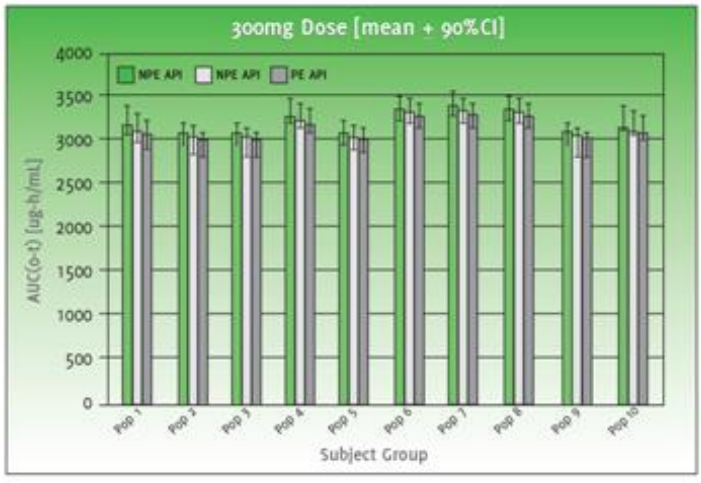
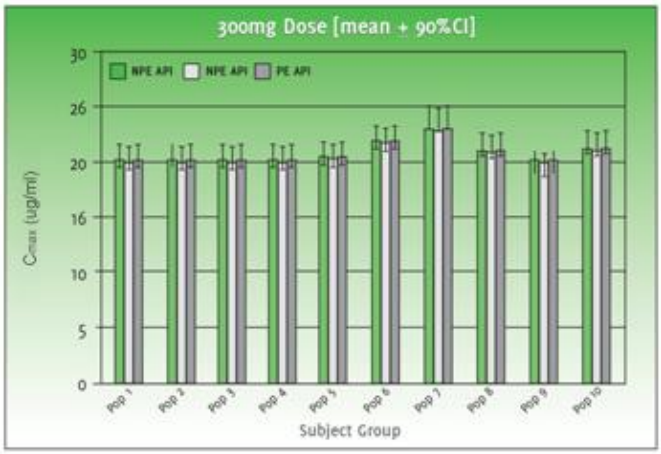


Figure 7: C_{max} comparison for tablets manufactured with the NPE API lots and the PE API lot



Conclusions

The BCS system currently allows for biowaivers for rapidly dissolving immediate-release (IR) products of Class I drugs. As demonstrated by Simulations Plus, the possibility of using modeling and simulation to extend biowaivers to IR products of Class II compounds is a breakthrough in formulation development. By eliminating bioequivalence studies, where appropriate, significant resource reductions in both costs and time to market for reformulated drug products can be realized while ensuring good drug product performance. Moreover, while the case study described here focuses on post-approval changes, the principle can be applied to generics when filing for ANDAs.