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Dissolution Modeling of Bead Formulations and Predictions of Bioequivalence for a Highly Soluble, Highly Permeable Drug

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Abstract: The objective of this study was to assess the impact of observed *in vitro* dissolution rate differences on *in vivo* pharmacokinetics for two enteric-coated bead formulations of a highly soluble, highly permeable drug. A new bead dissolution model was developed to quantitatively simulate the dissolution profiles of the two formulations. The model is based on the boundary layer diffusion model and can be used to simulate dissolution profiles for bead formulations using physicochemical properties of the formulation. The model was applied to show that the observed differences in dissolution profiles can be attributed completely to the difference in surface area of the beads for the two formulations. An absorption/pharmacokinetic model (GastroPlus) was used to predict the *in vivo* plasma concentration time profiles for the formulations using their respective *in vitro* dissolution profiles as input. The simulation results showed that the plasma concentration−time profiles were not significantly impacted by slower dissolution rates. Additionally, a sensitivity analysis was performed with a range of dissolution rate profiles. The fastest dissolution rate reached 80% dissolved in 41 min, while the slowest reached 80% in 114 min. Over this range, the predicted C_{max} decreased by 9% and the AUC decreased by 1%. An *in vivo* bioequivalence study on the two experimental formulations demonstrated the formulations were bioequivalent, consistent with predictions. The lack of sensitivity is attributable to the high permeability and long elimination half-life of the drug. The work presented in this article demonstrates the use of a bead dissolution model and an absorption/PK model to predict *in vivo* formulation performance.

Keywords: Dissolution; model; bioequivalence; absorption; bead formulation; enteric coating; delayed-release surface area; particle size; diffusion

Introduction

Dissolution models have been used by pharmaceutical scientists for some time with different levels of sophistication. They are often used to simulate either rotating disk dissolution[1−3] or particle dissolution.[4−10] Despite the fact that recent research[11] has shown the improved prediction accuracy of a reaction-limited model for dissolution, most models are still based on mass transfer-limited diffusion through a boundary layer and use the Noyes−Whitney equation[12] as a starting point. In this paper we describe a model for coated bead formulations. The model is similar

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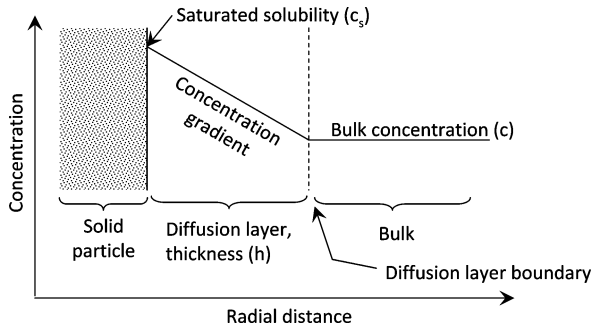

Figure 1. Schematic representation of the boundary layer dissolution model.

to the particle dissolution models, but takes into account the inert core of a coated bead.

The model is based on the familiar boundary layer model. A schematic representation of the model is given in Figure 1. The methodology and terminology follow those reported by other authors,[7,8] with two additional parameters to account for the solid inert core and the mass fraction of drug in the drug-containing layer. The drug layer in bead formulations is often a mixture of drug and binder. As will be shown, the boundary layer model equations can be modified to account for the dilution of drug with excipients. Despite the fact that the drug layer is not pure drug in a bead formulation, for sufficiently high drug load in the drug layer, all of the assumptions of the boundary layer model still apply.

The model drug used for the experimental work is a compound being developed by Eli Lilly and Company. The drug is a small-molecule hydrochloride salt, and it is highly soluble across the physiologic pH range. Caco-2 studies showed that the compound was also highly permeable. The compound has been shown to degrade rapidly in acid media; therefore the drug has been formulated as an enteric coated bead, which shields the compound from the acid environment of the stomach but allows release of the drug at the more neutral pH of the intestine.

After development of an original enteric coated bead formulation (formulation A), a new formulation for the drug product was being developed that contained higher drug load (formulation B). The drug load was increased by increasing the mass of the drug containing layer by 60% by spraying on a thicker layer. All other aspects of the formulation remained the same. During development, dissolution tests for formulation B consistently showed slower release relative to formulation A.

Dissolution of enteric coated formulations is performed, per the compendia,[13] as a two stage test, first applying an acid challenge stage, generally performed in 0.1 N hydrochloric acid, followed by dissolution in neutral (for example, pH 6.8) buffered media. The acid challenge stage confirms the integrity of the enteric coating and the buffer dissolution stage demonstrates the release of the product. Dissolution tests for the drug product pellets are performed using conditions of USP General Chapter ⟨711⟩, delayed release, method B. This approach uses apparatus I (baskets). The acid challenge stage is performed in 1000 mL of 0.1 N hydrochloric acid. At the end of the acid challenge, the medium is replaced with 1000 mL of pH 6.8 buffer.

Initially it was speculated that the dissolution apparatus could be causing the delayed release of formulation B. The baskets confine the formulation which potentially allows the pellets to agglomerate or the excipients to clog the basket mesh, impacting the rate of dissolution. To demonstrate the product release in the absence of the baskets, dissolution was performed using apparatus II (paddles). Delayed release, method B, is not practical for use with apparatus II since the sample has to be transferred to a new medium between the test stages. An alternate approach, using USP General Chapter ⟨711⟩, delayed release, method A, was used to allow testing without transferring the sample. This approach uses a reduced volume of the acid medium (750 mL of 0.1 N hydrochloric acid) for the acid challenge stage. At the end of the acid challenge stage, 250 mL of 0.20 M tribasic sodium phosphate is added to the acid to achieve a pH of about 6.8.

The drug development program required that formulation B be bioequivalent to formulation A. The above-mentioned dissolution model (Figure 1) was utilized to explain the observed *in vitro* results. Subsequent absorption/phamacokinetics (PK) simulation was used to predict the impact of this observed change in dissolution profile on the risk of nonbioeqivalence. This work led to an *in vivo* bioequivalence study to demonstrate the bioequivalence of formulations A and B.

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Experimental Section

Materials. The enteric coated pellet formulation contains multiple layers, including a nonpareil bead core, an active coating layer, a barrier layer, the enteric coating and a color coating. The active ingredient is coated on the formulation at a defined weight percent. The weight percent of API in formulation B is 60% higher than formulation A, while the barrier layer and enteric layer are applied with the same coating thickness as formulation A.

Dissolution was performed using media specified for delayed release testing in USP General Chapter, ⟨711⟩. Reagent grade hydrochloric acid and tribasic sodium phosphate were obtained. Media of 0.1 N hydrochloric acid, 0.20 M tribasic sodium phosphate and pH 6.8 buffer were prepared per instructions in the general chapter.

***In Vitro* Methods.** Dissolution tests for the drug product pellets were performed using conditions of USP General Chapter ⟨711⟩, delayed release, method B and method A. Both test approaches used a two hour acid challenge, followed by one hour of dissolution. The acid challenge stage was sampled at the end of the two hours. The buffer stage dissolution was sampled at 15 min intervals for one hour. Tests were performed on pellets, which were added by weight, equivalent to the highest clinical dose. Analysis of dissolution samples was performed using an isocratic reversed-phase HPLC assay.

For method B, apparatus I (baskets) was applied using the test criteria of formulation A. The 2 h acid challenge stage was performed in 1000 mL of 0.1 N hydrochloric acid equilibrated to 37 °C. At the end of the acid challenge, the medium was replaced with 1000 mL of pH 6.8 buffer, equilibrated to 37 °C prior to placing the product in the medium. The baskets were rotated at 100 rpm throughout the test.

Method A was applied for testing with apparatus II (paddles). A reduced volume of the acid medium (750 mL of 0.1 N hydrochloric acid) was used for the acid challenge stage. At the end of the acid challenge stage, 250 mL of 0.20 M tribasic sodium phosphate, prewarmed to the test condition of 37 °C, was added to the acid to achieve a pH of about 6.8. Dissolution was initiated upon addition of the tribasic sodium phosphate and after pH adjustment (if necessary). A high stirring rate (100 rpm) was used to ensure the pellets did not collect in the bottom of the vessel and agglomerate or form a cone.

Bead Dissolution Model. The bead dissolution model was developed using the nomenclature and derivation of Hintz and Johnson.[7] As these authors showed, starting with a Noyes−Whitney-type expression,[12]

$$-\frac{dX_s}{dt} = \frac{DS}{h}\left(C_s - \frac{X_d}{V}\right) \quad (1)$$

one can derive an expression for change in mass as a function of time for a collection of spherical particles:

$$-\frac{dX_s}{dt} = \frac{3DX_0^{1/3}X_s^{2/3}}{\rho h r_0}\left(C_s - \frac{X_d}{V}\right) \quad (2)$$

where X_s is the mass of solid drug at any time t, X_d is the mass of dissolved drug, X_0 is the initial mass of drug, D is the diffusion coefficient of the aqueous drug molecule, S is the surface area of the drug particle, h is the unstirred boundary layer thickness, C_s is the saturation solubility of the drug in the dissolution medium, V is the dissolution volume, ρ is the true density of solid drug and r_0 is the initial particle radius.

For a drug coated bead, a new expression equivalent to eq 2 can be derived by modifying the expression to account for the nonpareil bead core with a radius r_c. First, the number of beads, N_0, is given by

$$N_0 = \frac{3X_0}{4\rho f\pi(r_0^3 - r_c^3)} \quad (3)$$

where f is the volume fraction of drug in the drug-containing layer. In other published implementations of the unstirred boundary layer model, the true density of drug is used to relate the drug mass and volume, which then determines the surface area. Because in this case the drug layer is a mixture of drug and excipients, the volume and surface area of the bead is related to the mass by the product of ρ and f. The bead formulations studied here have drug layers that contain 75% v/v drug in a mixture of sucrose and hypromellose. Thus, $f = 0.75$ in all simulations. Using eq 3, the surface area of the beads (S) can be written as a function of the initial values for the physical dimensions and the current drug mass, X_s:

$$S = \frac{3X_0}{\rho f(r_0^3 - r_c^3)}\left[\frac{X_s}{X_0}(r_0^3 - r_c^3) + r_c^3\right]^{2/3} \quad (4)$$

Substituting eq 4 into eq 1 gives the final form of the bead dissolution model equation:

$$-\frac{dX_s}{dt} = \frac{3DX_0}{\rho f h(r_0^3 - r_c^3)}\left[\frac{X_s}{X_0}(r_0^3 - r_c^3) + r_c^3\right]^{2/3}\left(C_s - \frac{X_d}{V}\right) \quad (5)$$

The differential equation was solved by the Euler numerical method[14] using Mathcad 13.0 software (Parametric Technology Corp., Needham, MA).

The bead dissolution model assumes that the size of the nonpareil bead core (r_c) is time-invariant and monodisperse. The outer radius of the drug layer, however, is dynamic and polydisperse. At $t = 0$, the bead size distribution is divided into 30 discrete bins ($i = 30$), where each bin has a characteristic size ($r_{0,i}$) and mass ($X_{s,i}$). The initial bead size distribution is assumed to follow a log-normal distribution with a geometric standard deviation

(14) Boyce, W. E.; DiPrima, R. C. *Elementary Differential Equations and Boundary Value Problems*, 5th ed.; John Wiley & Sons: New York, 1992; pp 387−392.

of 1.05, which is an approximation of the bead size distribution observed by optical microscopy. At each integration time step, the differential equation is solved for each bin independently. Before the next time step, a new value is calculated for the bead size in each bin and the mass in each bin. All the bins contribute to the current bulk concentration (X_d/V) at every time step, thus while the differential equation for each bin is solved independently, the bins interact at each time step.

In pH 6.8 buffer, the solubility of the drug is 1.53 mg/mL. The true density of the drug is 1.26 g/cm^3 and the aqueous diffusion coefficient is estimated to be 7.72×10^{-6} cm/s from the molecular weight, using the estimator built into the GastroPlus absorption/PK simulation software. The manufacturer's claimed radius of 275 μm for the nonpareil bead core is used in all simulations. The recommendation of Lu and Johnson is used to estimate the diffusion layer thickness parameter, namely that $h =$ particle radius, with a constraint of $h \leq 30$ μm.[8] More recent work[15] suggests more sophisticated models for the diffusion layer thickness; however, the estimations of Lu and Johnson were found to be adequate for this study. While the model is capable of utilizing a time-variant value for h, the beads will always be larger than 30 μm, thus the value of the parameter is effectively fixed at 30 μm throughout the simulation.

Pharmacokinetic/Absorption Modeling. The potential impact of a slower dissolution profile on absorption was modeled using GastroPlus version 6.1.0003 (Simulations Plus, Inc., Lancaster, CA). The model was optimized by first utilizing intravenous PK data to determine distribution and elimination parameters. The PK data was described by a two-compartment model. The GastroPlus model parameters adjusted to optimize the fit are the volume of distribution, clearance and the second compartment rate constants, k12 and k21. The parameter values were determined by using the optimization feature of GastroPlus, with the *in vivo* concentration−time profile as the observed values. All other distribution and metabolism parameters were left at their default values. These parameters were then fixed for the remainder of the simulations.

The absorption parameters of the model were optimized utilizing *in vivo* PK data and corresponding *in vitro* dissolution data from formulation A. A simulated drug release function was created by taking the observed buffer stage *in vitro* data (see Figure 2a) and shifting it by 0.5 h to account for the delayed release of drug afforded by the enteric coating. The gastric empty time parameter was correspondingly set at 0.5 h. The permeability of the drug was shown by Caco-2 experiments to be high, so the permeability parameter for the model was set sufficiently high so that absorption was not permeability limited and was not further optimized. First-pass hepatic extraction was set based on the PK results from human PK studies. Using these parameters, the GastroPlus model provided a good fit to observed data with an average percent prediction error of 6.3%.

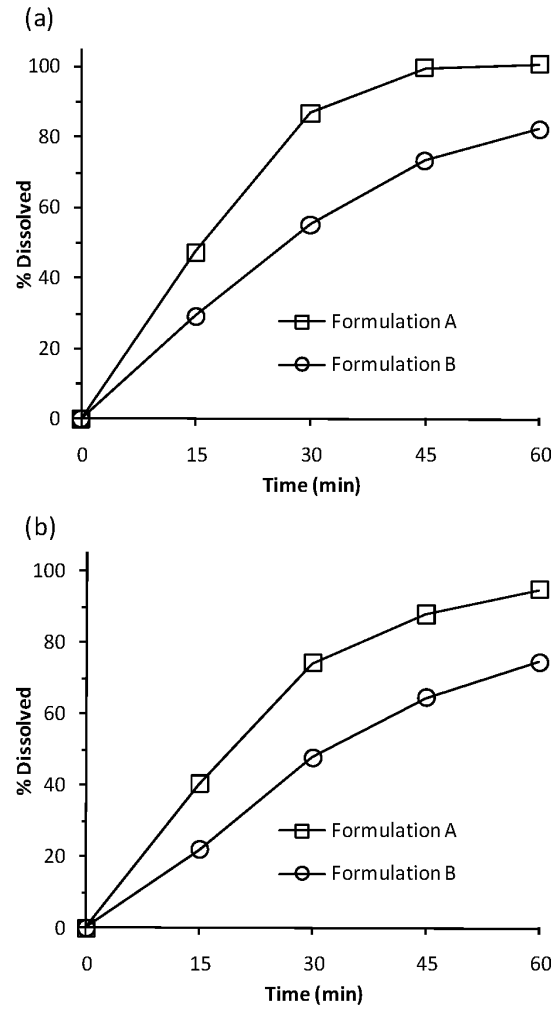

Figure 2. Average *in vitro* dissolution profiles ($n = 6$) of pellet formulations A and B by (a) USP method A and (b) USP method B. In all cases the standard error is 2% dissolved or less.

The impact of changes in dissolution profiles on *in vivo* PK profiles was simulated utilizing the identical model parameters with different simulated drug release profile inputs. To predict the PK profile of formulation B, a simulated dissolution profile was created from experimental data (see Figure 2) in the same manner as described above. A more general sensitivity analysis was also conducted by creating a simulated dissolution profile by fitting a Weibull function (eq 6) to the formulation A dissolution profile.

$$D(t) = 100 \times (1 - e^{[-(t-T)^b]/A}) \quad (6)$$

where $D(t)$ is the percent of dose dissolved as a function of time t, T is the time-shift parameter, fixed at 0.5 h, as

(15) Sheng, J. J.; Sirois, P. J.; Dressman, J. B.; Amidon, G. L. Particle Diffusional Layer Thickness in a USP Dissolution Apparatus II: A Combined Function of Particle Size and Paddle Speed. *J. Pharm. Sci.* **2008**, *97*, 4815–4829.

discussed above, b is a profile shape parameter, fixed at 1.70 to optimize the fit of the function to experimental data, and A is time-scale parameter. The Weibull function is used in lieu of experimental or simulated (model) release profiles because it provides a simple and general means of determining the sensitivity of simulated PK results to changes in release profile by varying a single parameter. GastroPlus simulations were run while adjusting the Weibull time-scale parameter (all other parameters fixed) to change the rate of dissolution.

Pharmacokinetic Study Design in Healthy Subjects. The study was designed as an open-label, randomized, single-dose, two-period crossover study. Subjects were randomly assigned to receive a single dose each of formulation A and formulation B in a crossover fashion. Thirty-three healthy male and female subjects, aged 18 to 70 years, entered and completed the study. Blood samples were obtained by venipuncture. Following single oral dose administration, sequential blood samples were collected at predose and up to 72 h post dose.

Pharmacokinetic Methods. The plasma concentrations of the drug were determined using a validated LC/MS/MS method. The interassay accuracy (% relative error) and the interassay precision (% relative standard deviation) during validation were <5%.

Pharmacokinetic parameters were calculated using non-compartmental method of analysis using WinNonlin Enterprise Edition Version 4.0.1 (Pharsight Corporation, St. Louis, MO). The primary pharmacokinetic parameters to assess bioequivalence were as follows: maximum observed plasma concentration (C_{max}) and area under the plasma concentration−time curve from time zero to infinity (AUC[0−∞]).

Statistical Methods. SAS Version 8.2, WINDOWS edition, was used for all statistical analyses. The PK parameters were logarithmically transformed, and the formulation comparison was evaluated by the least-squares geometric mean ratio of formulation B to formulation A. The 90% CI of the ratio was constructed for each parameter. A mixed-effect analysis of variance (ANOVA) was used to analyze the data. The model contained sequence, formulation and period as the fixed effects and subject nested within sequence as the random effect. Nonparametric analysis using Wilcoxon signed-rank test was used for evaluating t_{max}.

Results

***In Vitro* Results.** *In vitro* dissolution results for formulations A and B are shown in Figure 2. The *in vitro* profiles using USP method A are faster than those for method B for both formulations. However, both methods show that formulation B dissolves more slowly in the buffer stage of the dissolution test compared to formulation A. While these results show that the dissolution rate has some dependence on the selection of the test conditions, the fact that both methods show a similar difference between the two formulations confirms that the delay was not related to the dissolution test conditions and was the result of the formulation change.

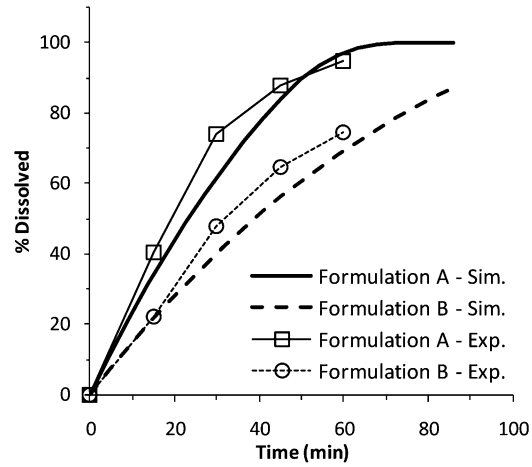

Figure 3. Simulated dissolution profiles using the bead dissolution model with physicochemical parameters for formulations A and B, compared to experimental dissolution data (USP method B) for formulations A and B, taken from Figure 2b.

Bead Dissolution Model. The bead dissolution model was used to understand the quantitative differences in the release profiles for formulations A and B. The simulated profiles are shown in Figure 3, along with the experimental data taken from Figure 2. One can see that the simulation slightly underpredicts the observed dissolution profiles. The prediction of the model can be significantly improved by optimizing physicochemical input parameters, such as solubility, diffusion coefficient and diffusion layer thickness. However, the goal of this work is to show that the predictive power of the model is sufficiently accurate for the intended purpose without the need to optimize parameters, which are taken directly from measured quantities or estimated by standard means. The model is a reasonable quantitative description of the release of drug from the bead, but more importantly, the model correctly predicts the differences in dissolution release profile between formulations A and B. For example, the simulation predicts an absolute different between formulation A and B at 30 min to be 22%, while the difference in experimental values at this same time point is 27%.

Pharmacokinetic/Absorption Modeling. The simulated PK profiles from GastroPlus modeling of formulations A and B are shown in Figure 4 along with the observed *in vivo* plasma concentrations for formulation A. The figure demonstrates the good agreement of the parametrized model and the *in vivo* results for formulation A. The average percent prediction error is 12.6%, excluding the 2 h data point which is on the steep rising edge of the absorption phase. The slower release profile of formulation B has a small impact on the overall PK profile. The modeled C_{max} of formulation B is 5% lower than formulation A, but the AUC is practically unchanged (<1%). The magnitude of changes in C_{max} and AUC from the simulations would not be considered a concern

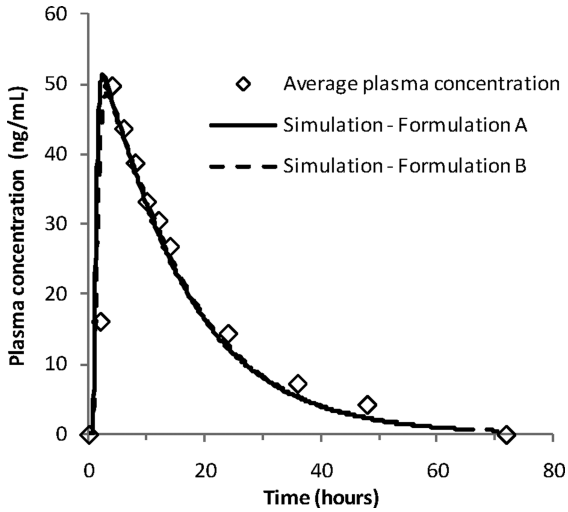

Figure 4. Simulated PK profiles for formulations A and B along with observed mean *in vivo* plasma concentrations for formulation A.

Table 1. Pharmacokinetic Parameter Results of Sensitivity Analysis Showing Impact of Changes to the Release Profile

	Weibull time-scale parameter (*A*)		
parameter	0.04	0.15[a]	1.1
time to reach 80% (min)[b]	41	56	114
relative C_{max}	1.00	1	0.91
relative AUC (0−∞)	1.00	1	0.99
t_{max} (h)	2.4	2.5	3.46

[a] The Weibull function fit to formulation A gives a time-scale parameter $A = 0.15$. [b] The time to reach 80% dissolved for the dissolution profile described by the Weibull function.

to demonstrate bioequivalence of the two formulations. Similarly, the modeled t_{max} of formulation A is 2.5 h, while the slower release profile of formulation B results in a t_{max} of 3.1 h.

The results of the sensitivity analysis are shown in Table 1. The PK parameters are relatively insensitive to changes in release profile. Over the range of release profiles that are from 15 min faster than formulation A up to 1 h slower (i.e., a range of 1.25 h), the AUC decreases only 1% for the slowest release rate, while the C_{max} decreases 9%. Over this same range, the t_{max} increases almost proportionally to the drug release rate. The t_{max} is approximately 1 h longer for the slowest release profile compared to the fastest.

In Vivo **Results.** The mean plasma concentration−time profiles were similar following oral administration of the same dose of formulations A and B (Figure 5). The ratios of geometric least-squares means and the corresponding 90% confidence intervals for AUC(0−∞) and C_{max} were within the bioequivalence criteria of 0.8 and 1.25 (Table 2). Therefore, formulation B meets the criteria for bioequivalence to formulation A. The median difference in t_{max} values for the two formulations is zero, and they were not statistically different ($p > 0.05$).

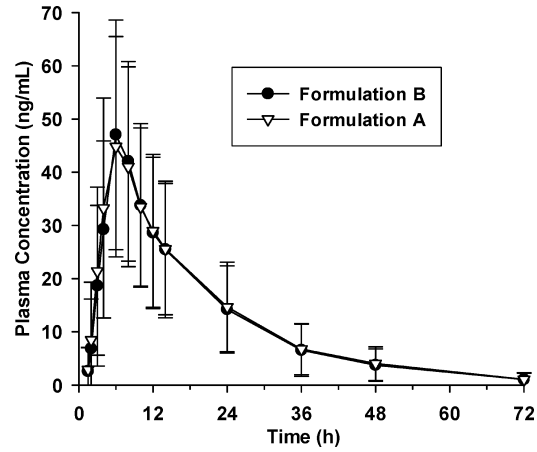

Figure 5. Arithmetic mean (SD) plasma concentration−time profile of drug following a single oral dose of formulations A and B.

Table 2. Relative Pharmacokinetic Parameters and Confidence Intervals Comparing Formulations A and B

parameter	ratio of geometric mean (B/A)	90% confidence interval
C_{max}	1.03	(0.95−1.11)
AUC(0−∞)	0.98	(0.92−1.05)

Discussion

The *in vitro* dissolution results for the enteric coated beads using USP method B (Figure 2) indicate that formulations A and B have different release profiles. While formulation B is expected to dissolve more slowly because of the lower bead surface area, a quantitative description of the difference in release profile is not obvious. As with most solid oral dosage forms, several formulation and experimental factors are known to impact the *in vitro* release rate for these formulations.[16] Of these factors, the impact of bead aggregation in the dissolution basket is the most difficult to estimate. Utilizing USP method A, the *in vitro* release profile of both formulations A and B is more rapid (Figure 2) compared to method B, presumably because there is no bead aggregation with method A. These experiments indicate that the difference in release rate (observed by both methods) is due to the differences between the formulations and not simply an artifact of the *in vitro* test. However, from these data alone, it is not clear if the observed difference between formulations is due purely to the difference in bead surface area or if other formulation factors are contributing.

The bead dissolution model is an extension of modeling work published in the literature by Johnson and others.[7,8] However, this is the first publication of a model that explicitly treats the inert core of a bead formulation. The model utilizes a discritized particle size distribution analogous to that of

(16) Abdou, H. M. *Dissolution Bioavailability and Bioequivalence*; Mack Publishing Company: Easton, PA, 1989; pp 73−100 and 115−143.

Johnson, which, as noted by Sertsou,[17] precludes an analytical solution to the differential equation. Mooney et al.[2,3] showed the value of accurately accounting for the pH variations throughout the diffusion layer for a rotating disk configuration. The bead dissolution model does not calculate diffusion layer pH; however, this could be added in further implementations of the model. In principle, the model could be adapted to account for absorption, as has been demonstrated by others.[4,7] The goal of this work was to utilize the bead dissolution model to determine the quantitative *in vitro* release rate difference that would be expected for formulations A and B based purely on the physicochemical parameters, and in this case, especially surface area. Absorption modeling was addressed in a more complete sense through subsequent GastroPlus modeling.

The results of the simulations for formulations A and B (Figure 3) are very similar to the observed experimental data. In these simulations, all parameters for both formulations are identical except for the surface area. Thus, the agreement between the simulations and the experimental data suggests that the differences in release rate observed *in vitro* are due purely to the difference in surface area. Importantly, the model does not have parameters that are optimized specifically for this study; the inputs to the model are based only on measured and estimated physicochemical parameters. This fact makes the model useful in a predictive sense. That is, it is not necessary to first have experimental data to calibrate the model; predictions can be completed before any formulations are made.

With a good understanding of the dissolution performance of the formulations, the absorption/PK simulations helped predict the impact on PK and bioequivalence. Given that intravenous and oral PK data existed to calibrate the absorption model, the optimization of the model parameters could be completed with some confidence. As a result, the fit of the model to observed PK results is quite good (Figure 4). The predictions of the plasma concentration−time profiles for formulation B (Figure 4) and the sensitivity analysis (Table 1) both show that PK is not sensitive to changes in drug input rate. The reason for the lack of sensitivity comes primarily from two properties of the drug molecule: high permeability and long elimination half-life. Because the permeability is high, the fraction absorbed or total exposure (AUC) is not impacted by even relatively large changes in drug input rate. The elimination half-life for the compound is approximately 12 h. With a long half-life such as this, C_{max} is only marginally impacted by changes in drug input rate. Even a 1 h change in drug input rate is relatively small compared to the 12 h half-life. The model would suggest that there is very low risk for bioequivalence failure for these two formulations.

The two-period crossover bioequivalence study showed that formulations A and B are bioequivalent by a confidence interval analysis. In fact, the ratios of geometric means for C_{max} and AUC were very near unity. However, the t_{max} in the bioequivalence study was longer than the value predicted in the simulations. Furthermore, t_{max} was longer in the bioequivalence study than in the previous PK studies. The previous PK study data was used to optimize the GastroPlus model, thus the model will reflect the t_{max} previously observed and not the value that was observed in the bioequivalence study. Even with this difference, the GastroPlus simulations are not predicting a t_{max} as long as that which has been observed in any study. This could be due to the method used to simulate the delay in release caused by the enteric coating, namely a 0.5 h delay in the release profile to simulate gastric residence. While the *in vitro* data show that in pH 6.8 buffer the formulations begin to release drug rapidly, the *in vivo* conditions may be different and may not lead to rapid enteric coating release. However, despite the problems simulating t_{max} accurately, bioequivalence between the two formulations is demonstrated as the simulations predicted.

In summary, a bead dissolution model was developed that was shown to successfully simulate dissolution of enteric coated bead formulations. The model can be used to simulate the effects of a variety of physicochemical parameters; in this case, it was utilized to show the effect of changing bead surface area. This modeling approach has inherent limitations similar to most modeling approaches. The accuracy of the simulation results depend on the accuracy of the physicochemical input parameters. Relating simulated dissolution rates to actual *in vivo* drug release rates requires detailed knowledge of the *in vivo* environment (e.g., pH, solubilization capacity afforded by bile salts, etc.) and how these parameters might impact formulation performance. Formulations that are sensitive to changes in the *in vivo* environment may have additional variability not predicted by the model. In these situations, additional work would be needed to understand the implications for variability in PK.

For the bead formulations studied here, it was shown that subsequent absorption/PK modeling with GastroPlus predicted that the difference in release rates caused by the change in bead surface area would not be expected to impact PK parameters. A two-period crossover bioequivalence study utilizing formulations A and B demonstrated bioequivalence between the two formulations. This work illustrates how *in vitro* and absorption/PK modeling can predict formulation bioequivalence, which can then be used in risk analysis for pharmaceutical development. In this case, the *in vitro* and modeling work demonstrated that the risk of non-bioequivalence was very low. The use of these modeling tools can guide drug product design and clinical study design to reduce the occurrence of unsuccessful bioequivalence studies. The work described in this paper in line with a general trend to more fully utilize modeling in drug development. The success

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of this work and others[18,19] suggests that regulatory agencies should consider granting waivers of *in vivo* bioequivalence studies in cases where the risk of non-bioequivalence can be shown to be very low, similar to other so-called biowiaver approaches.[20−22]

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