

Research Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development

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Mathematical Model-Based Accelerated Development of Extended-release Metformin Hydrochloride Tablet Formulation

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Abstract. A computational fluid dynamic (CFD) model was developed to predict metformin release from a hydroxypropylmethylcellulose (HPMC) matrix-based extended-release formulation that took into consideration the physical and chemical properties of the drug substance, composition, as well as size and shape of the tablet. New high dose strength (1000 mg) tablet geometry was selected based on the surface area/volume (SA/V) approach advocated by Lapidus/Lordi/Reynold to obtain the desired equivalent metformin release kinetics. Maintaining a similar SA/V ratio across all extended-release metformin hydrochloride (Met XR) tablet strengths that had different geometries provided similar simulations of dissolution behavior. Experimental dissolution profiles of three lots of high-strength tablets agreed with the simulated release kinetics. Additionally, a pharmacokinetic absorption model was developed using GastroPlus™ software and known physicochemical, pharmacokinetic, and *in vitro* dissolution properties of metformin to predict the clinical exposure of the new high strength (1000 mg) tablet prior to conducting a human clinical bioequivalence study. *In vitro* metformin release kinetics were utilized in the absorption model to predict exposures in humans for new 1000-mg Met XR tablets, and the absorption model correctly projected equivalent *in vivo* exposure across all dose strengths. A clinical bioequivalence study was pursued based on the combined modeling results and demonstrated equivalent exposure as predicted by the simulations.

KEY WORDS: diffusion; CFD; GastroPlus; HPMC; mathematical model; scale-up; surface area; volume.

INTRODUCTION

Hydroxypropylmethylcellulose (HPMC) is a commonly used drug release controlling polymer in a matrix tablet formulation. Its detailed characterization has been reported by Siepmann and Peppas (1). The same authors also summarized empirical and semi-empirical mathematical models reported in pharmaceutical literature to explain the drug release mechanism from HPMC-based systems (1). Additionally, a mathematical model showing the importance of tablet surface area/volume ratio was reported by Lapidus and Lordi (2,3). However, the detailed investigation of this concept and its practical utility were reported some time later by Reynolds *et al.* (4), who verified several key concepts. Tablets with same surface area, but different surface area/volume ratio did not result in

similar drug release. Tablets with larger surface area/volume ratio had faster drug release profiles. One of the most useful findings was that drug release from HPMC matrix tablet was comparable for similar surface area/volume ratios within the same tablet shape as well as among different shapes (4). This finding could be immensely useful to pharmaceutical scientists needing to develop additional higher or lower strength tablets of an established or to change tablet shapes to distinguish various tablet strengths. Adapting a modified release tablet surface area/volume ratio to produce a drug release profile similar to that of the reference tablet can increase the likelihood of bioequivalence between the test and reference formulations.

The rapid development of a high-strength (1000 mg) extended-release metformin hydrochloride (Met XR) tablet formulation was pursued through a mechanistic analysis that employed multiple fundamental modeling techniques to ensure robust performance. The high-strength tablet formulation was a common composition to existing commercial tablet strengths. Based on the scale-up and post-approval change (SUPAC) guidance for a modified release formulation, in absence of an *in vitro* *in vivo* correlation (IVIVC), a bioequivalence (BE) study would be needed if there is a change in manufacturing site, manufacturing process, or more than 10% change in the amount of release controlling excipient (5). Additionally, a higher tablet strength

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from the reference strength (case of this 1000 mg Met XR) would also require a BE study (6). To minimize the BE risk, three mathematical modeling approaches were utilized. Firstly, Lapidus and Lordi's model was applied to maintain a similar surface area/volume ratio during the scale-up of the new HPMC-based extended-release 1000-mg Met XR. Second, the dissolution behavior of the prototype tablet geometries were predicted using Gambit and Fluent modeling software before tablet manufacture or *in vitro* testing was pursued. Third, the physicochemical, pharmacokinetic, and *in vitro* release properties of high-strength metformin hydrochloride tablets were used to construct a GastroPlus pharmacokinetic absorption model to predict the clinical exposure of the new strength. This model-based development of a high-strength Met XR tablet formulation demonstrates a valuable approach for applying mechanistic models to obtain robust drug product clinical performance.

MATERIALS

Metformin hydrochloride was supplied by Merck Serono (Merck Serono, Calais, France). The following ingredients were used as received from the suppliers: sodium carboxymethylcellulose USP (FMC, Philadelphia, PA), hypromellose 2208 USP (Colorcon, West Point, PA), and magnesium stearate NF (Mallinckrodt, St. Louis, MO).

METHODS

Tablet Formulation. The tablet formulation design and the mechanism of metformin release have been previously published (7,8). The tablet formulation can be described as a two-phase system. The inner phase consists of fine metformin particles in intimate contact with sodium carboxymethylcellulose (SCMC). This drug-SCMC combination is then dispersed in a second continuous matrix of a second hydrophilic polymer, hypromellose. When a tablet formed from this blend (69% *w/w* metformin hydrochloride) comes in contact with fluid, the polymer hydrates and causes a tablet to develop a gel-like mass. Metformin slowly diffuses through the gel-like mass (7).

Metformin hydrochloride and sodium carboxymethylcellulose were mixed in a PMA 300 high shear granulator. The mix was granulated using purified water. The wet granules were wet milled using a comil and then dried to less than 2% *w/w* residual moisture in GPCG 120 (Glatt Particle Coater Granulator 120). The granulation batch size was 64 kg and four batches of granulation were combined for drying in GPCG 120. The dried granules were milled using Fitzmil and mixed with hypromellose and magnesium stearate in a bin blender. The final blend was compressed into 1450-mg tablet weight using Korsch XL 400 (Korsch Maschinenfabrik, Berlin, Germany) fitted with a capsule-shaped D tooling. Within the capsule shapes, seven different dimensions (length, width, thickness, and band thickness) were evaluated (Table I).

Dissolution. The tablet dissolution was conducted in 1000 mL in 50 mM pH 6.8 phosphate buffer, 50 mM pH 4.5 acetate buffer, or 0.1 N HCl at 37°C using the basket at 100 rpm. The tablet dissolution of Met XR 750 was conducted using the basket speed of 50 rpm. Dissolution of 2×500 Met XR was conducted using paddles at 100 rpm. Samples were taken at 60, 180, and 600 min. The sample volume was 10 mL.

For HPLC method for Met XR Dissolution, 50 mM pH 6.8 phosphate buffer was used as a mobile phase at the flow rate of 1.5 ml/min through a 2-mL sample loop with an in-line 2- μ filter. The sample injection volume was 15 μ l. Metformin was detected at the wavelength of 232 nm. The run time was 4 min.

Dissolution Simulation. A computational fluid dynamic (CFD)-based mathematical model was developed to predict metformin hydrochloride release from a matrix-based formulation that takes the physical and chemical properties of the drug substance, composition, and size and shape of the tablet into consideration, particularly to simulate the dissolution profile for an arbitrary shape and size of the tablet compared with the cylinder shape of the tablet normally used before, since CFD can mimic an arbitrary geometry of the tablet and has a well-established partial differential equation solver to obtain a converged solution easily. The geometry of the tablet was meshed using Gambit software (Fig. 1) and used in the dissolution simulations run on Fluent software.

GastroPlus Pharmacokinetic Absorption Model Development and Simulations. Using the physicochemical and pharmacokinetic properties of metformin hydrochloride, a pharmacokinetic absorption model was previously developed using GastroPlus™ V.7.0 software (9). The model was used to simulate the mean plasma concentrations for a wide range of drug release profiles and gastric emptying time for a 1000-mg dose of metformin. A wide range of drug release rates proportional to the square root of time that approximate the behavior of a swellable hydrophilic matrix were used to simulate the clinical exposure. These release profiles varied from 100 to 40% drug being released in 3 h, which corresponds to the mean transit time for the small intestine where metformin exhibits the greatest permeability. Gastric emptying times used in the simulations ranged from $T_{50}=0.25$ h up to $T_{50}=3.00$ h. The C_{max} and AUC (0–24) were determined from the simulated plasma concentrations and then plotted as a function of the percent drug released at 3 h and the simulated gastric emptying time. The model assumes that the drug release profiles represent the *in vivo* drug release from the formulations. These plots created a surface from which one can determine the drug release profile having the least impact from gastric emptying due to food and size exclusion effects.

Bioequivalence Study. The first bioequivalence (BE) study was conducted comparing 2×500 Glucophage XR (reference product) to 1×1000 mg Met XR (test product) in a 13 healthy subjects in randomized two period two treatment crossover study. The numbers of subjects was increased to 30 in the second BE study which was similar to the first BE study. The blood samples were collected after dosing at 15, 30, and 45 min and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, and 48 h. Plasma samples were analyzed using the previously reported method (7).

RESULTS AND DISCUSSION

Several mathematical models have been proposed to characterize the drug release (10,11). For the present study, a CFD-based model was developed to quantitatively describe

Table I. Dimensions of Tablet Tooling Design Considered for Met XR 1000 mg Tablet

	Metformin XR 750 As a reference	Capsule shape (Elizabeth carbide)	Modified Capsule (Natoli)	Modified capsule (Elizabeth carbide)	Oval (Elizabeth carbide)	Oval/modified capsule (Elizabeth carbide)	Modified capsule (Elizabeth carbide)
Drawing ID	R	A	B	C	D	E	F
Length (in.)	0.748	0.887	0.925	0.848	0.910	0.887	0.960
Width (in.)	0.3642	0.3450	0.3750	0.4750	0.4750	0.4100	0.3800
Thickness (in.)	0.2480	0.3290	0.2888	0.24350	0.2560	0.3030	0.2903
Band thickness (in.)	0.1300	0.2050	0.1706	0.1635	0.1560	0.1670	0.1563
SA (in ²)	0.7736	1.0347	1.0611	1.0912	1.0810	1.0331	1.0645
Vol (in ³)	0.0485	0.0754	0.0745	0.0745	0.0747	0.0754	0.0754
SA/Vol (1/in.)	15.94	13.73	14.24	14.64	14.48	13.70	14.12
Width-thickness (in.)	0.1162	0.0160	0.0862	0.2315	0.2190	0.1070	0.0897
Comments	Reference	Twining issue during coating	Too long to swallow easily	Orientation issue during tablet printing	Too long to swallow easily	Preferred	Too long to swallow easily

The parameters for selected tooling design is highlighted to facilitate comparison with the similar parameters for other tooling designs in inches, SA surface area

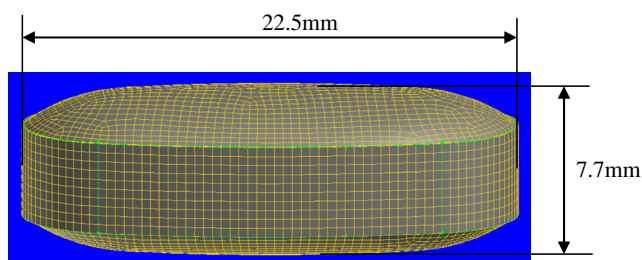
the drug transport in the matrix of the tablet and the drug release process. The following assumptions were made:

1. The drug is initially uniformly distributed in the tablet.
2. Only the drug diffuses in the tablet with a constant diffusivity, and the diffusion is isotropic.
3. Perfect sink condition is maintained at the surface of the tablet.
4. The oval tablet is used in the simulation shown in Fig. 1

Based on Fick's second law of diffusion, the drug mass transfer can be described by Eq. 1 (shown below) in the cylindrical coordinates. Here, c_d and D_d are the concentration and diffusion coefficient of the drug. This partial differential equation can be solved numerically using the CFD package FLUENT 14.5 and taking into account the given initial and boundary conditions as well as the drug diffusivity. The mesh (the computation domain) of Met XR1000 tablet for the CFD analysis was created by the preprocessor GAMBIT software (part of FLUENT package, Ansys Fluent 14.5 Document, 2013, ANSYS, Inc, Canonsburg, PA 15317) shown in Fig. 1. The detailed simulation settings and procedures were also published earlier (12).

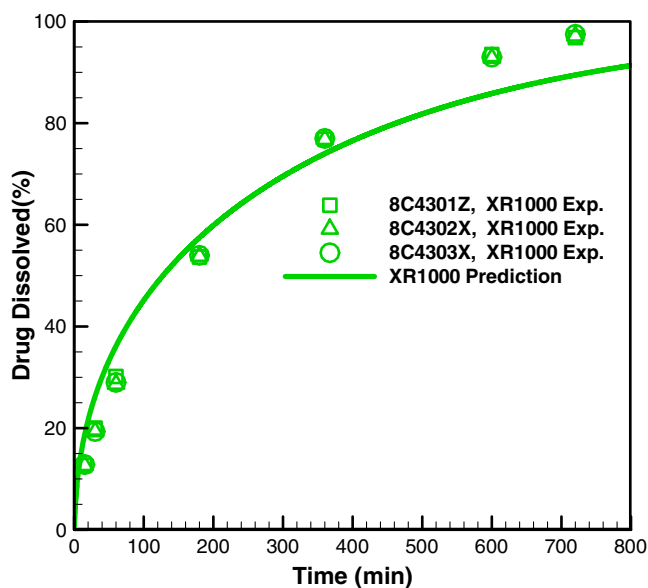
$$\frac{\partial c_d}{\partial t} = \left\{ \frac{\partial}{\partial r} \left(D_d \frac{\partial c_d}{\partial r} \right) + \left(\frac{D_d}{r} \frac{\partial c_d}{\partial r} \right) + \frac{\partial}{\partial z} \left(D_d \frac{\partial c_d}{\partial z} \right) \right\} \quad (1)$$

Initial conditions $t = 0, c_d = c_{d0}$ inside of tablet
Boundary condition $t > 0, c_d = 0$ on all surface of tablet

**Fig. 1.** Tablet tooling geometry and computational domain

The dissolution profile for the Met XR 1000 mg tablet was investigated by the model. The tablet geometry information is listed in Fig. 1 and Table I. CFD was applied to solve Eq. 1 to obtain the simulated dissolution profile for a tablet compressed using tooling E was shown as the solid line in Fig. 2 using the fitted model parameter, the diffusivity of the drug $D_d = 1.15 \times 10^{-10} m^2/s$, by the experimental data. As shown in Fig. 2, the simulated dissolution profile and actual dissolution of three separate lots of tablets compressed using tooling E were very similar for up to the first 400 min in the dissolution run. At the later time point, there was some divergence between the simulated and actual dissolution profiles probably because of an erosion of the HPMC-based tablet matrix (Fig. 2). The model has R^2 of 0.99; overall, the relative standard deviation between the experimental and predicted drug dissolved is 11.5% and these data further validated the model.

Compared to the CFD approach above which can be used in more detail to evaluate the effect of the tablet size and

**Fig. 2.** Simulated versus actual dissolution profiles of Met XR 1000 mg tablets compressed using E tooling

shape on the drug dissolution profile, Eq. 2 is an approximate solution (12) to Eq. 1. This was proposed by Lapidus and Lordi to describe a drug release from swellable HPMC tablet matrices (2). The relation between the dissolution profile and SA/volume ratio and diffusivity can also be seen from this equation.

$$\frac{M_t}{M_0} = 2 \left(\frac{SA}{Vol} \right) \left(\frac{D_{eff} t}{\pi} \right)^{\frac{1}{2}} \quad (2)$$

where M_t is the amount of drug dissolved at time t , M_0 is the drug in the original dry tablet and SA and Vol are the surface area and volume of the tablet, respectively. D_{eff} is the effective drug diffusivity in the tablet.

Lapidus and Lordi's model is adopted from Higuchi's model by using volume/surface area to approximate the characteristic diffusion length (2,13). Both Higuchi's model and the CFD method solved the mass transfer equation (drug) based on Fick's law within the tablet, but they have differences in the algorithm and computational domain. Higuchi's model gives an analytical solution for a typical computational domain (tablet) like plate, cylinder, and sphere, which is an infinite series and difficult to use. On the other hand, CFD uses the finite element volume (FEV) (13) approach to give a numerical solution for the arbitrary computational domain which can mimic any shape of the tablets.

Generally, the diffusivity in Fick's law for the control release has been obtained through fitting the experimental data by these models (13). In this work, the diffusivities for Lapidus and Lordi's model and CFD are 8.0×10^{-11} and $1.15 \times 10^{-10} \text{ m}^2/\text{s}$, respectively. With this diffusivity, Lapidus and Lordi's model has R^2 of 0.99 and the relative standard deviation between the experimental and predicted drug dissolved is 13.9%. When the diffusivity from CFD is used in the prediction by Lapidus and Lordi's model, a different drug release profile can be seen in Fig. 3. This difference was not caused by the model itself but the simplification in deriving Lapidus and Lordi's equation. Lapidus and Lordi (Higuchi (13) make an approximation by keeping the first term and omitting the rest of the series under the condition that the drug percent

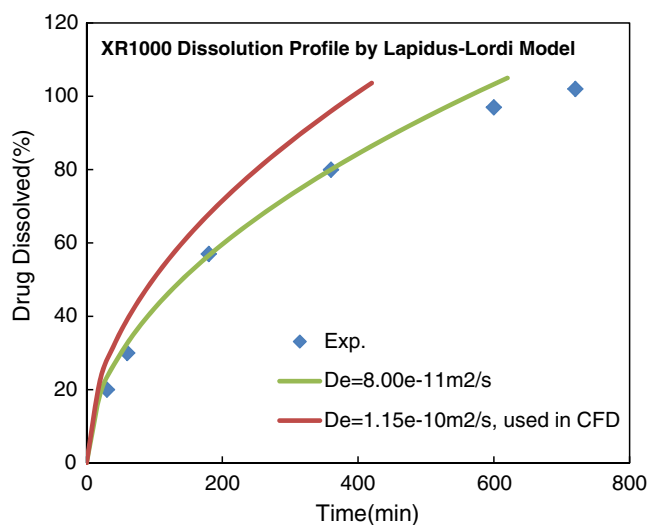


Fig. 3. The drug release profile with different diffusivities predicted by the Lapidus-Lordi model

release is less than 30% (a practical consideration for use). Additionally, the approximation about the characteristic diffusion length (volume/surface area) is used in Lapidus-Lordi's model compared with the typical characteristic diffusion length (plate $L/2$, cylinder $R/2$, sphere $R/3$), which is another source of the discrepancy. When the shape of the tablet is close to the typical geometry, the discrepancy is less. However, when the shape is far from the typical geometry, the discrepancy becomes larger. CFD model is also simplified compared to Siepmann's model (9,10) by implicitly using the effective diffusivity that includes the swelling effects. The diffusivity used in the CFD prediction of Met XR 1000 tablet dissolution profile is validated by Met XR750 tablet (reference product) due to the same formulation. Moreover, the CFD model can evaluate the effect of the complex geometry (tooling shape and size) on the dissolution profile by discerning the computational domain and avoid using volume/surface area as the characteristic diffusion length.

It can be demonstrated from Eq. 2 that when surface area (SA)/volume (Vol) ratio is kept constant, the drug release should be similar for tablets with different shapes. The practical utility of keeping tablet surface area/volume ratio constant to achieve a similar release profile using different tooling shapes or different doses was demonstrated by Reynold *et al.* (4). Based on this information, during the development of high-strength Met XR tablet, it was decided to keep its SA/Vol ratio similar to Met XR 750 mg which was shown bioequivalent to the reference product Met XR 500 mg (Glucophage™ XR 500) by comparing two tablets of Met XR 750 to three tablets of Met XR 500. Several tooling designs were evaluated to identify appropriate tooling for tablet compression. The desired surface area was not feasible with size "B" tooling because of the large target tablet weight of 1450 mg for the high-strength Met XR tablet. Six different tooling shapes (size "D") were evaluated for the development of high-strength Met XR tablets. Their descriptions, dimensions, and vendor's names are provided in Table I. The surface area and volume for each tooling shape was calculated using Gambit software (Gambit 2.4.6 software, 2006, Fluent Co., Lebanon, NH).

As shown in Table I, the SA/Vol ratio of Met XR 750 mg was 15.94 (1/in.). The various tooling designs had SA/Vol ratio varying from 13.70 to 14.64 (1/in.). According to Eq. 2, larger SA/Vol results in faster dissolution rate. Moreover, with the same volume, larger surface area can increase the mass transfer area results in faster dissolution rate. With similar value of SA/Vol of the different tooling designs in this study, they show the similar dissolution profile seen in the dissolution data of 1000 mg Met

Table II. Mean Dissolution Data of 1000 mg Met XR Compressed to Press Weight of 1450 mg Using Tooling of Different Shapes. The Values are % Metformin Dissolved

Time (minutes)	Met XR 750 as reference	Tooling A	Tooling C	Tooling E
30	21	19	20	20
60	30	29	29	30
180	56	55	54	57
360	79	77	77	80
600	94	93	93	97
720	97	96	98	102

$N=6$, standard deviation was around 1% for all the data.

Table III. Dissolution Profiles of Metformin XR 1000 mg Tablets Compared to 2×Metformin XR 500 mg Tablets in Three Different Dissolution Media. The Values are % Metformin Dissolved

Time point (min.)	Potassium phosphate buffer (pH 6.8)		Sodium acetate buffer (pH 4.5)		0.1 n hydrochloric acid solution (pH 1.2)	
	2×500 mg Met XR <i>f</i> ₂ =75	1×1000 mg Met XR	2×500 mg Met XR <i>f</i> ₂ =88	1×1000 mg Met XR	2×500 mg Met XR ¹ <i>f</i> ₂ =90	1×1000 mg Met XR
15	13	12	13	13	14	13
30	19	19	19	19	20	19
60	28	28	28	29	29	29
180	51	53	52	54	54	54
360	72	75	75	77	78	77
600	86	92	91	92	92	94
720	91	96	95	97	96	98

N=12, standard deviation was around 1% for all the data.

XR compressed using tooling A, C, or E (Table II). The dissolution data of 1000 mg Met XR compressed using tooling A, C, or E are shown in Table II. Dissolution data of Met XR 750 was shown as a reference (Table II). In addition to SA/Vol ratio, there were few additional factors taken into consideration in the identification of tooling. It was determined that with a 1450-mg tablet press weight, longer tablets would be difficult to swallow relative to comparatively shorter tablets. Based on this consideration, tooling B, D, and F were dropped since the tablet length would be larger than 0.9 in. Tablets compressed using tooling A showed significant twining (two or more tablets sticking together for their entire length) during the coating operation so this tooling shape was also dropped. Tablets compressed using tooling C did not have correct orientation to land in the preferred position for the printing operation. It is desirable to have a difference of about 0.100 in. between tablet thickness and width to land the tablet correctly in a tablet printer. For this reason, tooling C was not further considered. Thus, ease of swallowing, absence of twining during the coating operation, and preferred orientation during the printing operation led to

the selection of the oval/modified capsule-shaped tooling (E) for the development of high-strength XR tablets. A summary of the tooling-related elements is also mentioned in Table I comments.

Glucophage® XR 500 and 750 mg are commercial products in the USA. Since 1000 mg Met XR is a higher strength tablet than those already commercially available, a BE study was needed based on the guidance for bioavailability and bioequivalence studies for orally administered drug products (6) and guidance for extended-release oral dosage forms (5). Since Glucophage XR 500 mg was identified as a reference product for a BE study, dissolution of 2×Glucophage XR 500 tablets was compared against one Met XR 1000 mg in three different media namely 0.1 N HCl (pH 1.2), 50 mM sodium acetate buffer pH 4.5, and 50 mM potassium phosphate buffer (pH 6.8). As shown in Table III, dissolution of Met XR 1000 was similar to 2×Glucophage 500 mg in three different media with *f*₂ values ranging from 75 to 90. Dissolution profiles with *f*₂ values higher than 50 are considered similar (14).

Metformin pharmacokinetics has been extensively reported by numerous groups (9,15–17). It was shown that the

Table IV. GastroPlus Model Parameters

	Parameter	Value
Physical-chemical	Dose	1000 mg
	Log D	-3.37 (pH 4)
Physiology	Fed state	GastroPlus default values 2.2×10^{-4} cm/s
	Permeability (jejunum)	
Absorption scale factors	Duodenum	0.549
	Jejunum 1	0.540
	Jejunum 2	0.536
	Ileum 1	0.530
	Ileum 2	0.500
	Ileum 3	0.707
	Caecum	0.015
	Ascending colon	0.015
Pharmacokinetic	Clearance	0.61 [L/(h kg)]
	Volume of distribution (central)	0.578 L/kg
	K12	1.92 h^{-1}
	K21	1.03 h^{-1}
	K13	0.137 h^{-1}
	K31	0.237 h^{-1}

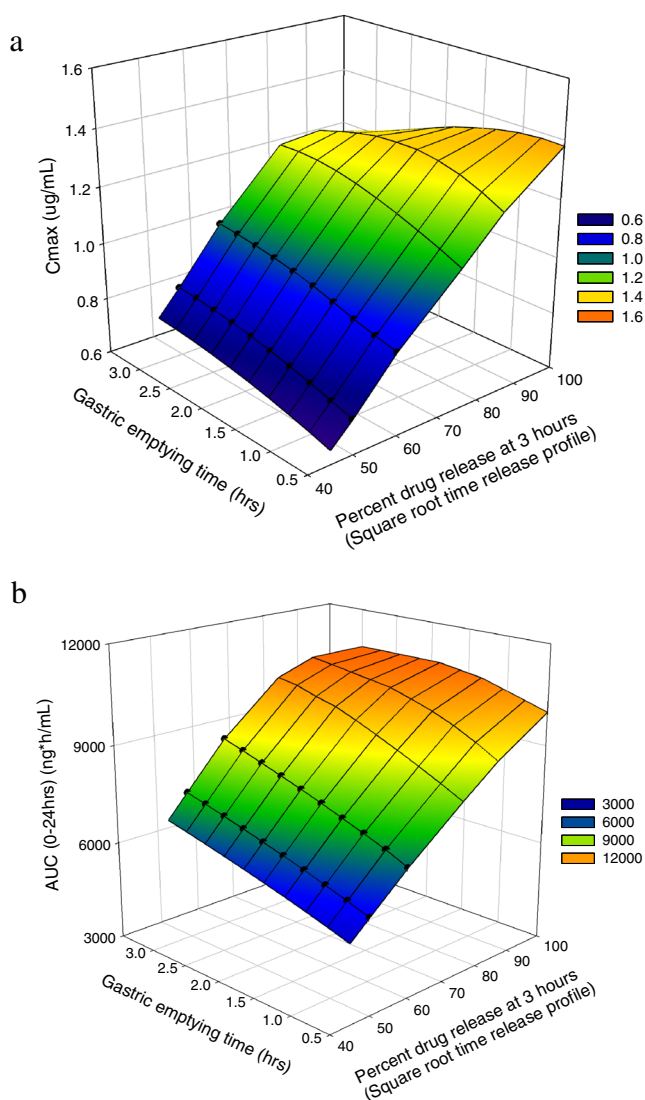


Fig. 4. C_{\max} and AUC (0–24) vs. gastric emptying and drug release (*in vivo* drug release proportional to the square root of time)

metformin bioavailability decreases as Glucophage XR dose is increased beyond the starting dose of 500 mg (7). Therefore, similarity in dissolution of 2×Glucophage XR 500 and 1000 mg Met XR similarity in dissolution may not lead to positive BE

results. In order to mitigate the risk of a BE failure, a PK absorption model was used to predict exposure in humans for 1000 mg Met XR. Using the physicochemical and pharmacokinetic properties of metformin, a pharmacokinetic absorption model was developed using GastroPlus™ V.7.0 software (9). Detailed parameters of the model are listed in Table IV. *In vitro* dissolution kinetics and the available human pharmacokinetic data were used to parameterize the absorption model. Figure 4 shows the simulated effect of drug release and gastric emptying on the pharmacokinetic parameters C_{\max} and AUC (0–24) for release proportional to the square root of time, which is the approximate behavior typically observed from swellable hydrophilic matrix tablets. In rare cases, a matrix could exhibit a constant surface area during *in vivo* release (no swelling) that would result in a zero order release and this occurrence can similarly be modeled to predict exposure. Plots in Fig. 4 include symbols (black circles) for the closest release profiles (50–60% dissolved at 3 h) that bracket the observed behavior for metformin XR tablets (Table III). These exposures agree closely with the observed clinical behavior and if anything very slightly under predict because square root of time release kinetics do well to represent diffusion-dominant *in vitro* dissolution for hydrophilic matrix tablets, but often do not describe some additional release from erosion anticipated to occur *in vivo*. Additionally, the Fig. 4-simulated AUC period was 24 h less than the 48 h PK monitoring period in the clinical bioequivalence study. The utility of these types of surface plots enables the formulator to easily select an *in vitro* release profile that will provide the necessary therapeutic C_{\max} and AUC.

The GastroPlus absorption model projected *in vivo* profile of the high-strength XR tablet to be equivalent to 2×500 mg Glucophage XR. Ultimate clinical BE studies comparing 1000 mg Met XR to 2×500 mg Met XR showed that the new tablet met the AUC criteria for BE indicating similar exposure. However, the C_{\max} was increased by 17%, and the 90% confidence interval ratio of C_{\max} geometric means extended above the BE range of 80 to 125% for the first BE study (Table V). Thus, the BE criteria for C_{\max} was not achieved (Table V). However, in the second BE study, both C_{\max} and AUC criteria were achieved (Table V). For a once daily metformin dosage form, overall exposure is more important from a treatment perspective given the wide clinical dose range of 500 to 2550 mg. Since Met XR 1000 mg met the AUC criteria in the both BE studies, it was selected for further development.

Table V. Results of Statistical Analysis of Metformin C_{\max} , AUC (inf.), and AUC (0–48 h)

Pharmacokinetic parameter (fed state)	Adjusted geometric means		BA ratio adjusted geometric means	
	Glucophage XR 2×500 mg	Met XR 1×1000 mg	Point estimate	90% C.I.
Study 1 (n=13)				
AUC (INF) (ng/ml.h)	9560	9701	1.015	(0.965, 1.067)
AUC (0–48 h) (ng/ml.h)	9419	9568	1.016	(0.966, 1.068)
C_{\max} (ng/mL)	735	861	1.171	(1.037, 1.323)
Study 2 (n=30)				
AUC (INF) (ng/ml.h)	9746.3	8713.4	0.894	(0.833, 0.959)
AUC (0–48 h) (ng/ml.h)	9246.8	8377.8	0.906	(0.848, 0.968)
C_{\max} (ng/mL)	1151.2	1055.9	0.917	(0.859, 0.980)

CONCLUSIONS

Three separate mathematical models were utilized for the accelerated development of Met XR 1000 mg tablets using the existing granulation of Met XR 750 mg. This approach kept the surface area/volume ratio of the new high-strength tablet similar to the commercial product Met XR 750 (Glucophage XR 750). Met XR 750 was bioequivalent to Glucophage XR 500 by comparing two tablets of Met XR 750 with three tablets of Met XR 500. Although the tablet weight of Met XR 1000 mg was increased by about 400 mg, the dissolution profile was similar to Met XR 750 and close to the predicted dissolution using Fluent software. Finally, the absorption model created using the GastroPlus software projected *in vivo* exposure (AUC) of 1000 mg Met XR equivalent to 2×500 mg Glucophage XR which was verified by actual BE studies. Thus, all three models not only accelerated the development of Met XR 1000 mg but increased the likelihood of success.

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