molecular pharmaceutics

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The Biowaiver Extension for BCS Class III Drugs: The Effect of Dissolution Rate on the Bioequivalence of BCS Class III Immediate-Release Drugs Predicted by Computer Simulation

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Received March 1, 2010; Revised Manuscript Received June 9, 2010; Accepted June 17, 2010

Abstract: The Biopharmaceutical Classification System (BCS) guidance issued by the FDA allows waivers for *in vivo* bioavailability and bioequivalence studies for immediate-release (IR) solid oral dosage forms only for BCS class I drugs. However, a number of drugs within BCS class III have been proposed to be eligible for biowaivers. The World Health Organization (WHO) has shortened the requisite dissolution time of BCS class III drugs on their Essential Medicine List (EML) from 30 to 15 min for extended biowaivers; however, the impact of the shorter dissolution time on AUC_{0-inf} and C_{max} is unknown. The objectives of this investigation were to assess the ability of gastrointestinal simulation software to predict the oral absorption of the BCS class I drugs propranolol and metoprolol and the BCS class III drugs cimetidine, atenolol, and amoxicillin, and to perform *in silico* bioequivalence studies to assess the feasibility of extending biowaivers to BCS class III drugs. The drug absorption from the gastrointestinal tract was predicted using physicochemical and pharmacokinetic properties of test drugs provided by GastroPlus (version 6.0). Virtual trials with a 200 mL dose volume at different drug release rates ($T_{85\%}$ = 15 to 180 min) were performed to predict the oral absorption (C_{max} and AUC_{0-inf}) of the above drugs. Both BCS class I drugs satisfied bioequivalence with regard to the release rates up to 120 min. The results with BCS class III drugs demonstrated bioequivalence using the prolonged release rate, $T_{85\%}$ = 45 or 60 min, indicating that the dissolution standard for bioequivalence is dependent on the intestinal membrane permeability and permeability profile throughout the gastrointestinal tract. The results of GastroPlus simulations indicate that the dissolution rate of BCS class III drugs could be prolonged to the point where dissolution, rather than permeability, would control the overall absorption. For BCS class III drugs with intestinal absorption patterns similar to those of cimetidine, atenolol or amoxicillin, the dissolution criteria for extension of biowaivers to BCS class III drugs warrants further investigation.

Keywords: BCS; cimetidine; dissolution; permeability; simulation; GastroPlus

Introduction

As a means to ensure consistency and reproducibility of the therapeutic performance of drug products, bioequivalence has been widely accepted as a standard test. In order to demonstrate bioequivalence, the C_{max} and area under the curve (AUC) of the plasma concentration−time profiles of the test drug must be statistically equivalent (i.e., fall within a 90% confidence interval (CI)) of the 80−125% range of mean of the reference product. In 2000, the U.S. Food and Drug Administration (FDA) released guidelines for the pharmaceutical industry, allowing for a "Biowaiver" that relied on the Biopharmaceutics Classification System (BCS), which classifies drugs according to the biopharmaceutical properties governing their ab-

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10.1021/mp100053q
Published on Web 06/17/2010

sorption and the controlling factors, permeability, solubility and product dissolution.[2,3] The European Medicines Agency (EMA), formally known as EMEA, has released guidance on the investigation of bioequivalence that includes the BCS-based biowaiver.[5] The FDA-issued and EMA-issued guidelines for industry concerning waivers based on *in vivo* bioavailability and bioequivalence studies for immediate-release (IR) solid oral dosage forms originated within the framework of BCS. According to these guidelines, the sponsors may request biowaivers for IR solid oral dosage forms of class I drugs, i.e. those exhibiting high solubility and high permeability. Under current FDA guidelines for biowaivers, BCS class I drug compounds are defined as highly soluble and highly permeable drugs when their highest IR dose strength is soluble at 37 °C in 250 mL or less of aqueous media over the pH range of 1.0−7.5 and their orally administered IR dose is more than 90% absorbed,[6,7] while EMA has defined highly soluble at 37 °C in 250 mL or less of buffer normally at pH 1.0, 4.6 and 6.8.[5,10] In addition, the test drug product and its reference product, i.e. its comparator, must show dissolution profile similarity in three media. Since *in vivo* dissolution of an IR oral dosage form of BCS class I drugs is relatively rapid compared to gastric emptying time, the drug products behave as if they are oral solutions. Therefore, the empirical demonstration of *in vivo* bioequivalence for BCS class I drug products is not necessary as long as the excipients used in the dosage form do not affect the absorption of the active drug. Hence, the demonstration of *in vitro* dissolution using recommended testing methods would provide sufficient assurance for human *in vivo* bioequivalence.[3] The current FDA requirement for the solubility class boundary to be highly soluble is relatively conservative; conversely, both the WHO and the EMA extend biowaivers to some class III drug compounds when they meet the criterion for very rapid dissolution drugs (>85% solubility at pH 1.2−6.8 in 15 min).[5]

The feasibility of granting biowavers to BCS class III drugs has been evaluated. BCS class III drugs are highly soluble, and their release properties are not the rate-limiting step for absorption; several studies have therefore suggested that biowaivers be extended to rapidly dissolved BCS class III drug products.[17,19−23]

The objectives of this paper were to predict oral absorption of BCS class I and III drugs with the simulation software

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Table 1. Chemical/Physiological/Pharmacological Parameters of BCS Class I and Class III Drugs for GastroPlus Simulation

		propranolol	metoprolol	atenolol	amoxicillin	cimetidine
MW		259.3	267.4	266.3	365.4	252.3
dose	mg	80[a]	100[a]	100[a]	875[a]	800[a]
dose vol	mL	200[b]	200[b]	200[b]	200[b]	200[b]
solubility	mg/mL	33[c]	16.9[d]	13.5[d]	3.4[d]	5.0[d]
log *P*		2.65[e]	1.72[e]	0.50[e]	−0.58[e]	0.79[e]
pK_a		9.5[f]	9.7[c]	9.4[g]	2.8/7.2[h]	6.8[c]
mean precipitation time	s	5	5	5	5	5
diffusion coeff	$\times 10^5$ cm^2/s	0.75	0.75	0.75	0.75	0.75
particle density	g/mL	1.2	1.2	1.2	1.2	1.2
human P_{eff}	$\times 10^{-4}$ cm^2/s	2.9[e]	1.5[a]	0.2[a]	0.3[a]	0.3[a]
body weight	kg	70	70	70	70	70
V_c[i]	L/kg	4.2[j]	4.5[k]	0.8[l]	0.6[m]	2.0[n]
total clearance	L/h/kg	0.7[j]	4.9[k]	0.07[o]	0.4[m]	0.7[n]

[a] Reference 1. [b] Reference 2. [c] Reference 8. [d] Reference 4. [e] References 9, 10. [f] Reference 11. [g] Reference 12. [h] References 13, 14. [i] Volume of central compartment. [j] Reference 15. [k] References 16, 17. [l] References 7, 18. [m] Reference 24. [n] Reference 25. [o] References 3, 26.

GastroPlus, and to assess the feasibility of extending biowaivers to BCS class III drugs based on their biopharmaceutical properties. In order to achieve these objectives, we predicted *in silico* the effects of dissolution kinetics on oral drug absorption, C_{max} and AUC, and bioequivalence. GastroPlus software was used to evaluate the influence of drug dissolution kinetics on oral absorption and the possibility of extending biowaivers to BCS class III drugs, as well as the significance of "rapid dissolution" and "very rapid dissolution" criteria for BCS class III drugs.

Materials and Methods

Computer Hardware and Software. GastroPlus program (version 6.0) of SimulationPlus, Inc. (Lancaster, CA) was run using an IBM computer with Intel Core 2 duo processors. This software allows the input of different dissolution velocities for pharmacokinetic predictions.

Simulation Design. The drug oral absorption was predicted on the basis of physicochemical, pharmacokinetic, and drug dissolution properties of 5 selected model drugs. The three different phases (I, II and II/III) of the interdigestive migrating myoelectric complex (IMMC) with two different dose volumes (50 and 200 mL) in humans have been reported, and it was shown that the intake volume could greatly affect the gastric emptying time[2] of some IMMC phases. However, there are no data available regarding IMMC in humans using a 250 mL dose volume; therefore, a 200 mL dose volume was chosen, consistent with volumes used in human studies and similar to the FDA recommendation for taking solid dosage forms with 250 mL of water.[2,3] Oberle and collegues have reported that the observed times to empty 50% of the dose (T_{50}^{obs}) from the stomach in each phase (I, II, and late II/III) are 22.8, 12.2, and 4.92 min, respectively.[2] The length of phase late II/III is 15 min, and the lengths of phase I and phase II are 4-fold and 3-fold longer than that of phase late II/III.[2] Based on those observations, the average gastric emptying time of the 200 mL dose volume was calculated using eq 1, which incorporates the lengths of the different phases (Table 2).

Table 2. Mean Gastric Emptying Parameters for 200 mL Volumes as a Function of Interdigestive Migratory Myoelectric Complex[a]

	phase[b]		
gastric emptying parameters	I[c]	II[d]	late II/III[e]
gastric emptying rate (min^{-1})	0.104	0.110	0.236
lag time (min)	15.7	4.99	1.7
T_{50}^{obs} (min)	22.8	12.2	4.92
length of phase (min)	60	45	15

[a] Data is reported as mean.[2] [b] Phase I: no contractions (no more than 2 contractions per 10 min). Phase II: intermittent activity. Phase III: 2−3 min regular contractions followed by duodenal phase III. [c] $n = 2$; 2 subjects. [d] $n = 15$; 6 subjects. [e] $n = 4$; 3 subjects.

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$$\text{mean GET} = (22.8 \times 4 + 12.2 \times 3 + 4.92 \times 1)/8 \quad (1)$$

The calculated mean GET of 200 mL dose volume ± standard deviation (SD) is 0.28 h (16.59 min) ± 0.19 h (11.6 min); this number was used for this virtual trial for 24 h monitoring instead of the GET default setting of 0.25 h (15 min). In virtual trials, the variations in population physiology such as gastrointestinal transit times, pH in GI compartments, pharmacokinetic parameters, etc. were defined as means with coefficients of variation in log space and were randomly selected within those ranges. Virtual trials were performed as references ($n = 500$) on each drug compound. Virtual trials ($n = 24$) with randomly selected physiological conditions were performed as samples with different release rates, which were fixed for all points from $T_{85\%} = 15$ min to $T_{85\%} = 180$ min as controlled release (Figure 1). The results of those predictions were compared with the reference results to determine bioequivalence.

Input Parameters for Pharmacokinetic Simulations. The physicochemical and biopharmaceutical properties of propranolol, metoprolol, cimetidine, atenolol, and amoxicillin used in the GastroPlus simulations are presented in Table 1.[1,2,4,8,9,11–13] Chemical, physiological, and pharmacological parameters for drugs cited in the literature are also presented in Table 1.[15,16,18,24–26] A mean precipitation time of 5 s was set in order to avoid exceeding the drug solubility for those predictions. Amoxicillin exhibits good oral bioavailability, despite its low lipophilicity and zwitterionic nature at physiological pH.[27,28] Because amoxicillin is a well-known substrate for the oligopeptide transporter PEPT1, which plays a major role in the intestinal absorption of β-lactam antibiotics,[27] the GastroPlus transporter table function (transporter, PepT1; type, influx; V_{max}, 0.001 μg/mL; K_m, 375 mg/s/mg protein) was used to predict the oral absorption of amoxicillin.[29]

Results: The Impact of Release Rate on Oral Drug Absorption

BCS Class I Drugs: Propranolol and Metoprolol. The oral absorption of propranolol and metoprolol during the average GET was predicted by GastroPlus virtual trials. Those prediction numbers, mean C_{max} and AUC_{0-inf} ± SD, were obtained with 500 virtual trials with $T_{85\%} = 30$ min as a reference and with 24 virtual trials as samples at different release rates (Tables 3 and 4). The 90% CI was calculated from the mean C_{max} and AUC_{0-inf} of its reference. Mean C_{max} and AUC_{0-inf} of propranolol and metoprolol at $T_{85\%} = 30$ min as a reference were compared with those of the other release rates of the same drug compounds. The ranges of C_{max} and AUC_{0-inf} for propranolol and metoprolol are shown in Tables 3 and 4. The differences between propranolol and metoprolol in their average values for C_{max} and AUC_{0-inf} between $T_{85\%} = 15$ min and $T_{85\%} = 30$ min were calculated and are shown in Tables 3 and 4. With the exception of $T_{85\%} = 180$ min, both BCS class I drugs exhibited similar C_{max} and AUC_{0-inf} values throughout all different release rates (propranolol, C_{max} 0.00−3.97%, AUC_{0-inf} 1.87−7.76%; metoprolol, C_{max} 0.31−7.07%, AUC_{0-inf} 3.65−10.26%) and demonstrated bioequivalence up to $T_{85\%} = 120$ min (Tables 3 and 4, Figures 2 and 3). The release rate would have less of an impact on the oral absorption of BCS class I drug products due to their highly permeable biopharmaceutical

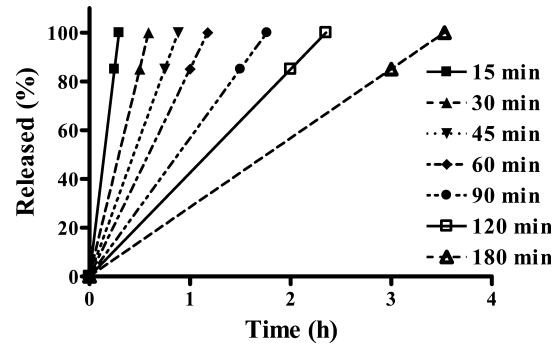

Figure 1. Release rate of the drug from the formulation in the GI tract used in the simulations. Lines represents the release versus time of a release pattern corresponding to 85% release in 15, 30, 45, 60, 90, 120, and 180 min.

Table 3. Simulated C_{max} and AUC of Propranolol with Different Release Kinetics[a]

release rate	C_{max} (μg/mL)	C_{max} % difference	AUC (ng/mL·h)	AUC % difference
solution	0.151 ± 0.009	0.00	1376.8 ± 77.0	3.56
$T_{85\%} = 15$ min	0.153 ± 0.008	1.32	1400.9 ± 70.9	1.87
$T_{85\%} = 30$ min	0.151 ± 0.008		1427.6 ± 70.4	
$T_{85\%} = 45$ min	0.154 ± 0.008	1.99	1392.0 ± 79.5	2.49
$T_{85\%} = 60$ min	0.149 ± 0.007	1.32	1350.0 ± 64.2	5.44
$T_{85\%} = 90$ min	0.149 ± 0.008	1.32	1352.2 ± 74.8	5.28
$T_{85\%} = 120$ min	0.145 ± 0.007	3.97	1316.8 ± 74.3	7.76
$T_{85\%} = 180$ min	0.122 ± 0.010	19.21	1122.6 ± 109.9	21.36

[a] Data is reported as mean ± SD.

Table 4. Simulated C_{max} and AUC of Metoprolol with Different Release Kinetics[a]

release rate	C_{max} (μg/mL)	C_{max} % difference	AUC (ng/mL·h)	AUC % difference
solution	0.077 ± 0.004	0.31	247.8 ± 16.9	3.65
$T_{85\%} = 15$ min	0.076 ± 0.004	1.30	244.1 ± 14.3	5.09
$T_{85\%} = 30$ min	0.077 ± 0.004		257.2 ± 14.0	
$T_{85\%} = 45$ min	0.078 ± 0.003	1.75	244.9 ± 12.5	4.79
$T_{85\%} = 60$ min	0.078 ± 0.004	2.23	247.7 ± 14.6	3.70
$T_{85\%} = 90$ min	0.076 ± 0.003	1.47	240.5 ± 15.2	6.52
$T_{85\%} = 120$ min	0.071 ± 0.004	7.07	230.8 ± 13.8	10.26
$T_{85\%} = 180$ min	0.057 ± 0.005	25.36	202.7 ± 22.1	21.22

[a] Data is reported as mean ± SD.

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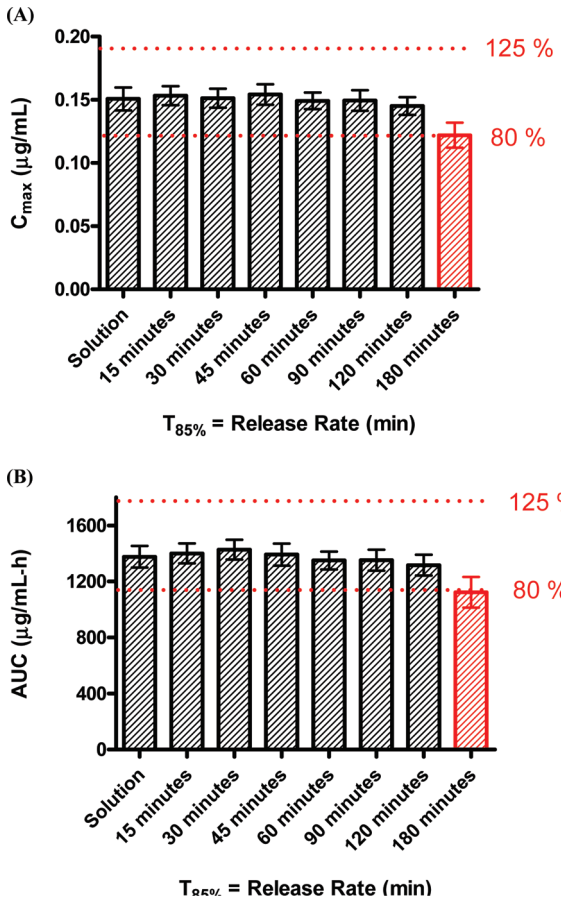

Figure 2. C_{max} (A) and AUC (B) of propranolol predicted by computer simulations. Data reported as mean ± SD 90% confidence interval (CI) of C_{max} (A) and AUC (B), the simulation being taken with a release rate corresponding to 85% release in 30 min as comparator. Black bars represent bioequivalence, and red bars represent outside of bioequivalence criteria, i.e. outside of 80% and 125% of the comparator.

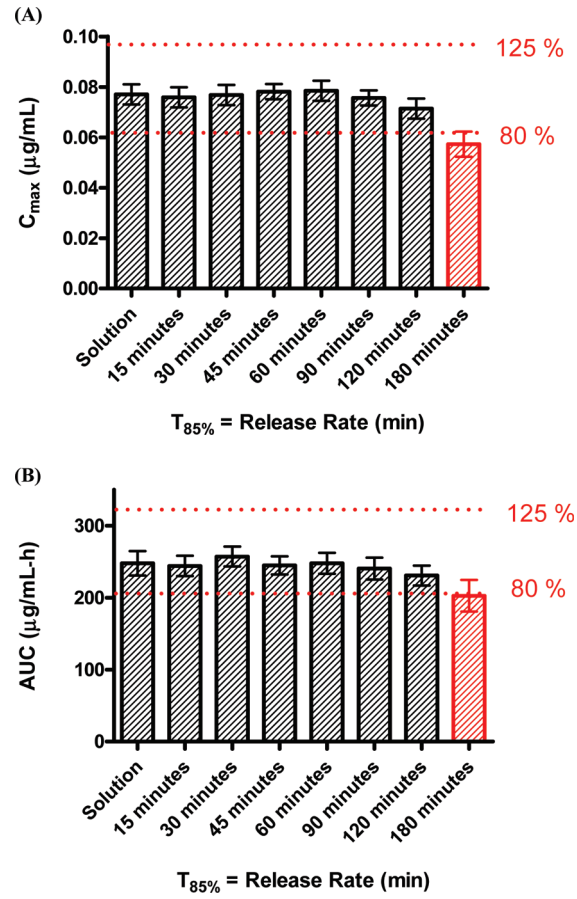

Figure 3. C_{max} (A) and AUC (B) of metoprolol predicted by computer simulations. Data reported as mean ± SD 90% confidence interval (CI) of C_{max} (A) and AUC (B), the simulation being taken with a release rate corresponding to 85% release in 30 min as comparator. Black bars represent bioequivalence, and red bars represent outside of bioequivalence criteria, i.e. outside of 80% and 125% of the comparator.

character throughout the whole intestine. Figures 7a and 7b show that BCS class I drugs were quickly absorbed immediately upon dissolving.

BCS Class III Drugs: Cimetidine, Atenolol, and Amoxicillin. Mean C_{max} and AUC_{0-inf} ± SD for cimetidine, atenolol, and amoxicillin under the mean GET were obtained by GastroPlus 500 virtual trials with a release rate of $T_{85\%}$ = 15 min as a reference and with 24 virtual trials at different release rates as sample sets (Tables 5−7). The 90% CI was calculated from the mean C_{max} and AUC_{0-inf} of its reference. The prediction results of sample groups with different release rates were examined along with their reference results and were determined to satisfy the bioequivalence criteria. With the extended biowaiver guidelines of the WHO and EMA, C_{max} and AUC_{0-inf} of $T_{85\%}$ = 15 min (>85% solubility (pH 1.2−6.8) in 15 min) as "very rapid dissolution" were compared with those of the other release rates. The ranges of C_{max} and AUC_{0-inf} for cimetidine, atenolol, and amoxicillin are shown in Tables 5−7. The differences in mean C_{max} for cimetidine, atenolol and amoxicillin between $T_{85\%}$ = 15 min and $T_{85\%}$ = 30 min were 1.76%, 2.11% and 4.39%, respectively. The differences in mean AUC_{0-inf} for cimetidine, atenolol and amoxicillin between $T_{85\%}$ = 15 min and $T_{85\%}$ = 30 min were 0.18%, 0.14% and 2.45%, respectively (Tables 5−7). The mean C_{max} and AUC_{0-inf} values of all tested BCS class III drugs between $T_{85\%}$ = 15 min and $T_{85\%}$ = 180 min were reduced by approximately 50%, and the prolonged release rate became the limiting step in their overall absorption. This reduction is likely the result of the

Table 5. Predicted C_{max} and AUC of Cimetidine with Different Release Kinetics[a]

release rate	C_{max} (µg/mL)	C_{max} % difference	AUC (ng/mL·h)	AUC % difference
solution	0.439 ± 0.032	3.30	1996.4 ± 140.2	0.89
$T_{85\%}$ = 15 min	0.454 ± 0.046		2014.3 ± 283.8	
$T_{85\%}$ = 30 min	0.446 ± 0.041	1.76	2010.6 ± 184.1	0.18
$T_{85\%}$ = 45 min	0.434 ± 0.037	4.41	1944.1 ± 155.0	3.49
$T_{85\%}$ = 60 min	0.422 ± 0.037	7.05	1895.8 ± 156.7	5.88
$T_{85\%}$ = 90 min	0.394 ± 0.044	13.22	1767.0 ± 205.8	12.28
$T_{85\%}$ = 120 min	0.338 ± 0.044	25.55	1504.8 ± 207.8	25.29
$T_{85\%}$ = 180 min	0.222 ± 0.033	51.10	991.1 ± 153.5	50.80

[a] Data is reported as mean ± SD.

Table 6. Predicted C_{max} and AUC of Atenolol with Different Release Kinetics[a]

release rate	C_{max} (μg/mL)	C_{max} % difference	AUC (ng/mL·h)	AUC % difference
solution	0.147 ± 0.022	3.52	1255.5 ± 190.9	6.25
$T_{85\%}$ = 15 min	0.142 ± 0.019		1181.6 ± 175.1	
$T_{85\%}$ = 30 min	0.139 ± 0.012	2.11	1179.9 ± 110.0	0.14
$T_{85\%}$ = 45 min	0.138 ± 0.020	2.82	1183.1 ± 180.1	0.13
$T_{85\%}$ = 60 min	0.134 ± 0.018	5.63	1130.1 ± 165.2	4.36
$T_{85\%}$ = 90 min	0.119 ± 0.020	16.20	1003.8 ± 191.6	15.05
$T_{85\%}$ = 120 min	0.108 ± 0.017	23.94	938.5 ± 165.8	20.57
$T_{85\%}$ = 180 min	0.069 ± 0.011	51.41	620.5 ± 94.7	47.49

[a] Data is reported as mean ± SD.

Table 7. Predicted C_{max} and AUC of Amoxicillin with Different Release Kinetics[a]

release rate	C_{max} (μg/mL)	C_{max} % difference	AUC (ng/mL·h)	AUC % difference
solution	2.996 ± 0.391	0.30	27430 ± 3564	2.8
$T_{85\%}$ = 15 min	3.005 ± 0.355		28220 ± 3697	
$T_{85\%}$ = 30 min	2.873 ± 0.315	4.39	27530 ± 3599	2.45
$T_{85\%}$ = 45 min	2.870 ± 0.359	4.49	27090 ± 3441	4.00
$T_{85\%}$ = 60 min	2.737 ± 0.348	8.92	27260 ± 3648	3.40
$T_{85\%}$ = 90 min	2.660 ± 0.279	11.48	24580 ± 4765	12.90
$T_{85\%}$ = 120 min	2.388 ± 0.461	20.53	22050 ± 4290	21.86
$T_{85\%}$ = 180 min	1.134 ± 0.244	62.26	10040 ± 2177	64.42

[a] Data is reported as mean ± SD.

combination of a limited absorptive window and an increase in the release rate. Cimetidine and atenolol demonstrated bioequivalence up to $T_{85\%}$ = 60 min of release rate (Figures 4 and 5). Amoxicillin exhibited bioequivalence in C_{max} up to $T_{85\%}$ = 45 min, while it exhibited bioequivalence in AUC_{0-inf} up to $T_{85\%}$ = 60 min (Figure 6). Figure 7 illustrates the limited drug absorption of BCS class III drugs and that their poor absorption is clearly the result of their low permeability rather than their dissolution rates (Figures 7c−7e).

Discussion

In this computer-based prediction of oral drug absorption, the chemical, physiological, and pharmacological parameters for GastroPlus are shown in Table 1. Because the phases of IMMC affect GET and gastrointestinal motility,[2] which in turn may lead to differences in drug absorption, the mean GET was calculated using eq 1 and applied to the prediction of oral drug absorption. Virtual trials were performed using the GastroPlus preloaded physiological conditions Human Physiological-Fasted and Opt LogD Model. In those virtual trials, dose, dose volume, molecular weight, log P, pK_a, particle density, and diffusion coefficient of drug compounds were fixed. All other parameters for virtual trials such as effective human permeability, intestinal transit time and pharmacokinetic clearance were defined as variables, which were randomly created within 10−20% log-normal distribution based on their mean values except GET. The physiological compartment parameters were adjusted so that BCS class I drugs were absorbed in the entire small intestine and

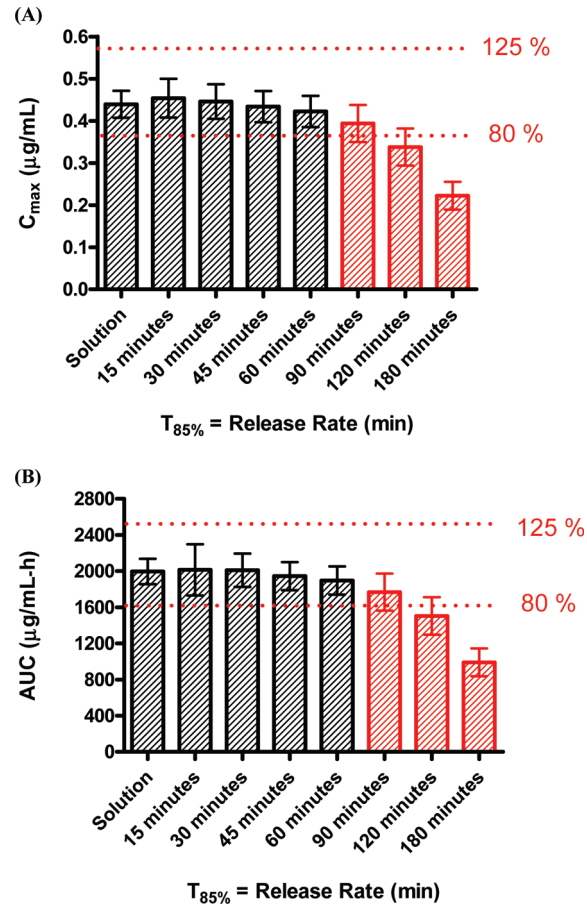

Figure 4. C_{max} (A) and AUC (B) of cimetidine predicted by computer simulations. Data reported as mean ± SD 90% confidence interval (CI) of C_{max} (A) and AUC (B), the simulation being taken with a release rate corresponding to 85% release in 15 min as comparator. Black bars represent bioequivalence, and red bars represent outside of bioequivalence criteria, i.e. outside of 80% and 125% of the comparator.

large intestine but not in the stomach. For BCS class III drugs, site-dependent absorption has been reported.[30,31] If the absorptive site of BCS class III drugs is the ileum, those highly soluble BCS class III drugs would be completely dissolved before reaching the distal intestine. Therefore, the absorptive sites for BCS class III drugs were modified to include only proximal intestine, duodenum and jejunum, and exclude the ileum, large intestine and stomach.

The FDA guidelines currently allow biowaivers only for BCS class I drugs, while the WHO and EMA guidelines recommend biowaivers for BCS class III drug products with very rapid dissolution (>85% dissolved in 15 min).[3,5] The current FDA Guidance is considered quite conservative, allowing biowaivers for products containing only BCS class I drugs. Extending biowaivers to BCS class III has been

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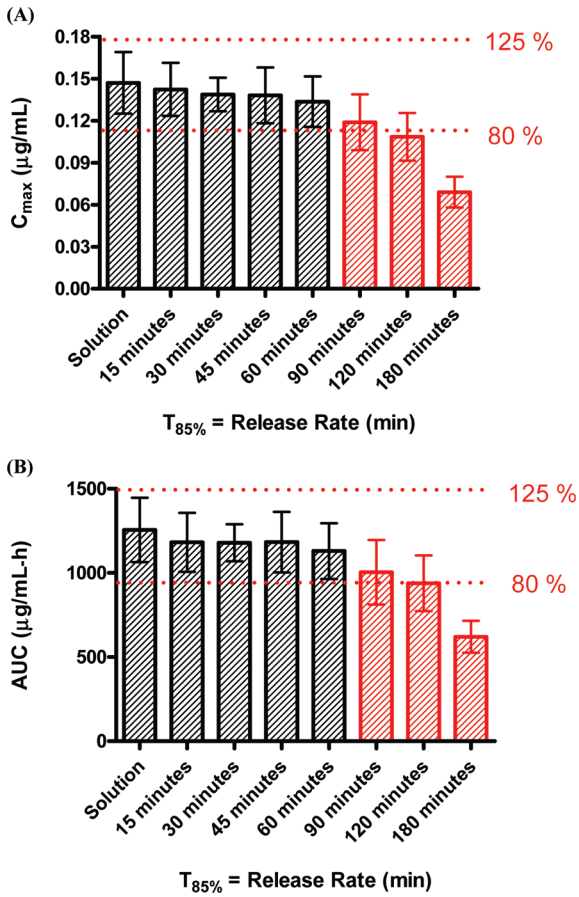

Figure 5. C_{max} (A) and AUC (B) of atenolol predicted by computer simulations. Data reported as mean ± SD 90% confidence interval (CI) of C_{max} (A) and AUC (B), the simulation being taken with a release rate corresponding to 85% release in 15 min as comparator. Black bars represent bioequivalence, and red bars represent outside of bioequivalence criteria, i.e. outside of 80% and 125% of the comparator.

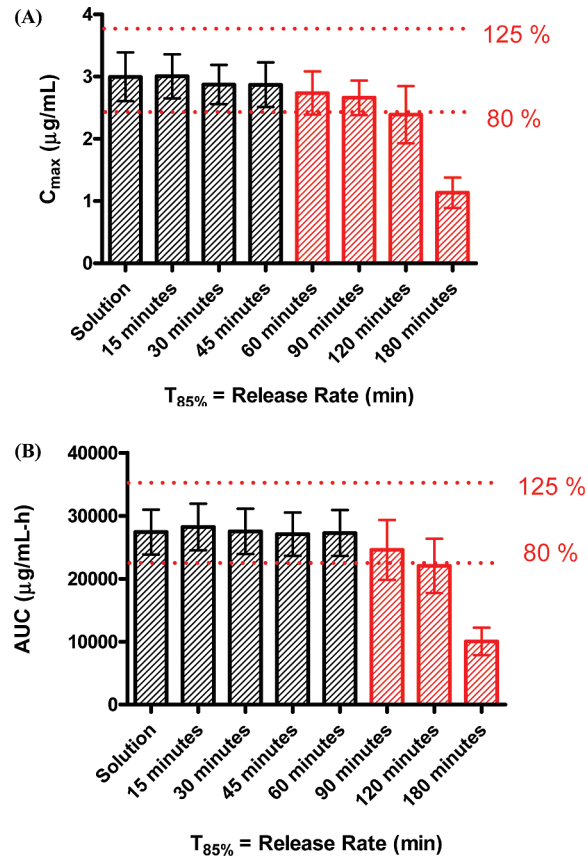

Figure 6. C_{max} (A) and AUC (B) of amoxicillin predicted by computer simulations. Data reported as mean ± SD 90% confidence interval (CI) of C_{max} (A) and AUC (B), the simulation being taken with a release rate corresponding to 85% release in 15 min as comparator. Black bars represent bioequivalence, and red bars represent outside of bioequivalence criteria, i.e. outside of 80% and 125% of the comparator.

proposed.[21] The utilization of the BCS-based approach to establish bioequivalence with *in vitro* studies without *in vivo* studies clearly has had regulatory impact for biowaivers of BCS class I drugs. In order to ensure the quality of drug products, the biowaivers for BCS class III compounds have to be carefully evaluated before exempting *in vivo* bioequivalence studies.[32,33] It has been argued from an empirical standpoint that biowaivers for some class II and III compounds should be extended.[20,34−36] Cheng and colleagues, for example, have demonstrated the feasibility of granting a biowaiver for the BCS class III drug metformin based on *in vivo* clinical studies, while Jantratid and colleagues suggested the possibility of a biowaiver for cimetidine.[20,35]

It is generally accepted that, for highly soluble−highly permeable drugs, the rate of drug absorption is limited by gastric emptying time. The range of gastric emptying time during fasting conditions is approximately 15−60 min.[2,37] In this series of predictions, the stomach transit time was set at 16.59 min. With an average gastric emptying time of approximately 15 min, those drug products with very rapid dissolution would behave similarly to oral drug solution products. Therefore, biowaivers for drug products with rapid dissolution rates would be acceptable.

In our predictions, physiological parameters were modified to reflect no absorption in the stomach for BCS class I and III drugs. For BCS class III drugs, zero permeability (no absorption) in the ileum and colon were the parameters used, consistent with published data regarding site-dependent absorption for this class.[30,31] When the dissolution of BCS class III products is rapid and the absorptive site is the ileum, they behave more similarly to an oral solution and therefore bioequivalence studies should be waived.[3] The colonic absorption would not affect the overall absorption of BCS

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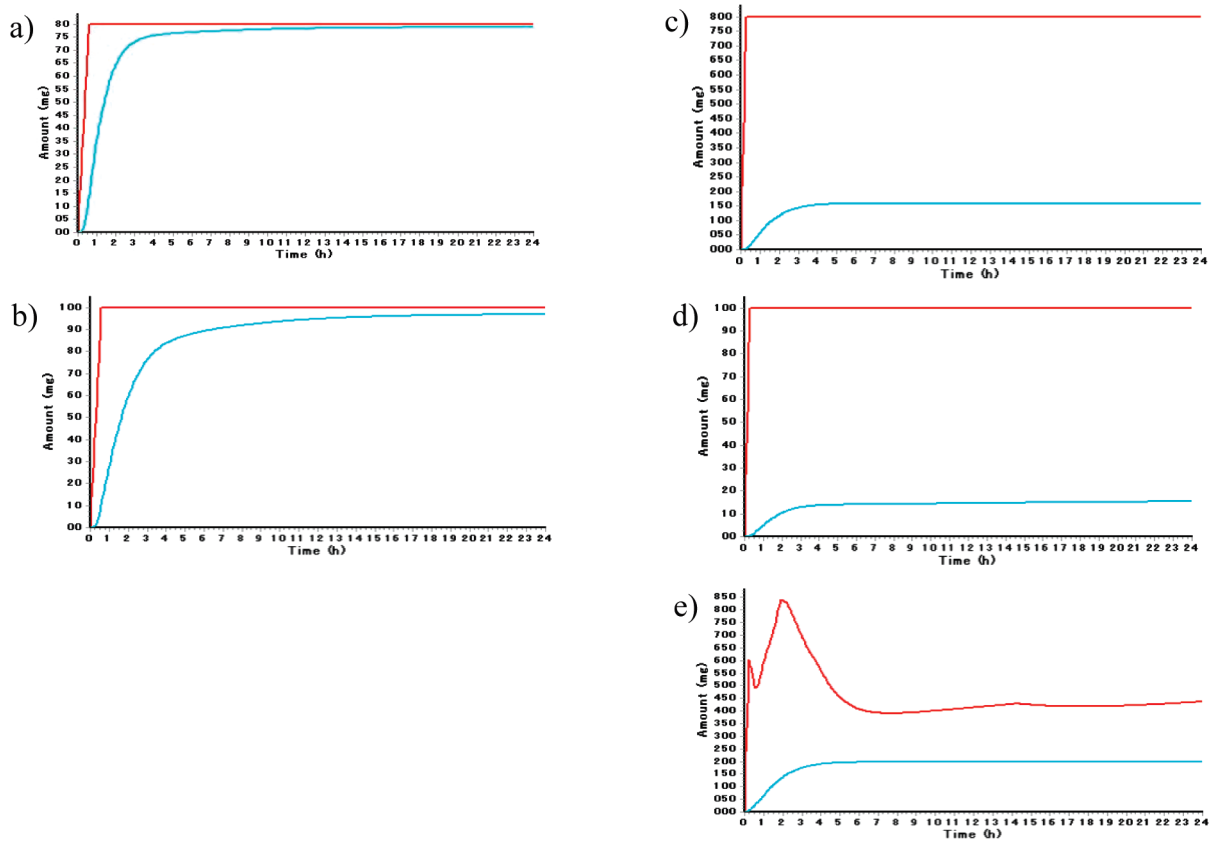

Figure 7. Amount of absorbed drug calculated by computer simulation as a function of the release rate. Red line represents amount of released drug as a function of time, and blue line represents amount of absorbed drug as a function of time: (a) propranolol, release rate corresponding to 85% in 30 min; (b) metoprolol, release rate corresponding to 85% in 30 min; (c) cimetidine, release rate corresponding to 85% in 15 min; (d) atenolol, release rate corresponding to 85% in 15 min; (e) amoxicillin, release rate corresponding to 85% in 15 min. These results were obtained by GastroPlus Single Simulation.

class I drugs because of their high permeability and the completion of absorption before reaching the colon. In the case of BCS class III drugs, their incomplete absorption might occur due to their low permeability and limited residence time in the small intestine when formulated in a controlled release dosage; as a result, the colonic absorption might have a greater impact on AUC_{0-inf}. However, when colonic absorption of BCS class III drugs was taken into account, AUC_{0-inf} differences were small (less than 2%) and C_{max} differences were not observed (data not shown). This result reflects the lower impact of colonic absorption for oral drug absorption and agrees well with a previous report.[17]

In this series of BCS class I drug absorption, the predicted propranolol and atenolol absorption profiles exhibited bioequivalence up to $T_{85\%} = 120$ min as compared to the reference result of $T_{85\%} = 30$ min, including bioequivalence between very rapid dissolution (>85% solubility in 15 min) and rapid dissolution (>85% solubility in 30 min); the results of bioequivalence between very rapid dissolution and rapid dissolution agreed well with previous reports.[17,38] On the other hand, the predicted BCS class III drug absorption exhibited bioequivalence up to $T_{85\%} = 60$ min as compared to the reference result of $T_{85\%} = 15$ min, except in the case of amoxicillin. For oral drug absorption of amoxicillin, the predicted AUC_{0-inf} demonstrated bioequivalence up to $T_{85\%} = 60$ min, similarly to other tested BCS class III drugs, but the predicted C_{max} of amoxicillin displayed bioequivalence

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only up to $T_{85\%} = 45$ min. This result suggests that the C_{max} criterion is more rigorous than AUC_{0-inf} for verifying bioequivalence. The predicted oral absorption profiles in terms of C_{max} and AUC_{0-inf} of all tested BCS class III drugs were similar, and those results demonstrated bioequivalence between $T_{85\%} = 15$ min and $T_{85\%} = 30$ min dissolution rates. The results of this study clearly reveal that the permeability of BCS class III compounds is the rate-limiting step for oral drug absorption, rather than their dissolution. Prolonging the release rates from $T_{85\%} = 15$ min to $T_{85\%} = 120$ or 180 min of BCS class III drugs resulted in a reduction of C_{max} and AUC_{0-inf} values that ranged from 20.53 to 64.42%, thus reflecting the overall decrease in absorption. The predictability of oral absorption for BCS class III drugs was clearly limited due to their low permeability throughout different dissolution rates as compared to the results of BCS class I drugs (Figures 7a−7e). Those results exhibited comparable pharmacokinetic parameters and suggested the extendibility of biowaivers to class III, in agreement with previous reports[17,37,39] (Tables 5−7, Figures 4−6). By exhibiting bioequivalence with extended release rates, those results of oral drug absorption suggest that large differences in release rates in the GI tract between test product and comparator can be tolerated.

The drug absorption from intestine is influenced by physiological factors (gastrointestinal motility, gastric emptying time, transit time), biopharmaceutical properties (gastrointestinal stability, solubility, dissolution, metabolism, and permeability), and drug−excipient interactions. However, most excipients used in solid oral IR products of class III drugs reportedly have little effect on drug absorption.[21,31,36,40] Taken together, the results reported here suggest that the current dissolution criteria are conservative and that extending the biowaiver to include IR dosage forms of BCS class III drug products is feasible. For high solubility and low permeability drugs, their permeability is the rate-limiting step for oral drug absorption. Therefore, biowaivers for BCS class 3 drug products with suitably rapid dissolution would ensure the quality of pharmaceutical products.

Acknowledgment. We thank Dr. John Chung for his valuable help with GastroPlus software.

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