Regular Article

Bioequivalence Dissolution Test Criteria for Formulation Development of High Solubility-Low Permeability Drugs

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Received September 20, 2022; accepted January 4, 2023

The purpose of the present study was to provide the experimental and theoretical basis of bioequivalence (BE) dissolution test criteria for formulation development of high solubility-low permeability drugs. According to the biowaiver scheme based on the biopharmaceutics classification system (BCS), for BCS class III drugs, a test formulation and a reference formulation are predicted to be BE when 85% of the drug dissolves within 15 min ($T_{85\%} < 15$ min) in the compendial dissolution test. However, previous theoretical simulation studies have suggested that this criterion may possibly be relaxed for use in practical formulation development. In the present study, the dissolution profiles of 14 famotidine formulations for which BE has been clinically confirmed were evaluated by the compendial dissolution test at pH 1.2 and 6.8. The plasma concentration–time profiles of famotidine formulations were simulated using the dissolution data. In addition, virtual simulations were performed to estimate the range of dissolution rates to be bioequivalent. The fastest and slowest dissolution rates among the famotidine formulations were $T_{85\%} = 10$ min and $T_{85\%} = 60$ min at pH 6.8, respectively. The virtual simulation BE study suggested that famotidine formulations can be bioequivalent when $T_{85\%} < 99$ min. In the case of BCS III drugs, the rate-limiting step of oral drug absorption is the membrane permeation process rather than the dissolution process. Therefore, a difference in the dissolution process has less effect on BE. These results contribute to a better understanding of the biowaiver approach and would be of great help in the formulation development of BCS class III drugs.

Key words biowaiver, biopharmaceutics classification system, bioequivalence, famotidine, dissolution test

Introduction

In new drug development, product life-cycle management, and generic drug development, the assessment of bioequivalence (BE) between reference and test formulations is required. To confirm BE with high evidence level, a clinical BE study is required. However, clinical BE studies are costly and time intensive. In addition, it is ethically not preferred to administer a drug to healthy volunteers. Therefore, to reduce the number of clinical BE studies, the biowaiver scheme based on the biopharmaceutics classification system (BCS-BWS) has been proposed for regulatory submissions. BCS-BWS predicts BE on the basis of the classification of a drug molecule by its equilibrium solubility and intestinal permeability (BCS classification) and compendial dissolution testing. BCS-BWS was first introduced by the U.S. Food and Drug Administration (FDA) in 2000 and then adopted by the European Medicines Agency (EMA), WHO, and many other regulatory agencies.[1–5]

However, several previous studies have pointed out that BCS-BWS can be improved.[6–10] For example, currently, the dissolution test criterion for BCS class III drugs (high solubility and low permeability) is 85% dissolution ($T_{85\%}$) within 15 min.[5] However, many BCS class III drugs have achieved clinical BE even when their $T_{85\%}$ values significantly deviated from this criterion.[11–14] In addition, theoretical analyses have suggested that a longer $T_{85\%}$ value may be a more appropriate criterion for BCS class III drugs because the dissolution process is not the rate-limiting step.[9,15] However, more experimental evidence is required to support this hypothesis.

BCS-BWS is usually discussed in terms of regulatory submissions (regulatory biowaiver). From this perspective, conservative dissolution criteria are required to reduce false-positive predictions. However, at the same time, this will also increase false negatives. Besides regulatory biowaiver, BCS-BWS is also widely used to guide formulation design during formulation development. Currently, compendial dissolution tests are routinely used in industrial formulation research with an implicit assumption that they can predict BE based on BCS-BWS (research biowaiver). From this perspective, false-negative predictions should be avoided not to reduce the chance of successful product development.

The purposes of the present study was to investigate the practical dissolution test criteria for the BE assessment of BCS class III drugs in formulation development. Regulatory biowaiver is out of the scope of this study. Famotidine was used as a model drug. The *in vitro* dissolution rates of nine famotidine immediate-release tablet products (IRT A to I) and five orally disintegrating tablet products (ODT A to E) were measured by the compendial dissolution test. To theoretically discuss the dissolution criteria, the plasma concentration (C_p)–time profiles were simulated by varying the dissolution rate.

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Experimental

Materials A total of 14 famotidine 20-mg formulations were used as test formulations: nine IRTs and five ODTs. Previous clinical studies have shown BE between the original formulation (IRT A) and other IRTs, as well as IRT A and the original ODT (ODT E), and ODT E and other ODTs. A 10-mm porous ultra-high molecular weight polyethylene cannula filter was purchased from ProSense (Netherlands).

Methods

Dissolution Test

Dissolution tests were performed using a DT 626 rotating-paddle apparatus (ERWEKA GmbH, Heusenstamm, Germany) with the Japanese Pharmacopeia dissolution buffer (900 mL, pH 1.2 and 6.8, 37 ± 0.5 °C, 50 rpm). Ten-milliliter aliquots of dissolution medium were withdrawn at 5, 10, 15, 30, and 60 min through a cannula filter. The concentration of famotidine was determined by UV spectroscopy with a SpectraMax 190 spectroscope (Molecular Devices LLC, Sunnyvale, U.S.A.). The detection wavelength of famotidine was 266 nm. The experiments were performed in triplicate.

Computer Simulation

Differential equations expressing the dissolution, intestinal membrane permeation, and elimination were used to simulate the C_p–time profiles.

$$\frac{dX_{undissolv}}{dt} = -k_{diss} X_{undissolv} \quad (1)$$

$$\frac{dX_{dissolv}}{dt} = k_{diss} X_{undissolv} - k_{perm} X_{dissolv} \quad (2)$$

$$\frac{dX_{plasma}}{dt} = k_{perm} X_{dissolv} - k_{el} X_{plasma} \quad (3)$$

where $X_{\mathrm{undissolv}}$ is the undissolved drug amount, X_{dissolv} is the dissolved drug amount, X_{plasma} is the drug amount in the plasma, k_{diss} is the dissolution rate coefficient, k_{perm} is the permeability rate coefficient, and k_{el} is the elimination rate coefficient.

The small intestine and the body were considered as one compartment. The small intestinal transit time (T_{si}) was set to 210 min unless otherwise noted.[16] The stomach and colon were omitted because they do not contribute to oral drug absorption for most drugs.[17–21] The intestinal and first-pass hepatic metabolism was neglected because famotidine is mainly excreted in the urine.[22] The k_{diss} value of each famotidine formulation was calculated by fitting Eq. (1) to the *in vitro* dissolution profiles (least-squares method). The C_p was calculated as $C_p = X_{\mathrm{plasma}}/\mathrm{Vd}$. The Vd and k_{el} values were obtained from the literature (i.v. data).[22] The Euler method with an integration time interval of 1 min was used to numerically integrate Eqs. (1) to (3).

Estimation of Permeation Rate Coefficient

The k_{perm} value was calculated using the GUT framework as follows[23]:

$$k_{perm} = \frac{2DF}{R_{SI}} \cdot P_{eff} \quad (4)$$

where DF is the degree of flatness, R_{SI} is the radius of the small intestine, and P_{eff} is the *in vivo* effective intestinal membrane permeability.[24] P_{eff} can be expressed as follows:

$$P_{eff} = \frac{PE}{\frac{1}{P'_{ep}} + \frac{1}{P_{UWL}}} = \frac{PE}{\frac{1}{VE \cdot f_u \cdot P_{ep}} + \frac{1}{P_{UWL}}} \quad (5)$$

where P'_{ep} is the effective epithelial membrane permeability, P_{UWL} is the unstirred water layer permeability, PE is the plica expansion factor, VE is the villi expansion factor, and f_u is the bile micelle unbound fraction in the intestinal fluid. For most BCS class III drugs, $P'_{ep} << P_{UWL}$.[15,23] Famotidine is absorbed predominantly *via* the paracellular pathway.[25] The bile micelle binding of famotidine was assumed to be negligible ($f_u = 1$) because the octanol-water partition coefficient ($\log P_{\mathrm{oct}}$) of famotidine is very low (−0.63).[26,27] In this case, Eq. (5) can be approximated as follows:

$$P_{eff} \approx PE \cdot VE \cdot P_{ep} \quad (6)$$

The P_{ep} value of famotidine was assumed to be the same as the apparent Caco-2 permeability ($P_{app} = 7.4 \times 10^{-7}$ cm/s at 0.1 mM).[25] $DF = 1.7$, $R_{SI} = 1.5$ cm, $PE = 3$, and $VE = 10$ were used in the k_{perm} calculation.[28–30]

Results

BCS Classification of Famotidine The physicochemical and biopharmaceutical properties of famotidine are shown in Table 1. Famotidine is a base drug with a pK_a of 7.06. The dose/solubility ratio was calculated to be <13 mL (lowest solubility at pH 7.5 = 1.53 mg/mL, highest dose strength = 20 mg).[12] The lipophilicity value ($\log D_{\mathrm{oct}}$ at pH 6.5 = −1.3),[12] Caco-2 permeability value (7.4×10^{-7} cm/s at 0.1 mM),[25] and the fraction of a dose absorbed (Fa) in humans (Fa% = 40–49%)[31] suggest that famotidine is a low-permeability drug. Therefore, famotidine was classified as BCS class III.

Dissolution Profiles of Famotidine Formulations The results of the dissolution test are shown in Fig. 1 and Table 2. All IRTs except IRT H achieved 85% dissolution within 15 min at pH 1.2. On the other hand, only IRT B and IRT C achieved 85% dissolution within 15 min at pH 6.8. The $T_{85\%}$ of

Table 1. Parameters of Famotidine

Parameters	Values
MW	337
pK_a	7.06 (Base)[a]
Octanol-water partition coefficient ($\mathrm{Log}\,P_{\mathrm{oct}}$)	−0.63[b]
Octanol-water distribution coefficient ($\mathrm{Log}\,D_{\mathrm{oct}}$)	−1.3 (pH 6.5)[a]
Solubility	1.53 mg/mL (pH 7.5)[a]
Caco-2 permeability (P_{app})	7.4×10^{-7} cm/s (0.1 mM)[c]
	5.3×10^{-7} cm/s (0.3 mM)[c]
	3.9×10^{-7} cm/s (0.5 mM)[c]
	3.4×10^{-7} cm/s (0.7 mM)[c]
	3.3×10^{-7} cm/s (1 mM)[c]
	2.4×10^{-7} cm/s (2 mM)[c]
Elimination half-life ($t_{1/2}$)	2.9 h[d]
Elimination rate coefficient (k_{el})	0.29 h^{-1}[e]
Total clearance (CL_{tot})	25.5 L/h[d]
Volume of distribution (Vd)	87.9 L[d]
Absolute bioavailability	39.6–49.0%[d]

a) Ref.[12] *b*) Calculated from $\mathrm{Log}\,D_{\mathrm{oct}}$ (pH 6.5) using the Henderson–Hasselbalch equation. *c*) Ref.[25] *d*) Ref.[22] *e*) Calculated from CL_{tot} and Vd ($k_{\mathrm{el}} = CL_{\mathrm{tot}}/V\mathrm{d}$).

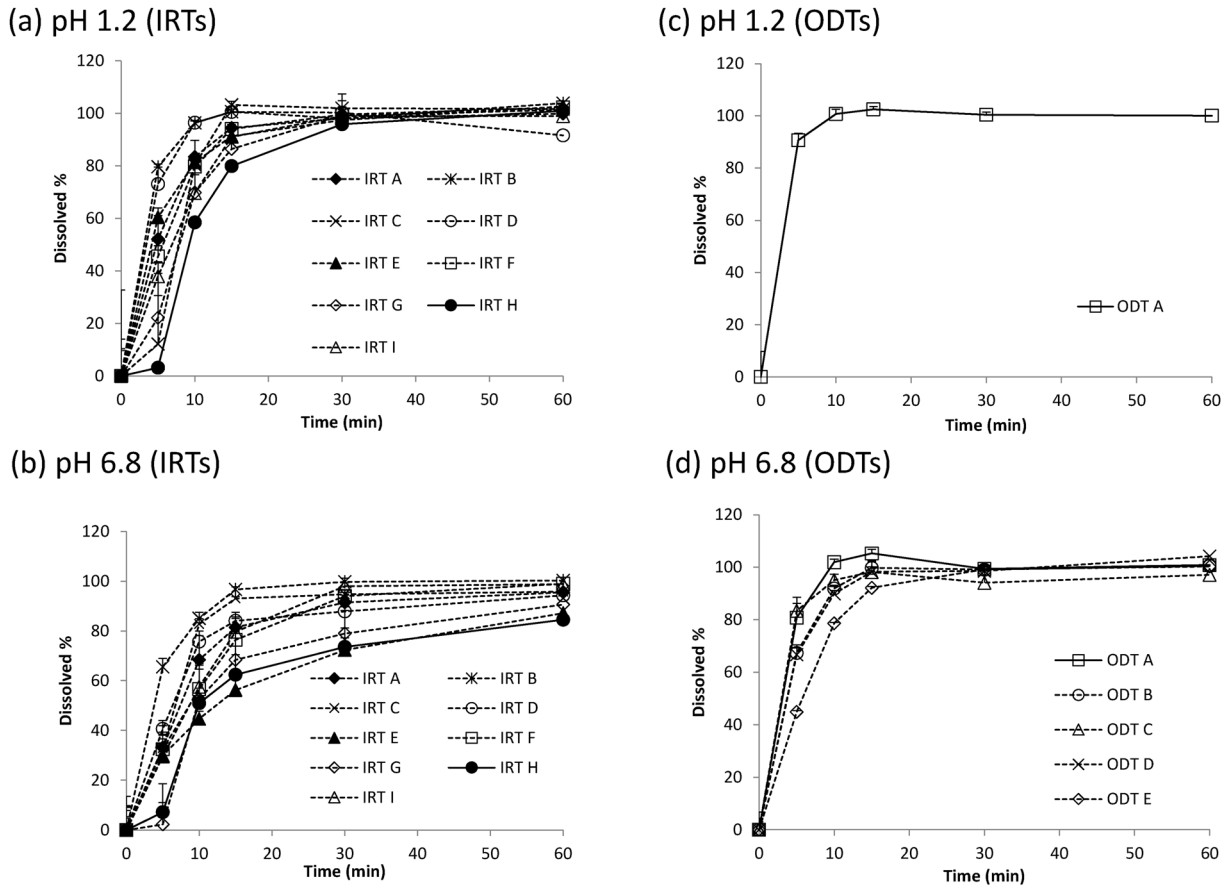

Fig. 1. Dissolution–Time Profiles of Famotidine Immediate-Release Tablet Products (IRTs) at pH 1.2 (a) and 6.8 (b) and of Orally Disintegrating Tablet Products (ODTs) at pH 1.2 (c) and 6.8 (d)

Table 2. *In Vitro* Percent Dissolution at 15 min and Time to Reach 85% Dissolution ($T_{85\%}$) of Test Formulations (pH 1.2 and 6.8)

Formulation	pH 1.2		pH 6.8	
	Percent dissolution at 15 min	$T_{85\%}$ (min)	Percent dissolution at 15 min	$T_{85\%}$ (min)
IRT A	94	15	81	30
IRT B	101	10	97	10
IRT C	103	15	93	15
IRT D	101	10	84	30
IRT E	91	15	80	30
IRT F	94	15	76	30
IRT G	86	15	68	60
IRT H	80	30	62	60
IRT I	91	15	56	60
ODT A	103	5	105	10
ODT B	—[a)]	—[b)]	100	10
ODT C	—[a)]	—[b)]	98	10
ODT D	—[a)]	—[b)]	98	10
ODT E	—[a)]	—[b)]	92	15

a) Not measured because it was expected to be >85%. *b*) Not measured because it was expected to be <15 min.

the famotidine formulations ranged from 5 to 30 min at pH 1.2 and from 10 to 60 min at pH 6.8.

All ODTs achieved 85% dissolution within 15 min at pH 6.8. The dissolution rate at pH 1.2 was not evaluated for the ODTs (except for ODT A) because famotidine is expected to dissolve faster at pH 1.2 than at pH 6.8. Therefore, the $T_{85\%}$ values of all ODTs were expected to be <15 min. The $T_{85\%}$ of ODT A at pH 1.2 was <5 min.

Estimation of Permeation Rate Coefficient (k_{perm}) The k_{perm} value was predicted from the apparent permeability in Caco-2 cell monolayers. The C_p–time profiles of ODT A were simulated using the predicted k_{perm} value (0.18 h^{-1}) to evaluate the validity of this value. ODT A was selected because the dissolution process of ODT A is very fast ($T_{1/2}$ = 2.3 min) so that it can be regarded as a good approximation of solution administration to neglect the effect of drug dissolution. The simulated C_p–time profile was close to the observed C_p–time profile of ODT A in the clinical study[32] (Fig. 2), suggesting that the k_{perm} value estimated from Caco-2 P_{app} value by using the GUT framework was appropriate.

In this study, the C_p–time profiles were simulated in a bottom-up prediction manner without using any parameter fitting to the oral pharmacokinetics (PK) data (only the intravenous (i.v.) PK data and the k_{perm} value estimated from the Caco-2 P_{app} data were used). The Fa and C_{max} values were appropriately simulated, whereas the area under the curve (*AUC*) and C_p–time profile were slightly underestimated. From the viewpoint of bottom-up prediction accuracy,[21] the discrepancy between the simulated and observed C_p-time profiles was rather slight, suggesting that the model parameters appropriately captured the biopharmaceutical characteristics of the famotidine formulation without using any parameter fitting. Therefore, the k_{perm} value estimated from the Caco-2 P_{app} value was

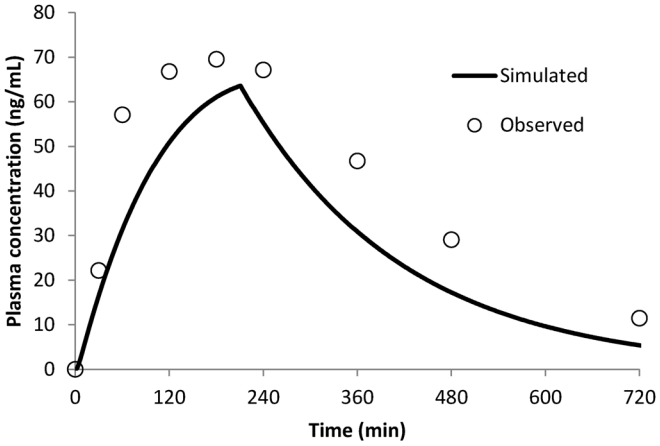

Fig. 2. Observed and Simulated Plasma Concentration–Time Profiles of Famotidine ODT A in Humans

used in the following studies. To avoid ambiguity about data interpretation,[33] parameter fitting was not used for k_{perm} (or P_{eff}) estimation. The *p.o.* and i.v. data used in this study were from different populations. Therefore, the post-absorptive PK parameters such as total clearance could be different between the *p.o.* and i.v. data. To accurately estimate a k_{perm} value from clinical PK data, a cross-over study is required. In addition, to identify the k_{perm} value from clinical PK data, an intra-duodenum administration of a solution formulation is required.[34]

Computer Simulation of the C_p–Time Profile Based on the results of the dissolution tests, ODT A and IRT H showed the highest and lowest dissolution rates at pH 6.8, with k_{diss} values of 18 and 3.1 h^{-1}, respectively. The amount of the drug dissolved in the small intestine and the C_p–time profile were simulated using these k_{diss} and k_{perm} values. The simulation results showed that the *AUC* and C_{max} values of these formulations would be equivalent (Fig. 3a and Table 3), even though

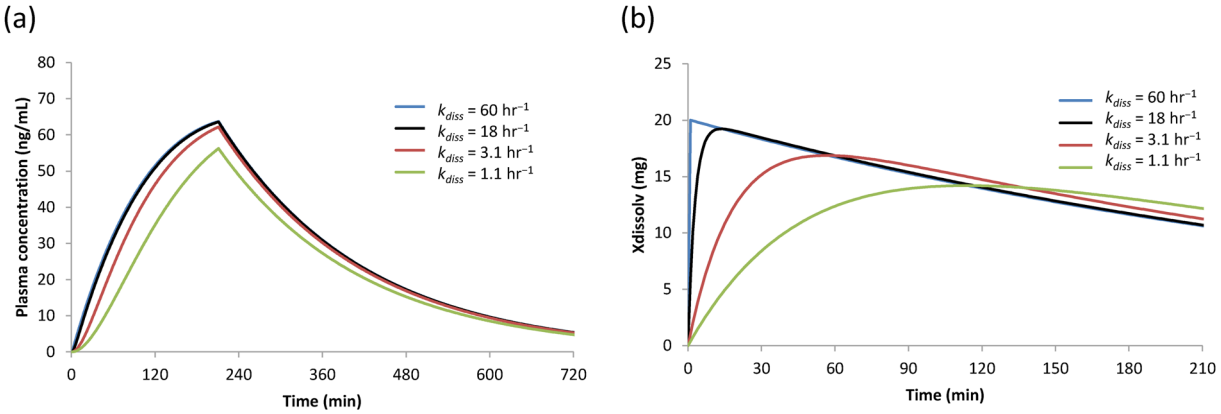

Fig. 3. Effect of Dissolution Rate Coefficient (k_{diss}) on the Plasma Concentration–Time Profiles (a) and Dissolved Drug Amount–Time Profiles (b) of Famotidine Formulations

Table 3. Observed and Simulated *AUC*, C_{max}, and T_{max} of Famotidine Formulations

		k_{diss} (h^{-1})	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	Fa%
ODT A	Observed[a]	—	565 ± 99	77 ± 18	2.7 ± 1.2	(39.6–49.0)[c]
	Simulated	18	365	64	3.5	46.6
IRT H	Observed[b]	—	550 ± 104	80 ± 22	3.2 ± 1.0	(39.6–49.0)[c]
	Simulated	3.1	344	62	3.5	43.9

a) Ref.[32] except for Fa%. *b*) Ref.[54] except for Fa%. *c*) Ref.[22]

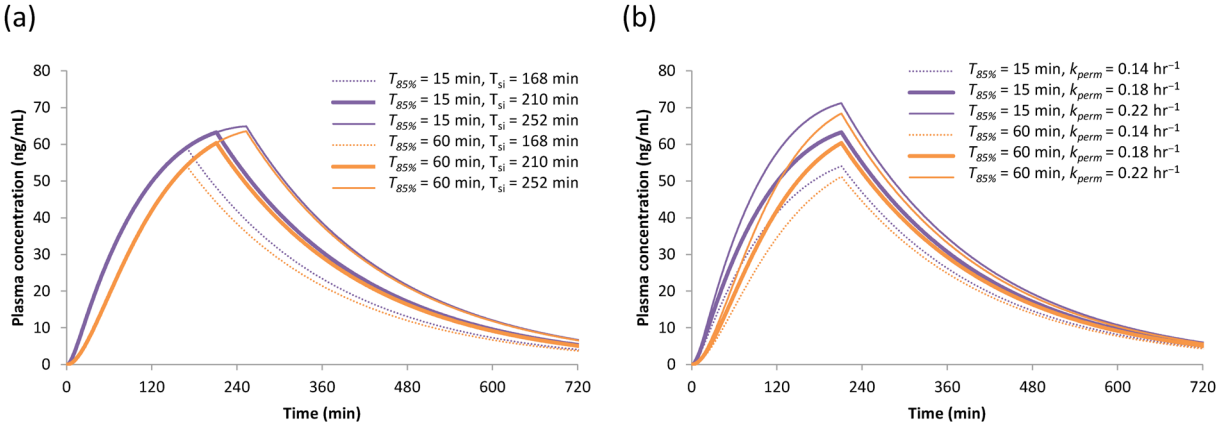

Fig. 4. Effect of Small Intestinal Transit Time (T_{si}) (a) and Permeability Rate Coefficient (k_{perm}) (b) on the Plasma Concentration–Time Profiles of Famotidine Formulations

Table 4. Simulated AUC and C_{max} of Famotidine Formulations with Different Dissolution Rate Coefficient (k_{diss}) Values

k_{diss} (h^{-1})	$T_{85\%}$ (min)[a]	AUC_{0-24h} (ng·h/mL)	AUC_{0-24h} percent difference	C_{max} (ng/mL)	C_{max} percent difference
60[b]	2[b]	368		64	
18	6	365	99	64	100
3.1	36	344	93	62	98
1.1	99	294	80	54	88

a) The $T_{85\%}$ values were calculated as $T_{85\%} = -\ln(1-0.85)/k_{diss}$. *b*) $k_{diss} = 60\,h^{-1}$ ($T_{85\%} = 2$ min) was used as the infinite dissolution rate.

Table 5. Simulated AUC and C_{max} of Famotidine Formulations with Different $T_{85\%}$ and Small Intestinal Transit Time (T_{si}) Values

$T_{85\%}$ (min)	T_{si} (min)	AUC_{0-24h} (ng·h/mL)	AUC_{0-24h} percent difference	C_{max} (ng/mL)	C_{max} percent difference
2[a]	210	368		64	
15	168	302	92	59	93
15	210	359	98	63	99
15	252	409	111	65	102
60	168	264	72	54	85
60	210	325	88	60	95
60	252	380	103	64	100

a) $T_{85\%} = 2$ min was used as the infinite dissolution rate.

Table 6. Simulated AUC and C_{max} of Famotidine Formulations with Different $T_{85\%}$ and Permeability Rate Coefficient (k_{perm}) Values

$T_{85\%}$ (min)	k_{perm} (h^{-1})	AUC_{0-24h} (ng·h/mL)	AUC_{0-24h} percent difference	C_{max} (ng/mL)	C_{max} percent difference
2[a]	0.18	368		64	
15	0.14	304	83	54	85
15	0.18	359	98	63	99
15	0.22	408	111	71	112
60	0.14	274	74	51	80
60	0.18	325	88	60	95
60	0.22	372	101	68	107

a) $T_{85\%} = 2$ min was used as the infinite dissolution rate.

there was a difference in the amount of the drug dissolved in the intestine at <90 min (Fig. 3b).

Furthermore, simulation results with varying k_{diss} values showed that any formulations with $T_{85\%} < 99$ min ($k_{diss} = 1.1\,h^{-1}$) are expected to show BE (Fig. 3a and Table 4).

The effects of k_{perm} and T_{si} on the C_p–time profiles of famotidine were also simulated by changing them by ±20%. As shown in Fig. 4, Tables 5, and 6, famotidine absorption was susceptible to changes in k_{perm} and T_{si}. However, the effect of k_{perm} and T_{si} on the C_p–time profiles was not mitigated by reducing $T_{85\%}$ from 60 to 15 min.

Discussion

In BCS-BWS, the first step is to classify a drug molecule by equilibrium solubility and intestinal membrane permeability. The second step is to perform compendial dissolution tests of the formulations.

In the first step, a drug molecule is classified into one of four categories: BCS class I (high solubility/high permeability), BCS class II (low solubility/high permeability), BCS class III (high solubility/low permeability), or BCS class IV (low solubility/low permeability).[5] When the highest dose is soluble in ≤250 mL in the physiological gastrointestinal pH range of pH 1.2–6.8, the drug molecule is classified as highly soluble. When the Fa in humans is ≥85%, the drug molecule is classified as highly permeable.

In the second step, the dissolution rate of drug products is evaluated. Rapid dissolution ($T_{85\%} < 30$ min) and very rapid dissolution ($T_{85\%} < 15$ min) are required for a biowaiver of BCS class I and III drugs, respectively.[5] In contrast, BCS class II and IV drugs are not eligible for a biowaiver.

Famotidine is a BCS class III drug. Therefore, according to BCS-BWS, the dissolution criterion is >85% dissolution at 15 min at pH 1.2 and 6.8. All formulations used in this study have shown BE in clinical studies. However, several famotidine formulations did not comply with this BCS-BWS criterion, especially at pH 6.8. Therefore, the BE prediction by BCS-BWS for these formulations was false negative. One possible reason for the discrepancy is that the dissolution process has less impact on C_{max} and AUC because the rate-limiting step of oral drug absorption of famotidine is the intestinal permeation process, rather than the dissolution process. We examined this assumption by computer simulation. In the case of basic drugs, such as famotidine, the dissolution rate is lower at neutral pH than at acidic pH. Furthermore, the main absorption site is the small intestine. Therefore, a computer simulation using the dissolution data at pH 6.8 was performed. This is the most conservative scenario for a basic drug. Even in this scenario, the simulation results suggest that the dissolution criterion of current BCS-BWS may be relaxed for famotidine.

Previous theoretical analyses have suggested the dissolution criterion for a BCS class III drug[7,15,35] (Table 7). These analyses showed that the criterion of $T_{85\%}$ for BCS class III was 23–44 min with a safety margin of 3, which is approxi-

Table 7. $T_{85\%}$ Criteria of BCS Class III Drugs Determined by Theoretical Analysis

Gastrointestinal transit model	Parameters of model drugs			Critical $T_{85\%}$ (min)	$T_{85\%}$ criteria (Critical $T_{85\%}/3$) (min)	Ref.
	Gastric emptying	k_{perm} (h^{-1})	k_{el} (h^{-1})			
One-compartment model	Not applicable	0.057	0.069–0.69	85	28	15)
	Not applicable	0.57	0.069–0.69	133	44	
Multi-compartment model (S1I3)	$t_{1/2} = 0.01$ h	0.25	0.48	90	30	35)
	$t_{1/2} = 0.5$ h	0.25	0.48	>120	>40	
	$t_{1/2} = 0.01$ h	0.8	1.8	69	23	
	$t_{1/2} = 0.5$ h	0.8	1.8	>120	>40	
Multi-compartment model (S1I7C1)	Solution: 3.5 h^{-1} Solid: $t_{1/2} = 0.4$–1.4 h	0.1–0.8	0.014–0.9	>120	>40	7)

mately 2 to 3 times larger than the criterion in BCS-BWS ($T_{85\%} = 15$ min). The results of this study are in good agreement with the results of the previous theoretical analyses.

The result of the present study was in good contrast to what has been suggested for BCS class I drugs. Regarding the dissolution criteria, several studies have pointed out that an elimination half-life ($t_{1/2}$) should be considered for BE of C_{max} values.[7,8,15] BCS class I drugs with short elimination $t_{1/2}$ values probably may not show BE of C_{max} values.[36–38] From the viewpoint of BE of C_{max} values, the dissolution criterion of BCS class I with a short half-life should be set more strictly than that of BCS class III drugs. According to the previous theoretical analysis, the dissolution criterion for a BCS class I drug ($k_{perm} = 5.7\ h^{-1}$) with an elimination $t_{1/2}$ of 60 min should be $T_{85\%} = 14$ min for BE of C_{max}, with a safety margin of 3.[15] This is stricter than the current criterion for BCS class I drugs in BCS-BWS ($T_{85\%} = 30$ min). In the future, further investigation is needed to validate the dissolution criteria using clinical data for not only BCS class III drugs but also class I drugs with a short half-life.

Another possible reason for BCS-BWS resulting in a false-negative prediction for famotidine is that the *in vitro* dissolution test in this study may be overly discriminative. The agitation condition required by WHO was 75 rpm for the paddle apparatus, whereas that by FDA and EMA was 50 rpm.[10] When the agitation is stronger, the discrimination power decreases. If the 75-rpm paddle method can adequately describe the *in vivo* dissolution of famotidine formulations, the 50-rpm paddle method may have been overly discriminative. However, it has been reported that the agitation strength in humans corresponds to 10–30 rpm.[39–42] Furthermore, it has been reported that the 75-rpm paddle method was less discriminative and predictive of the *in vivo* dissolution.[36]

It should be noted that the above discussion does not necessarily mean that BCS class III drugs are suitable for a biowaiver. The oral absorption of BCS class III drugs can be affected by changes in T_{si} and/or membrane permeability by some excipients (Fig. 4). The effect of excipients on oral drug absorption may explain the strict criterion set for BCS class III drug products. However, it is unclear whether bioinequivalence due to the excipient's effects on T_{si} and/or membrane permeability can be offset by using a strict dissolution criterion for BCS class III drugs. The study results suggest that it is difficult to reduce the risk of bioinequivalence by changes in T_{si} or membrane permeability even when complying with the dissolution criteria of $T_{85\%} = 15$ min.

In addition, it is questionable whether or not the practical content of excipients can affect T_{si}. For example, sugar alcohols, such as mannitol and sorbitol, may affect T_{si} in a dose-dependent manner.[43,44] According to previous findings, the oral administration of 2 g of mannitol reduced T_{si} by ≤60%,[45] resulting in a reduction in the oral absorption of low-permeability drugs.[46–48] In the present study, mannitol is used in ODT A, C, D, and E, but not in the other formulations. These formulations show clinical BE. Matsui *et al.* investigated the mannitol content in marketed oral drug products and estimated the no-effect threshold.[49] They showed that at least 50 mg of mannitol did not affect oral absorption when the formulation rapidly dissolved. Several surfactants have also been reported to affect membrane active transporters.[50–52] However, commonly used excipients would not greatly affect the passive epithelial membrane permeability of BCS class III drugs except for P-glycoprotein substrates.[53] Further investigation is needed regarding the effects of excipients on oral absorption in terms of quantity as well as quality.

The above discussion does not mean that the criteria of regulatory BCS-BWS should be changed. For a regulatory biowaiver, it is appropriate to set conservative dissolution criteria to reduce false-positive predictions. However, for formulation development, false-negative predictions can narrow the formulation design space and increase unnecessary formulation optimization efforts. Given that many BCS III drugs show clinical BE despite not satisfying the regulatory BCS-BWS criteria,[11–14] different criteria could be more appropriate for formulation design.

Conclusion

The clinical BE famotidine formulations showed a wide range of dissolution rates in the compendial dissolution test. The computer simulation results indicated that, in the case of famotidine, it is possible to show BE between formulations dissolving within $T_{85\%} < 99$ min. These results may be of great help in the development of high solubility-low permeability drugs that have physicochemical and biopharmaceutical properties similar to famotidine. However, further investigations using various BCS class III drugs are required to generally apply the findings of this study to all BCS class III drugs.

Conflict of Interest The authors declare no conflict of interest.

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