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REVIEW

A Proposal of Conducting Bioequivalence Trials with Gastric pH Modulators for Two Oral Formulations Demonstrating Different Dissolution Profiles at Elevated pH

Hao Zhu[1,*], Xiaomei Chen[1], Mariam Ahmed[1], Yaning Wang[1], Qi Liu[1], Ramana S. Uppoor[1], Colleen Kuemmel[1] and Mehul Mehta[1]

In this paper, a special case for bioequivalence evaluation of oral formulations is discussed. Drug formulations with different forms of active moieties (e.g., free base and salt) may yield different dissolution characteristics and, thus, differ in absorption at elevated gastric pH. However, routine bioequivalence trials using subjects with normal gastric pH (i.e., ~ 1) may fail to identify these differences because dissolution/absorption profiles of the two formulations at normal gastric pH are similar. In the case of palbociclib, it is confirmed that the free base and salt formulations showed different absorption in patients with different gastric pH. Significant reduction in drug absorption was observed only in patients with elevated gastric pH using free base formulation. The discovery that the free base had significantly reduced absorption hinged on the inclusion of enough patients with elevated gastric pH to detect a difference in a bioequivalence trial. This raises a concern, as demonstrated through simulation, that dissolution/absorption differences in other formulations could be missed in routine bioequivalence trials. Aside from differences in active pharmaceutical ingredients (APIs), other factors, such as changes in excipients or manufacturing methods, may also lead to exposure differences between formulations at elevated gastric pH. For formulations containing different forms of the same active moiety or the same API and showing different dissolution profiles at elevated pH (i.e., pH ~ 4–6.8), evaluation of bioequivalence with gastric pH modulators (e.g., a H_2 blocker) in addition to routine bioequivalence assessments may help to ensure therapeutic equivalence in patients with elevated gastric pH.

According to § 320.1 (21CFR320.1), bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[1] To demonstrate bioequivalence, a clinical trial using pharmacokinetic end points is typically performed. A bioequivalence test to demonstrate that the true mean ratios of the major pharmacokinetic parameters are used to describe rate and extent of drug absorption between two formulations are within a predefined range (i.e., bioequivalence limits). Demonstrating bioequivalence between two formulations provides an important regulatory pathway to support approval of a new formulation (e.g., a new dosage form or a new salt form) or a generic substitute.[2,3]

In this paper, we focus on a special case in bioequivalence evaluation. For different formulations using the same active moiety, dissolution characteristics may vary at different pH levels. Although most people in the general population have a gastric pH around 1, a certain percentage of patients, which may vary across different diseases, may have an elevated pH due to various factors, including physiology (e.g., aging), pathology (e.g., achlorhydria), or medication (e.g., acid-reducing agent).[4,5] Subjects with an elevated gastric pH may show differences in the rate and extent of absorption of two formulations of the same active moiety due to pH-related differences in drug dissolution. Thus, therapeutic equivalence may not be ensured between the two formulations in patients with elevated gastric pH, even though pharmacokinetic end points may meet bioequivalence criteria in a routine bioequivalence trial conducted in subjects with normal gastric pH (~ 1).

To investigate this issue, we analyzed data from new drug application submissions, modeling and simulation, and literature reports. Based on these analyses, we propose that bioequivalence trials be conducted with gastric pH modulators (i.e., proton pump inhibitors or H_2-blockers) for formulations containing either different forms of the same active moiety (e.g., salt and free base) or the same active pharmaceutical ingredients (API) and showing different dissolution profiles at elevated pH (i.e., pH 4–6) to ensure similar exposure and, thus, therapeutic equivalence.

THE CASE OF PALBOCICLIB

The case of palbociclib demonstrates that a formulation may exhibit significant reduction in dissolution/absorption in subjects with elevated gastric pH. The extent

[1]Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. *Correspondence: Hao Zhu (hao.zhu@fda.hhs.gov)
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of reduction in absorption at various pH levels can be formulation-dependent.

Palbociclib, as a weak organic base, is indicated for the treatment of breast cancer.[6] Two formulations using different active pharmaceutical ingredients (APIs) were developed at different stages during clinical development.[7–9] The early clinical trials used an isethionate salt formulation. A free base formulation was developed for subsequent clinical trials and commercialization.[7,8] A crossover bioequivalence trial was conducted to bridge the free-base and the isethionate salt formulations. The free-base formulation marginally failed the bioequivalence test when compared with the isethionate salt formulation. The lower limit of the 90% confidence interval for the ratio of the peak plasma concentration (C_{max}) was ~ 76%, slightly lower than the acceptance limit of 80%.[7] Based on C_{max} or area under the curve (AUC) ratio distribution, it seems that a subgroup of subjects in the bioequivalence trial showed low exposures only when receiving the free-base formulation.[7] Nevertheless, the data suggested that the majority of the subjects showed similar exposures independent of the formulations received, because the point estimate ratios of C_{max} and AUC were close to 1.[7]

To further confirm the finding from the bioequivalence trial that a subgroup of subjects receiving free base formulation showed low exposure, a comparison was conducted across multiple phase I clinical trials. Among all subjects receiving different formulations at the same dose, only some subjects receiving free-base formulations yielded low C_{max}, lower than 20% of the median C_{max} across all the trials. In addition, it was found that the subjects with low exposure did not represent the majority of the subjects, because the median exposures in the free-base formulation group were similar to those from other formulation groups. The subjects showing low exposure accounted for 13% of the total subjects receiving the free base formulation.[7,8]

The subgroup of subjects with decreased exposure when receiving the free base formulation is likely to be the subjects with increased gastric pH based on the dissolution characteristics of the formulations. When the pH is <4.3, the solubility of palbociclib is >0.5 mg/mL, which means that 125 mg of palbociclib free base can be completely dissolved in 250 mL of buffer. However, the solubility drastically decreases when the pH increases, approaching zero near pH 7.[8] Along with the solubility changes, the dissolution rate and extent, as illustrated in **Figure 1a**, are significantly decreased when pH increases.

A drug–drug interaction trial further suggested that the subgroup of subjects with low exposure when receiving the free-base formulation are the subjects with increased gastric pH. The trial was to evaluate the extent of absorption reduction of the palbociclib free base formulation in subjects with concomitant use of rabeprazole, a proton pump inhibitor. The trial showed an average of 80% reduction in palbociclib C_{max} in subjects stabilized with rabeprazole. The observed palbociclib C_{max} for all subjects stabilized with rabeprazole were similar to that from the subgroup of subjects showing low exposure in other phase I trials.[8] Furthermore, four subjects who showed low exposure receiving the palbociclib free base formulation alone demonstrated no further exposure change when receiving palbociclib in combination with rabeprazole.[7]

In summary, the data suggest that there are two groups of subjects with different absorption patterns of palbociclib likely based on their gastric pH levels. For the majority of subjects (~ 87%) with normal gastric pH (i.e., gastric pH close to 1), the drug dissolution and absorption patterns between the free base and isethionate salt formulations are similar. However, for the subgroup of subjects with presumed elevated gastric pH (~ 13%), the rate and extent of drug dissolution between the free-base formulation and the isethionate salt formulation differ substantially. Hence, subjects in this subgroup receiving the free base formulation yield significantly low exposure.

SIMULATION STUDY

In the case of palbociclib, formulations with different APIs—salt and base—may vary in absorption in subjects with elevated pH. This raises the concern that differences in absorption could be missed in the absence of subjects with varying gastric pH in routine bioequivalence trials for other drug formulations. To explore this observation and seek a potential solution, a series of simulations were conducted. It is noted that the quantitative outcomes from the simulation (e.g., percentage of simulated trials passed bioequivalence testing) can be affected by the simulation models, model assumptions, and parameter values used. However, the concept can be generalized for other formulations with similar features.

METHODS

Simulation models

The model applied for simulation consisted of three components: a dissolution model, a pharmacokinetic model, and a gastric pH distribution model. A schematic of the dissolution and pharmacokinetic models is illustrated in **Figure 2**. The dissolution model was used to describe the cumulative dissolution curve over time at different pH for a free-base and salt formulation. The pharmacokinetic model linked the amount of drug released into gastric fluid over time and the pharmacokinetic profile of each formulation. The gastric pH distribution model was developed to describe the distribution of subjects with different gastric pH in a general population. Parameters used for simulation were derived based on a new drug application submission and literature reports.

Dissolution model

The dissolution model was developed based on the theory that the different dissolution rates for a salt and a free base are due to different surface pH (i.e., pH within diffusion layer) and not the bulk pH.[10,11]

The Nerst–Brunner equation[12–14] was used to describe the drug dissolution rate (Eq. 1), where M_t is the amount of drug dissolved at time t, M is the remaining undissolved solid drug amount, M_0 represents the initial amount of drug (the value can be assumed to be 1 for a single dose), C_s is the drug solubility at the particle surface, C_t is the drug concentration in bulk solution at time t, and z is determined by diffusion coefficient, diffusion layer thickness, initial particle size, particle density, and shape factor.[12]

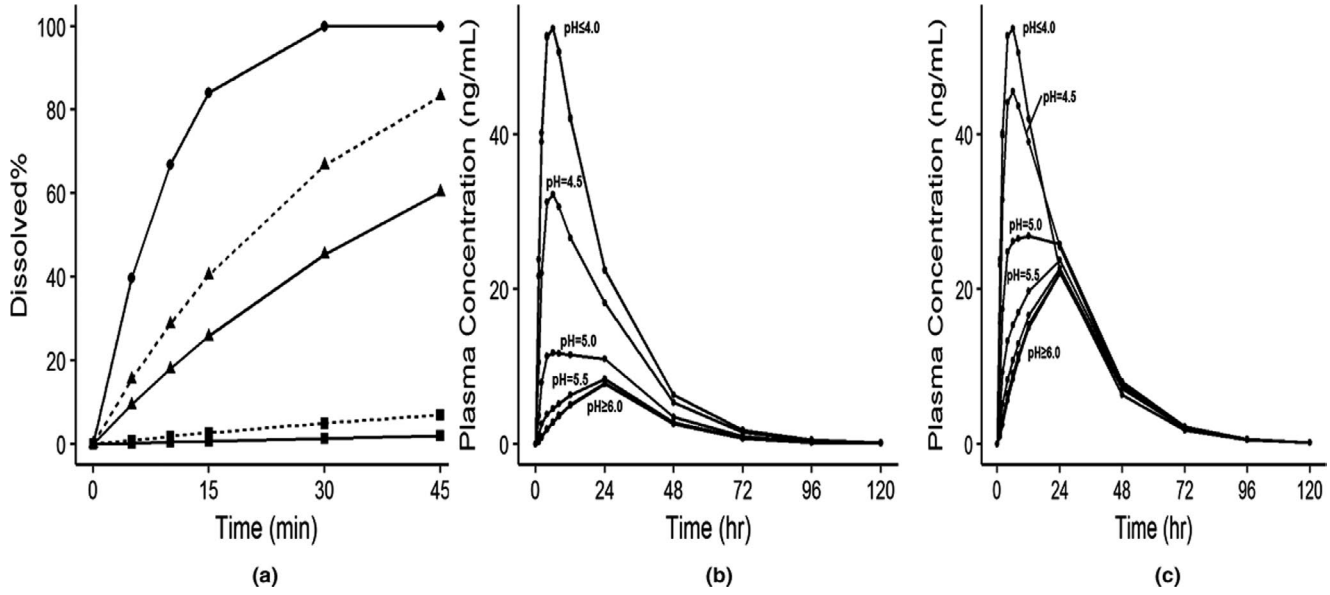

Figure 1 Simulated dissolution (**a**) and pharmacokinetic profiles (**b,c**) for the free-base and salt formulations. Dissolution profiles in **a**: solid lines are the simulated dissolution profiles for base and dashed lines are the simulated dissolution profiles for salt: square: pH = 6.8; triangle: pH = 4.5; and circle: pH = 1.2. **b,c:** Mean pharmacokinetic profiles for free-base formulation in **b** and salt formulation in **c** at pH ≤ 4.0, pH = 4.5, pH = 5.0, pH = 5.5, and pH ≥ 6.0.

$$\frac{dM_t}{dt} = z \cdot M_0^{\frac{1}{3}} \cdot M^{\frac{2}{3}} \cdot (C_s - C_t) \quad (1)$$

The pH-solubility profile of a basic drug is determined by two curves represented by the two equations (Eqs. 2 and 3) for totable solubility (S_T) for free base and salt, respectively[10,11]:

$$S_{T,\text{base}}(\text{pH} \geq \text{pH}_{\max}) = [\text{BH}^+] + [\text{B}]_S = [\text{B}]_S \left(1 + 10^{(\text{p}K_a - \text{pH})}\right) \quad (2)$$

$$S_{T,\text{salt}}(\text{pH} \leq \text{pH}_{\max}) = [\text{BH}^+]_S + [\text{B}] = [\text{BH}^+]_S \left(1 + 10^{(\text{pH} - \text{p}K_a)}\right) \quad (3)$$

where pK_a is the acid dissociation constant with the value of 7.86, and [BH$^+$] and [B] are the concentrations of ionized base and free base in aqueous medium. The subscript *S* represents solubility of the specific form. Eq. 2 only accounts for the solubility of free base ($[B]_S$ = 0.0002 mg/mL), and Eq. 3 accounts for the solubility of salt ($[\text{BH}^+]_S$ = 2.2 mg/mL). The pH_{max} (= 3.82) is the point of pH where two curves intersect. The total solubility is the minimum of the two equations at a certain pH. More specifically, the solubility is determined by Eq. 2 for $\text{pH} \geq \text{pH}_{\max}$ and by Eq. 3 for $\text{pH} \leq \text{pH}_{\max}$. Based on values of pKa and pH_{max}, the term $10^{\text{pH}-\text{p}Ka}$ in Eq. 3 is $<10^{-4}$, thus negligible (i.e., the dissolved free base is removed from the Eq. 3, leading to Eq. 4).

$$S_{T,\text{salt}}(\text{pH} \leq \text{pH}_{\max}) = [\text{BH}^+]_S \left(1 + 10^{\text{pH}-\text{p}K_a}\right) \approx [\text{BH}^+]_S \quad (4)$$

To further match the dissolution and pharmacokinetic data, the solubility of the free base was increased to 0.0117 mg/mL as solubility increases in the gastrointestinal tract due to the effect of bile (C_s = 0.0117 mg/mL at pH > 6.1). Eq. 5 summarizes the overall solubility-pH profile.

$$C_s = S_T = \begin{cases} [\text{BH}^+]_S & \text{for pH}_{\text{surface}} \leq 3.82 \\ [\text{B}]_S(1 + 10^{pK_a - \text{pH}_{\text{surface}}}) & \text{for } 3.82 < \text{pH}_{\text{surface}} \leq 6.1 \\ 0.0117\ \text{mg/ml} & \text{for pH}_{\text{surface}} > 6.1 \end{cases} \quad (5)$$

Eq. 5 uses the pH at the solid surface of drug particle instead of bulk pH in the dissolution model, so pH is replaced with $\text{pH}_{\text{surface}}$ (i.e., pHsur). That is because previous literature[11,15,16] reported that the dissolution rate is not determined by the solubility at the bulk pH (pH_{bulk}) but by the solubility based on the pH at the solid surface ($\text{pH}_{\text{surface}}$). Solid surface pH is different from bulk pH depending on the drug property (acid/base, solubility, pK_a, etc.), as well as drug form (free acid/base, salt). The $\text{pH}_{\text{surface}}$ is possible to be measured through experiments.[11,17] However, there was no such experiment reported for the studied compound. Alternatively, an empirical polynomial equation was obtained based on the available salt dissolution data to describe the relationship between $\text{pH}_{\text{surface}}$ and pH_{bulk} for the salt formulation of the specific compound studied (Eq. 6):

$$\text{pH}_{\text{surface}} = \begin{cases} \text{pH}_{\text{bulk}} & \text{for pH} \leq 2.83 \\ -0.08 * \text{pH}_{\text{bulk}}^2 + 1.4526 * \text{pH}_{\text{bulk}} - 0.64 & \text{for pH} > 2.83 \end{cases} \text{[Salt only]}$$
$$\text{pH}_{\text{surface}} = \text{pH}_{\text{bulk}} \text{[Base only]} \quad (6)$$

Table 1 Pharmacokinetic parameters applied for pharmacokinetic simulation

Parameter	Symbol	Unit	Value
Diffusion parameter	z	mL × $mg^{2/3}$ × $minute^{-1}$	0.215
Volume of dissolved drug compartment	$V2$	mL	250
Volume of distribution	$V3$	L	2,100
Clearance	CL	L/hour	90
Absorption constant rate	K_a	$hour^{-1}$	0.6

which indicates $pH_{surface}$ of salt formulation was less than pH_{bulk} at high pH_{bulk}, a similar trend suggested by previous studies[11,17] for other weak bases. The pH was assumed the same through diffusion layer for free base (Eq. 6).

Pharmacokinetic model

For the simulation, a one-compartment pharmacokinetic model with first-order absorption and first-order elimination was used with parameters estimated from a clinical pharmacokinetic trial (**Table 1**). The interindividual variability for the pharmacokinetic parameters was assumed to be 22%. The average gastric emptying time was assumed to be 1 hour, as the pH of bulk solution switched from gastric pH to intestinal pH (pH = 7) at 1 hour. It is to note that the absorption rate constant should be interpreted as a function of gastric emptying constant and permeation constant. The total absorption time was set to 24 hours. A proportional error model was used, specifying a normal distribution with a mean of zero and an SD of 0.22.

Gastric pH distribution model

A statistical model was applied to describe gastric pH distribution among the general population, which was obtained through a literature report.[18] Due to the bimodal and skew distribution of gastric pH, a mixture model of truncated lognormal and truncated normal distribution was developed (Eq. 7).

$$Y = I \times Y_1 + (1 - I) \times Y_2 + 0.75 \quad (7)$$

In the mixture model, Y is the gastric pH for the individual of interest. I is an indicator, which follows Beroulli distribution taking the values of 1 and 0, with the probability of 90% to take the value of 1. Y_1 follows lognormal distribution with a geometric mean of 0.64 and a percentage coefficient of variance of 100%. Y_2 follows normal distribution with a mean of 6.3 and an SD of 0.45. The simulated values of Y_1 and Y_2 were truncated between 0 and 6.5.

Simulation studies

Forty subjects with different gastric pH levels were simulated using the gastric pH distribution model. Each simulated subject received two formulations, starting with the salt or the free base formulation (reference and test formulation, respectively), in a crossover manner. Dissolution profiles for both formulations at the intended gastric pH level were generated for each subject. Subsequently, individual pharmacokinetic profiles after the administration of the test or reference formulation were simulated. The calculated C_{max} and AUC were applied for bioequivalence testing. When the 90% confidence intervals for the ratios (test:reference) of C_{max} and AUC values were within the bioequivalence limits of 80–125%, the trial was considered a success. Two hundred simulations were conducted, and the percentage of the successful trials was calculated.

A second simulated trial was performed in subjects with a fixed gastric pH ranging from 1–6. Only 20 subjects with a fixed gastric pH were simulated. Similar to the first simulation, the dissolution and pharmacokinetic profiles were generated for both the reference and the test formulation. The 90% confidence intervals for both the C_{max} and AUC ratios (test:reference) within the bioequivalence limits of 80–125% were considered a success.

Trial subjects with different gastric pH levels were simulated in R (version 3.3.2, http://www.r-project.org) using a gastric pH distribution model. A nonlinear mixed effect model (NONMEM, version VII; ICON Development Solution, Ellicott City, MD) combining the dissolution and pharmacokinetic models was used to perform trial simulations. Simulated pharmacokinetic profiles were further assessed with the R package of PKNCA (version 0.8.1) to obtain major pharmacokinetic parameters, such as C_{max} and AUC. The bioequivalence test was performed with SAS (version 9.4; SAS Institute, Cary, NC), and final results were summarized using R.

Simulation results

The dissolution profiles from the free-base and salt formulation (i.e., test and reference, respectively) were generated

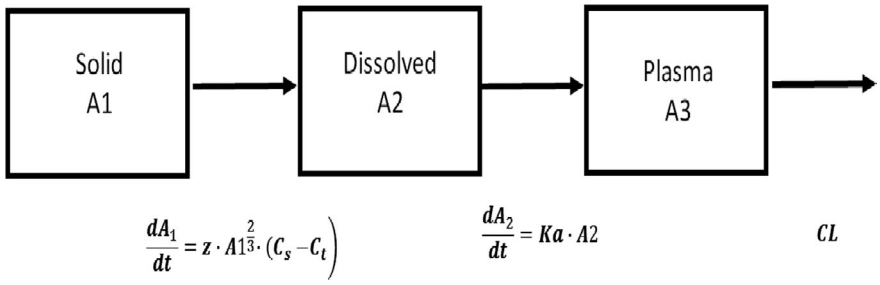

Figure 2 Schematic presentation of the dissolution and pharmacokinetic model.

using the dissolution model. The dissolution patterns for both formulations are similar at pH 1.2 (**Figure 1a**). At pH 4.5, the dissolution profiles diverge with the salt formulation showing greater dissolution over time. Both formulations have relatively low dissolution at pH 6.8.

The mean pharmacokinetic profiles following the administration of the free base and the salt formulations are shown in **Figure 1b,c**. At low gastric pH (e.g., pH ~ 1–2), the pharmacokinetic profiles are similar between the two formulations. However, at pH ≥ 4.5, the pharmacokinetic profiles differ between formulations within the first 48 hours after administration.

To simulate a bioequivalence trial, we assumed that subjects were randomly enrolled from a general population. A mixture model was used to generate subjects with various gastric pH levels following the anticipated distribution in the general population. **Figure 3a** shows the simulation reasonably describes the gastric pH distribution in the general population. Both the simulations and data from the literature[4] show the gastric pH for most subjects is around 1 and a relatively small subject population with gastric pH > 4.

A total of 40 simulated subjects were randomized to the crossover trial simulation to evaluate the bioequivalence of the free base and salt formulation (test and reference, respectively). Over 45% of the 200 pharmacokinetic simulations passed routine bioequivalence testing (**Figure 3b**). The results were largely affected by the number of subjects with an elevated gastric pH. As the percent of patient enrolled with gastric pH > 4 rose, the percent of trials meeting bioequivalence criteria decreased (**Figure 3c**).

Additional simulations were conducted in 20 simulated subjects with homogenous gastric pH. The predicted pharmacokinetic profiles in subjects with a fixed gastric pH between pH 1 and 6 are shown in **Figure 4**. These data were used for bioequivalence testing (**Table 2**). Consistent with the results of other simulations in this study, the two formulations successfully meet bioequivalence criteria in subjects with low gastric pH (pH 1–4) but failed in subjects with elevated gastric pH. Elevated pH (pH 5–6) led to a greater decrease in exposure to the free-base formulation in comparison to the salt formulation (75–86% vs. 44–56% for C_{max}, 61–77% vs. 12–32% for AUC_{∞}; **Table 2**).

Summary of simulation studies

It is demonstrated that the pharmacokinetic profiles and exposures are significantly different between a free base formulation and a salt formulation in subjects with elevated gastric pH. Thus, two formulations shown to be bioequivalent in subjects with normal gastric pH may yield significantly different exposures and pharmacokinetic profiles in subjects with elevated gastric pH. In addition, we show that depending on the enrolled subjects, a routine bioequivalence assessment may or may not be able to identify the difference in drug absorption in the subgroup of subjects with elevated gastric pH. Additionally, to conduct a bioequivalence trial in subjects receiving a gastric pH modulator seems to provide a potential solution. This approach

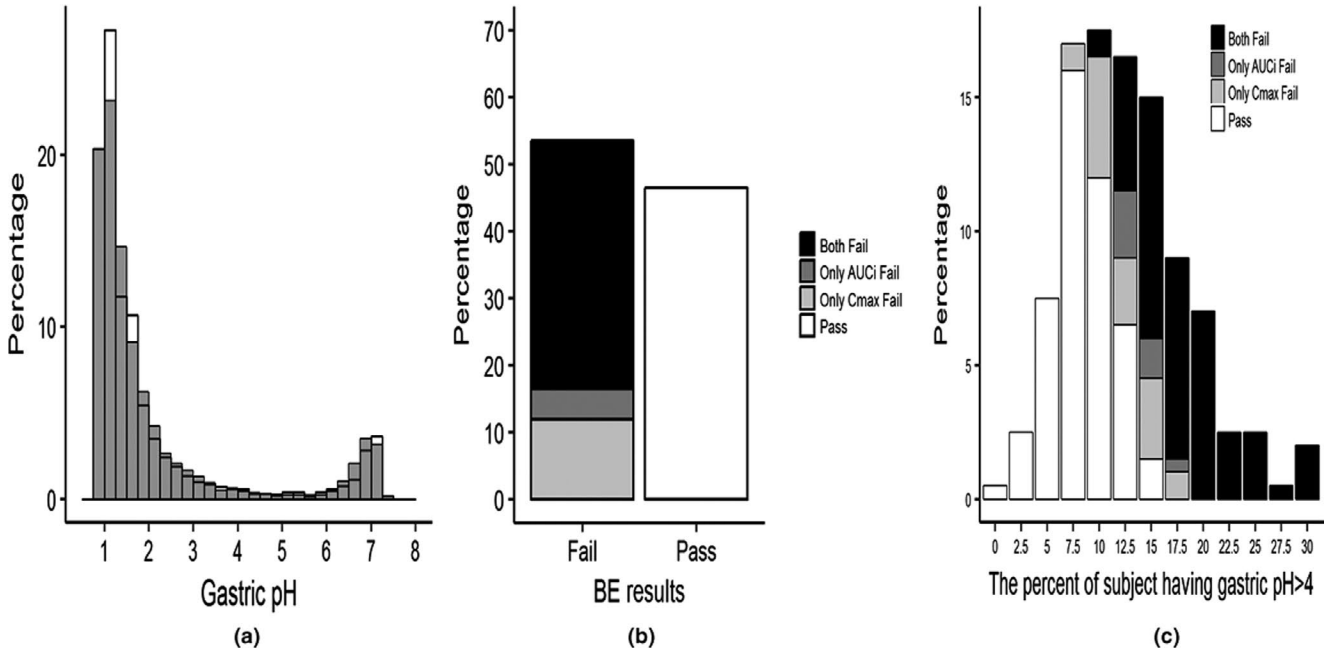

Figure 3 Bioequivalence (BE) simulation results in subjects with a gastric pH distribution similar to the general population. (**a**) Simulated gastric pH distribution vs. reported gastric pH distribution: The open areas represent the gastric pH distribution reported in the literature.[4] The gray areas represent the simulated gastric pH distribution. (**b**) Percentage of the failed bioequivalence trials. Fail represents the simulated trials failed the bioequivalence test. Pass represents the simulated trials passed the bioequivalence test. The reasons (area under the curve (AUC) or peak plasma concentration (C_{max})) for failed bioequivalence tests are also presented. (**c**) Percentage of the simulated trials meeting bioequivalence criteria vs. failing the bioequivalence test as a function of percentage of subjects with gastric pH > 4.

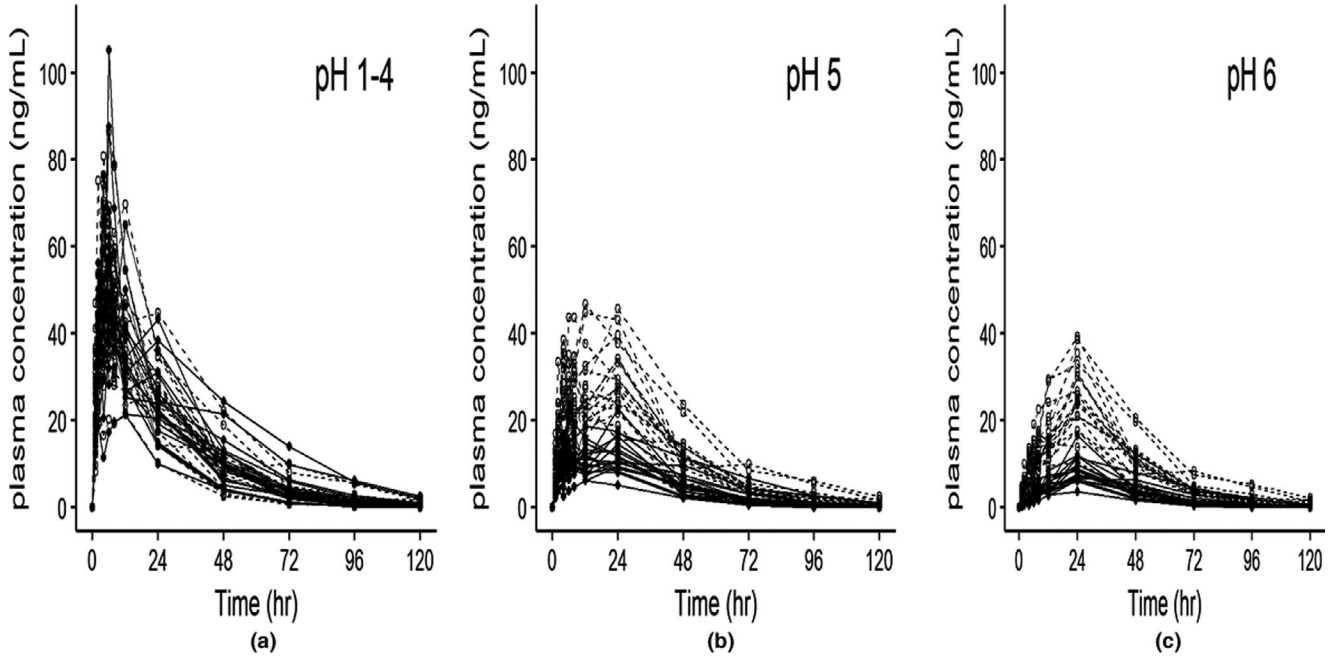

Figure 4 Simulated pharmacokinetic profiles for subjects receiving a free-base (test) or salt formulation (reference) at different gastric pH. Solid lines represent pharmacokinetic profiles in subjects receiving a free base formulation (test). Dashed lines represent the pharmacokinetic profiles in subjects receiving an isethionate formulation (reference). (**a**) Gastric pH levels are between 1 and 4, (**b**) gastric pH = 5, (**c**) gastric pH = 6. Subjects are simulated.

Table 2 Bioequivalence results of crossover trial simulation with homogeneous gastric pH values (*n* = 20)

Gastric pH	Parameter (units)	Adjusted geometric mean		Ratio of mean base/ salt	90% CI for ratio
		Base	Salt		
1–4	C_{max} (ng/mL)	56.02	55.2	101.49	(93.51–110.15)
	AUC_{last} (ng×hour/mL)	1,389	1,417	97.97	(93.73–102.41)
	AUC_{inf} (ng×hour/mL)	1,403	1,433	97.88	(93.61–102.35)
5	C_{max} (ng/mL)	13.87	31.12	44.57	(41.57–47.78)
	AUC_{last} (ng×hour/mL)	538	1,238	43.46	(41.43–45.59)
	AUC_{inf} (ng×hour/mL)	545	1,256	43.42	(41.37–45.56)
6	C_{max} (ng/mL)	7.98	24.37	32.74	(29.34–36.53)
	AUC_{last} (ng×hour/mL)	322	964	33.45	(31.7–35.29)
	AUC_{inf} (ng×hour/mL)	327	980	33.42	(31.67–35.27)

AUC, area under the curve; AUCinf, area under the curve from zero to infinity; AUClast, area under the curve from zero to the last observed time point; CI, confidence interval; C_{max}, peak plasma concentration.
The test formulation is the free-base formulation and the reference formulation is the salt formulation. Subjects are simulated.

applies also for formulations whose dissolution characteristics differ in subjects with elevated gastric pH.

LITERATURE REPORTED RELATIVE BIOAVAILABILITY STUDY WITH A GASTRIC PH MODULATOR

The following is a reported case of prasugrel where two formulations (i.e., a free base and a chloride salt), which yielded similar average pharmacokinetic profiles and exposures based on a routine relative bioavailability trial, showed distinctively different pharmacokinetic profiles and exposures (52% and 72% reduction in C_{max} for salt and free-base formulations, respectively) with concomitant use of a proton pump inhibitor.[19] The case seems to be consistent with our simulation conclusions. More importantly, the reported trial provides an example for the design of a bioequivalence trial with a gastric pH modulator.

The reported trial was a randomized, four-period, 2 × two-way crossover trial. The relative bioavailability of tablets containing prasugrel free base and prasugrel hydrochloride salt (test and reference, respectively) given with and without lansoprazole, a proton pump inhibitor, was investigated (**Figure 5**).[19] The study contained four treatment arms. Subjects received the test formulation in period 1 then were switched to the reference formulation in period 2 or vice versa under fasting conditions. In

	A vs. B		C vs. D	
Period				
Period1	A	B		
Period2	B	A		
Period3			C	D
Period4			D	C

Figure 5 Design of the relative bioavailability trial. Treatment A: test without proton pump inhibitor (PPI); treatment B: reference without PPI; treatment C: test after four consecutive doses of PPI; treatment D: reference after four consecutive doses of PPI.

periods 3 and 4, the same regimen was followed except prior to each period subjects received four consecutive doses of lansoprazole. Between each period, there was a washout phase.[19]

IDENTIFICATION OF OTHER FORMULATION FACTORS THAT MAY IMPACT BIOAVAILABILITY AT ELEVATED GASTRIC PH BASED ON LITERATURE

Thus far, it has been demonstrated that formulations with changes in APIs (e.g., a free base vs. salt) may have different bioavailability in subjects with elevated gastric pH. A literature search was conducted to identify other formulation factors that may lead to changes in drug dissolution in subjects with elevated gastric pH.

PubMed searching was conducted using the key words "gastric pH/acidity" in combination with "bioequivalence/bioavailability/absorption/pH-dependent absorption" and "formulation." A total of 12 publications were identified containing nonclinical and clinical bioavailability studies.[19–30] Half of these were based on nonclinical pharmacokinetic studies[20–26], and the other half were based on clinical pharmacokinetic studies.[19,27–30] The publications are mainly focused on formulations with active moieties that are weak bases and have pH-dependent solubility. Most compounds are considered as Biopharmaceutics Classification System class II and class IV compounds. Dogs and rabbits were the main species used for nonclinical studies. The normal gastric pH in dogs is higher than humans. Therefore, a pretreatment of pentagastrin, which stimulates secretion of gastric acid, was performed in dog studies. For both nonclinical and clinical pharmacokinetic studies, the elevated gastric pH was mainly achieved by coadministration of multiple doses of a proton pump inhibitor or an H_2-blocker.

Beyond changes in API, alteration of excipients can also lead to changes in the dissolution pattern of a formulation at elevated gastric pH. In particular, the addition of acidic excipients may lead to improved dissolution and absorption of a free-base formulation, especially when pH increases. For example, at elevated gastric pH, BMS-561389, a weak base compound, had ~ 90% reduction in drug absorption; however, the new formulation containing 16% tartaric acid had ~ 20% reduction in drug absorption in a canine model.[21]

Changing API and excipients together may further affect the drug dissolution pattern at different pH. As reported by Mitra *et al*.,[20] the C_{max} and AUC ratios of compound A under high gastric pH vs. low gastric pH were <0.1 for the capsule using the free-base API in a dog model. This suggests that drug dissolution was reduced by at least 90% at elevated gastric pH. However, ~ 20–30% reduction in drug release was observed at elevated gastric pH for a capsule using the hydrochloride salt as API and including citric acid as excipient.

Changes to the coating of pH-sensitive polymers may also alter drug release and absorption patterns at different gastric pH. For instance, a posaconazole oral suspension with no coating showed ~ 50% reduction in drug absorption at elevated gastric pH in healthy volunteers.[29] However, there is minimal change in drug absorption at elevated gastric pH from a tablet with enteric coating in another group of healthy subjects.[28] Posaconazole demonstrated increased solubility at decreased pH. The enteric coating prevented drug release only at low pH, hence yielding similar drug dissolution at different pH.[28,29]

Different formulation techniques may yield formulations with different dissolution characteristics at elevated gastric pH. For example, an albendazole formulation prepared through physical mixture showed ~ 80% reduction in C_{max} and AUC at elevated gastric pH, whereas the same compound prepared through solid dispersion had ~ 40% reduction in C_{max} and AUC in rabbits.[25] X-ray diffraction showed a crystalline structure for the formulation prepared by physical mixture and an amorphous state for the formulation prepared by solid dispersion. This result was thought to be related to the different dissolution patterns observed at different pH ranges.[25]

In summary, nine cases were reported where the dissolution and absorption pattern may differ for different formulations with the same active moiety at elevated gastric pH. Multiple formulation factors, including different APIs (e.g., free base vs. salt), excipients (e.g., with or without acidifying excipients), and formulation techniques (e.g., physical blend vs. solid dispersion) may significantly contribute to the different dissolution and absorption characteristics at different gastric pH ranges.

CONSIDERATIONS FOR INCLUDING A BIOEQUIVALENCE TRIAL WITH A GASTRIC PH MODULATOR

A bioequivalence trial with a gastric pH modulator may provide additional information to ensure therapeutic equivalence of a formulation in patients with elevated gastric pH. Evaluation with a gastric pH modulator would not be advised when dissolution profiles of different formulations are similar at elevated pH (i.e., pH ~ 4–6.8). An appropriately designed dissolution test in media between the pH ranges of 1–6.8 can serve as a screening tool. Formulations with similar dissolution profiles in this range are unlikely to yield substantially different exposures in subjects with elevated gastric pH. Science is evolving. Additional tools and information, such as physiologically-based pharmacokinetic modeling and simulation or

nonclinical/clinical studies with different formulations used in combination with a gastric pH modulator, respectively, may provide insights on whether the suggested bioequivalence study is necessary as the community gains more experience.

Although the examples in this paper illustrated formulation-dependent differences in dissolution and absorption at elevated gastric pH, it is possible that two formulations could have similar dissolution at elevated pH and different dissolution profiles at low pH. This would imply that the two formulations differ in the rate and extent of absorption at normal gastric pH. However, a bioequivalence trial without a gastric pH modulator may be sufficient to detect this, provided that most of the enrolled subjects have a gastric pH around 1.

Studies of palbociclib suggest that elevated gastric pH had a limited effect (13%) on AUC of the free-base formulation under fed conditions.[7–9] This is because food can affect bioavailability by modulating gastric pH and changing the solubility of the unionized form of the drug. However, it is unclear whether the reduced drug absorption due to elevated gastric pH can always be mitigated by food effect. As shown for GDC-0941, food may not be able to compensate for the reduced exposure caused by elevated pH.[31] Therefore, it is uncertain whether bioequivalence demonstrated through a fed bioequivalence trial is sufficient to ensure therapeutic equivalence in subjects with elevated gastric pH levels.

Overall, these cases suggest that a bioequivalence trial with a gastric pH modulator may be useful for formulations containing different forms of the same active moiety (e.g., salt and free base) or the same API and showing different dissolution profiles at elevated pH. We think this approach may ensure that such different formulations achieve similar absorption and, thus, therapeutic equivalence in subjects with various gastric pH levels.

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