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Development and Application of a Biorelevant Dissolution Method Using USP Apparatus 4 in Early Phase Formulation Development

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Abstract: Dissolution testing is frequently used to determine the rate and extent at which a drug is released from a dosage form, and it plays many important roles throughout drug product development. However, the traditional dissolution approach often emphasizes its application in quality control testing and usually strives to obtain 100% drug release. As a result, dissolution methods are not necessarily biorelevant and meaningful application of traditional dissolution methods in the early phases of drug product development can be very limited. This article will describe the development of a biorelevant *in vitro* dissolution method using USP apparatus 4, biorelevant media, and real-time online UV analysis. Several case studies in the areas of formulation selection, lot-to-lot variability, and food effect will be presented to demonstrate the application of this method in early phase formulation development. This biorelevant dissolution method using USP apparatus 4 provides a valuable tool to predict certain aspects of the *in vivo* drug release. It can be used to facilitate the formulation development/selection for pharmacokinetic (PK) and clinical studies. It may also potentially be used to minimize the number of PK studies, and to aid in the design of more efficient PK and clinical studies.

Keywords: Biorelevant; dissolution; USP apparatus 4; flow-through cell; formulation development; formulation rank order; food effect; *in vivo* drug release; rate profile

Introduction

Dissolution testing determines the rate and extent at which the drug is released from its pharmaceutical dosage form. It plays many important roles in new drug product development, especially for solid oral dosage forms.[1,2] For example, it is frequently used as a quality control (QC) tool to ensure consistent lot-to-lot quality for commercial small molecule drug products; it can serve as an *in vitro* surrogate for *in vivo* bioequivalence studies and *in vivo* and *in vitro* correlation (IVIVC) studies,[3−8] and it can also provide valuable information and guidance for formulation development. Throughout the drug development process, dissolution

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testing serves different roles at the various clinical development phases. For example, when used during the early phases of clinical development, the utility of dissolution testing as a QC tool is limited since the formulations are often simplified (e.g., neat drug or blend in a capsule); also, frequently, only one lot of a drug product is manufactured using the same formulation for the early clinical studies. However, experimental dissolution data could be very useful to guide formulation development during this stage, especially for drugs with dissolution-limited absorption. While in the late phases of development or at the commercial stage, dissolution as a QC tool is critical to ensure lot-to-lot consistency and compliance with the agreed-upon regulatory specification criteria; it can also serve as an alert to see if any of the product quality attributes have changed as compared to the historical results.

The primary role of the traditional compendial dissolution test is anchored in its QC purpose where 100% drug release is targeted regardless of the extent of *in vivo* drug dissolution. When dealing with poorly water-soluble drugs, it is often necessary to modify the dissolution media to achieve 100% drug release at the later dissolution time points. The dissolution medium selected for the test is often not biorelevant, and extreme conditions may include using high organic solvent content (e.g., 40% isopropyl alcohol), highly basic conditions (e.g., pH 12), or very high surfactant concentrations.[9] Although these modifications to the media are necessary to achieve 100% *in vitro* drug release in dissolution testing, these types of media are clearly not biorelevant. Thus, prediction of the drug's *in vivo* behavior using the resulting dissolution data becomes quite challenging, especially in the early phases of drug development where *in vivo* data is not yet available. In addition, the method is frequently developed using only a single lot of an early stage dosage form, and therefore the true discriminating power of the method is not clear. As a result, it is common that an early phase *in vitro* dissolution method is either over-discriminating, i.e., drug products with different *in vitro* profiles show similar *in vivo* drug release profiles or under-discriminating, i.e., similar *in vitro* dissolution profiles result in different *in vivo* drug release behavior. Therefore, application of the traditional QC dissolution method to guide early stage formulation development is somewhat limited. Since a dissolution method traditionally has product-specific dissolution test conditions, it is difficult to compare one dissolution release profile to another because the medium and the test conditions are very different. Also, since setting meaningful criteria for method transfer between laboratories is a challenge at this stage, differences in testing results from laboratory to laboratory are also quite common, particularly when multiple testing sites are involved.

Many studies have been conducted and are still currently ongoing to understand the *in vivo* drug release process, to develop media that better represent the *in vivo* conditions, and to better predict *in vivo* drug release.[10−17] However, detailed knowledge regarding exactly what happens *in vivo* to an oral solid dosage form after administration is still limited. It is known, however, that the dosage form experiences very different pH environments and hydrodynamic conditions in the human gastrointestinal tract (GIT), and that the transit times and volumes are different through the stomach, small intestine, and colon. The environment and transit times through the GIT also vary from individual to individual, and can vary even for the same individual

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depending on the fasted/fed condition or even the type of meal the individual has had.[18,19]

In order to better predict *in vivo* drug release and to have a relatively consistent method such that one can compare the dissolution profiles across different drug products, it is important to evaluate the *in vitro* dissolution in a biorelevant environment.[20−26] Biorelevant dissolution testing is conducted in an environment that closely mimics the *in vivo* physiological conditions regarding the pH environment, hydrodynamics, and duration of exposure. This approach allows *in vitro* dissolution testing conditions to be more relevant to the actual *in vivo* intraluminal environment and to allow for the *in vitro* dissolution to be evaluated in a more consistent fashion for the solid oral dosage form. Therefore, the application of biorelevant dissolution testing allows *in vitro* dissolution to potentially have more predictive power in terms of *in vivo* drug release.

Different types of USP dissolution apparatus have been previously used to study biorelevant dissolution conditions.[27−34] The flow-through cell methodology in drug release testing of oral dosage forms was first used in the 1950s and the apparatus was finally included in the USP in 1990 as USP apparatus 4.[35,36] The USP apparatus 4 system may be used in an open or closed configuration. The USP apparatus 4 open system was used in this study based on the following advantages: (1) sink conditions can be maintained for poorly soluble drugs throughout the dissolution run; (2) it is easy to change media and modify flow rate to simulate *in vivo* conditions; (3) it simulates intraluminal hydrodynamics more efficiently; (4) it can be modified for different dosage forms, including testing of tablets, capsules and powders; and (5) it measures the *in vitro* release rate profile of the dosage form as an output that is similar to the shape of an *in vivo* profile.

The primary objective of this study was to develop a biorelevant dissolution method to predict the rank order of *in vivo* drug release, to predict potential food effect on *in vivo* drug performance, and to potentially guide formulation development/selection and therefore influence the design of future PK and clinical trials. This method was developed using model compounds with different physicochemical properties. In contrast to the traditional dissolution method development, this method does not aim to achieve 100% *in vitro* drug release.

Experimental Section

Materials and Instruments. A USP apparatus 4 system (Sotax CE 7 Smart semiautomated system, Sotax Corporation, Horsham, PA) with online fiber optics detection (Opt Diss Fiber Optic UV Spectrophotometer with Opt Diss Flow Through Manifold for USP 4 (Distek, North Brunswick, NJ)) was used for the studies.

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Advil tablets, 200 mg (Wyeth Consumer Healthcare), and Motrin tablets, 200 mg (Ortho-McNeil-Janssen Pharmaceuticals), were purchased from Longs Pharmacy. Danazol capsules, 200 mg (Barr Laboratories), and Prevacid SoluTabs, 15 mg and 30 mg (TAP Pharmaceutical), were purchased from Burt's Pharmacy for research purposes. All corresponding standards were purchased from USP and prepared in ethanol (Pharmco-Aaper, 200 proof).

All Amgen development compounds were developed and formulated at Amgen Inc. PK and clinical data were obtained from internal Amgen development studies.

Simulated gastric fluid (SGF (pH 1.2), no pepsin), simulated intestinal fluid (SIF, pH 6.8), fed state simulated intestinal fluid (FeSSIF, pH 5.0), and fasted state simulated intestinal fluid (FaSSIF, pH 6.8)[37−39] were prepared by Amgen Inc.

Method Development. The method development approach used in this work was different from traditional *in vitro* dissolution method development, in which the aim typically is to achieve 100% drug release without necessarily taking into account the *in vivo* drug performance. Instead, the known *in vivo* plasma profiles of several model compounds were used to guide the generic biorelevant dissolution method development in this study. In addition, only biorelevant dissolution media, such as simulated gastric fluid (SGF), simulated intestinal fluid (SIF), fasted state simulated intestinal fluid (FaSSIF), and fed state simulated intestinal fluid (FeSSIF), were utilized. The intent of this approach was to utilize conditions that closely mimic the *in vivo* physiological environment regarding pH and hydrodynamics, and to focus on the *in vivo* vs *in vitro* profile comparisons.

Model Compounds. BCS class II compounds have the physicochemical characteristics of low solubility and high permeability, where dissolution is typically a rate-limiting step in the drug absorption process.[40,41] Several commercially available BCS class II compounds with known *in vivo* plasma profiles were used as model compounds to guide the biorelevant dissolution method development. To systematically evaluate the dissolution behavior, the compounds were divided into the following three different categories: (1) acidic compounds, which include ibuprofen (both Advil tablets, 200 mg (Wyeth Consumer Healthcare), and Motrin tablets, 200 mg (Ortho-McNeil-Janssen Pharmaceuticals)), naproxen (both Naprosyn tablets, 500 mg (Roche Laboratories), and Naprelan tablets, 500 mg (Hi Tech Pharmacal)), and warfarin (Coumadin tablets, 2 mg, 5 mg and 10 mg (Bristol-Myers Squibb Co.)); (2) neutral compounds, which include carbamazepine (Tegretol tablets, 200 mg (Novartis)) and danazol (danazol capsules, 200 mg (Barr Laboratories)); and (3) basic compounds, which include ketoconazole (ketoconazole tablets, 200 mg (Mylan)), lansoprazole (Prevacid SoluTabs, 15 mg and 30 mg (TAP Pharmaceutical), and raloxifene (Evista tablets, 60 mg (Eli Lilly)). A variety of salt forms (free base, salt, etc.) and dosage forms (immediate-release tablets, enteric-coated tablets, and sustained-release products) were used for both method development and dissolution testing purposes. Ibuprofen tablets, both Advil and Motrin, were primarily used for method development.[42,43] The resulting method was used to run all other model compounds and development dosage forms.

Biorelevant Media. Various biorelevant media that mimic the physiological conditions in the GIT have been reported to facilitate the prediction of *in vivo* drug release.[12,17,19,37–39,44−46] Four standard biorelevant dissolution media, SGF, SIF, FeSSIF and FaSSIF, were used in this study. The media were chosen to represent, respectively, similar pH/components in the stomach, in the intestinal tract, or the fasted or fed conditions in the intestine. No other media, organic solvents, or surfactants were used, even though they might be commonly used in the traditional *in vitro* dissolution testing.

Rate Profiles vs Cumulative Profile. Results from traditional dissolution tests are normally reported using a cumulative profile, i.e. % dissolved vs time, whereas results from PK studies are normally presented as a rate profile, i.e. a plot of concentration vs time. Recently, a study was performed in which the dissolution results were presented as rate profiles (concentration vs time) in order to facilitate direct qualitative comparison of the *in vivo* and *in vitro* profiles.[28,47] The rate profiles were collected as a default in this study, while the cumulative profiles (% dissolved vs time) were also calculated later to monitor the overall drug dissolution in the system.

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Systematic Method Development. Various parameters were evaluated during dissolution method development including flow rate (2 mL/min to 20 mL/min), biorelevant dissolution media, flow-through cell size (12 mm i.d. vs 22.6 mm i.d.) and the impact of a sample holder. The necessity of using SGF first and then changing the media to SIF to mimic the pH gradient in the GIT was also evaluated during the development. The development work was largely conducted using 200 mg Advil and Motrin tablets[42,43] with other model compounds used for confirmation and comparison purposes. Online UV signals were monitored using a product specific wavelength in each case.

Results

Initial Method Optimization. Flow rates in the range of 2 mL/min to 20 mL/min were evaluated with the 22.6 mm i.d. flow-through cell using SIF as the medium. The results indicated that when the flow rate changed within this range, the rank order of the drug release profiles remained the same. The appearance of the dissolution profiles, however, varied slightly as the flow rate changed, with sharper profiles for the higher flow rates and "flattened" profiles for slower flow rates. When the flow rate was at or below 6 mL/min, the resulting curves were more erratic and the signals became much noisier. A similar observation was noted when the small flow cell (12 mm i.d.) was used, which might be attributed to the reduced homogeneity of the hydrodynamic flow in the system.

The necessity of using SGF first and then changing the media to SIF (to attempt to mimic the GIT conditions) was evaluated during the method development. The results indicated that, for the acidic and neutral compounds, SIF may be used directly for the entire experiment instead of using SGF first and then switching to SIF, since the rank order and profiles remain the same in both cases. However, for most of the basic compounds, the use of SGF is needed before changing the medium to SIF. For drug products where disintegration rather than dissolution is the rate-determining step, the midrun media switch should probably be considered as well. It was also observed that when an 8 mL/min flow rate was used, a 5 min hold time in SGF prior to switching to SIF provided a better match of the *in vivo* profiles yet maintained the appropriate rank order of the model compounds tested. When a significantly longer duration (e.g., 30 min) was used for SGF before the medium was switched to SIF, the discriminating power was lost and an *in vitro* "drug release burst" was observed.

As a result of the systematic method development described above, the following conditions were selected: flow rate = 8 mL/min, flow-through cell = 22.6 mm i.d., 1 mm glass beads and with a sample holder. When the medium was switched from SGF to SIF, a hold time of 5 min was used for the initial SGF condition. A filter with 0.7 μm pore size was routinely used. Glass wool was used to reduce backpressure when needed. All analysis was conducted using online UV detection with an appropriate UV wavelength that was compound-dependent. The rate profile (concentration vs time) was collected initially, and the cumulative profile (% dissolved vs time) was calculated later if needed. The resulting method was used directly without further product-specific development for all applications described. See Figure 1 for *in vivo* profiles that guided the biorelevant dissolution method development and the resulting *in vitro* profiles of ibuprofen.[42,43] Selection of a specific biorelevant dissolution media depends on the purpose of the study. For example, if the evaluation of the food effect is the main objective of the study, FaSSIF or FeSSIF should be used instead of the SIF.

Applications of the Biorelevant Dissolution Method Using USP Apparatus 4. Four case studies are presented below using commercially available products or Amgen development products to demonstrate the applications of this biorelevant dissolution method.

Case Study I: Lot-to-Lot Variability (Compound A). Compound A is a BCS class II compound, and is a weak base with a pK_a of 1.5. It was formulated as 10 mg immediate-release (IR) tablets that were manufactured at Amgen for early phase clinical studies. As shown in Figure 2, the dissolution profile of the original clinical supply lot (lot 1) using the biorelevant USP apparatus 4 dissolution method looked qualitatively very similar to the first in human *in vivo* profile.

However, lot 2, the remanufacture of the same formulation, exhibited slightly slower *in vitro* dissolution compared to the original lot 1, when using the applicable quality control release method (USP apparatus 2, 900 mL, 0.1 N HCl, 50 rpm). Since the quality control release method was developed using a single lot instead of using lots with variable profiles, the discriminating power of this method was unknown. As a consequence, it was difficult to determine whether or not lot 2 was suitable to be used as a resupply lot since there were no quantitative criteria established yet for the *in vitro* release profile at this early stage of clinical development. The USP apparatus 4 biorelevant dissolution results, however, showed that the resupply lot (lot 2) was significantly different from the original lot, lot 1 (Figure 2), with the cumulative % dissolved for compound A at only 60% compared to that of the original lot. The results therefore indicated that lot 2 was not suitable to be used as a resupply material for clinical studies.

Further investigation indicated that during the manufacturing of the resupply lot, the process parameters were modified while still using the same formulation composition. The resupply lot was manufactured using a higher granulating fluid level (35% for lot 2 vs 30% for lot 1) and higher impeller speed during the granulating process, resulting in denser granules with larger particle size and better flow properties. When compressed, these lot 2 granules produced

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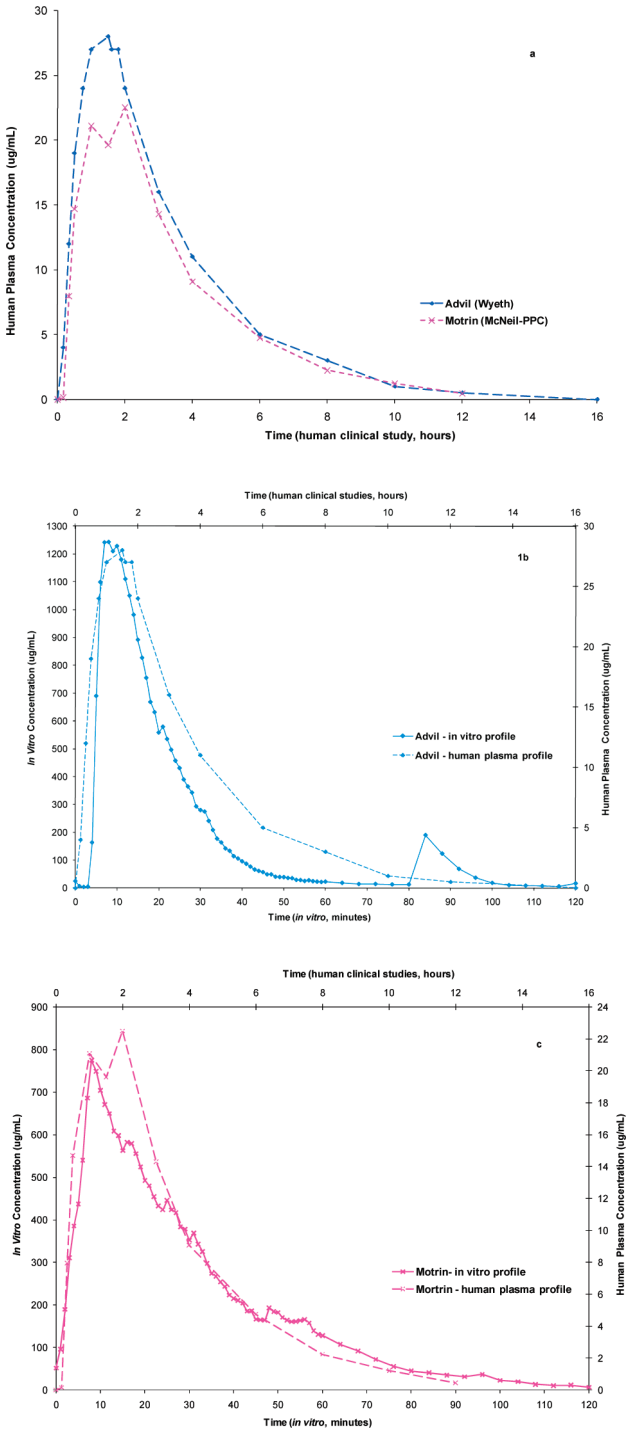

Figure 1. The *in vivo* profiles of ibuprofen that guided the biorelevant dissolution method development (a) and the resulting *in vitro* profiles of ibuprofen using USP apparatus 4 compared to the corresponding *in vivo* profiles (b, c).

tablets that had slower disintegration and dissolution properties than those from lot 1.

A nonclinical crossover study (beagle dogs, $n = 4$) using the original lot (lot 1) and the resupply lot (lot 2) indicated that the resupply lot had an approximately 70% reduction in C_{max} (maximum concentration) and an approximately 65%

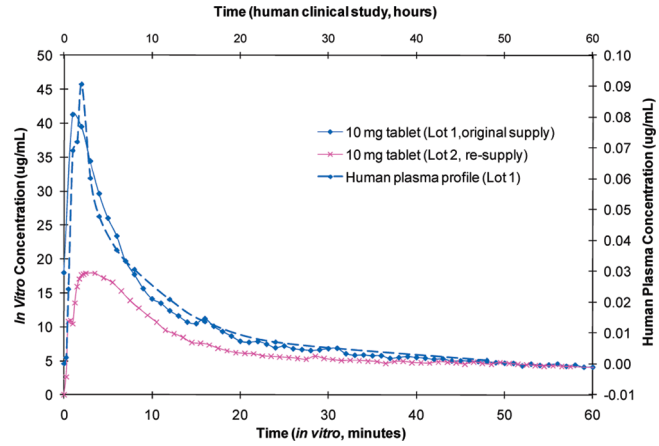

Figure 2. Comparison of *in vivo* plasma profile from human clinical studies (blue dotted line/diamond) against dissolution profiles from USP apparatus 4 for 10 mg tablets of compound A (solid blue line/diamond, original lot; solid pink line/cross, resupply lot).

reduction in AUC (area under the curve), confirming the conclusion obtained from the *in vitro* dissolution results (USP apparatus 4). As a result of the investigation, lot 2 was not used as a clinical resupply lot.

Case Study II: Effect of pH Modifier (Compound B). Compound B is a BCS class II compound; it is a mesylate salt of a weak base with low aqueous solubility (solubility of 0.13 μg/mL in pH 6.8 phosphate buffer), a pK_a of 5.1, and a log P value of 3.3. In order to maintain a supersaturated condition at high pHs, fumaric acid was used as a pH modifier in two 100 mg strength prototype formulations (lots 2 and 3), with the two formulations without pH modifiers serving as controls (lots 1 and 4). Lot 2 contains 15% of fumaric acid (intragranular), and lot 3 contains a total of 20% of fumaric acid (15% intragranular and 5% extragranular). HPMC-K3 was presented in all formulations in order to minimize precipitation and to maintain supersaturation. The biorelevant dissolution results using SGF, pH 1.2 (5 min) followed by SIF, pH 6.8 (120 min) predicted that these formulations would have similar *in vivo* bioavailability and that the formulations with pH modifiers would have similar *in vivo* performance compared to those without pH modifiers. All lots tested using the *in vitro* biorelevant dissolution method show relatively similar concentration vs time profiles and similar cumulative % dissolved, achieving approximately 20% cumulative % dissolved at the end of the ~120 min experiment. Several pharmacokinetic studies (male beagle dogs, $n = 5$) indicated that there is no significant difference in terms of AUC for all formulations tested (Figure 3a), which conforms well with the *in vitro* data (Figure 3b).

However, when the experiments were conducted in SIF directly, the data showed a noticeable difference between the formulations with and without pH modifiers (Figure 4). Lots 2 and 3 exhibited significantly higher dissolution compared to lots 1 and 4. As noted earlier, lots 2 and 3 each contain an acid modifier (i.e., fumaric acid) which was a formulation attempt to establish an acidic microenvironment to enhance *in vivo* dissolution. The results indicated that

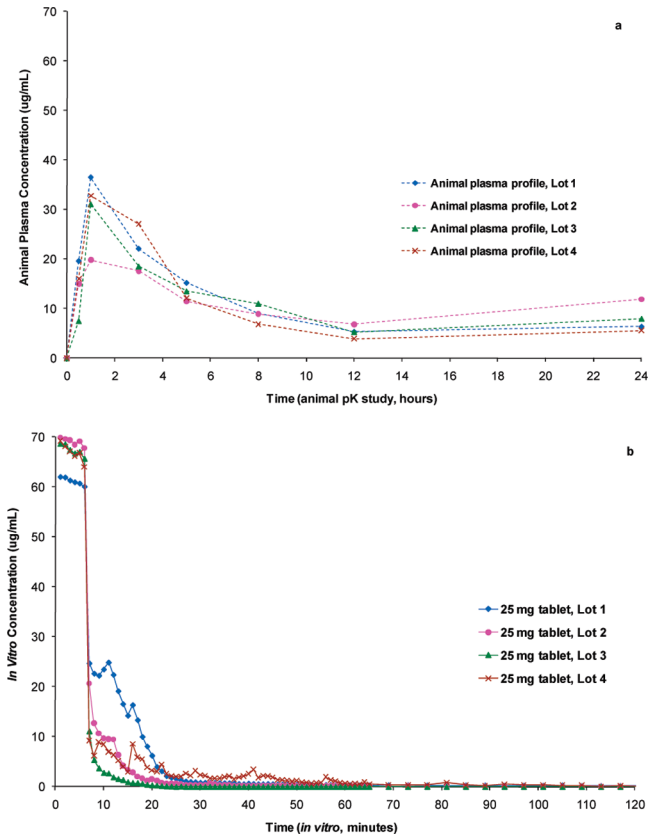

Figure 3. Comparison of *in vivo* profiles from animal PK studies (a, dotted lines) against dissolution profiles from USP apparatus 4 testing for compound B using SGF followed by SIF (b, solid lines).

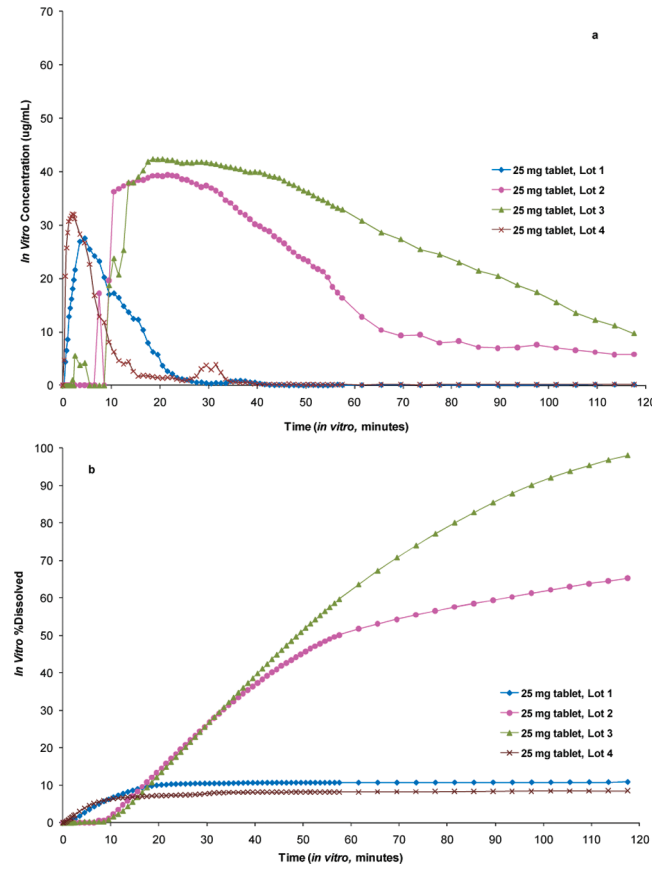

Figure 4. Dissolution profiles in SIF for tablets of compound B using USP apparatus 4 (a, rate profiles; b, cumulative profiles).

when the drug was released in a higher pH (neutral or alkaline), the use of a weak acid as a pH modifier is a good strategy to enhance drug bioavailability. However, if the drug disintegrated and was released in a lower pH (more acidic) environment, e.g., in the stomach, the weak acid may not function effectively as the intended internal pH modifier.

As a comparison, the Prevacid SoluTabs, which are enteric-coated and contain two weak acids, methacrylic acid and citric acid,[48] were tested using the same dissolution method. Prevacid SoluTabs were used as a proton pump inhibitor to treat various acid-related disorders, and the active ingredient in Prevacid SoluTabs is lansoprazole, which is a BCS class II compound and is a weak base with a pK_a value of 4.15. The observations in the *in vitro* studies using 15 mg Prevacid SoluTabs were very different from those for compound B (Figure 5). This might be due to the fact that since the Prevacid SoluTabs contain enteric-coated microgranules, the drug therefore could only be released in the neutral or alkaline environment of the duodenum. As a result, the two weak acids present in this tablet formulation were able to more effectively function as pH modifiers in this environment.

Case Study III: Rank Ordering of Development Formulations (Compound C). Compound C is an Amgen clinical development candidate and is a BCS class II compound. It is a weak acid with pK_a values of 4.0 and 7.9,

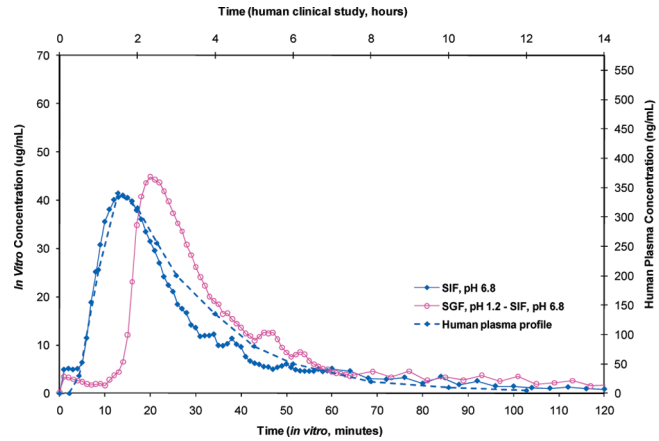

Figure 5. Comparison of *in vivo* human plasma profile from 15 mg Prevacid SoluTabs (dotted line[49,50]) against dissolution profiles of 15 mg Prevacid SoluTabs using USP apparatus 4 (solid blue line/diamond, in SIF directly; solid pink line/empty circle, 5 min in SGF and then 120 min in SIF).

a measured log *P* value of 4.5 and aqueous solubility of 32 μg/mL. Two separate 25 mg immediate-release formulations were developed for early clinical development with similar excipients except that the first formulation (identified as lot 1) contains Avicel (PH 101), lactose monohydrate (Impal-

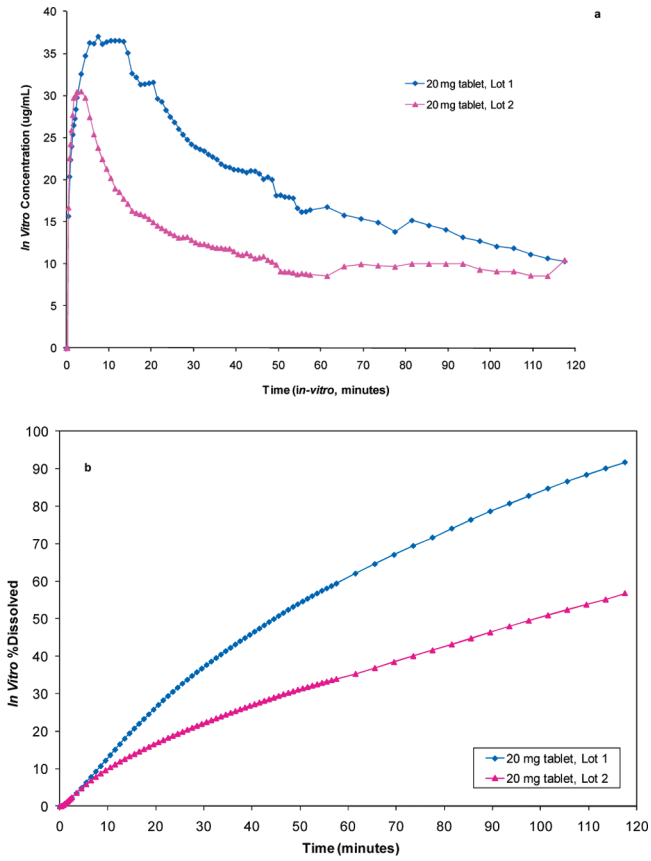

Figure 6. Dissolution rate profile (a) and cumulative profiles (b) of two formulations of 25 mg compound C tablets in SIF using USP apparatus 4.

pable 313) and HPMC, and the second formulation (lot 2) contains Avicel PH 102−lactose monohydrate (FastFlo 316) without HPMC. Forced degradation studies as well as QC dissolution results using USP apparatus 2 are very comparable for the two formulations. However, USP apparatus 4 dissolution results in SIF indicated that lot 1 would have a much better *in vivo* performance compared to that of lot 2 (Figure 6). This prediction was later confirmed by an *in vivo* nonclinical PK study data (cyno monkeys, $n = 4$), which indicated that although the t_{max} values for lots 1 and 2 are similar, lot 1 has approximately three times the C_{max} and approximately four times the AUC compared to that of lot 2 (Figure 7). Based on these observations, lot 1 was selected for further clinical development.

Case Study IV: Assessment and Prediction of Food Effect. The effect of food on the absorption and hence on the bioavailability of small molecule drugs has been shown

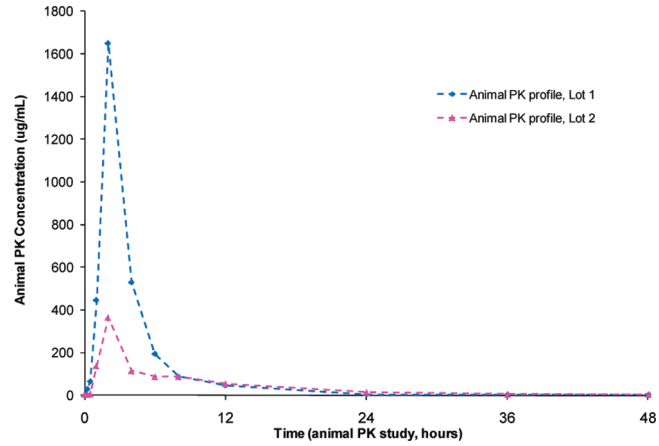

Figure 7. Comparison of *in vivo* nonclinical profiles (in cyno monkeys) of 25 mg tablets of compound C.

to be one of the critical elements impacting successful drug development.[51−53] There is a great need to understand and predict food effects early in development to maximize overall drug bioavailability and help design the most effective animal and human studies. Encouragingly, the food effect may be evaluated *in vitro* using USP apparatus 4 by comparing the results obtained with FeSSIF and FaSSIF as dissolution media while keeping all other parameters the same. Numerous compounds have been tested using this approach to assess or confirm different drug release rates under fasted or fed conditions.[54] Results for lansoprazole (30 mg Prevacid SoluTabs), danazol (200 mg danazol capsules), and an Amgen development compound (compound D) are summarized here (Figures 8, 9 and 10, respectively). Lansoprazole is recommended to be administered under fasted conditions. In agreement with this recommendation, the results from the biorelevant dissolution testing using USP apparatus 4 also indicated that lansoprazole would have significantly higher bioavailability in the fasted state (Figure 8). It was reported that danazol exhibited at least three times higher bioavailability in the fed state compared to that in

(48) Prevacid® SoluTabs, www.PDR.net.
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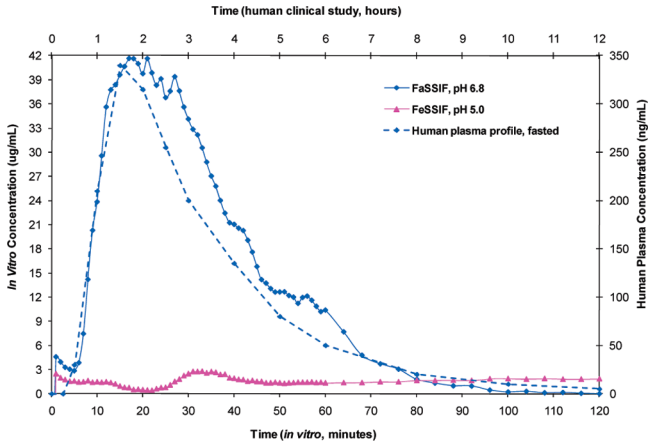

Figure 8. Dissolution profiles of 15 mg Prevacid SoluTabs in FeSSIF (solid pink line/triangle) and FaSSIF (solid blue line/diamond) using USP apparatus 4 compared to the human clinical plasma profile in the fasted state (dotted blue line/diamond).[49,50]

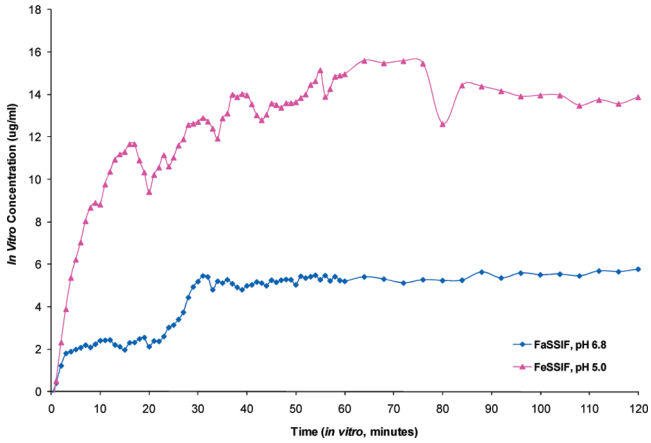

Figure 9. Dissolution profiles of danazol 200 mg capsules in FeSSIF (solid pink line/triangle) and FaSSIF (solid blue line/diamond) using USP apparatus 4.

the fasted state.[55,56] Analysis of the dissolution profiles of danazol using USP apparatus 4 confirmed this observation (Figure 9).

Compound D is a BCS class II compound; it is a weak acid with pK_a values of 4.0 and 7.9 and a measured log *P* value of 4.5. Its aqueous solubility is approximately 32 μg/mL. Compound D was formulated as immediate-release 25 mg tablets. Analysis of the dissolution profiles using the USP apparatus 4 method with both FeSSIF and FaSSIF suggested that this product would have a significant negative food effect with higher bioavailability in the fasted condition compared

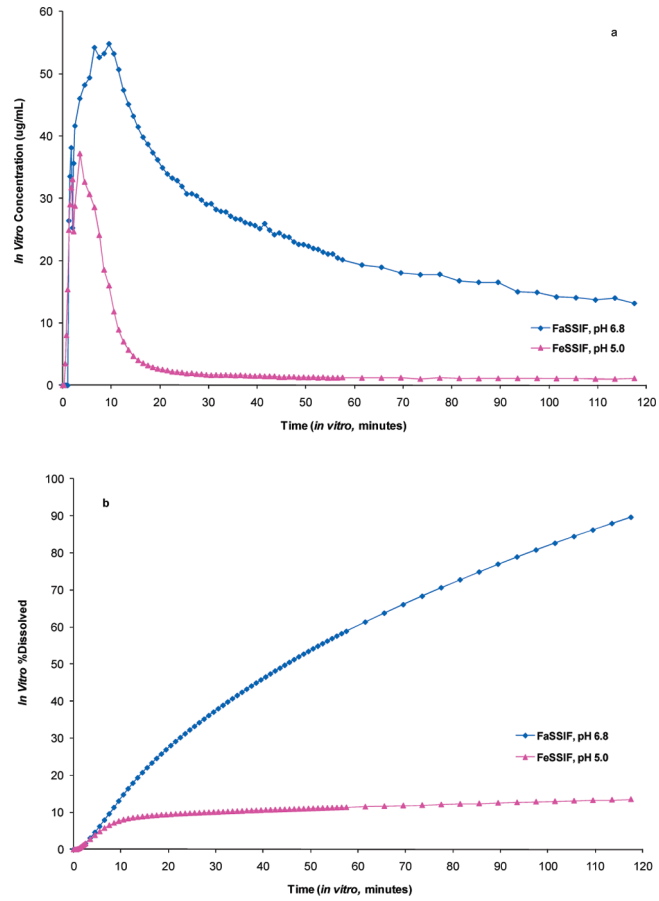

Figure 10. Dissolution profiles of 25 mg compound D tablets in FeSSIF (pink solid line/triangle) and FaSSIF (blue solid line/diamond) using USP apparatus 4 (a, rate profile; b, cumulative profile).

to that of the fed condition (Figure 10). This result was later confirmed in a partial-crossover human PK study ($n = 6$) where C_{max} values of 58.3 and 18.6 ng/mL and AUC values of 335 and 114 h.ng/mL for the fasted and fed state, respectively, were observed.

Discussion

One of the most important applications of dissolution testing is to predict the *in vivo* performance of solid oral dosage forms. However, the simple aqueous buffer solutions traditionally used for QC purposes usually do not represent the physiological conditions in the human GIT. Prediction of intraluminal performance in the proximal gut generally requires adequate simulation of conditions in the stomach and the proximal part of the small intestine with respect to pH and hydrodynamic conditions.[17] That is why it is important to study the *in vitro* dissolution behavior in an environment that mimics *in vivo* conditions.

Over the years, significant progress has been made in dissolution media composition to better reflect the physiological conditions and the influence of the digestive process at various locations in the GIT, e.g., stomach or small intestine, as well as at various conditions, e.g., fasted or fed, such that the *in vitro* dissolution could be studied in an

(55) Charman, W. N.; Toger, M. C.; Boddy, A. W.; Barr, W. H.; Berger, B. M. Absorption of Danazol After Administration to Different Sites of the Gastrointestinal Track and the Relationship to Single-and Double-Peak Phenomena in the Plasma Profiles. *J. Clin. Pharmacol.* **1993**, *33*, 1207–1213.

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environment that more closely mimics the conditions in the human GIT.[17] Compared to the progress made in preparing various types of biorelevant dissolution media, advances in mimicking the hydrodynamics in the GIT have been less than satisfactory due to the complexity of the human GIT. Compared to other available dissolution systems, the USP apparatus 4 open system offers many significant advantages. In this system, fresh solvent from the reservoir continuously passes through the cell to bring the dissolved material out of the cell, analogous to the way material passes through the human GIT, to efficiently maintain the sink conditions for a poorly soluble drug. The design of the pump, the presence of the glass beads, the defined shape of the flow cell, etc. help to better control the flow with less turbulence as compared to other dissolution apparatus. Therefore, the flow-through cell open system has the potential to better simulate the intraluminal hydrodynamics, which is critical to study the *in vivo* drug performance in an *in vitro* setting. The combination of the flow-through cell open system as well as the biorelevant dissolution media allows the *in vitro* dissolution testing to be conducted in an environment that mimics the physiological conditions of the GIT and therefore can potentially predict the *in vivo* drug performance of a solid oral dosage form in a qualitative manner.

In addition to the USP apparatus 4 open system with biorelevant dissolution media, the authors also utilized the available *in vivo* human profiles of commercially available drugs to guide the *in vitro* dissolution method development to ensure that the selected method parameters, such as flow rate, were optimized in terms of the hydrodynamics. This approach allowed the development of a biorelevant *in vitro* dissolution method with a standard set of parameters that is potentially applicable to a wide range of solid oral dosage forms. Although this method was initially developed and verified using BCS class II compounds, experiences with a broad range of commercial as well as development compounds covering the BCS spectrum demonstrated that the method has applicability beyond BCS class II compounds. This enables the method to be used with a generic set of conditions and parameters without much product-specific development, which not only saves method development time but also unnecessary use of dosage forms early in the development phase of a compound when drug substance is often scarce.

Traditional dissolution results are typically expressed in a cumulative fashion, i.e. % dissolved vs time. Cumulative profiles have been commonly used to compare lot-to-lot consistency and product quality during shelf life as well as f2 calculations for biowaiver studies. However, for the purposes of predicting *in vivo* drug performance and empirical comparison of the *in vivo* and *in vitro* profiles, the rate profile, instead of the cumulative profile, is of more interest since most of the *in vivo* plasma profiles are expressed in a rate profile fashion (concentration vs time). This would potentially facilitate qualitative comparisons of the *in vivo* and *in vitro* profiles.

Lot-to-lot equivalency is sometimes challenging to determine, especially when the discriminating power of the dissolution method is not fully understood and the *in vivo* and *in vitro* correlation (IVIVC) has not yet been established. In Case Study I, the process parameters utilized in the manufacturing of the resupply lot led to a slower dissolution profile using the traditional dissolution method (0.1 N HCl), but the results were not conclusive. The biorelevant USP apparatus 4 method using SIF was able to determine that the recently manufactured lot of tablets was not suitable to resupply an ongoing clinical trial, and this finding was later confirmed by animal pharmacokinetic studies. This might be due to the combination of the pH-dependent solubility properties of the compound as well as the different hydrodynamic patterns for USP apparatus 2 and USP apparatus 4. Compound A exhibits a solubility of 0.06 mg/mL ($\sim 6\times$ sink) in 0.1 N HCl and 0.037 mg/mL ($< 4\times$ sink) in SIF. Therefore, the results from the USP apparatus 4 method appear to have better biorelevant discriminating power. The potential outcome of these types of studies is to reduce the number of future PK studies as greater understanding is gleaned from these *in vitro* studies.

It is worthwhile to note that compound A, a weak base with pK_a of 1.5, is one of the exceptions where SIF may be used directly instead of switching the medium from SGF (pH 1.2) to SIF (pH 6.8), presumably due to its low pK_a and the relatively flat solubility curve in this pH range. For the other weak bases with a higher pK_a, a medium switch is recommended to better reflect the in *vivo* dissolution behavior.

This biorelevant dissolution method was also used to evaluate whether a formulation with a pH modifier can provide better *in vivo* dissolution and bioavailability, as was seen in Case Study II. Results from USP apparatus 4 dissolution testing as well as the PK study indicated that there are no significant advantages observed for the prototype formulations of compound B with fumaric acid as a pH modifier (lot 2 and 3), compared to the lots without pH modifier (lot 1 and 4). This might be due to the fact that compound B, a mesylate salt of a weak base formulated as immediate-release tablets, disintegrated and was released in the stomach where strongly acidic conditions are commonly observed. The designed microenvironment expected to be modified by the weak acid was therefore difficult to establish in the strongly acidic environment. However, the pH modifier effect was clearly observed for the Prevacid SoluTabs, which are formulated as delayed-release orally disintegrating tablets using enteric-coated microgranules. Although the tablets are designed to disintegrate quickly in the mouth, the enteric-coated microgranules allow the drug to travel through the upper GIT and to be released in the neutral or alkaline environment of the duodenum. As a result, the weak acids in the Prevacid SoluTabs, i.e., methacrylic acid and citric acid, were able to function effectively as pH modifiers in this neutral or alkaline environment. The presence of the

enteric-coated microgranules also explains the similar dissolution profiles observed with or without the medium switch (Figure 5), which is very different from the case study for compound B. The different observations made for compound B and Prevacid SoluTabs indicated that the use of a delayed release strategy, *e.g.,* enteric coating, may significantly enhance the effectiveness of a weak acid as a pH modifier in a dosage form. Otherwise, when the dosage form disintegrates and the drug is released in the stomach at low pH, the weak acid in the dosage form may be "washed away" and therefore the desired effect of the pH modifier might not be seen. This case study also indicated that in order to evaluate the effect of the pH modifier for immediate-release solid oral dosage forms, an SGF to SIF dissolution media switch is needed.

Aside from assessments of product stability and drug product processability, the *in vitro* dissolution profile should be one of the most important parameters when selecting formulations for development. However, this objective is often challenging when trying to use traditional dissolution testing results, i.e., when dissolution method development typically aims for 100% drug release and uses product-specific non-biorelevant dissolution media. The generic dissolution method described here, which utilizes USP apparatus 4 and biorelevant dissolution media, provides a valuable approach to address this unmet need for early phase formulation development. This is especially true when an *in vitro*/*in vivo* correlation has not been previously established, as seen in Case Study III. In Case Study III, lot 1 of compound C has significantly better bioavailability compared to that of lot 2, as confirmed by the monkey PK studies. This may be mainly attributable to the presence of HPMC in lot 1, which significantly improved the wettability of the compound and consequently enhanced the *in vivo* and *in vitro* dissolution of compound C. This case study also suggested once again that different dissolution methods are needed to fulfill the various roles that *in vitro* dissolution plays throughout the drug product development lifecycle. The traditional QC dissolution method alone is not going to satisfy the multiple needs and various uses for the *in vitro* dissolution testing.

Similar to troglitazone (a poorly soluble lipophilic weak acid) reported previously,[27] danazol, a poorly soluble neutral compound, demonstrated a significant positive food effect in the fed state. This may be explained by the fact that danazol is a lipophilic compound with a log *P* of 4.2.[57] The increased concentration of bile salts and lecithin in the fed state presumably plays a key role to enhance the solubility of danazol. On the other hand, the negative food effect observed for compound D, a weak acid with pK_a values of 4.0 and 7.9 and a measured log *P* of 4.5, might be attributable to the pH-dependent solubility increase of the disalt. All results obtained thus far using many commercially available compounds correspond well in a qualitative fashion to the *in vivo* data.[54] The results from Case Study IV suggested that the food effect may be assessed *in vitro* using this biorelevant dissolution method with FeSSIF and FaSSIF as the media. When applied at the appropriate time in a product's development lifecycle, this approach may provide valuable information to understand whether a mitigation strategy is needed to minimize a potential food effect. The results may also facilitate the design of more efficient pharmacokinetic studies or clinical trials later in development. Results from Case Study IV also suggested that the food effect of individual drugs needs to be assessed on a case-by-case basis, and it remains challenging to predict the food effect in a reliable fashion solely based on physicochemical properties and solubilization capacity of bile salts and surfactants.

As mentioned before, the primary objective of this study was to develop a biorelevant dissolution method to predict the rank order of *in vivo* drug release, to predict potential food effect on *in vivo* drug performance, and to potentially guide formulation development/selection. However, throughout the course of the study, empirical similarities (without any mathematical modeling or conversion) have surprisingly been observed between the *in vivo* and *in vitro* rate profiles (concentration vs time). Many of the calculated correlation coefficients (r^2) for the profiles were observed to be higher than 0.9 (individual results not shown in this report). The compounds that exhibited this apparent correlation were compound A, ibuprofen (both Advil and Motrin tablets, 200 mg), carbamazepine (Tegretol tablets, 200 mg), and lansoprazole (Prevacid SoluTabs, 15 and 30 mg). Most of the dosage forms in this study are immediate-release formulations for which establishing a true IVIVC has been known to be a challenge for decades. All of the observed cases are BCS class II compounds for which dissolution is a rate-limiting step in the drug absorption process. Presumably, the systematic method development approach guided by the known *in vivo* profiles, the hydrodynamic characteristics of the USP apparatus 4 open system (which continuously removes the dissolved material and maintains sink conditions), the biorelevant dissolution media that mimic the *in vivo* GIT environment, and the physicochemical characteristics of BCS class II compounds may together have contributed to these findings. More work is currently ongoing to further understand and explain these empirical observations and their applicability in developing conceptually simple *in vitro*/*in vivo* relationships.

Conclusion

The biorelevant dissolution method described here is generic in the sense that it is broadly applicable for solid oral dosage forms, and it does not require significant product-specific method development for products containing different active ingredients. This method made it possible to compare dissolution profiles for various drug

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products using the same set of operating parameters and conditions in a biorelevant fashion. In addition, these method conditions may potentially be used directly to rank order *in vivo* drug product performance for different formulations, and to assess potential food effects prior to performing animal PK studies and human clinical trials. This approach thus provides a valuable tool to compare *in vitro* drug release in a biorelevant environment, and to potentially predict certain aspects of *in vivo* performance across different types of pharmaceutical compounds and solid oral dosage forms.

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