Review Article

Regulatory Perspectives on Strength-Dependent Dissolution Profiles and Biowaiver Approaches for Immediate Release (IR) Oral Tablets in New Drug Applications

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Abstract. Dissolution profile comparisons are used by the pharmaceutical industry to assess the similarity in the dissolution characteristics of two formulations to decide whether the implemented changes, usually minor/moderate in nature, will have an impact on the *in vitro/in vivo* performance of the drug product. When similarity testing is applied to support the approval of lower strengths of the same formulation, the traditional approach for dissolution profile comparison is not always applicable for drug products exhibiting strength-dependent dissolution and may lead to incorrect conclusions about product performance. The objective of this article is to describe reasonable biopharmaceutic approaches for developing a biowaiver strategy for low solubility, proportionally similar/non-proportionally similar in composition immediate release drug products that exhibit strength-dependent dissolution profiles. The paths highlighted in the article include (1) approaches to address biowaiver requests, such as the use of multi-unit dissolution testing to account for sink condition differences between the higher and lower strengths; (2) the use of a single- vs. strength-dependent dissolution method; and (3) the use of single- vs. strength-dependent dissolution acceptance criteria. These approaches are cost- and time-effective and can avoid unnecessary bioequivalence studies.

KEY WORDS: biowaivers; immediate release oral dosage forms; multi-unit dissolution testing; strength-dependent dissolution acceptance criteria; strength-dependent dissolution profiles.

INTRODUCTION

In vitro dissolution/release testing has emerged as an informative and useful tool for the development and quality control of drug products. It is a valuable tool in the drug development phase for appropriate drug substance selection, formulation optimization, selection of appropriate formulations to advance *in vivo* testing, and optimization and/or process control of manufacturing steps (1, 2). Additionally, *in vitro* dissolution testing is a simple and cost-effective quality control (QC) tool to ensure batch-to-batch consistency and identify minor/moderate manufacturing deviations before batch release (3). *In vitro* dissolution testing has

pivotal and extensive applications in regulatory submissions. It is employed to bridge minor/moderate formulation/manufacturing changes that are within the limits defined in the Scale-Up and Post-Approval Changes (SUPAC) FDA guidance (level 1 and 2 changes) that may occur during the product's life cycle (pre-approval and post-approval stages of drug product development) (4–6).

In vitro dissolution/release plays an important role in demonstrating product strength equivalence for strengths not tested in bioequivalence trials. The need to demonstrate bioequivalence/dose proportionality between product strengths exists during a product's life cycle in the following scenarios: (1) addition of lower strengths and/or higher strengths not tested in clinical trials and (2) major manufacturing/formulation change that is supported by bioequivalence between pre-change and post-change drug products at the highest strength. In accordance with 21CFR320.22(d)(2) (7) and FDA guidance on bioavailability (BA) and bioequivalence (BE) (8), for studies submitted in regulatory applications such as new drug applications (NDAs) and investigational new drug applications (INDs), comparable *in vitro* testing is one of the criteria considered for the demonstration of bioequivalence/dose proportionality between product strengths and for granting biowaivers to strengths not studied *in vivo*. Dissolution profile comparisons (when applicable) by appropriate statistical approaches (9)

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can provide acceptable evidence of bioequivalence between pre-change and post-change drug products and/or reference strength and test strength.

Dissolution through *in vitro-in vivo* correlation (IVIVC) may be utilized to document bioequivalence for post-change product and product strength equivalence without further conducting *in vivo* studies and setting certain drug product specifications (10–12). Furthermore, in the Quality by Design (QbD) paradigm, dissolution has the potential to link material/process/product variables to the clinical efficacy/safety of the drug product and provide regulatory flexibility in a drug product's life cycle (13, 14). The importance of developing a dissolution method that is not only discriminating but also biopredictive has been recently discussed in scientific conferences (15). Development of biopredictive *in vitro* dissolution methods with clinical relevance will largely enhance the possibility to establish a successful IVIVC/R and thereby enable dissolution to be effectively used as a bridge between the drug product's critical material attributes (CMAs)/process parameters (CPPs) and *in vivo* performance. Thus, *in vitro* dissolution testing can be a time and cost-effective alternative to bioequivalence studies in many important aspects of drug product development, particularly for solid oral dosage forms.

In vitro dissolution testing results and conclusions can be influenced by complex processes/parameters. Hence, the efforts on thorough evaluation of the method are necessary to ensure that reliable information is generated to assess and assure quality control during drug development (13). One such scenario that has not received much attention is the impact that strength-dependent dissolution profiles may have on the dissolution method development, setting dissolution acceptance criteria, and discriminating capability of the method for all strengths. Strength-dependent dissolution behavior would also impact the outcome of dissolution profile comparisons between product strengths and pre-change and post-change products during drug product life cycle for biowaiver purposes. The above scenario is the focus of this article.

In vitro strength-dependent dissolution profile is defined as the difference in drug dissolution profiles among strengths of the same oral drug product; i.e., there is dissolution dissimilarity across product strengths (e.g., similarity factor $f_2 < 50$). Such dissolution behavior has been observed with both compositionally proportional and non-proportional formulations. The compositionally proportional and non-proportional formulations have been defined in FDA guidance (8). In accordance with this guidance, the dissolution profile comparison in at least three different pH media is recommended to demonstrate equivalence/dose proportionality between product strengths (e.g., approval of lower strengths not tested in clinical trials) for biowaiver purposes. It is likely that the dissolution profile comparison test in single or multiple media among product strengths with strength-dependent dissolution pattern will fail. Dissimilar dissolution profiles would indicate the need for costly and time-consuming BE studies on multiple or all strengths, but that conclusion may be misleading and *in vivo* studies may not be necessary. This raises further questions such as *what factors can cause strength dependent dissolution behavior? How can this misleading situation be avoided in in vitro settings?* The

information presented in this article is intended to provide a high-level overview of some scientific considerations for dissolution method development, the challenges with biowaivers for drug products with strength-dependent dissolution profiles, and provides alternative approaches to comparative dissolution analysis for ascertaining the feasibility of a biowaiver strategy in drug development for product exhibiting strength-dependent dissolution.

METHODS

The analysis in the present study was conducted on the biopharmaceutical information contained in approved NDA submissions from 2010 to 2014 for multiple-strength immediate release (IR) tablet formulations. A screening approach was utilized to identify IR tablet examples that demonstrated strength-dependent dissolution profiles. The screening efforts were concentrated on identifying multiple-strength IR tablet products containing biopharmaceutical classification system (BCS) class 2 or 4 drugs as these drugs are likely to produce strength-dependent dissolution pattern in the instances when sufficient sink conditions in the testing conditions are not maintained across all strengths. Further, products with BCS class 2 or 4 drugs can also demonstrate strength-dependent dissolution as a function of differences in formulation and/or manufacturing process parameters even though sufficient sink conditions exist. Thus, the information gathered from the NDA submissions and relevant scientific review documents not only considered BCS class and pH solubility profile but also formulation properties (compositionally proportional *vs.* non-proportional), the approved dissolution method and acceptance criteria, dissolution behavior in multiple-dissolution media, relevant biopharmaceutical questions (e.g., biowaiver) that were addressed, and approaches followed to address and resolve biowaiver questions. The biopharmaceutical information for the identified drug product examples and the related regulatory review performed by the FDA provided a representation of products exhibiting strength-dependent dissolution behavior and successful *in vitro* dissolution biopharmaceutical strategies used to address the issue. About 10% of the submissions identified contained strength-dependent dissolution. The FDA's biopharmaceutical review practice related to the identified product examples served as the basis for the recommendations presented in this article on approaches for (1) single (same method for all strengths) *vs.* strength-dependent (different methods among strengths) dissolution testing for quality control purpose, (2) single- *vs.* strength-dependent dissolution acceptance criteria settings, and (3) dissolution profile comparisons for biowaiver purposes for drug products with strength-dependent dissolution profiles.

RESULTS

The screening process identified five IR drug products (tablets) for oral administration with multiple strengths (BCS class 2) approved from 2010 to 2014 that demonstrated strength-dependent dissolution profiles. An additional oral new drug IR tablet product approved in 2015 was considered for the research objective. The biopharmaceutical relevant information and approaches employed for addressing the

biowaiver questions on these six drug product examples are presented in Table I.

The preliminary analysis of the collected data revealed that strength-dependent dissolution occurred in both single entity and fixed dose combination (FDC) drug products. Most of the identified drug products contained BCS class 2 drugs except for one FDC drug product that contained BCS class 3 drugs. Strength-dependent dissolution for drug products was observed either with the approved QC dissolution method and other dissolution media for pH profiling or just in the multiple-dissolution media for pH profiling. The later scenario existed with drugs demonstrating pH-dependent solubility and drug products that showed sink condition across all strengths using the QC method with or without surfactant. Further analysis of the data indicated that for compositionally proportional formulations, strength-dependent dissolution profiles can be attributed, as expected, to several factors such as sink differences among strengths in the selected dissolution medium (e.g., media pH, volume, and ionic strength) and manufacturing process differences (e.g., hardness). For compositionally non-proportional formulations, in addition to the above, formulation differences among strengths can also be a contributing factor. It was found that factors responsible for strength-dependent dissolution for drug products that had sufficient sink conditions in both QC and other multiple medium were likely related either to manufacturing process (for compositionally proportional formulations; drug products 2 and 3 in Table I) and/or formulation differences (for compositionally non-proportional formulations; drug product 6 in Table I). Whereas, the strength-dependent dissolution profiles for drug products observed in several of the tested multiple-dissolution media were likely due to insufficient sink conditions as a function of pH-dependent solubility (drug products 1, 4, and 5 in Table I). The absence of sink condition was concluded based on the aqueous solubility of the drug in the respective dissolution medium and the resulting difference in volume of medium necessary for complete drug dissolution among strengths. Despite the presence of strength-dependent dissolution profiles, there was no pattern in terms of the use of strength-dependent acceptance criteria for neither group of the drug products evaluated. Specifically, the acceptance criteria were the same for all strengths in most cases except one (drug product 3 in Table I).

The strength-dependent dissolution behavior of the drug products in Table I indicated that dissolution profile comparison (when applicable) by the traditional approach (e.g., comparison of lower vs. higher strengths of the same drug product using single tablet unit) is not feasible. This is because a dissolution similarity test between strengths of these products is likely to fail, which may not necessarily translate into lack of similarity *in vivo* and may lead to incorrect conclusions about when *in vivo* studies are needed. This challenge on biowaiver requests for drug products demonstrating strength-dependent dissolution was addressed by approaches submitted in NDAs and developed during the review of the application for lower/intermediate strengths. For the sake of brevity, we describe approaches for only two of the identified drug product examples in detail, one under each compositionally proportional and non-proportional formulation categories. The rest of the cases and approaches employed to address a biowaiver request are briefly presented and summarized.

Case Example 1: An Example of Horizontal Dissolution Profile Comparison for Biowaiver Purposes

This case describes strength-dependent dissolution behavior of approved drug product 1 presented in Table I. The drug product 1 consists of a BCS class 2 drug with pH-dependent aqueous solubility. All four approved strengths are compositionally proportional. The drug product underwent a major manufacturing process change from the clinical trial to the to-be-marketed (TBM) formulation which required a BE study to support the change. The manufacturing process change was supported by the demonstration of bioequivalence at the highest strength and dissolution similarity ($f_2 \geq 50$) for two intermediate strengths in comparison to the highest strength. However, the dissolution profile comparison did not support the waiver of conducting BE studies for the lowest strength as the similarity test failed due to differences in dissolution profiles among the strengths (Fig. 1). Since strength-dependent behavior was not observed using the QC method, the dissolution acceptance criteria were set to the same value for all strengths. Further analysis of this behavior suggests that sink condition differences are likely to be the cause for the observed differences in dissolution profiles among strengths. Based on the drug solubility in non-QC media (pH 4.5 and 6.8), the difference in volume of medium required for complete dissolution/solubilization of drug between lowest and highest strengths is eightfold. In general, a failed dissolution similarity test is a strong indicator that additional information is needed to confirm that there is likely no difference in clinical performance, which often means conducting an *in vivo* BE study. However, to address this issue of dissolution dissimilarity for the lowest strength, dissolution profile comparison between pivotal clinical trial and to-be-marketed formulation (i.e., horizontal dissolution profile comparison) of lowest strength was assessed. Horizontal dissolution comparison refers to the dissolution profile comparison between the same strength of the drug product (e.g., pre-change vs. post-change at the same strength). This is in contrast to vertical dissolution profile comparison approach which is commonly followed for demonstration of BE between the lower and higher strengths of the same drug product based on *in vitro* testing. In this case, example of horizontal dissolution profile comparison, the pivotal clinical trial, and to-be-marketed formulations represents pre-change and post-change products, respectively, for the lowest strength. This comparison resulted in dissolution similarity and supported the approval of a biowaiver for the lowest strength. It is worth mentioning that this approach was taken, given that the lower strength (pre-change formulation) was tested in clinical trials which allowed the collection of pharmacokinetic (PK) information. The question arises, *if no clinical information (e.g., PK data) had been provided for the lower strength tested in the pivotal clinical trials, would it still be feasible to apply this approach?* The answer relies on whether dissolution similarity and/or BE requirements were met for the lower strength tested in pivotal clinical trials. If the answer is “no” (e.g., no clinical information provided for the lowest strength), a feasible *in vitro* approach to address this problem is illustrated in case example 2. If the answer is “yes,” one of the examples below illustrates the case with the use of BE data (namely, indirect BE link) generated as part of the drug product development strategy.

Table 1. Relevant Biopharmaceutical Information for Approved IR Tablet Drug Products that Demonstrated Strength-Dependent Dissolution Profiles

No.	Drug product	BCS class	Solubility behavior	Number of approved strengths	Compositionally proportional (yes/no)	Approved QC dissolution medium	Strength-dependent dissolution behavior ^a	Strength-dependent acceptance criteria (yes/no)	Reason for strength-dependent dissolution behavior	Biopharmaceutical regulatory question addressed	Approach to address the biopharmaceutical question ^b
1	Single drug entity	Class 2	pH dependent (solubility decreases with increase in pH)	4	Yes	Acidic (pH 2 without surfactant)	Observed in basic medium (pH 4.6 and 6.8)	No	Sink condition differences	Biowaiver request for lower strengths	Biowaiver based on horizontal dissolution profile comparison ^c (single-unit dissolution)
2	Single drug entity	Class 2	pH dependent (solubility decreases with increase in pH)	4	Yes	Water with surfactant	Observed in QC and non-QC medium (pH 1.2, 4.5, and 7.5 with surfactant)	No	Hardness differences	Biowaiver request for lower strengths	Biowaiver based on indirect BE bridge ^d
3	Single drug entity	Class 2	pH independent	4	Yes	Acidic (pH 4.5 without surfactant)	Observed between lowest strengths in QC and multimedia (pH 1.2 and 6.8)	Yes	Hardness differences	Biowaiver request for lowest strength	Biowaiver based on indirect BE bridge
4	Single drug entity	Class 2	pH dependent (solubility decreases with increase in pH)	2	Yes	Basic (pH 6.8 with surfactant)	Observed in multimedia (pH 4.5 and 6.8)	No	Sink condition differences	Biowaiver request for lower strength	Biowaiver based on vertical dissolution profile comparison ^e (multiple unit dissolution) ^f
5	Fixed dose combination (FDC)—two drug entities	Class 2	Drug A, pH independent and drug B, pH dependent (solubility decreases with decrease in pH)	4	No	Basic (pH 6.8 with surfactant)	Observed for drug B in acidic medium (pH 1.2 and 4.5)	No	Sink condition differences	Biowaiver request for intermediate strengths	Biowaiver based on vertical dissolution profile comparison (multi-unit chain-bracketing approach ^g)
6	FDC—two drug entities ^h	Class 3	Both drugs (drugs A and B) are highly soluble over the entire physiological pH range	3	No	Basic (pH 6.8 without surfactant)	Present for drug A between two lower strengths vs. higher strength in QC and multimedia (water and pH 1.2 and 4.5)	No	Formulation differences	Biowaiver request for intermediate strength	Biowaiver based on BE bracketing ^f

^a Strength-dependent behavior observed across all strengths unless specified in Table^b In addition to the approaches listed in the Table, other biowaiver requirements recommended in the FDA BA/BE guidance for NDAs and INDs were also fulfilled^c Horizontal dissolution profile comparison represents the dissolution comparison between the same strength of the drug product (e.g., pre-change vs. post-change product at the same strength)^d Indirect BE bridge refers to the use of data from BE studies not conducted directly between the drug product strength under review and the reference strength (e.g., strength(s) evaluated in pharmacokinetic (PK) studies)^e Vertical dissolution profile comparison represents the dissolution comparison between different strengths of the same drug product (e.g., lower strength vs. higher strength and intermediate vs. lower or higher strength)^f Multiple-unit dissolution represents dissolution testing using more than one unit of the dosage form in the same dissolution vessel^g Multiple-unit chain-bracketing approach refers to the application of brackets in dissolution profile comparison when multiple units are needed to account for differences in sink conditions among strengths of the same formulation which have the same QC dissolution method^h This fixed dose combination product containing two drug entities has both immediate release (IR) and extended release (ER) components. Drugs A and B are present in the IR and ER components of the product, respectivelyⁱ BE bracketing approach under strength-dependent dissolution scenario is defined as demonstration of product strength equivalence/dose proportionality for intermediate strength(s) based on *in vivo* bioequivalence between strengths representing the extremes in formulation/process differences and for which the intermediate strength dissolution profile is within the dissolution bounds of bioequivalent strengths

Fig. 1. Mean ($n = 12$) dissolution profiles of four strengths of drug product 1 in dissolution medium, a pH 4.5 and b pH 6.8

Case Example 2: An Example of Dissolution Testing Using Multi-Unit Chain-Bracketing Approach for Biowaiver Purposes

Drug product 5 (summarized in Table I) is a FDC product containing two drug entities (i.e., drugs A and B) both belonging to BCS class 2. Of the two drug entities, only drug B with pH-dependent solubility demonstrated strength-dependent dissolution. All four approved strengths are compositionally non-proportional. The drug product underwent a major formulation change post-approval. The information submitted to support the change included (1) a biowaiver request for intermediate strengths, (2) an *in vivo* BE study for the test and reference product for both drug entities at the highest and lowest strengths, (3) evidence of consistent manufacturing process among strengths, and (3) multimedia (QC medium and pH 1.2, 4.5, and 6.8) dissolution profile comparisons for all strengths. Bioequivalence was demonstrated between the highest and lowest strengths vs. the corresponding strengths of the reference product. The formulation change was further supported for drug A at intermediate strengths by similarity testing ($f_2 > 50$) in multiple-dissolution media in comparison to the highest strength. However, for drug B, the dissolution comparison for intermediate strengths with respect to highest strength at pH 1.2 and 4.5 indicated dissimilarity ($f_2 < 50$; Fig. 2). Strength-dependent dissolution at pH 4.5 was only observed for the highest strength (Fig. 2b). To rule out the potential effect of differences in sink conditions, a multiple-unit (multi-unit) dissolution testing approach was followed. Specifically, drug B

dissolution profiles of intermediate strength in pH 1.2 and 4.5 media were obtained using two tablet units in a single vessel and were compared to that of one tablet unit of highest strength. Vertical dissolution profile comparison indicated similarity ($f_2 \geq 50$) which demonstrated that dissolution dissimilarity was due to differences in sink conditions achieved among the different strengths in the conditions tested. The approach taken in this example, namely, “multi-unit” approach, illustrates the importance of accounting for sink condition differences among strengths when dissolution profile comparisons are applied to drug products with strength-dependent dissolution for biowaiver purposes. It should be noted that for drug products not proportionally similar in composition, a dissolution-bracketing approach is a feasible option, provided that the proposed highest and lowest strengths meet the criteria through the bioequivalence bracketing approach. This approach allows demonstration of BE between intermediate strengths and lowest/highest strengths using comparative dissolution testing. In this example, the multiple-unit approach implemented was applied to the strengths not tested *in vivo* but bracketed by the *in vivo* BE study conducted for the highest and lowest strengths.

Multiple-unit (multi-unit) chain-bracketing approach refers to the application of brackets in dissolution profile comparison when multiple units are needed to account for differences in sink conditions among strengths of the same formulation which have the same QC dissolution method. For instance, consider a drug product containing four strengths (e.g., 10, 20, 40, and 80 mg) that are compositionally proportional and demonstrate strength-dependent dissolution due to sink condition

Fig. 2. Drug B mean ($n=12$) dissolution profiles of four strengths of drug product 5 in dissolution medium, **a** pH 1.2 and **b** pH 4.5

differences. A biowaiver is being requested for the strengths not tested in bioavailability study (e.g., pharmacokinetic studies) based on dissolution profile comparisons in addition to all the requirements set forth under CFR 320.22 (for oral solid dosage forms). Due to the strength-dependent dissolution profiles, if (due to method constraints) more than two units cannot be employed in dissolution testing to account for sink condition differences between two lowest strengths (e.g., 8×10 and 4×20 mg) vs. highest strength (1×80 mg), the multi-unit dissolution comparison may be performed between higher intermediate strength (2×40 mg) and highest strength (1×80 mg), lower intermediate strength (2×20 mg) and higher intermediate strength (1×40 mg), and lower strength (2×10 mg) and lower intermediate strength (1×20 mg; Fig. 3). Alternative approaches (as shown in Fig. 3) should be properly justified with supporting data. Similarly, if the above drug product example was a compositionally non-proportional formulation and BE is demonstrated at extreme strengths, double-unit dissolution comparison for higher (2×40 mg) and lower (1×20 mg) intermediate strengths can be performed with highest (1×80 mg) and lowest (2×10 mg) strengths, respectively (Fig. 4), provided that the comparison meets the compositional proportional requirements as explained above.

Overview of Other Case Examples: Biowaiver Based on Indirect Bioequivalence Bridge and/or Bioequivalence Bracketing Approach

The question arises as “*what if sink conditions are not the cause of the observed strength-dependent dissolution*”? The

drug product examples 2, 3, and 6 in Table I highlight this scenario. The biowaiver approaches for these drug products are based on bioequivalence studies conducted as part of the drug product development program. These BE studies provided an indirect link (indirect BE bridge) to support the approval of product strengths exhibiting strength-dependent dissolution. Specifically, indirect BE bridge refers to the use of data from BE studies not conducted directly between the

Fig. 3. Illustration of a multiple-unit (multi-unit) chain-bracketing dissolution testing approach for biowaiver purpose applied to a compositionally proportional drug product that exhibits strength-dependent dissolution testing

Fig. 4. Illustration of a multiple-unit (multi-unit) chain-bracketing dissolution testing approach for biowaiver purpose applied to a compositionally non-proportional drug product that exhibits strength-dependent dissolution

drug product strength under review and the reference (e.g., strength(s) evaluated in PK studies) and for which a typical BE bracketing approach is not feasible (e.g., the strength is out of the bracket).

Drug product 3 is an immediate release formulation marketed in four strengths with compositionally proportional formulations. A change in formulation and manufacturing site (alternate site) was implemented for the pivotal clinical trial formulation (CTF). Data from a BE study which included the three highest strengths (Fig. 5) were provided to support the approval of these three strengths. The lowest strength (strength 4; Fig. 5) was not part of this BE study. Instead, dissolution profile comparisons with similarity testing between this and all higher strengths were performed (Fig. 5). The similarity test failed due to faster dissolution of the lowest strength. Data

provided suggested that differences in several manufacturing attributes (e.g., hardness ranges) are likely to be the cause for the observed strength-dependent dissolution profiles among the lower strength and all other strengths. Despite the dissolution dissimilarity between the lowest and higher strengths, the biowaiver for the TBM lowest-strength formulation manufactured at the alternate site (site B; Fig. 5) was justified based on (1) dissolution similarity between CTF and TBM formulations at the lowest strength and (2) indirect demonstration of bioequivalence between CTF and TBM formulations of lowest and highest strengths, respectively. In particular, the CTFs of lowest and highest strengths were shown to be bioequivalent. Further, the CTF and TBM formulations of highest strengths were bioequivalent. Overall, the comparative PK study data and dissolution data for the CTF and TBM formulations provided the additional support needed to conclude that the risk of bioinequivalence between the TBM lowest and highest strengths was low, despite observing dissolution dissimilarity. Thus, both horizontal dissolution profile comparison and indirect bioequivalence bridge addressed the primary question of granting a biowaiver for lowest strength demonstrating strength-dependent dissolution.

It should be noted that, in this example, the dissolution acceptance criteria were set based on the *in vitro* performance of each strength (namely, “strength-dependent dissolution acceptance criteria”). The implementation of strength-dependent dissolution acceptance criteria as part of the drug product specifications is recommended since it enhances the discriminating power of the dissolution method for the strength in consideration. However, it should be noted that in the presence of a BE bridge, dissolution acceptance criteria should be set based on the slowest-dissolving strength or formulation that was found BE to the fastest-dissolving strength or target formulation (e.g., formulation tested in pivotal clinical trials).

Another example that illustrates the application of indirect bioequivalence bridge in addition to BE bracketing approach to support the approval of lower strengths is shown in Fig. 6. Drug product 6 (summarized in Table 1) is an

Fig. 5. Illustration of BE bracketing and indirect BE approaches for biowaiver purposes applied to a compositionally proportional drug product that exhibits strength-dependent dissolution

Fig. 6. Illustration of BE bracketing and indirect BE approaches for biowaiver purposes applied to a compositionally non-proportional drug product that exhibits strength-dependent dissolution

immediate release/extended release fixed dose combination product containing BCS class 3 drugs. The drug product is compositionally non-proportional across three strengths. Of the two drug entities, only the IR component showed strength-dependent dissolution in the QC and additional media for one of the three strengths (i.e., the highest strength). This strength-dependent dissolution profile behavior is likely due to formulation difference between lower/intermediate and higher strengths. The data submitted to support the approval of the intermediate strength was based on (1) BE data comparing the highest and lowest strengths and (2) dissolution profile comparisons between the intermediate and highest strengths.

The dissolution profile comparison between intermediate and higher strengths did not indicate similarity (Fig. 6); however, further analysis and assessment of the data indicated that the approval of the intermediate strength could be supported based on the following additional data: (1) demonstration of BE between the lowest and highest strengths, (2) dissolution profile of the intermediate strength being within the dissolution bounds of lowest and highest strengths, (3) dissolution similarity between the intermediate and lowest strengths, and (4) equivalent systemic exposure from intermediate strength in comparison to other two strengths based on cross-study comparison. BE bracketing approach under strength-dependent dissolution scenario as evident from above example is defined as demonstration of product strength equivalence for intermediate strength(s) based on *in vivo* bioequivalence between strengths representing the extremes in formulation/process differences and for which the intermediate strength dissolution profile is within the dissolution bounds of bioequivalent strengths.

DISCUSSION

Strength-dependent dissolution profiles for compositionally proportional and non-proportional formulations though not a common observation may have critical implications on whether a biowaiver request for the required *in vivo* BE study(ies) can be granted. Efforts were therefore initiated with the objective to understand (1) the need for strength-dependent dissolution methods and acceptance criteria and (2) issues related to the dissolution profile comparisons among strengths of the drug product that shows strength-dependent dissolution for biowaiver purposes. Our efforts were focused on IR oral tablets. The strength-dependent dissolution/release for other oral and non-oral dosage forms will be a subject of future investigations. This review article summarizes some scientifically based and practical approaches and considerations for using *in vitro* dissolution to support BA/BE study waiver requests for drug products with strength-dependent dissolution profile characteristics. Current approaches for selecting dissolution method and acceptance criteria for drug products with strength-dependent dissolution characteristics were also considered in this review work.

The cause-effect for strength-dependent dissolution behavior can be ascribed to several factors such as sink condition differences in the dissolution testing conditions among strengths, quality attribute/process differences (e.g., hardness, shape, and size), formulation differences (i.e., compositionally non-proportional formulation), and

interactions between these factors. For instance, the differences in tablet hardness and shape/size among strengths may impact disintegration and surface area to volume ratio, respectively, and consequently the dissolution rate. These factors that cause strength-dependent dissolution *in vitro* may not necessarily impact the *in vivo* performance across product strengths. For example, failing to demonstrate comparative dissolution for a lower strength not tested in BE studies may trigger conduct of an *in vivo* bioequivalence study. However, when considering whether an *in vivo* BE study is needed or if alternate *in vitro* approaches may be scientifically reasonable, the following questions should be assessed: (1) *Is the observed strength-dependent dissolution behavior due to sink condition differences?* (2) *Is a single-dissolution method adequate for a drug product demonstrating strength-dependent dissolution profiles?* (3) *How does the strength-dependent dissolution behavior impact the setting of dissolution acceptance criteria?* (4) *If a single method is found to be adequate for a drug product and shows strength-dependent dissolution, is there a feasible approach for dissolution profile comparison to demonstrate product strength equivalence and support biowaiver?*

Sink condition may exist for one or more lower strengths but not for higher strengths during multimedia dissolution testing, resulting in dissolution profile differences among product strengths causing strength-dependent dissolution profiles. The BCS class 2 or 4 drugs are likely to show strength-dependent dissolution if sufficient sink conditions are not maintained for all strengths. Although the use of surfactant is a common practice to maintain sink conditions, it may render the dissolution method under-discriminating for lower strengths if a relatively high surfactant concentration is employed. Therefore, efforts should be made, as part of the dissolution method development, to ensure that the method selected has sufficient discriminating ability for all strengths being considered. If this is not the case, the possibility of having two different QC methods (e.g., different media volume) should be explored with appropriate justification. Alternatively, strength-dependent dissolution acceptance criteria should be considered to increase the discriminating ability of the method per strength. The need for implementing strength-dependent dissolution methods or acceptance criteria should be guided by the presence of a biopredictive dissolution method (14, 15). Therefore, an effort should also be made in determining the relationship between dissolution profiles and systemic exposure [peak concentration (C_{max}) and area under the curve (AUC)] rendering the dissolution method biopredictive.

If the selected method shows strength-dependent dissolution behavior, efforts should be made during the dissolution method development stage to determine whether this behavior is due to sink condition differences in a defined volume of medium. Addressing this issue early during drug product development will help guide decisions on the most appropriate biopharmaceutical strategy to support product development changes. For example, when dissolution testing is used for biowaiver purposes, the multi-unit dissolution testing approach described above allows for the lower strength(s) to have the same dissolution testing conditions including solubility capacity of the dissolution medium compared to the higher strength(s) to mitigate sink condition issues. However,

an excessive number of units tested may change the hydrodynamics and should be appropriately justified. It should be noted that the multi-unit dissolution testing approach should be considered only when addressing biowaiver requests through dissolution profile comparisons. Specifically, dissolution for release and during stability testing should follow the USP dissolution testing standards or as agreed upon with the regulatory Agency. If the profiles are dissimilar from multi-unit dissolution, the quality-attribute differences (e.g., hardness, shape, and size) resulting from manufacturing processes may be the reason causing strength-dependent dissolution. For compositionally non-proportional formulations, in addition to quality attribute differences, formulation differences when multi-unit dissolution is not similar can also lead to strength-dependent dissolution. In some cases, strength-dependent dissolution acceptance criteria may be scientifically appropriate for quality control when the above behavior due to product attribute/formulation differences is observed and should be discussed with regulatory authorities. Thus, assuming that potential sink condition differences among strengths have been addressed, Table II provides a layout of possible approaches to consider for dissolution testing, acceptance criteria settings, and biowaivers for compositionally proportional and non-proportional IR tablet drug products exhibiting strength-dependent dissolution.

It is expected that after correction for sink conditions using the so-called “multi-unit chain-bracketing dissolution approach,” compositionally proportional drug products with observed strength-dependent dissolution profiles will have similar dissolution profiles among strengths, provided same manufacturing process controls. Under these circumstances, dissolution profile comparisons should be conducted between lower and higher strengths (vertical dissolution profile comparison). Correction for sink condition differences will facilitate vertical dissolution profile comparison between strengths tested *in vivo* vs. not tested *in vivo*, which otherwise would have indicated dissimilarity between strengths due to sink condition differences. The use of relatively high concentration of surfactant in the dissolution medium may compromise the discriminating ability of the QC dissolution method for the lower strengths. Therefore, a strength-dependent dissolution acceptance criterion should be considered to increase the discriminating ability per strength (formulation type 1; Table II), in the absence of BA/BE data indicating otherwise. In addition, this will avoid the development of more than one method (e.g., strength-dependent dissolution method) streamlining the drug product development. It should be noted that development of more than one method may be necessary when the discriminating ability of a single method is not demonstrated for all strengths.

Potential lack of similarity in dissolution profiles (through vertical dissolution profile comparison) for

Table II. Approaches for Dissolution Method, Dissolution Acceptance Criteria, and Biowaivers for Compositionally Proportional and Non-Proportional IR Tablet Drug Products Exhibiting Strength-Dependent Dissolution Profiles

No.	Formulation type	Dissolution comparison across strengths after correction for sink conditions ^a	Dissolution method for quality control purposes	Dissolution acceptance criteria ^b	Dissolution comparison approach for product strength equivalence (biowaiver purpose) at pre- and post-approval stages
1	Compositionally proportional	Dissolution similar	Single method with single unit (same for all strengths)	(1) Strength-dependent criteria ^c and (2) strength-independent criteria ^d	Vertical dissolution comparison using the multi-unit chain-bracketing dissolution approach for strength(s) not tested in PK studies
2	Compositionally proportional	Dissolution dissimilar	Single method with single unit (same for all strengths)	(1) Strength-dependent criteria ^c and (2) strength-independent criteria ^d	Horizontal dissolution comparison (if feasible, e.g., formulation change biowaiver) using single unit for strength(s) not tested in PK studies ^e
3	Compositionally non-proportional	Dissolution similar	Single method with single unit (same for all strengths)	(1) Strength-dependent criteria ^c and (2) strength-independent criteria ^d	Vertical dissolution comparison using the multi-unit chain-bracketing dissolution approach for strength(s) (e.g., intermediate strengths) not tested in PK studies
4	Compositionally non-proportional	Dissolution dissimilar	Single method with single unit (same for all strengths)	(1) Strength-dependent criteria ^c and (2) strength-independent criteria ^d	Horizontal dissolution comparison (if feasible, e.g., formulation change biowaiver) using single unit for strength(s) not tested in PK studies ^e
5	Compositionally non-proportional	Dissolution dissimilar	Strength-dependent method with single unit	(1) Strength-dependent criteria ^c	(1) Vertical dissolution comparison using the multi-unit chain-bracketing dissolution approach for strength(s) (e.g., intermediate strengths) not tested in PK studies or (2) horizontal dissolution comparison (if feasible, e.g., formulation change biowaiver) using single unit for strength(s) not tested in PK studies

^a Use of multiple units for correction of sink condition if applicable

^b Dissolution acceptance criteria based on the dissolution profile obtained using a single unit

^c Strength-dependent criteria are suggested when strengths are not bioequivalent or comparative BA/BE data are not available

^d Strength-independent criteria or same criteria for all strengths are recommended if justified by *in vivo* bioequivalence data. Specifically, dissolution acceptance criteria setting based on the lowest dissolution profile among bioequivalent strengths are suggested

^e Additional data (e.g., PK data) may be needed to justify that the observed dissolution differences (e.g., $f_2 < 50$) do not have an *in vivo* impact

compositionally proportional (formulation type 2; Table II) and compositionally non-proportional drug products (through vertical dissolution profile comparison among comparable strengths) (formulation type 4; Table II) with observed strength-dependent dissolution profiles despite accounting for sink condition differences may be due to different quality attributes and/or formulation differences, respectively. Therefore, without data indicating the presence of an over-discriminating method, *in vivo* data (PK data) may be necessary to demonstrate that the observed *in vitro* differences (e.g., $f_2 < 50$) are of no clinical relevance. When addressing major formulation/manufacturing changes, the approval of lower strengths not tested in PK studies may be supported by dissolution profile comparisons among similar strengths (horizontal comparison), provided that the reference (pre-change) strength acceptability has been previously justified (refer to case study drug product 3, for proportionally similar composition drug product).

The presence of strength-dependent dissolution profiles for products that are compositionally non-proportional is expected (even after sink condition differences among strengths are accounted for) since differences in formulation among strengths are likely to cause differences in dissolution profiles. However, it may be the case where no differences are observed even in the presence of an otherwise discriminating/biopredictive dissolution method. For example, the implemented changes in formulation across strengths have no impact on dissolution and the observed strength-dependent dissolution profile is likely due to sink condition differences. Under this condition, for biowaiver purposes, a multi-unit chain-bracketing dissolution approach for the strengths not tested clinically (e.g., intermediate strengths) may be employed (formulation type 3; Table II). Vertical dissolution profile comparison between strengths with the same dissolution method is suggested to qualify lower strengths during either pre- or post-approval (manufacturing/formulation changes). When it comes to the implementation of the selected dissolution method for QC purpose, if an appropriate discriminating ability is not developed across strengths, strength-dependent dissolution methods may be considered, especially when dissimilarity in the dissolution profiles is found (formulation type 5; Table II). Alternatively, strength-dependent dissolution acceptance criteria may be appropriate to increase the discriminating ability of the method across strengths.

The approaches described above may prove useful when developing biopharmaceutical strategies to address *in vitro* dissolution-based biowaiver challenges for drug products with strength-dependent dissolution. However, the use of multi-unit chain-bracketing dissolution approach for biowaiver purposes raises questions on the potential effect multiple tablet units in a single-dissolution vessel may have on *in vitro* hydrodynamic conditions. Multiple tablet units in a single-dissolution vessel may affect positioning of the tablets/disintegrated particles and produce physical hindrance to drug release/dissolution. The position of the tablet in the dissolution vessel is known to influence drug dissolution/release rate (16). The heterogeneity in shear rate as a function of the position in the dissolution vessel is one of the causes of variability in the dissolution rate. This further can be confounded by agitation rate employed, shape and size

of tablets, mechanism of drug release, and type of tablets (fast vs. slow disintegrating). The above impact which is dynamic over experiment time can be expected to influence the release of drugs from the product in multi-unit dissolution as well and produce variability in the results. Therefore, the effect of single unit vs. multiple units on the dissolution performance (profile and variability) in media that exhibited strength-dependent dissolution was independently investigated. The profiles and variability in dissolution of single and double units of lowest strength and single unit of highest strength of drug product 4 (Table I) were compared. This approach provided equivalent sink conditions across both strengths. The preliminary analysis revealed the absence of an impact of multi-units on dissolution variability. Further investigation on drug product 1 (Table I) to study the impact of more than two units (single and four units of lowest strength and single unit of highest strength) on dissolution profile and variability provided the same above conclusion. However, the impact of multi-units on dissolution can be drug product specific, and hence, it would be valuable to evaluate the effect of the multi-unit approach on hydrodynamics and dissolution variability before its application for biowaiver purposes. It is worth reiterating that multi-unit dissolution is suggested for comparative *in vitro* testing for biowaiver purposes. The multi-unit approach for quality control is usually not necessary and hence not encouraged.

CONCLUSION

In this study, IR tablet drug products with strength-dependent dissolution as a function of dissolution sink conditions, formulation, and quality attribute differences among strengths were identified. The impact of strength-dependent dissolution behavior on selecting dissolution method and acceptance criteria, and biowaiver request strategies, was presented through case examples. Dissolution profile comparison (when applicable) by traditional approach for strength-dependent dissolution behavior of the drug products is likely to fail, which may not necessarily translate into lack of similarity *in vivo*. The challenge posed by this behavior may be addressed by determining whether this is due to sink condition differences across strengths in the dissolution medium. Addressing the sink condition differences by applying the multi-unit chain-bracketing approach is one way to allow for a direct vertical comparison of the dissolution profiles between the lower and higher strengths, that when successful (e.g., $f_2 > 50$) may demonstrate that *in vivo* BE studies are not warranted. The implementation of single- vs. strength-dependent dissolution method and acceptance criteria will largely be determined by existence of *in vivo* BA/BE data generated during the development program linking dissolution profiles to systemic exposure.

The alternative approaches, horizontal dissolution profile comparison, and indirect bioequivalence bridge, for waiving BE studies for IR oral drug products, were presented to avoid misleading conclusions about the need for a bioequivalence study based on *in vitro* dissolution dissimilarity due to strength-dependent dissolution. These approaches are expected to save time and resources by avoiding unnecessary BE studies. However, under circumstances of strength-

dependent dissolution, the outlined approaches should be thoroughly evaluated for its applicability to support biowaivers. Efforts will be continued to study other dosage forms for strength-dependent dissolution and further investigate the effect of the multi-unit approach on dissolution hydrodynamics and variability.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest There are no conflicts of interest to declare.

Disclaimer This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

REFERENCES

1. Wang Q, Fotaki N, Mao Y. Biorelevant dissolution: methodology and application in drug development. *Dissolut Technol.* 2009;16(3):6–12.
2. Anand O, Lawrence XY, Conner DP, Davit BM. Dissolution testing for generic drugs: an FDA perspective. *AAPS J.* 2011;13(3):328–35.
3. Shah VP. Dissolution: a quality control test vs. a bioequivalence test. *Dissolut Technol.* 2001;8(4):6–7.
4. Duan JZ, Riviere K, Marroum P. In vivo bioequivalence and in vitro similarity factor (f_2) for dissolution profile comparisons of extended release formulations: how and when do they match? *Pharm Res.* 2011;28(5):1144–56.
5. U.S. Food and Drug Administration/Center for Drug Evaluation and Research. FDA guidance for industry: immediate release solid oral dosage forms: scale-up and postapproval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation. November 1995. <http://www.fda.gov/downloads/Drugs/Guidances/UCM070636.pdf> (Accessed on 11 June 2015).
6. U.S. Food and Drug Administration/Center for Drug Evaluation and Research. Guidance for industry: SUPAC-MR: modified release solid oral dosage forms: scale-up and postapproval changes: chemistry, manufacturing, and control; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation. September 1997. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf> (Accessed on 03/31/2015).
7. Code of Federal Regulations (CFR), Title 21CFR320.22. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22> (Accessed on 05/18/2015).
8. U.S. Food and Drug Administration/Center for Drug Evaluation and Research. FDA draft guidance for industry: bioavailability and bioequivalence studies submitted in NDAs or INDs—general considerations. March 2014. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf> (Accessed on 03/23/2015).
9. Stevens RE, Gray V, Dorantes A, Gold L, Pham L. Scientific and regulatory standards for assessing product performance using the similarity factor, f_2 . *AAPS J.* 2015;17(2):301–6.
10. Kaur P, Jiang X, Duan J, Stier E. Applications of *in vitro*–*in vivo* correlations in generic drug development: case studies. *AAPS J.* 2015;1–5.
11. Kesisoglou F, Hermans A, Neu C, Yee KL, Palcza J, Miller J. Development of *in vitro*–*in vivo* correlation for amorphous solid dispersion immediate-release suvorexant tablets and application to clinically relevant dissolution specifications and in-process controls. *J Pharm Sci.* 2015.
12. U.S. Food and Drug Administration/Center for Drug Evaluation and Research. Guidance for industry: extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. September 1997. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070239.pdf> (Accessed on 05/06/2015).
13. Dickinson PA, Lee WW, Stott PW, Townsend AI, Smart JP, Ghahramani P, *et al.* Clinical relevance of dissolution testing in quality by design. *AAPS J.* 2008;10(2):380–90.
14. Suarez SS, Marroum PJ, Hughes M. Biopharmaceutic considerations in drug product design and in vitro drug product performance. In: Shargel L, Yu ABC, editors. *Applied biopharmaceutics and pharmacokinetics*. Seventhth ed. New York: McGraw-Hill Education; 2016. p. 415–67.
15. Suarez S. Establishing clinically relevant drug product specifications: FDA perspective. *AAPS Annual Meeting and Exposition*. Chicago, IL, 2012. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341185.pdf> (Accessed on 09/23/2015).
16. Baxter JL, Kukura J, Muzzio FJ. Hydrodynamics-induced variability in the USP apparatus II dissolution test. *Int J Pharm.* 2005;292(1):17–28.