dx.doi.org/10.14227/DT310424P174

Demonstrating Discriminatory Power of a Dissolution Method Using DDDPlus: Case Study of an Extended-Release Formulation and Use in Regulatory Justifications

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ABSTRACT

Introduction: Dissolution testing is an important attribute that provides insight into in vivo performance, batch-to-batch uniformity and consistent clinical quality. Demonstrating discriminatory power of the dissolution method ensures that any changes in manufacturing processes or composition can be reflected through dissolution. Although discriminatory power is demonstrated through multiple experiments, modeling software such as Dose Disintegration and Dissolution Plus (DDDPlus) can be utilized. In the present case, for an extended-release formulation containing a class 3 (Biopharmaceutics Classification System) API, the regulatory agency indicated that the dissolution method lacked discriminatory power with respect to polymer content based on pilot test formulations in humans. Although formulations with varying polymer concentration showed differences in in vivo results, the in vitro dissolution were similar. DDDPlus was used to investigate the root cause for the lack of discriminatory power. **Methods:** A DDDPlus model was developed and validated using formulations with different polymer content. Simulated formulations with up to 70% less polymer content were used to test the model, and a cut-off for polymer content resulting in dissolution dissimilarity was determined. **Results:** When the polymer level was less than 50% of the original, similarity failure was observed, but formulations with higher polymer levels achieved similarity. This was attributed to the presence of highly soluble class 3 API in the formulation (> 50% w/w) coupled with a relatively low polymer level (20% w/w). This justification was accepted by the regulatory agency and further re-development of dissolution method was not necessary. **Conclusion:** This work opens new avenues for demonstrating discriminatory power of a dissolution method using software such as DDDPlus, which can reduce analytical workload, increase productivity, and speed up regulatory filings.

KEYWORDS: Discriminatory power, dissolution, DDDPlus, extended-release

INTRODUCTION

Dissolution is an important step that governs drug absorption, bioavailability, and efficacy. Because of this, dissolution testing of dosage forms plays a significant role in characterizing the in vivo performance of orally administered drug products. During the new chemical entity (NCE) development, dissolution testing in multiple pH conditions with biorelevant fluids (e.g., simulated intestinal fluids) is used to understand precipitation behavior and impact of food and/or proton pump inhibitors (PPI) (*1–3*). Subsequently, dissolution testing is used to bridge formulations between various clinical phases, scale-up, and commercial manufacturing (*4*). In the generic product development process, dissolution testing is widely used to establish bioequivalence between innovator and generic formulations and subsequently to support biowaivers and site transfers as well as scale-up and post-approval changes (SUPAC) (*5–7*). When dissolution is coupled with physiologically based pharmacokinetic and biopharmaceutic models (PBPK/PBBM), the results can predict in vivo performance (*7–9*). In addition, quality control (QC) dissolution methods are used during routine manufacturing to ensure product quality and batch-to-batch consistency (*7*).

Discriminatory power is a prerequisite for any dissolution method that is used for QC purposes, which is defined as the ability of the dissolution method to discriminate

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between batches manufactured with different critical process parameters (CPP), critical material attributes (CMA), or critical formulation variables (CFV) that may have impact on bioavailability, i.e., critical bioavailability attributes (CBA) (*10*). During the dissolution method development, discriminatory power is demonstrated through intentional formulation changes and corresponding dissolution evaluation. For example, the impact of active pharmaceutical ingredient (API) particle size, compression force, and polymer concentration on dissolution behavior can be evaluated. An ideal dissolution method should be able to discriminate changes in these parameters. Based on the outcome of discriminatory testing, appropriate ranges can be defined for the variables to assure desired in vivo performance. Recently, agencies such as the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) mandated demonstration of discriminatory power of the dissolution method by through its ability to reject nonbioequivalent batches (*11*). Absence of discriminatory power can result in an inability to detect changes in formulation variables, thus limiting utility of the dissolution method for QC purposes as well as predicting in vivo performance. Although discriminatory power of the dissolution method is routinely established through experimentation, modeling software such as Dose Disintegration and Dissolution Plus (DDDPlus) can be used to simulate experimental outcomes (*12*, *13*). Thus, in the present article, DDDPlus was used to demonstrate the discriminatory power of the dissolution method.

The test product in this study is an extended-release tablet containing an API belonging to class 3 of the Biopharmaceutics Classification System (BCS). The API has a drug load of more than 50% (w/w), with methocel K100M used as rate-controlling excipient (approximately 20% w/w). The regulatory agency indicated that the dissolution method lacks discriminating ability with respect to polymer content, considering the behavior of pilot test formulations in humans. The pilot test formulations resulted in bio-inequivalence (especially the upper 90% T/R ratio); however, no differences in dissolution results were observed. The agency recommended to re-develop the dissolution method and demonstrate discriminatory ability with intentional and meaningful variations of polymer content (±10–20% changes in the specified values). Multiple attempts were made to demonstrate the discriminatory power of the dissolution method, but none were successful. To investigate the root cause for the lack of discriminatory power, DDDPlus was used.

This study aims to demonstrate the utility of DDDPlus in establishing discriminatory power of a dissolution method for an extended-release formulation and for regulatory justification. Using a validated DDDPlus model, a threshold for polymer concentration that can result in a lack of dissolution similarity with pivotal test formulations may be identified, thereby demonstrating discriminatory power of the dissolution method. This approach to demonstrating discriminatory power using DDDPlus is considered novel and may be utilized in regulatory justifications.

METHODS

Materials

The solubility and other characteristics of API are presented in Table 1. The API was obtained from the local market for the determination of solubility. The API was formulated as extended-release formulation using methocel K100M (approximately 18% w/w) at drug load of more than 50% (w/w). All other excipients were conventional excipients such as PVP K-30, colloidal silicone dioxide, magnesium stearate, microcrystalline cellulose, dicalcium phosphate, and croscarmellose sodium.

Table 1. DDDPlus Model Input Parameters

Property	Model Input	Reference
Dosage form	CR polymeric matrix tablet	Controlled-release dosage form
Dimensions of dosage form	Tablet volume: 2.071 cm^3 Tablet surface area: 7.679 cm^2	Based on tooling information, oblong nature of dosage form
Solubility	pH 1.2: 329.6 mg/mL pH 3: 327.8 mg/mL pH 4.5: 326.8 mg/mL pH 6.8 (reference solubility): 329.4 mg/mL	In-house
Other properties	API density: 1.2 g/mL Diffusion coefficient: 1.201 $cm^2/s \times 10^5$ Log P: –0.82	Default values or ADMET Predicted values
Dissolution conditions	900 mL of 50 mM pH 6.8 phosphate buffer USP apparatus 2 at 75 rpm	Quality control media conditions
Dissolution model	Constant porosity model	Suitable dissolution model
Calibration constant	API: 0.0996 Polymer: 1.5	Optimized using reference formulation
Simulation length	600 min	Quality control media dissolution duration

CR: controlled release; API: active pharmaceutical ingredient; USP: United States Pharmacopeia.

The amount of methocel K100M that were used in various formulations for DDDPlus model development, validation, and application are presented below.

- *Model development:* Pivotal and pilot reference formulations – 317.5 mg (18% w/w)
- *Model validation:* Pivotal test formulation: 275 mg (20% w/w), pilot test 1: 280 mg (20.51% w/w), pilot test 2: 317 mg (22.56% w/w), batches manufactured intentionally with –20% polymer (220 mg, 16% w/w) and +20% polymer (330 mg, 24.2% w/w) relative to the pivotal test formulation
- *Model application:* Hypothetical batches manufactured with polymer content of –10% (247.5 mg), –20% (220 mg), –50% (137.5 mg), –60% (110 mg), and –70% (82.5 mg) relative to the pivotal test formulation

Dissolution Studies

Dissolution testing of all the batches was performed for QC purposes with 900 mL of 50-mM pH 6.8 phosphate buffer at 37 °C as the medium, using United States Pharmacopeia apparatus 2 at 75 rpm. Samples (5 mL) were collected at 0, 60, 150, 180, 240, 360, 480, and 600 mins, replaced with fresh medium, and analyzed by high-performance liquid chromatography (HPLC).

The DDSolver, an add-in for Microsoft Excel was used to calculate similarity factor (f_2) values for comparison of dissolution profiles. Twelve replicates were used for similarity factor calculations.

DDDPlus Modeling

DDDPlus (version 6, Simulations Plus, Lancaster, CA), was utilized to simulated in vitro dissolution for all formulations.

Model Development

A detailed modeling workflow for DDDPlus is described in Figure 1. The base model was developed using the input parameters listed in Table 1. The pH vs solubility profile (at pH 1.2, 4.5, 6.8) were input using an spd file. The default value of API density was used, and log P and the diffusion coefficient were calculated using ADMET Predictor (Simulations Plus). Considering the matrix formulation, CR polymeric matrix was selected as the dosage form. Oblong was chosen as dosage form shape, and the dimensions of tablet were entered to obtain tablet volume as 2.071 cm^3 and tablet surface area as 7.679 cm^2. Similar dimensions were utilized for all other trials during model development and validation. The same dissolution conditions were used to mimic QC testing (900 mL of 50-mM pH 6.8 phosphate buffer at 37 °C in USP apparatus 2 at 75 rpm for 600 mins). Constant porosity was selected as dissolution model. The base DDDPlus model was developed with reference formulation by entering the composition into the Formulation tab. During initial model development, calibration constants of the API and polymer were used to achieve the optimal fit between observed and predicted dissolution data.

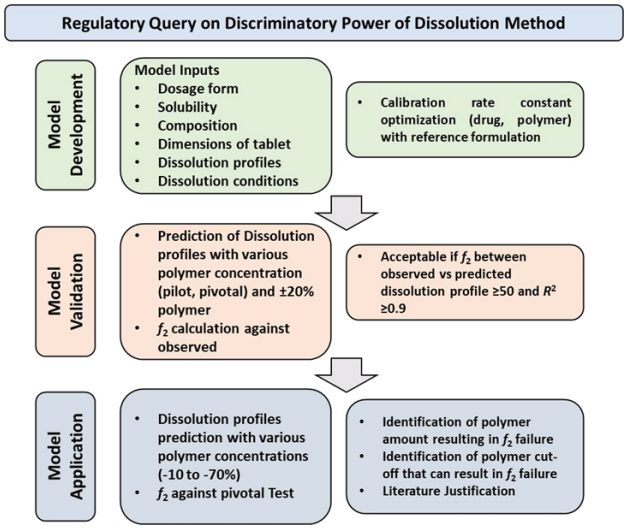

Figure 1. DDDPlus model workflow for demonstrating discriminatory power of a dissolution method.

Model Validation

A model validation exercise was performed with formulations containing different amounts of release-controlling polymer content. The pivotal test formulation (275 mg polymer), both pilot test formulations (280 and 317 mg), and two batches intentionally manufactured with ±20% polymer content (220 and 330 mg) were used. In the Formulation tab, the polymer amount was changed to account for formulation composition change. The simulations were ran, and the validation was performed using two metrics to compare the observed and predicted dissolution values: similarity factor (f_2) and regression coefficient (R^2) (*14*, *15*). Successful prediction is indicated by f_2 greater than 50 and R^2 greater than 0.9.

Model Application

To demonstrate discriminatory power, dissolution profiles were simulated in the validated model using simulated formulation compositions with polymer content of –10% (247.5 mg), –20% (220 mg), –50% (137.5 mg), –60% (110 mg), and –70% (82.5 mg) relative to the pivotal test formulation (275 mg). Similarity factors were used compare the observed and simulated dissolution profiles against the pivotal test formulation. A boundary of polymer content that resulted in f_2 failure with respect to the pivotal test formulation was identified.

RESULTS

Solubility and Dissolution

Across the pH conditions, the solubility values were found to be higher than 300 mg/mL (Table 1). Approximately 3.4 mL of aqueous fluids are required to dissolve a complete dose of 1000 mg, thereby confirming the highly soluble nature of the API. However, the API is formulated as an extended-release formulation controlled by methocel K100M. The release profiles of pilot and pivotal test and reference formulations are provided in Figure 2. The dissolution data indicate that release is controlled over a period of 10 h, after which almost complete release is achieved at the end of the dissolution.

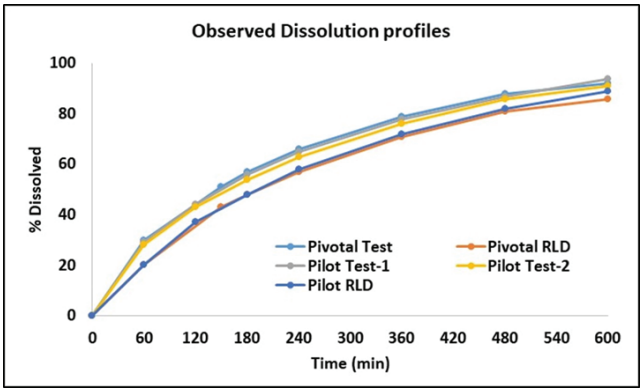

Figure 2. Observed dissolution profiles of various formulations. RLD: reference listed drug.

DDDPlus Modeling

Model Development

Critical aspects such as dosage form and tablet dimensions were considered appropriately in the developed DDDPlus model. The model was developed with pivotal and pilot reference formulations. Initial simulations indicated that the dissolution profiles of reference product were not predicted well and thus it was necessary to optimize the calibration constants of API and polymer. With the optimized calibration constants, the model predicted pivotal reference formulations well, as indicated in Table 2 and Figure 3. For both pilot and pivotal reference formulations, f_2 and R^2 values for the observed versus predicted profiles were considered similar, indicating the suitability of the model.

Model Validation

Results of the model validation exercise with various polymer levels are provided in Table 2 and Figure 3. Across all the predictions, f_2 and R^2 values indicated that the model was valid. Based on the regulatory agency query, additional batches with ±20% polymer content were manufactured, and dissolution profiles were generated. Predictions were performed for these batches as well (available as Supplemental Table S1), and the f_2 and R^2 values were more than 50 and 0.9, respectively, further indicating the validity of the model. Overall, the validation exercise was successful as the model was able to accurately predict dissolution profiles across formulations with varying levels of the polymer content.

Model Application

Results of DDDPlus simulations with varying polymer levels from –10% to –70% w/w are presented in Table 3 and in Figure 4. With decreasing polymer concentration, an increase in the dissolution rate was observed, as expected. When compared to the pivotal test formulation, f_2 values

Table 2. Model Validation for Pilot and Pivotal Test Formulations and Reference Products

Test Formulations												Reference Products							
Pivotal Test Formulation (275 mg polymer)				Pilot Test 1 Formulation (280 mg polymer)				Pilot Test 2 Formulation (317 mg polymer)				Pilot Reference Formulation (317.57 mg polymer)				Pivotal Reference Formulation (317.57 mg polymer)			
Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff	Time (min)	Obs (%)	Pred (%)	Diff
0	0	0	NA	0	0	0	NA	0	0	0	NA	0	0	0	NA	0	0	0	NA
60	30	32	2	60	29	32	3	60	28	31	3	60	20	30	10	60	20	30	10
150	51	51	0	120	44	46	2	120	43	44	1	120	37	42	5	150	43	47	4
180	57	56	-1	180	56	56	0	180	54	53	-1	180	48	52	4	180	48	52	4
240	66	65	-1	240	65	65	0	240	63	62	-1	240	58	60	2	240	57	60	3
360	79	79	0	360	78	79	1	360	76	76	0	360	72	73	1	360	71	73	2
480	88	92	4	480	87	92	5	480	86	87	1	480	82	84	2	480	81	84	3
600	92	100	8	600	94	100	6	600	91	98	7	600	89	94	5	600	86	94	8
f_2 = 83				f_2 = 78				f_2 = 87				f_2 = 65				f_2 = 64			
R^2 = 0.97				R^2 = 0.98				R^2 = 0.98				R^2 = 0.95				R^2 = 0.93			

Obs: observed release data; pred: predicted release data; f_2: similarity factor; R^2: regression coefficient.

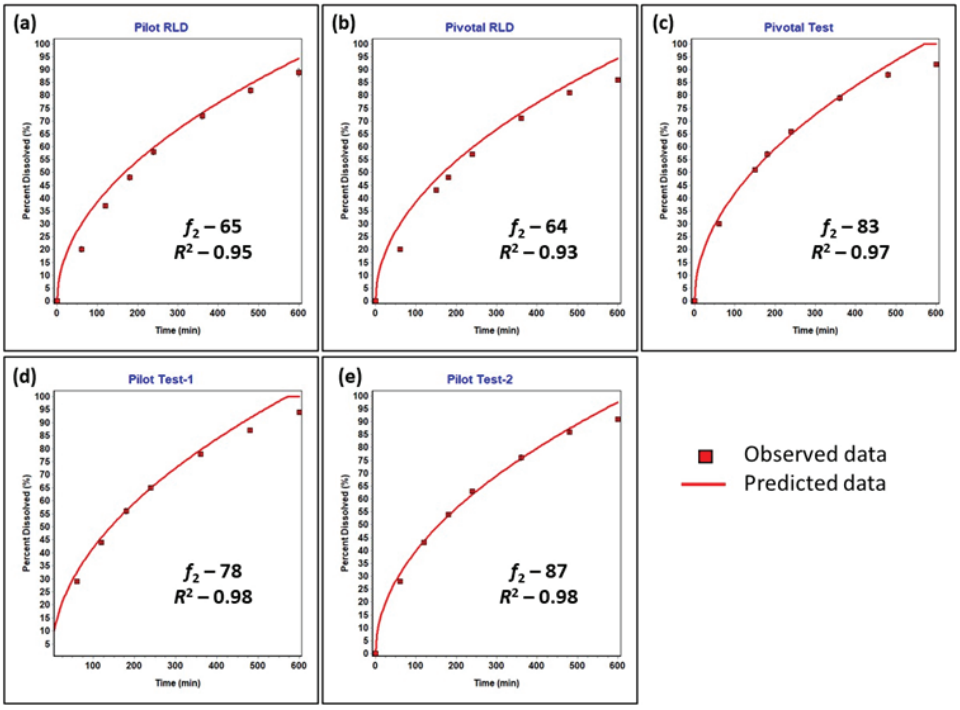

Figure 3. DDDPlus predictions for reference and test formulations. RLD: reference listed drug.

Table 3. Predicted Dissolution Data with Various Polymer Concentrations and f_2 Calculations

Time (min)	Pivotal Test Formulation (275 mg Polymer)			Time (min)	Simulated Formulations (%)				
	Obs (%)	Pred (%)	Diff		–10% polymer (247.7 mg)	–20% polymer (220 mg)	–50% polymer (137.5 mg)	–60% polymer (110 mg)	–70% polymer (82.5 mg)
0	0	0	NA	0	0	0	0	0	0
60	30	32	2	60	33	35	38	39	40
150	51	51	0	150	53	55	60	62	63
180	57	56	-1	180	58	60	65	67	69
240	66	65	-1	240	67	69	76	78	80
360	79	79	0	360	82	85	93	95	98
480	88	92	4	480	95	98	100	100	100
600	92	100	8	600	100	100	100	100	100
f_2 (obs vs pred) = 83				f_2	72 (vs obs) 80 (vs pred)	63 (vs obs) 67 (vs pred)	49 (vs obs) 51 (vs pred)	46 (vs obs) 47 (vs pred)	43 (vs obs) 44 (vs pred)

Obs: observed release data; pred: predicted release data; diff: difference

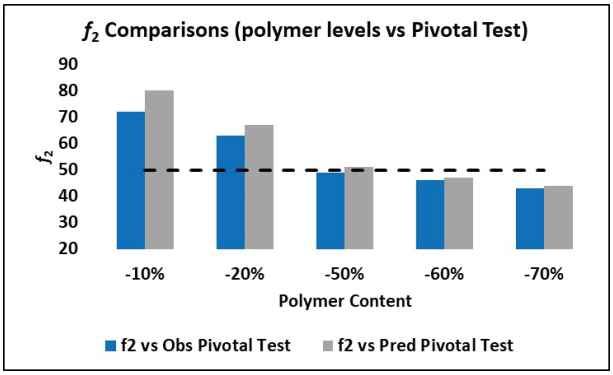

Figure 4. Dissolution similarity analysis between pivotal test and formulations with different polymer content. Obs: observed data; pred: predicted data.

indicated similar dissolution profiles for formulations with up to 20% less polymer content; however, the dissolution profiles were not similar for formulations with 50%, 60%, and 70% less polymer content.

These results indicate that when the polymer level is reduced beyond half of original formulation (i.e., beyond –50%), the dissolution method can discriminate between formulations, but polymer reductions up to 50% could not be discriminated on the basis of dissolution.

DISCUSSION

Demonstrating the discriminatory ability of a dissolution method can ensure manufacturing as well as clinical

quality (*16*, *17*). Identification of critical attributes as a part of discriminatory dissolution testing and integration through PBPK/PBBM modeling is an upcoming area (*10*). Such approaches can aid in development of patient-centric quality standards, thereby ensuring that patients receive drug products with acceptable quality.

In this study, a BCS class 3 API was formulated as an extended-release formulation with methocel K100M as rate-controlling polymer. Like any other controlled-release product, polymer content has been identified as critical attribute that can impact product performance. Although dissolution profiles were similar for the two pilot formulations in humans (Figure 2), some differences were observed in the bioequivalence study results between both formulations, wherein test 2 formulation exhibited slightly higher ratios than the test 1 formulation (Supplemental Table S2). Considering this, regulatory agency indicated that the dissolution method lacks discriminatory power and suggested to re-develop the dissolution method. As none of the formulation trails taken were successful to demonstrate discriminatory ability, a novel approach using DDDPlus was described in this article.

A DDDPlus model was developed using pivotal reference formulation through optimization of calibration rate constants for the API and polymer. The calibration constant is a fitted parameter that enables dissolution model to simulate the dissolution rate and extent for a particular ingredient. Further, constant porosity model was chosen as this options allows to turn on porosity vs time calculations to be off in the polymeric matrix model and assumes constant porosity throughout the dissolution process. The model validation consisted of testing the predictability of the model with various levels of polymers. The model validation results from Table 2 (and Supplemental Table S1) indicated that the observed and simulated profiles are similar, thus confirming the validity of the model. Typically, for PBPK or PBBM models, prediction error is utilized; however, in DDDPlus simulations, the metrics f_2 and R^2 were found to be appropriate and acceptable (*18*).

Using the validated model to demonstrate discriminatory ability, a range of virtual formulations with up to 70% reduced polymer content relative to the pivotal test formulation were simulated. Manufacturing a formulation with 50–70% less polymer content was not possible as tablet could not be formed, thus studying the observed dissolution is not feasible. Because of this limitation, it was not possible to validate the model against a failing result (i.e., failed f_2 vs pivotal test batch). In such cases, designing hypothetical formulations and studying their behavior through DDDPlus is an appropriate choice for demonstrating discriminatory power. When dissolution profiles of these formulations are compared against the pivotal test formulation (observed and simulated), those with less than half of the original polymer content resulted dissimilarity based on f_2 calculation. Thus, the dissolution method is considered to be discriminatory, but only at when the polymer concentration is reduced by half of the original amount and beyond (i.e. beyond -50%).

The reasons for lack of discriminatory power in the dissolution method, in this case at polymer ranges up to –50% of original amount, can be multi-fold. The API is BCS class 3 in nature, with a drug load of more than 50% (w/w) and polymer content of only 20% (w/w). Although drug release is controlled by polymer, a high drug load in a highly soluble API could explain the apparent lack of discriminatory power of the dissolution method. Literature from polymer manufacturer Colorcon also indicated that for a highly soluble drug like Metformin HCl manufactured with methocel K100M or K200M at a drug load of 50% (w/w), dissolution discriminatory power was not observed at polymer levels of 20–30% (w/w). High viscosity grade K200M did not result in a difference in dissolution; hence, the absence of an impact for lower viscosity grade polymer K100M is evident (*19*). These findings are in line with observations made in the present study. Our observations are also in line with other DDDPlus studies that were conducted to simulate in vitro dissolution for establishing IVIVC, develop biorelevant media, and gain mechanistic insight into drug absorption behavior through reduction of lab experiments (*12*, *13*, *20*).

As an additional point of consideration, the regulatory agency's concerns were based on pilot study results of only 15 subjects (Supplemental Table S2), and the upper confidence interval for the test 2 formulation was beyond 125% (leading to bioinequivalence), which needs to be interpreted with caution because wide confidence intervals may not represent actual in vivo variability. It can be seen from the pivotal test formulation study with 30 subjects that the 90% confidence intervals were further narrowed. Thus, there is no significant discrepancy between in vivo results and in vitro dissolution, and the dissolution method is adequate. This justification was accepted by the regulatory agency and redevelopment of dissolution method was not necessary.

Overall, this research is considered to be novel, as it highlights (1) the importance of the dissolution method's discriminatory power during pharmaceutical

development and (2) the application of DDDPlus for regulatory justifications to minimize analytical experimentation and enhance productivity. As an extension, integration of these dissolution data into PBPK or PBBM models can provide insight into in vivo behavior (*21*).

CONCLUSION

In the present work, a novel way of demonstrating the discriminatory power of a dissolution method for an extended-release formulation was developed, validated, and applied utilizing DDDPlus. This work highlights importance of utilizing in silico simulations to reduce the number of experiments, enhance productivity, and speed up regulatory submissions. This approach is particularly useful in cases where formulations cannot be manufactured due to practical considerations, yet dissolution method discrimination needs to be established. When such modeling tools are coupled with strong rationale and relevant literature references, they yield significant insight into dissolution behavior of the drug product. Extension of these dissolution data into PBPK or PBBM models can provide insight into in vivo behavior and correlate in vitro dissolution similarity with in vivo bioequivalence.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

DISCLOSURES

This study was sponsored by Dr. Reddy's Laboratories Ltd. The authors have no other conflicts of interest.

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