



# Discriminative Dissolution Method Development Through an aQbD Approach

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## Abstract

Using a one-factor-at-a-time approach for dissolution method and discrimination analysis can be time-consuming and may not yield the optimal and discriminative method. To address this, we have developed a two-stage workflow for the dissolution method development followed by demonstration of discrimination power through an analytical Quality by Design (aQbD) approach. In the first stage, an optimal dissolution method was achieved by determining the method operable design region (MODR) through a design of experiment study of the high-risk method-related parameters. In the second stage, we established a Formulation-Discrimination Correlation Diagram strategy to examine the method discrimination capability, through which one can determine the method discriminative design region (MDDR) and visualize the impact of each formulation parameter and their interactions on dissolution. The application of aQbD principles into a workflow provides a scientific-driven guidance for robust method development and demonstrating discrimination power for dissolution methods.

**Keywords** analytical quality by design · discriminative dissolution method · method discriminative design region · method operable design region

## Introduction

Quality control and monitoring play a crucial role in ensuring the consistent safety and effectiveness of drug products during and after manufacturing [1, 2]. These controls are typically achieved through release testing followed by stability evaluation once the batch is manufactured. For orally administered drug products in solid-dosage form, it is necessary to conduct a test to confirm proper release of the drug in accordance with the proposed release mechanism [3, 4]. Dissolution testing, an *in vitro* test used to characterize the release of drug product, is a critical quality control assessment due to its potential correlation with clinical performance [5–8]. Dissolution testing offers a way of projecting how and when the drug will release *in vivo*, based on an

understanding of the drug's physicochemical properties and its dissolution performance under various dissolution conditions [9–12]. Even if an *in vitro/in vivo* correlation cannot be established, having an *in vitro* dissolution method capable of discriminating against formulation variability is still crucial, as it helps identify potential discrepancies in clinical performance caused by unexpected formulation or process variations [11, 13].

The general procedure to develop a dissolution method includes (1) understanding the properties of drug substance and drug product, (2) evaluating sink conditions, (3) optimizing the dissolution conditions, and (4) evaluating the dissolution profiles and finalizing the method conditions [14–21]. One-factor-at-a-time (OFAT) approach is commonly used for process and method optimization [22, 23]. Although this approach is straightforward and easy to implement, it may take longer to identify the optimal conditions that yield an appropriate dissolution profile with sufficient discrimination power. In some cases, the OFAT approach may not lead to the best method conditions. An alternative approach for method development is through Quality by Design (QbD), a systematic approach that incorporates prior knowledge, design of experiments, quality risk management, and knowledge management to achieve more desirable

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operational outcomes [24–26] and has been widely introduced by the US Food and Drug Administration with the goal of embedding quality into pharmaceutical products to ultimately protect patient safety [27–29]. QbD approach has been extended to the development of analytical methods to have the quality built into a method [30], known as analytical Quality by Design (aQbD), including high-performance liquid chromatography (HPLC) methods [31–35], Karl Fischer Titration for water content [36], and dissolution method for release characterization [37]. Employing aQbD for analytical method development, including defining the analytical target profiles, method scouting, determination of potential critical method attributes, method development through design of experiments, and method validation, allows one to have a more thorough understanding of the method parameters and their impacts on method performance, and thereafter identify the optimal conditions for a robust method [30, 38–40]. However, few studies have implemented an aQbD approach for dissolution method development [24, 37, 41], and aQbD strategy for demonstration of method discrimination power has not been established.

Discrimination of a dissolution method is a critical part of dissolution development as it is the ability to distinguish changes in the pharmaceutical product that potentially impact *in vivo* performance [13, 42, 43]. To demonstrate that a method is discriminative, a commonly employed procedure includes conducting a risk assessment to identify parameters that may impact dissolution profiles significantly, evaluating different conditions for each parameter, developing formulations, conducting dissolution testing, and performing dissimilarity analysis [14, 15, 44, 45]. However, this approach carries the risk of failing to show the discrimination under the arbitrarily chosen conditions. It is desirable to have a comprehensive understanding how formulation or process parameters impact the dissolution profile to determine if the method is truly discriminative.

In light of the gaps identified here for demonstrating discrimination during aQbD development, this work aims to provide a methodology for including discrimination considerations into an aQbD workflow. Accordingly, a two-stage workflow through aQbD approach for the development of a robust and discriminative dissolution method is presented. The first stage of the workflow is intended to provide a phase-appropriate method for early phase clinical programs, and the second stage of the workflow will serve to demonstrate the method discrimination as required for late phase and commercial regulatory filings. A method operable design region (MODR) is established to define the conditions that ensure method robustness and attainment of release targets. To demonstrate the discrimination power of the method, a Formulation-Discrimination Correlation Diagram strategy is established for the first time. The method discriminative design region (MDDR) within

the Formulation-Discrimination Correlation Diagram specifies the range of formulation parameters where the method exhibits discrimination power, indicating its ability to detect meaningful changes in the manufacturing process or formulation.

## Material and Methods

### Materials

The drug substances (Biogen, Cambridge, MA), silicified microcrystalline cellulose (SMCC 90, JRS Pharma, Patterson, NY), croscarmellose sodium (CCM-Na, Merck KGaA, Billerica, MA), colloidal silicon dioxide (Aerosil 200, Evonik, Sanford, ME), magnesium stearate (MgSt, Spectrum, New Brunswick, NJ), sodium phosphate (Thermo Fisher Scientific, Fair Lawn, NJ), and sodium hydroxide (LabChem, Zelienople, PA), were used as received. Acetonitrile, methanol, isopropanol, ammonium hydroxide solution, and ammonium acetate were purchased from Fisher Chemical (Fair Lawn, NJ). All solvents were of HPLC grade.

### Sink Conditions

To evaluate sink conditions, a specific quantity of the active pharmaceutical ingredient (API) was transferred to a medium, ensuring that the concentration was maintained at three times the concentration at which the drug product completely dissolves in the dissolution vessel. The medium was subsequently agitated at high speed using a magnetic stirrer under ambient condition for a minimum duration of 24 h, and the clarity of the medium was visually examined and recorded.

### Particle Size Distribution

Particle size distribution analysis was conducted using a Mastersizer 3000 particle size analyzer employing laser light diffraction. Approximately 100 mg of the powder was weighed and added to a 10-mL aqueous solution of 1% Triton X-100. The resulting mixture was vortexed for 30 s to ensure proper dispersion. Subsequently, the suspension was transferred to the dispersion unit, which was set to agitate at a speed of 2000 rpm. Sonication was then performed for 60 s at 60% energy to further enhance dispersion. The measurements were carried out in triplicate.

### Formulation and Tablet Compression

SMCC 90 was chosen as the dry binder due to its exceptional flowability and compatibility. Croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate were used as

the disintegrant, flow aid, and lubricant, respectively. The API powder, along with all other excipients, was sieved and then combined in a 100-ml plastic bottle. The bottle was manually rotated for a duration of 5 min to facilitate particles sliding and thorough mixing of the components.

Tablets were manufactured using a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France). The TSM-B simulation profile of a rotary tablet press, specifically the Korsch XM 12, was employed with a tableting speed of 30 rpm. The Styl'One Evolution was equipped with a round concave 7.94-mm TSM-B tooling (Natoli, Saint Charles, Missouri). The blend was manually filled into the die wall, ensuring that the tablet weight was controlled at approximately 187 mg.

## Design of Experiment

The dissolution method was optimized using a fractional design of experiments (DoE) approach. Three method-related parameters, including paddle speed, pH of dissolution medium, and concentration of surfactant, were identified as high-risk factors affecting the drug release profile. To optimize the method, three pH levels (1.2, 4.5, and 6.8), two paddle speeds (50 and 75 rpm), and three concentrations of sodium dodecyl sulfate (SDS) (0.3%, 0.6% and 1.0%) were selected for investigation. Combinations of these parameters were generated using the Fusion QbD software. In total, twelve combinations were studied to determine their impact on the dissolution profile and identify the optimal method conditions.

To assess the discrimination power of the dissolution method, three medium/high-risk formulation/process-related parameters affecting the dissolution performance were identified: particle size distribution, disintegrant level in formulation composition, and tablet compression force. To evaluate the impact of these parameters, fifteen formulations were prepared. Subsequently, the dissolution profiles of these formulations were statistically analyzed using the same module. This analysis allows for the assessment of how variations in particle size distribution, disintegrant level, and compression force influenced the dissolution behavior of the formulations.

## Dissolution Testing

Dissolution testing was conducted using an apparatus II dissolution instrument (Distek Evolution 4300) with a rotation speed controlled within a range of 50 to 75 rpm. For the optimization of the dissolution method, three dissolution media with different pH levels were prepared. The volume of each dissolution medium was maintained at 900 mL, and the temperature was set at  $37.0 \pm 0.5^\circ\text{C}$ . Aliquots were withdrawn from the dissolution vessels at 10 min, 20 min, 30 min, 45

min, and 60 min. Additionally, an infinity time point of 75 min (at 250 rpm) was included. An automated dissolution sampler was employed to withdraw the samples, which passed through a 10- $\mu\text{m}$  HDPE filter fitted into a cannula. The collected samples were subsequently subjected to analysis by HPLC using a Waters Sunfire C18 column ( $50 \times 4.6$  mm, 3.5  $\mu\text{m}$ ) and a UV detector set to a wavelength of 230 nm. The column temperature was maintained at  $35^\circ\text{C}$ . Two mobile phases were prepared as follows: 0.1% trifluoroacetic acid (TFA) in water and 0.1% TFA in acetonitrile. The flow rate was set to 1.5 mL/min. The concentration of API was determined by comparing the peak areas of the dissolution samples to those of a standard solution.

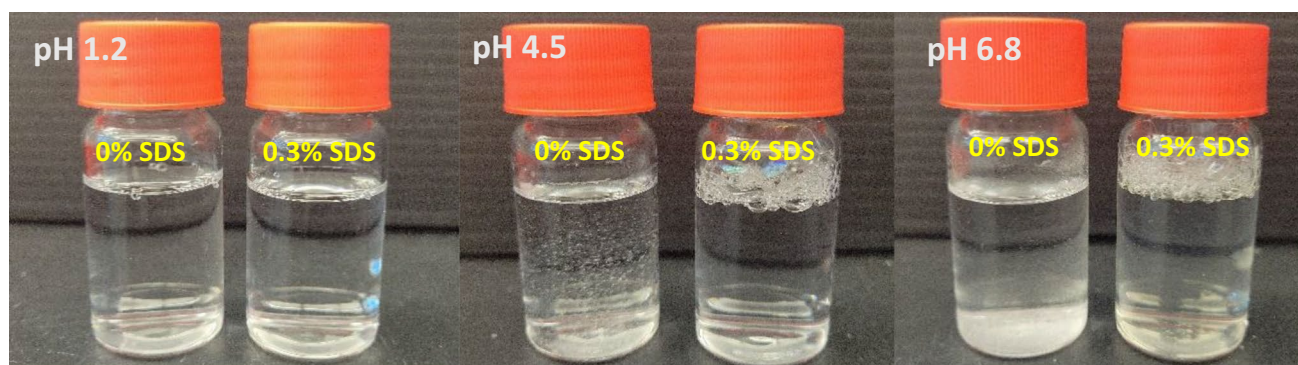
## Results and Discussions

### Sink Condition Evaluation

The drug substance has low solubility and high permeability, characteristics consistent with a Biopharmaceutics Classification System (BCS) Class 2 compound [46, 47]. Various media with different pH levels and surfactant concentrations were evaluated for sink condition determination. Sodium dodecyl sulfate (SDS), a commonly used surfactant in dissolution methods [48, 49], was selected to enhance the solubility of API by improving wetting of the API particle surfaces in the medium. The concentration of the API was maintained at three times that the concentration of complete dissolution of the drug product in the vessel medium, assuming a volume of 900 mL. This ensured that sink conditions would be maintained throughout the dissolution determination, making the release profile of the drug product solely influenced by its quality attributes [50]. After agitation at  $37^\circ\text{C}$  for 24 h, the clarity of the medium was assessed through visual observation and recorded (Fig. 1). The clarity results are presented in Table I. Sink conditions were achieved under pH 1.2 without SDS and pH 4.5 and 6.8 with 0.3% SDS added to the medium. Previous reports have suggested that SDS may reduce the solubility of the API, particularly under low pH conditions due to the formation of less soluble salts between ionized SDS and API [51]. However, in this work no salt formation was observed. Furthermore, a preliminary study indicated that the solubility of the API decreases as the pH increases (Table S1). Considering that sink conditions were achieved under pH 6.8 with 0.3% SDS, it is expected that sink condition will be maintained within the pH range of 1.2 to 6.8 when SDS concentration is above 0.3%.

### Design of Experiment for Dissolution Method Development

Based on the clarity screening, a sink condition can be established within the pH range of 1.2 to 6.8 when the SDS



**Fig. 1** Sink condition evaluation under various media

**Table I** Clarity Observation Under Various Sink Conditions

Conditions		Clarity observation (fully, not fully dissolved)
pH	%SDS	
1.2	0	Fully dissolved
	0.3%	Fully dissolved
4.5	0	Not fully dissolved
	0.3%	Fully dissolved
6.8	0	Not fully dissolved
	0.3%	Fully dissolved

concentration exceeds 0.3%. The reference drug product used in the dissolution method development was prepared with an API particle size ( $D_{50}$ ) of approximately 25  $\mu\text{m}$ , compression force of 8 kN, and a disintegrant content of 5%. Initial dissolution testing conducted with apparatus I under pH 1.2 conditions, without SDS, revealed that the drug product achieves 100% release within 10 min. However, it is important to note that a rapid-release method may not offer sufficient discrimination power. Considering the recommendations of regulatory agencies, a slower dissolution process by way of applying a dissolution window at early time points is preferred [50]. Consequently, further method evaluation will focus on pH 4.5 and 6.8 conditions.

The process development module within Fusion QbD, a statistical tool designed for process and method optimization utilizing the DoE, was implemented to optimize the dissolution conditions. Table II outlines the method parameters considered for the DoE study, with the medium volume consistently set at 900 mL. The study encompassed two pH conditions, two paddle speeds, and three surfactant concentrations. In total of 12 method combinations are assessed and presented in Table III.

Figure 2 illustrates the release profiles of the reference drug product obtained under various method conditions outlined in Table III. It is evident that the drug product exhibited rapid release at 10 min across all method conditions. This initial rapid release can be attributed to the high level of disintegrant

**Table II** Parameters and Corresponding Conditions for the Dissolution Method DoE Study

Parameters	Conditions
pH	4.5, 6.8
Vessel volume (mL)	900
Paddle speed (rpm)	50, 75
Surfactant	0.3%, 0.6%, 1%

**Table III** Combinations of Method Conditions in Dissolution Method DoE Study

No	pH	Paddle speed (rpm)	SDS%
1	6.8	50	1
2	4.5	75	1
3	6.8	50	0.6
4	6.8	50	0.3
5	4.5	50	0.6
6	4.5	50	1
7	4.5	75	0.3
8	6.8	75	1
9	6.8	75	0.3
10	4.5	50	0.3
11	4.5	75	0.6
12	6.8	75	0.6

present in formulation composition (5%) as well as the small particle size of API, with a  $D_{50}$  value of approximately 25  $\mu\text{m}$ . After 30 min, a noticeable divergence in the release profiles became apparent. For methods employing a paddle speed 50 rpm, the release demonstrated a plateau at approximately 70%. This phenomenon aligns with the concept of coning, where excipients covering the API hinder the release of the drug product under low paddle speeds. In contrast, methods employing a paddle speed of 75 rpm demonstrated a plateau close to 100%. To ensure complete release of the drug product, a higher paddle speed was required in such cases.



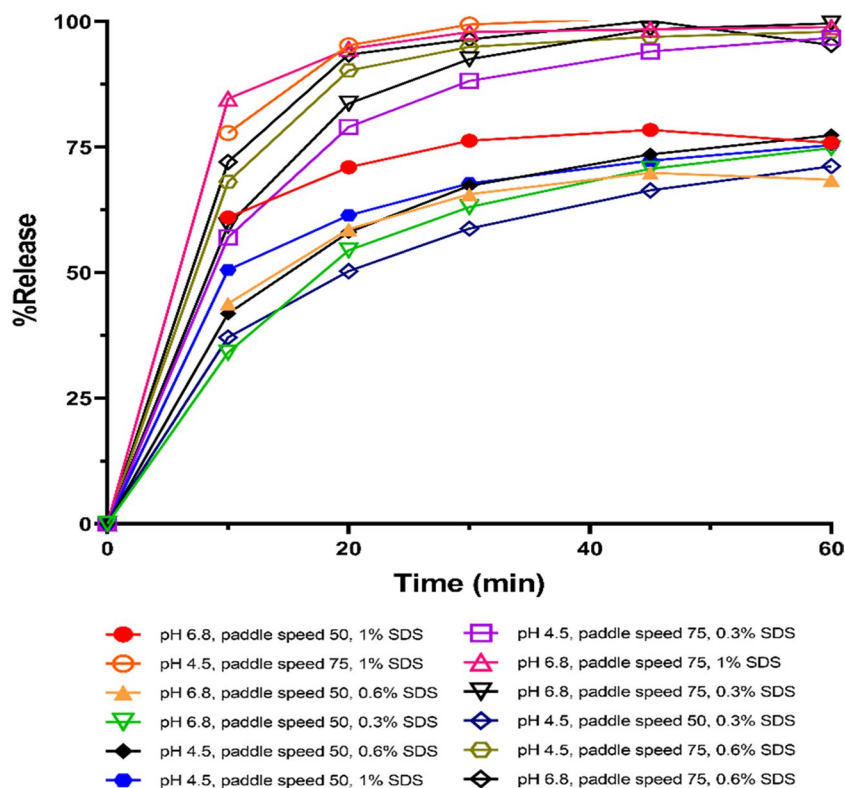


Fig. 2 Release profiles of the reference drug product in dissolution method DoE study ( $n=2$ , data shows the average)

Table IV Release Targets of the Reference Drug Product at 10 and 45 min

Time point	Release target (%)
10 min	0–60
45 min	85–110

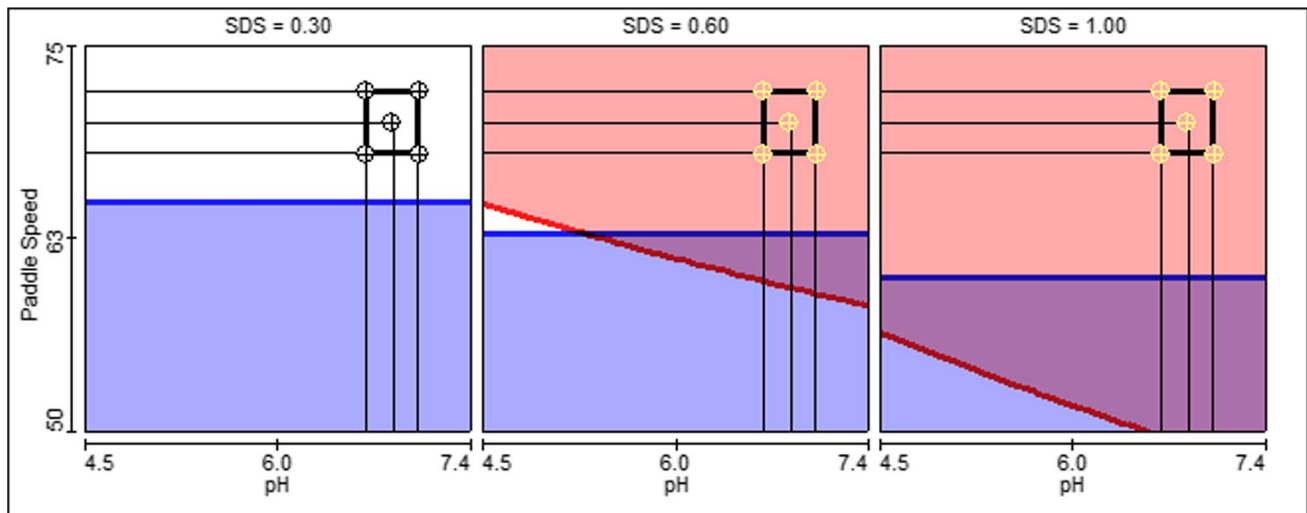
### Optimization of Dissolution Conditions

Considering the previous discussion on the preferred dissolution profile, which involves a dissolution window at early time points and complete release at late time points, it is crucial to establish specific release targets for the reference drug product. The release targets at 10 and 45 min were proposed as 0–60% and 85–110%, respectively (Table IV). These targets create a subregion within the range of conditions depicted in Fig. 2. By defining this subregion, certain portions of the profile set are included while others are excluded, ensuring the optimization of conditions in accordance with the desired dissolution profile.

The drug release profiles obtained from the dissolution method DoE study, along with the defined release targets, enable the process development module to model, process, and optimize the method conditions. In Fig. 3, the unshaded region represents the acceptable performance region where both release targets can be achieved. The red and blue regions indicate failure to meet the release target at 10 min and 45 min, respectively. Since the change in solubility within the pH range of 6 to 8 is expected to be negligible (as indicated in Table S1),

the performance graphs were extrapolated to pH 7.4. The edge of failure at 10 and 45 min exhibited a sloping and horizontal trend with pH, respectively, suggesting that pH within the range of 4.5 to 7.4 is likely to impact early release points but have minimal effect on late release points when SDS concentration and paddle speed are held constant. However, both paddle speed and SDS concentration had a significant impact on the release profile. The horizontal boundary of the blue shaded region and other regions in Fig. 3 indicates the minimum paddle speed required to achieve a release higher than 85% at 45 min, even at high SDS concentration. This suggests the potential occurrence of the coning effect under low paddle speed, which is consistent with the analysis of profiles in Fig. 2. The presence of SDS in this study enhanced the solubility of the API, and this might be due to the improved wettability of the system, leading to higher solubility and faster dissolution [52]. This aligns with the performance region graph in Fig. 3, where the red and blue boundary shift downwards as the SDS concentration increases, suggesting lower hydrodynamic power (reflected by paddle speed) is required to achieve 60% release (10 min) and full release (45 min) at the higher SDS concentrations.

The acceptable performance region (unshaded area) is considerably large at an SDS concentration of 0.3%, making it suitable for further method optimization. Conversely, at SDS concentration of 0.6% or 1.0%, the performance graph is predominantly covered by the red and blue regions, indicating that either the release at 10 min is too rapid or



**Fig. 3** The performance graphs of the reference drug product in the dissolution method DoE study (red region fails 10 min target, blue region fails 45 min target, and unshaded region meet both targets)

full release at 45 min cannot be achieved. Consequently, the SDS concentration was fixed at 0.3% for the subsequent optimization process. The method operable design region (MODR) was defined with targeted conditions of paddle speed set at  $70 \pm 2$  rpm and pH maintained at  $6.8 \pm 0.2$  (Fig. 4). Dissolution testing was conducted at the corner and center conditions of MODR, and the resulting dissolution profiles were collected. These results demonstrate that all the method conditions (A, B, C, D, and T) successfully meet the release targets at both 10 and 45 min, affirming the accuracy and reliability of the MODR. Further details of the release results are found in Table V. Therefore, the center method of the MODR was verified, with paddle speed, pH, and SDS concentration maintained at 70 rpm, 6.8 and 0.3%, respectively. The results indicated that the release profile obtained under the center method conditions adhered to the desired release criteria, and it was selected as the optimized method for the reference drug product.

Robustness is one of the critical quality attributes of an analytical method. Comparing to the center method condition, the corner method conditions of MODR varied the method parameters of pH ( $\pm 0.2$ ) and paddle speed ( $\pm 2$  rpm). These variations represented normal instrument and media variability during the dissolution testing. The release profiles of the corner methods are well within the release targets (Table V), confirming the robustness of the dissolution method developed through the aQbD approach.

## Discriminatory Power

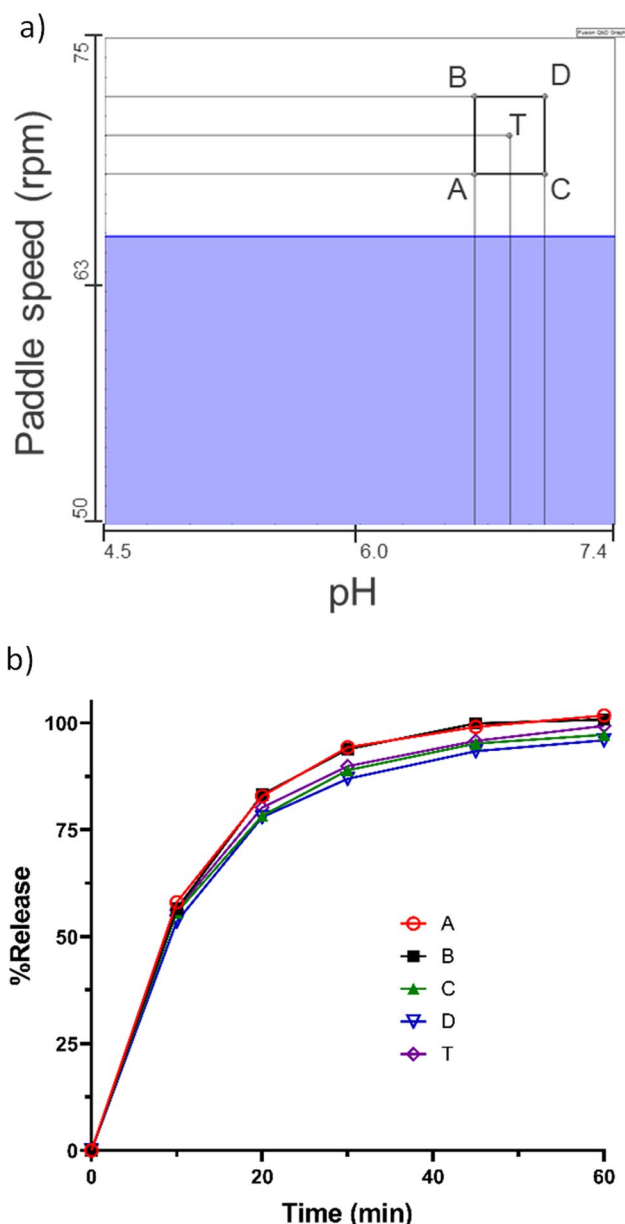
### Risk Assessments

In late-stage clinical development, demonstrating the discrimination power of a dissolution method is crucial

for ensuring the quality control of drug product prior to release. To evaluate the method's ability to discriminate between different formulations, a comprehensive risk assessment of the dissolution testing was conducted. This assessment involved an examination of various factors, including the manufacturing process, API properties, excipients, and method parameters. Figure 5 illustrates an Ishikawa diagram, which indicates potential sources of influence on the dissolution profile. Considering the importance of API exposed surface area and timing of exposure to the dissolution profile, particle size, compression force, and disintegrant quantity were identified as medium- or high-impact factors and were selected for further investigation, which is consistent with other studies [10].

### Formulation DoE Study

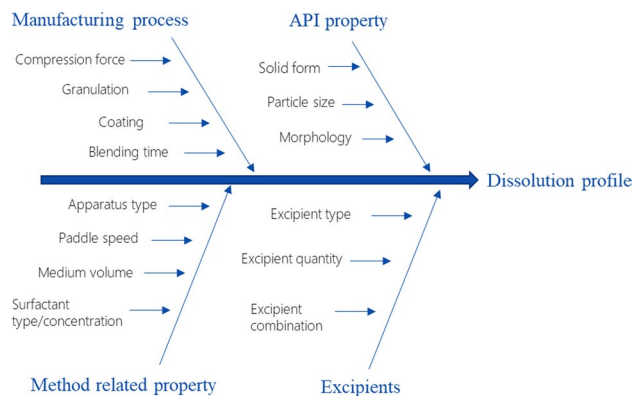
In general, the process for demonstrating the discriminatory power of the method involves three steps. First, risk assessment is performed based on the understanding of API and formulation properties. Second, the deviated formulations are prepared with specific parameter variations based on the knowledge of the drug product. Lastly, dissolution testing is performed, and the differences in dissolution profiles are compared [10, 11, 14, 15, 18, 45]. However, there is a risk that the deviated formulations may not show noticeable difference of dissolution profile comparing to that of the reference drug product. In such cases, it is possible that the deviations of the formulation/process parameters are not large enough to manifest the difference in dissolution, and further formulation development may be required. To mitigate this risk, a Formulation-Discrimination Correlation Diagram is proposed for



**Fig. 4** a performance graph under 0.3% SDS concentration, and b release profiles of the reference drug product under the method conditions at the corners and center of MODR ( $n=2$ , data shows the average)

**Table V** The Release Profiles of Method Conditions in the MODR ( $n=2$ )

Conditions	pH	Paddle speed	SDS%	10 min	45 min
A	6.6	68	0.3	55.7	95.2
B	6.6	72	0.3	58.1	99.1
C	7.0	68	0.3	53.5	93.4
D	7	72	0.3	56.6	99.9
T	6.8	70	0.3	56.3	95.8



**Fig. 5** Risk assessment of dissolution profile using Ishikawa diagram approach

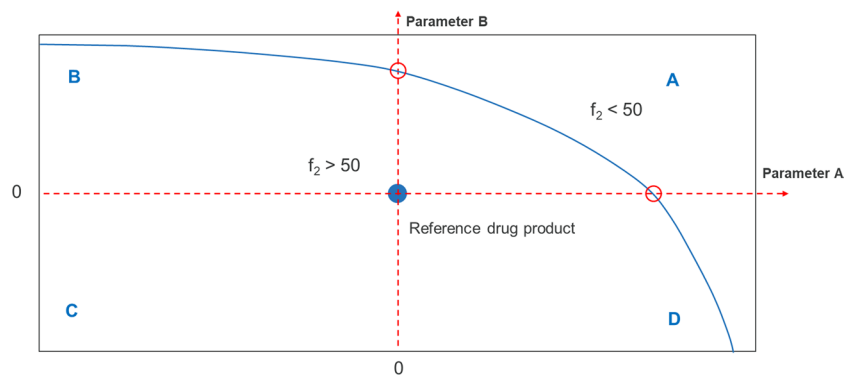
the first time (Fig. 6). This approach allows visualization of the impact of each parameter as well as their correlation on the dissolution profile. The Formulation-Discrimination Correlation Diagram can serve as a scientifically driven guide for selecting influential factors for discrimination evaluation and determining the adequacy of the method’s discrimination capability.

To demonstrate the discriminatory power, various approaches can be employed, such as visual comparison,  $f_1$  or  $f_2$  factor, establishing release variation through intermediate precision, and other statistical tools [13, 53]. In this study, the  $f_2$  factor was adopted to evaluate discrimination by comparing the release profile of each deviated formulation with that of the reference drug product. This is a model independent statistical approach accepted per FDA guidance [54]. The  $f_2$  value was calculated using Eq. (1), where  $R_t$  and  $T_t$  are the cumulative percentage dissolved at each of the selected  $n$  time points of the reference and test product, respectively. A value of  $f_2$  higher than 50 indicates similarity, while a value lower than 50 indicates dissimilarity between the deviated formulation and the reference drug product [50, 54].

$$f_2 = 50 \cdot \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad (1)$$

The Formulation-Discrimination Correlation Diagram is divided into four zones, A, B, C, and D, and the area above and below the blue curve represents the formulations which have  $f_2$  value lower and higher than 50, respectively, when comparing to the reference drug product. The zone C represents formulations with smaller value of parameter A and B comparing to the reference drug product, and therefore, faster releases are expected. Since the reference drug product presents a rapid release already (Fig. 4b),  $f_2$  of the formulations in zone C will likely have a value higher than 50. The same principle applies to zone

**Fig. 6** Formulation-Discrimination Correlation Diagram for the design of formulation DoE study



B and D. Zone A represents formulations with larger values of parameters A and B, and the dissolution profiles are expected to be slower. The design of formulation DoE study within this zone is preferred since the discriminative region ( $f_2 < 50$ ) is the largest and the threshold of each parameter indicating discrimination can be determined (red circles). Therefore, three variations for each formulation/process parameter were proposed, resulting in a total of 15 formulations in the DoE. The specific variations for each parameter are found in Table VI. Subsequently, these formulations were prepared and compressed into tablet drug products, as outlined in Table VII.

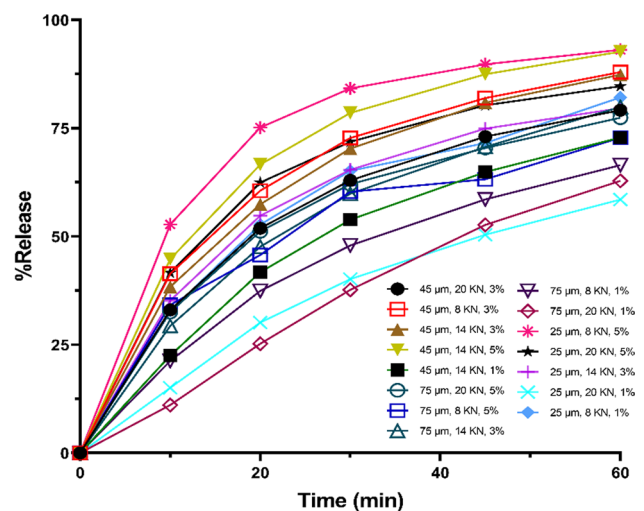
To demonstrate the approach of correlation diagram, the release profiles of the formulations in the DoE study were collected and are presented in Fig. 7. The release profiles of the formulations in the DoE were compared to that of the reference drug product. The resulting correlation diagram is shown in Fig. 8, which aligns with the proposed concept in Fig. 6. In both Fig. 8a and b, each graph is divided into two distinct regions: an unshaded region where the  $f_2$  value is above 50, indicating similarity to the reference drug product, and a shaded region referred to as the method discriminative design region (MDDR), where the  $f_2$  value is below 50, indicating dissimilarity to the reference drug product. The modelling results depicted in Fig. 8a reveal that the method lacks discrimination of compression force, as compression force deviated formulations fall within the unshaded region. This is probably due to the similar tablet hardness over the compression force of 8–20 kN (data is not shown here). However, when the particle size ( $D_{50}$ ) of the API exceeds approximately 60  $\mu\text{m}$ , it is expected that differences in

**Table VII** Formulations DoE Study for Discriminatory Power Analysis

No	Particle size ( $\mu\text{m}$ )	Compression force (kN)	Disintegrant level (%)
1	45	20	3
2	45	8	3
3	45	14	3
4	45	14	5
5	45	14	1
6	75	20	5
7	75	8	5
8	75	14	3
9	75	8	1
10	75	20	1
11	25	8	5
12	25	20	5
13	25	14	3
14	25	20	1
15	25	8	1

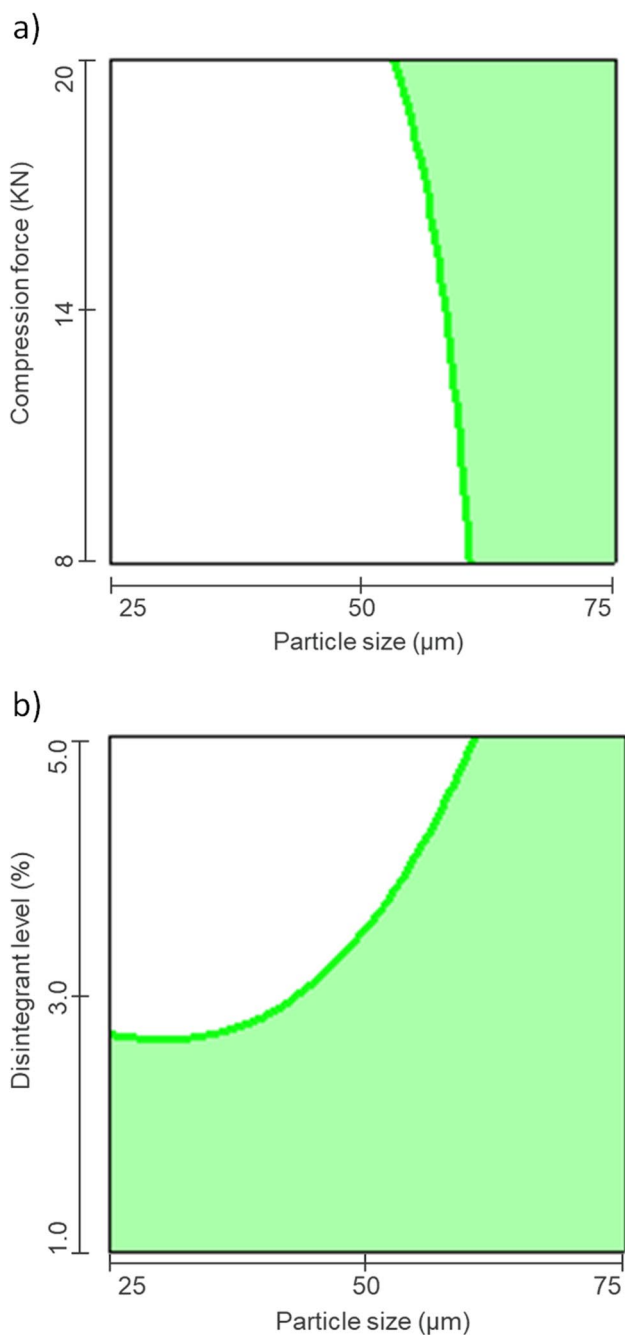
**Table VI** Formulation Parameters and Conditions for Discriminatory Power Evaluation

Parameter	Proposed conditions
Particle size ( $D_{50}$ )	25, 45, 75
Compression force (kN)	8, 14, 20
Disintegrant (%)	1, 3, 5



**Fig. 7** Dissolution profiles of formulations in the DoE study ( $n=2$ , data shows the average)





**Fig. 8** Formulation-Discrimination Correlation Diagram under the condition of **a** 5% disintegrant level and **b** 8 kN compression force

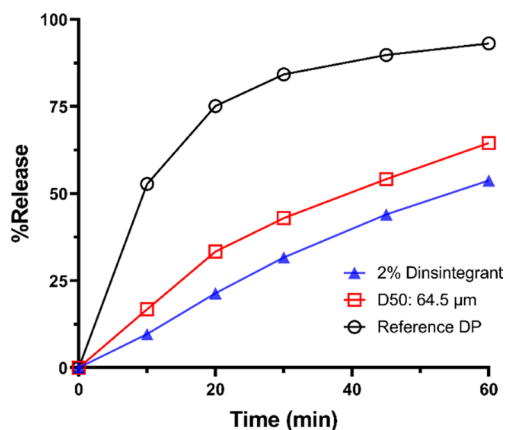
dissolution will be observed when compared to the reference drug product. Similarly, in Fig. 8b, discrimination is anticipated when the disintegrant content in the formulation falls below approximately 2.5%, as formulations within that range exhibit dissimilarity in dissolution profiles. Therefore, the Formulation-Discrimination Correlation Diagram, as demonstrated in Fig. 8a and b, provides a visual representation of the regions where the method shows discrimination with

respect to specific formulation parameters. This information can guide the selection and optimization of parameters to enhance the discriminatory power of the dissolution method.

To further verify the Formulation-Discrimination Correlation Diagram, especially the MDDR, two deviated formulations were prepared and tested. The first formulation contained 2% disintegrant, and the second formulation had a larger particle size ( $D_{50}$  of approximately 64.5 µm) while keeping the disintegrant content at 5%. Upon comparing the dissolution profiles of the two deviated formulations with the reference drug product (Fig. 9), the  $f_2$  values for the formulation with 2% disintegrant and the formulation with an API particle size of  $D_{50}$  64.5 µm are 16 and 22, respectively, indicating the dissimilarity of the deviated formulations to the reference drug product. The agreement between the experimental results and the correlation diagram further demonstrates that the MDDR accurately identifies the regions where the dissolution profiles of the formulations deviate from the reference drug product, providing a reliable guide for assessing the discriminatory power of the dissolution method.

### Conclusion

This study establishes a two-stage workflow for the development of dissolution method and demonstration of method discrimination power, employing an analytical Quality by Design approach. For programs in early phase, where method development and timeline are both crucial, aQbD approach allows for efficient screening and optimization of method parameters. For late phase programs, Formulation-Discrimination Correlation Diagram strategy built upon the method development in the early phase provides a scientifically driven approach for demonstrating the discriminatory power of the dissolution method.



**Fig. 9** Dissolution profiles of the reference drug product and two deviated formulations

By visually presenting the impact of formulation/process parameters and their correlations on the dissolution profile, the Formulation-Discrimination Correlation Diagram guides analytical scientists in determining if the method is discriminative and if any further method development is necessary.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1208/s12249-023-02692-8>.

**Author Contribution** All authors contributed through experiment discussion, data review, manuscript writing, editing, and reviews.

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## Declarations

**Conflict of Interest** Hongbo Chen and John-David McElderry are Biogen employees and may hold Biogen stock.

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