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Dissolution Method Development for Regulatory Approval: A Comprehensive Review and Case Study

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ABSTRACT

In vitro dissolution testing is an important tool for any oral drug product. It is useful for product development and to ensure the in vivo performance of drug products throughout their commercial life without conducting clinical or bioequivalence studies after regulatory approval. It also plays a role in maintaining batch-to-batch consistency, providing quality assurance, supporting biowaiver and post-approval changes, etc. Guidelines from regulatory agencies provide expectations about the dissolution method and acceptance criteria; however, pharmaceutical manufacturers may fail to comply with the requirements or the expectations of the agencies, resulting in dissolution deficiencies. Furthermore, updates in dissolution testing may not be effectively communicated to non-industry scientists who are involved in dissolution or drug delivery research. This article provides a comprehensive review of the current American and European regulatory guidance for solid oral dosage forms followed by a case study to demonstrate how a dissolution method should be developed, which can be used as a framework for any drug product.

KEYWORDS: Dissolution method development, dissolution specification, discriminatory power, dissolution apparatus, dissolution medium

INTRODUCTION

This article focuses on the two main regulatory agencies, the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA). In general, other health authorities consider the development approach followed by these two agencies appropriate and accept the same dissolution methods with supporting rationale. Both agencies have their own guidance and expectations about the dissolution method and acceptance criteria. The FDA and EMA guidance documents are non-binding recommendations from the agencies, so alternative approaches can also be used and justified provided that the dissolution method has sufficient discriminatory power to assess the critical quality attributes (CQAs) of a drug product. This article provides a comprehensive review of the requirements, expectations, significance, and rationale for selection of dissolution test conditions and acceptance criteria. This article also provides a framework for dissolution method development, including examples and case studies for easy interpretation by pharmaceutical scientists.

United States FDA Guidelines

In 1997, the FDA published two guidances for industry that discuss the dissolution method and specifications for acceptance (*1*, *2*):

- *Dissolution testing of immediate release solid oral dosage forms*
- *Extended-release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations*

For generic product development, the FDA recommended to consider the *United States Pharmacopeia* (USP) and the dissolution method database maintained by the Office of Generic Drugs (*3*). The historical approach for dissolution method development for generic drugs was as follows (*4*). If the dissolution method is published in the *USP* drug-specific monograph, then directly use the same dissolution method for the generic product. If the dissolution method is not in the USP or no monograph has been published, then refer and follow the method

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published in the FDA's dissolution method database. If the above-mentioned conditions are not suitable, then develop a new dissolution method.

The FDA's perspective on developing the dissolution method recently changed from a historical approach to a biopharmaceutical approach. Considering this, the FDA published the following guidance since 2017 (*4*–*7*):

- *Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a Biopharmaceutics Classification System (BCS)*
- *M9 biopharmaceutics classification system-based biowaivers*
- *Dissolution testing and acceptance criteria for immediate release solid oral dosage form drug products containing high solubility drug substances*

Immediate-Release Dosage Forms

For immediate-release (IR) drug products, the BCS should be considered when selecting the dissolution method and acceptance criteria (*4*). The dissolution acceptance criteria should be 80% of drug release within 30 min.

For drug products containing highly soluble drug substances, the following dissolution methods should be used (*7*).

- *Method A*: Basket apparatus; 0.1 N HCl medium, 500 mL volume; 100 rpm agitation speed; without surfactant.
- *Method B*: Paddle apparatus; 0.1 N HCl medium, 500 mL volume; 50 rpm agitation speed; without surfactant. A sinker can be added as per the need, and agitation speed can be increased to 75 rpm with justification.

With appropriate justification, other test conditions can be used and accepted by regulatory agencies. For IR drug products containing highly soluble drug substances, the dissolution test can be replaced with the disintegration test in the finished product specifications with adequate justification (*8*).

For drug products containing poorly soluble drug substances, both *USP* and FDA databases should be used as a starting point to see what conditions have already been approved. The selection of the dissolution method should be based on its feasibility and discriminatory power for the proposed drug product. A new method can be developed and validated if the USP and or FDA methods are not available or found inadequate. The selection of the time point should be where not less than (NLT) 80% of the drug is dissolved.

Extended-Release Dosage Forms

Irrespective of the method availability in the USP or FDA dissolution method database, it is expected that a product-specific discriminatory dissolution method should be developed, thoroughly evaluated, and validated for extended-release (ER) dosage forms. When setting the product specifications, a minimum of three time points should be selected to cover the initial, middle, and final phases of the dissolution profile. Dissolution acceptance criteria for the initial and middle time points should be based on a mean target value ± 10%. The last time point should cover at least 80% of the drug release. The target value is based on the mean drug release of the lot/batch used in the clinical study.

Fixed-Dose Combination Products

Fixed-dose combination (FDC) drug products can be the combination of two or more drug substances with similar or different release mechanisms (IR and/or ER). For FDC drug products, both USP and FDA databases should be used as a starting point to see the conditions that have already been approved for the FDC or the single component drug products (*9*).

The development of a dissolution method for FDC drug products is challenging due to the differences in physicochemical properties of the drug substances. Individual dissolution methods can be developed for each drug substance in the FDC product; however, it is expected to have a single dissolution method because of the analytical efficiency, time and cost savings, feasibility during the commercial-release testing, and reduction in the burden during the stability study. Essentially, the method should be robust and reproducible during routine quality control testing.

IR-FDC drug products comprising multiple highly soluble drug substances can be evaluated with a similar approach as an IR drug product containing a single component. Similarly, the dissolution test can be replaced with the disintegration test with adequate justification.

In IR-FDC drug products comprising substances with different solubilities, precedence should be given to the poorly soluble component over the highly soluble component because its dissolution is rate-limiting in the in vivo absorption. The selection of the time point should be where NLT 80% of the drug is dissolved.

In FDC drug products comprising substances with different release mechanisms, precedence should be given to the ER component, followed by the IR component if it is poorly soluble. When setting the acceptance criteria, depending on the release mechanisms of each component, a similar approach for IR or ER drug products containing a single component can be followed.

Delayed-Release Dosage Forms

Delayed release (DR) dosage forms commonly have an enteric coating. There can be other DR mechanisms based on the rationale behind the product design (e.g., to protect against irritation of the stomach mucus membrane, to prevent acidic degradation of the drug, or for targeted drug delivery in the gastrointestinal (GI) tract [i.e., colon targeting]). DR dosage forms can be non-disintegrating (coated tablets) and disintegrating (tablets or capsules containing coated multiple-unit pellet systems).

In general for conventional DR dosage forms, a minimum of two time points is required to meet the specifications. The first point controls the drug release in the acid stage (0.1 N HCl), usually NMT 10% in 2 h, and the second time point controls drug release in the higher pH buffer stage (pH 6.8), usually NLT 80% in 45 min. If DR dosage forms are designed for pulsatile, controlled release, or targeted delivery in the GI tract, the selection of a stage 2 dissolution medium, time points, and acceptance criteria can be set as per the expectations for each release mechanism (*10*, *11*).

European Medicines Agency Guidelines

Just like the FDA follows the *USP*, the EMA follows the *European Pharmacopeia* (*EP*). However, *EP* only has monographs for drug substances, and not drug products. Recently, *EP* has started to publish drug product monographs, including dissolution methods for drug products.

The *British Pharmacopoeia* (*BP*) includes both drug substances and drug product monographs. Earlier BP monographs were acceptable for developing drug products for European territories; however, in February 2020, the UK withdrew from the European Union and become a "third country" (*12*). So, drug products that are developed for the European market must follow and comply with EP and EMA specifications and guidance.

In addition to the general chapters by the EP for the dissolution testing, EMA has published guidelines that discuss dissolution method expectations and acceptance criteria (*13*, *14*):

- *Guideline on quality of oral modified release products*
- *Reflection paper on the dissolution specification for generic oral immediate release products*

For all dosage forms, a product-specific dissolution method with discriminatory power should be developed and validated irrespective of method availability in any public database.

Immediate-Release Dosage Forms

For IR dosage forms, the dissolution method should be developed irrespective of the drug solubility class. Dissolution acceptance criteria should be 75–85% drug release in a given period of time. The target value is the mean drug release of the lot/batch used in the clinical study minus 10%.

Extended-Release Dosage Forms

When setting the product specifications for ER dosage forms, a minimum of three time points should be selected. The first time point is to eliminate dose dumping or to ensure the loading dose (20–30% drug release). The second time point is to define the drug-release pattern (50% drug release), and the acceptance criteria should be ± 10% to the mean target value. The last time point is to ensure at least 80% of the drug release. The target value is the mean drug release of the lot/batch used in the clinical study.

Fixed Dose Combination Products

In FDC drug products comprising drug substances with different solubilities and/or release mechanisms, precedence should be given to the ER component and/or poorly soluble components. Acceptance criteria can be derived using the same principles recommended by the EMA or *EP* for individual IR or ER drug products containing a single component.

Delayed-Release Dosage Forms

For conventional DR dosage forms, expectations of the EMA are the same as the FDA. *USP* general chapter <711> and *EP* general chapter <2.9.3> have been harmonized. For non-conventional DR dosage forms, selection of a stage 2 dissolution medium, time points, and acceptance criteria can be set according to the expectations of the EMA or *EP* for each release mechanism.

DISSOLUTION METHOD DEVELOPMENT

A product-specific dissolution method should be developed in the sequence of activities given in Figure 1.

Drug Solubility and Solution Stability

An analytical method should be developed for detecting the drug using suitable detection techniques. The solubility of the drug should be determined in aqueous

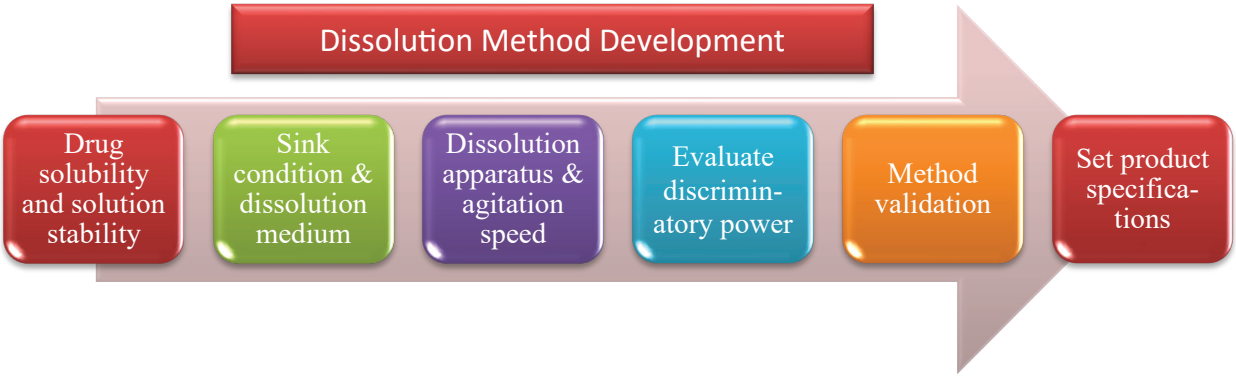

Figure 1. Flow diagram of dissolution method development.

media with a pH in the range of 1–6.8 at 37 ± 1 °C. Solution stability in each medium should be ensured using the stability-indicating assay or impurity method of the analysis. Drug solubility and stability are useful for determining the solubility class and for the selection of dissolution medium. If the highest dose of the drug substance is soluble in 250 mL of the aqueous medium with a pH in the range of 1–6.8, then that drug is considered highly soluble (*5*, *6*, *7*).

For FDC drug products, an in-depth evaluation of the physicochemical properties of each drug substance, like pH solubility, solution stability, and drug-to-drug interaction in the physiological pH range should be performed. In general for FDC drug products, an analytical method with high performance liquid chromatography (HPLC) is preferred over UV-visible spectroscopy to avoid interference in the absorbance at a particular wavelength. However, UV-visible spectroscopy methods are acceptable with the appropriate demonstration of specificity and lack of interference for the active ingredients.

Sink Conditions and Selection of Dissolution Media

To use any aqueous medium as a dissolution medium, it should be capable of maintaining the sink condition and have sufficient solution stability to cover the duration of time required to perform the dissolution test and analyze the sample aliquots. The sink condition is at least three times the volume needed to obtain a saturated solution based on the highest strength of the drug product (*10*, *15*, *16*). The preferred dissolution media volume for USP apparatus 1 and 2 (basket and paddle, respectively) is 500 900, or 1000 mL, and in the worst case, 1800 mL. For the USP apparatus 3 (reciprocating cylinder), media volume can be in the range of 200–300 mL per vessel.

For IR dosage forms containing highly soluble drugs, 500 mL of 0.1 N HCl should be directly used according to the FDA (*7*). In other cases, the choice of the medium should be based on the ability to maintain the sink condition and stability of the solution. If the drug substance has pH-independent solubility and stability, then the preferred dissolution medium can be 0.1 N HCl or purified water. If a drug substance has poor solubility in all pH ranges, then the solubility study can be conducted by adding the minimum effective concentration of the surfactant. The choice and concentration of surfactant should be based on the evaluation and appropriate justification. Commonly, sodium lauryl sulfate, polysorbate 20, and polysorbate 80 are used as surfactants in the dissolution medium. If adequate solubility to satisfy sink conditions exists only over a narrow pH range, then an appropriate buffer should be selected to maintain the pH range.

If FDC drug products contain drug substances with different solubilities, a pH should be selected that meets the sink condition for the low soluble drug. If FDC drug products contain multiple poorly soluble drug substances with different pH solubilities or pH-dependent solution stabilities, then multiple pH media and buffers should be evaluated (even within narrow pH ranges) to accommodate the sink condition and solution stability of multiple drug substances.

Dissolution of conventional DR dosage forms can be performed in 0.1 N HCl followed by a pH 6.8 phosphate buffer. The acid-stage dissolution ensures or validates the efficiency of enteric-coating polymers to avoid drug release or degradation beyond the specified limit, commonly no more than (NMT) 10%. If the drug is insoluble in 0.1 N HCl, then the acid-stage dissolution performance can be checked by developing the acid medium with the addition of surfactants. In some cases, the drug can be degraded in 0.1 N HCl, where the acid stage dissolution can be performed by detecting the degradant products alone or along with the parent drug substance.

Selection of Dissolution Apparatus and Agitation Speed

There are seven compendial dissolution apparatus used in the pharmaceutical industry, depending on the dosage form (*10, 11*):

- USP apparatus 1 (basket): used for tablets, capsules, suppositories, and floating dosage forms
- USP apparatus 2 (paddle): used for tablets, capsules (with or without sinkers), and suspensions
- USP apparatus 3 (reciprocating cylinder): used for IR, ER, and DR tablets
- USP apparatus 4 (flow-through cell): used for implants or when sink conditions cannot be achieved using another apparatus
- USP apparatus 5 (paddle over disc): used for transdermal delivery systems
- USP apparatus 6 (rotating cylinder): used for transdermal delivery systems
- USP apparatus 7 (reciprocating disc): used for transdermal delivery systems and ER tablets

USP apparatus 1 and 2 (baskets and paddle, respectively) is widely used for dissolution testing of solid oral dosage forms, as they are feasible and easily available. In some cases, where a basket or paddle apparatus is not feasible, another USP apparatus can be used. Evaluation of the dissolution apparatus should consider the product design initially, then further considerations should be made based on the observations during the evaluation. The paddle apparatus can be used for IR and ER dosage forms. Sinkers can be used for dosage forms that float or stick to vessel walls. The basket apparatus can be used for dosage forms that tend to float. In certain cases, drug products in the dissolution vessel form a cone or hip if there is a significant amount of insoluble material. In those cases, the agitation speed can be increased or apex vessels can be used with appropriate justification. A non-compendial low-volume apparatus with mini paddles and baskets can be adequately qualified and used with appropriate justification (e.g., low-dose drug products).

The recommended agitation speed is 100 rpm for the basket apparatus and 50 rpm for the paddle apparatus. A paddle with an agitation speed of 75 or 100 rpm can be used with an optimization study and the justification. Sometimes, 50 rpm agitation does not create sufficient hydrodynamics to uniformly disintegrate or dissolve the drug product, resulting in incomplete drug release or unit-to-unit variation. The agitation speed is also important to achieving the discriminatory power of the dissolution method. An increase in agitation speed often reduces the discriminatory capacity of the dissolution method, with a low agitation speed causing the variation.

USP apparatus 3 (reciprocating cylinder) can be used for IR, ER, and DR dosage forms like matrix tablets or formulations containing coated multi-particulate systems, which may not completely disintegrate into fine particles in the earlier rows and pass through the mesh of the cylinder. Apparatus 3 can be useful when drug release is pH-dependent, in which case it becomes appropriate to adjust pH over the course of the dissolution run. Agitation for apparatus 3 is considered in the form of dips per minute (dpm). When developing a dissolution method using apparatus 3, it is necessary to optimize the dips, which generally range from 5–30 dpm.

USP apparatus 4 (flow-through cell) is used for products containing drugs that have limited solubility. For USP apparatus 4, the media flow rate is critically controlled. Standard flow rates are 4, 8, and 16 ml/min. Other flow rates and modified flow-through cells can be used depending on the need and with justification, for example, powder dosage forms.

USP apparatus 7 is useful for ER dosage forms containing coated multi-particulate systems or for osmotic-controlled release delivery systems.

For handling the sequential dissolution in the case of DR dosage forms, two methods are commonly discussed in *USP* <711> and *EP* <2.9.3>.

Method A: Perform the acid-stage dissolution using 750 mL of 0.1 N HCl with a paddle or basket apparatus for 2 h followed by sampling and testing for acid-stage drug release. After 2 h, add 250 mL of 0.20 M tribasic sodium phosphate to each vessel to make 1000 mL of pH 6.8 buffer. If required, the pH adjustment can be done using 2 N HCl/NaOH.

Method B: Perform the acid-stage dissolution using 1000 mL of 0.1 N HCl with a paddle or basket apparatus for 2 h followed by the sampling and testing for acid-stage drug release. After 2 h, drain the 0.1 N HCl from each vessel with careful attention so that the drug product under study should not be lost, and pour 1000 mL of pH 6.8 buffer (previously equilibrated at 37 ± 0.5 °C) in each vessel.

Another option is to directly replace each vessel of 0.1 N HCl with another vessel containing 1000 mL of pH 6.8

buffer (previously equilibrated at 37 ± 0.5 °C) followed by the transfer of drug product from the stage 1 vessels to the stage 2 vessels. In each case, stage 2 dissolution can be performed commonly up to 45 min or on a case-by-case basis as per the adopted dissolution time point, considering the release mechanism or design of the drug product.

Dissolution of DR dosage forms can also be performed using apparatus 3 and 4. The use of apparatus 3 makes it easier for the sequential dissolution as the 0.1 N HCl can be added in the first row and the pH 6.8 buffer in the second row using media volumes in the range of 200–300 mL.

Discriminatory Power Evaluation and Method Validation

Discriminatory power is the ability of the dissolution method to detect changes in the drug product. The rationale behind the requirement for discriminatory power is as follows.

For a new drug product or a new generic drug product, in vivo clinical or bioequivalence (BE) studies are conducted after the completion of the formulation, analytical, and process development (which are submitted in the dossier to the agency for marketing approval). Dissolution specifications are finalized based on the dissolution data of batches used in the in vivo clinical/BE studies. Throughout the commercial life of the drug product, batches are expected to have the same in vivo performance, which is indirectly ensured by using the in vitro dissolution test as a quality control tool (*13*, *14*). Dissolution is identified as a CQA for most formulations (exceptions can be IR dosage forms containing highly soluble drugs) and is often utilized to determine the Proven Acceptable Ranges (PAR) and generate the design space. The study of any individual unit operation or parameter while keeping other parameters constant will give the PAR. By changing more than one factor at a time, multidimensional combinations and interactions of input variables and process parameters can be evaluated. If a factor demonstrates the ability to assure quality, then that factor generates design space (*17*). For example, the factors that can affect dissolution are the granulation process (input raw materials attributes, granulating fluid quantity, particle size distribution of the granules, etc.), lubrication process (lubricant level, lubrication time, etc.), compression process (compression force, tablet hardness, etc.), coating process (weight build-up, spray rate, curing temperature, curing time, etc.), and stability measures (temperature, humidity, hold time, etc.). Therefore, the discriminatory dissolution method is essential for developing a control strategy by controlling Critical Material Attributes (CMAs), fixing the processing equipment, and defining acceptable ranges for the Critical Process Parameters (CPPs). So, with this rationale, the selected dissolution method should be capable of detecting acceptable and unacceptable characteristics that can be possible during the commercial life of the product.

Once a tentative dissolution method (including medium, volume, apparatus, and agitation speed) has been chosen, then the method should be evaluated for discriminatory power by preparing different formulations with meaningful changes to the composition and/or process. The term 'meaningful change' here signifies any change in the raw material, composition, or manufacturing process that is possible during routine operation that may affect the in vivo performance of the product (e.g., differences in particle size or polymorphic forms of the drug substance, differences in lot-to-lot polymer viscosity, changes in functional excipient level like polymer, disintegrant, binder, lubricant level, etc). Manufacturing process changes can be granulation parameters, milling parameters, tablet hardness, polymer coating spray rate, coating weight build-up, curing temperature, curing time, etc. Complete removal of any excipient or change in the process design to prove the discrimination is not supported.

To check the discrimination, a dissolution profile of the final formulation should be compared to a formulation with meaningful changes. The comparison of dissolution profiles may be done using similarity factor analysis, i.e., difference factor (f_1) or similarity factor (f_2). An f_1 value above 15 or an f_2 value below 50 signifies that the dissolution profiles are different (*18*). A difference in the dissolution profile indicates the discriminatory power of the method. Discriminatory power can also be proved if the optimized formulation complies with the proposed dissolution acceptance criteria while formulations with meaningful changes fail to comply with the same. The choice of any one method should be based on the method's comparative discriminatory capacity. To achieve maximum discriminatory power, the dissolution method can be evaluated by varying the media volume, agitation speed, apparatus, etc. Not all formulation or process changes are expected to result in a significant dissolution profile difference, but the dissolution test should be able to discriminate expected differences due to the underlying drug release mechanism(s).

There is a possibility of the dissolution method being over-discriminatory and leading to the rejection of batches

that may not have a concern for in vivo performance. If the manufacturing process is in a state of control that is capable of consistently producing a product that meets specifications, an overly discriminating dissolution test may be justified.

If there is a concern that the process may produce batches that are out of specification, then the best approach to reducing this risk is to establish the IVIVC by performing an in vivo study on the batches produced with the most extreme dissolution profiles, followed by the setting of in vitro dissolution acceptance criteria based on the acceptable and non-acceptable in vivo behavior of the formulation.

The finalized discriminatory dissolution method should be validated as per ICH Q2 guidance and *USP* <1092> (*10*, *19*).

Setting Product Specifications

The dissolution profile of the test batch used in the clinical or BE study should be used to determine the drug product's final specification. In case of IR products where a BCS-based biowaiver is applied, the Q value can be set between 15 and 30 mins. Table 1 and 2 provides the understanding for setting the dissolution specifications for the American and European market, respectively (*2*, *4*, *7*, *13*, *14*, *20*). Hypothetical examples are included in Tables 1 and 2 to make it easy to understand the expectations of the regulatory agencies.

Briefly, the best possible approach to setting the dissolution acceptance criteria for an IR drug product is mean drug release of the clinical/BE batch at a given time point minus 10% (Q). For an ER drug product, the target value is the mean drug release of the clinical/BE batch ± 10% for early time points and minus 10% for the last time

Table 1. Dissolution Specifications for the USA Market (2, 4, 7)

Type	Conditions	Acceptance Criteria (US FDA)	Hypothetical Examples	
			Mean drug release of test lot used in clinical/ BE study	Acceptance criteria
IR	Highly soluble drugs	Single point specification: NLT 80% in 30 min	15 min: 82% 30 min: 93%	30 min: NLT 80%
IR	Complete drug release ≤ 60 min	Single point specification: NLT 80% in specified time interval	15 min: 65% 30 min: 82% 45 min: 93% 60 min: 99%	45 min: NLT 80%
IR	Complete drug release > 60 min	Minimum 2 time points: 1st time point: < 60 min 2nd time point: > 60 min & 80% release	15 min: 35% 30 min: 42% 45 min: 63% 60 min: 72% 75 min: 85% 90 min: 96%	60 min: NLT 60% 90 min: NLT 80%
ER	Conventional ER	Minimum 3 time points (initial, middle, and final phase) & 80% release[a]	1 h: 18% 5 h: 52% 10 h: 93%	1 h: NMT 30% 5 h: NLT 42% & NMT 62% 10 h: NLT 80%
ER	Modified ER with bi-phasic or multi-phasic release	Minimum 3 time points (initial, middle, and final phase) & 80% release[a]	0.5 h: 25% 4 h: 55% 8 h: 96%	0.5 h: NLT 15% & NMT 35% 4 h: NLT 45% & NMT 65% 8 h: NLT 85%
DR	Conventional enteric-coated drugs	Minimum 2 time points: Acid stage: usually NMT 10% in 2 h Buffer stage: usually NLT 80% in given time interval	Acid stage: 2 h: 4% Buffer stage: 15 min.: 65% 30 min.: 82% 45 min.: 93% 60 min.: 99%	Acid stage, 2 h: NMT 10% Buffer stage, 45 min: NLT 80%
DR	DR with ER mechanism	Minimum 1 time point in acid stage and 3 time points in buffer stage. Acid stage: NMT 10% in 2 h Buffer stage: Initial, middle, and final phase & 80% release[a]	Acid stage: 2 h: 4% Buffer stage: 1 h: 22% 2 h: 52% 6 h: 93%	Acid stage, 2 h: NMT 10% Buffer stage: 1 h: NLT 12% & NMT 32% 2 h: NLT 42% & NMT 62% 6 h: NLT 80%

[a]Acceptance based on mean target value ± 10%; mean target value is the mean drug release of the test lot used in the clinical/BE study.
FDA: Food and Drug Administration; IR: immediate release; ER: extended release, DR: delayed release; BE: bioequivalence; NLT: not less than; NMT: not more than.

Table 2. Dissolution Specifications for the Europe Market (13, 14, 20)

Type	Conditions	Acceptance Criteria (EMA)	Hypothetical Examples	
			Mean drug release of test lot used in clinical/BE study	Acceptance criteria
IR	Complete drug release ≤ 45 min	Single point specification: Q value = bio batch mean drug release – 10%. Q value is usually 75–85%. Q value above 85% is considered irrelevant.	15 min: 92% 30 min: 99%	15 min: NLT 80%
			15 min: 79% 30 min: 93%	30 min: NLT 80%
			15 min: 65% 30 min: 82% 45 min: 99%	45 min: NLT 85% i
IR	Complete drug release > 45 min	Minimum 2 time points: 1st time point: < 45 min 2nd time point: > 45 min & 80% release	15 min: 35% 30 min: 42% 45 min: 63% 60 min: 72% 75 min: 85% 90 min: 96%	45 min: NLT 50% 90 min: NLT 85%
ER	Conventional ER drug products	Minimum 3 time points: 1st time point: 20–30 % release 2nd time point: 50% release 3rd time point: ≥ 80% release[a]	2 h: 22% 6 h: 52% 12 h: 93%	2 h: NLT 12% & NMT 32% 6 h: NLT 42% & NMT 62% 12 h: NLT 80%
ER	Modified ER with bi-phasic or multi-phasic release	Minimum 3 time points: 1st time point: 20–30 % release 2nd time point: 50% release 3rd time point: ≥ 80% release[a]	0.5 h: 25% 4 h: 55% 8 h: 96%	0.5 h: NLT 15% & NMT 35% 4 h: NLT 45% & NMT 65% 8 h: NLT 85%
DR	Conventional enteric-coated drugs	Minimum 2 time points: Acid stage: usually NMT 10% in 2 h. Buffer stage: usually NLT 80% in given time interval.	Acid stage: 2 h: 4% Buffer stage: 15 min: 65% 30 min: 82% 45 min: 93% 60 min: 99%	Acid stage, 2h: NMT 10% Buffer stage, 45 min: NLT 80%
DR	DR with ER mechanism	Minimum 1 time point in acid stage and 3 time points in later buffer stage. Acid stage: usually NMT 10% in 2 h. Buffer stage: 1st time point: 20–30 % release 2nd time point: 50% release 3rd time point: ≥ 80% release[a]	Acid stage: 2 h: 4% Buffer stage: 1 h: 22% 2 h: 52% 6 h: 93%	Acid stage, 2 h: NMT 10% Buffer stage: 1 h: NLT 12% & NMT 32% 2 h: NLT 42% & NMT 62% 6 h: NLT 80%

[a]Acceptance based on mean target value ± 10%; mean target value is the mean drug release of the test lot used in the clinical/BE study.
EMA: European Medicines Agency; IR: immediate release; ER: extended release, DR: delayed release; NLT: not less than; NMT: not more than.

point. For a DR drug product, the target in the acid stage is NMT 10% after 2 h, and the buffer stage target depends on the release mechanism (IR or ER) or design of the drug product.

Any deviation from the range specified above can be justified by performing the additional clinical/BE studies using the batches with extreme dissolution profiles. During the stability study, it is expected that the product should meet the acceptance criterion that was derived based on the batches linked to the clinical/BE studies, any change in the dissolution behavior during the stability study can trigger an out-of-specification value followed by an investigation. If needed, to support the change in dissolution data, acceptance criteria can be revised by demonstrating additional BE (i.e., dissolution profile) between the batch with changes vs. the batch used in the early clinical/BE studies (*13*).

CASE STUDY

A dissolution method development case study is presented in the subsequent sections for a better understanding of each element. The case study considers a model drug and ER tablet dosage form; however, the same procedure can be applied to any dosage form.

Materials

Metformin hydrochloride ER tablets (50 mg) was selected as a model drug for this study. Metformin hydrochloride (Harman Finochem), lactose monohydrate (DFE), povidone (BASF), colloidal silicon dioxide (Evonik), magnesium stearate (Petergreven), hypromellose (Lotte),

ethylcellulose (DuPont), triethyl citrate (Stearinerie Dubois), talc (Emerys), and isopropyl alcohol (Runa Chemicals) were obtained from Centaur Pharmaceuticals Pvt Ltd. Hydrochloric acid (37%), sodium hydroxide, potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium acetate, glacial acetic acid were of analytical grade.

Optimized Formulation Development

A formulation was optimized with a reservoir system, and the target was to achieve an ER profile. The tablet core was prepared using granules manufactured using an aqueous wet granulation process, compression using 8.2 mm round punches, and B-tooling tablet press with a target tablet weight of 250 mg. To smooth the core surface and to serve as a barrier between the core and the controlled-release polymer coating, a 3% w/w subcoating was layered over the core tablets. After subcoating, controlled-release polymer coating (15% w/w) was performed using a hydrophilic-hydrophobic polymer combination. The last film coating used an Opadry premix (3% w/w). The formulation composition is listed in Table 3 (formulation #1).

Analytical Method Development

An ultraviolet (UV) spectrophotometer (1800 series, Shimadzu) was used with 1-cm quartz cuvettes. Drug standard solutions with a final concentration of 10 µg/mL were prepared using various buffer solutions (0.1 N HCl, pH 4.5 acetate, pH 6.8 phosphate buffer, and water). Absorbance was measured for each standard solution using the UV spectrophotometer at a wavelength ranging from 200 to 400 nm. The pattern of the spectrum and absorbance maxima was evaluated in each medium. The UV spectrophotometer method was found to be feasible. Spectra with 0.1 N HCl showed a solvent effect, giving a sharp peak close to 200 nm. The absorbance maximum was 233 nm in pH 4.5 acetate, pH 6.8 phosphate buffer, and water. A concentration of 10 µg/mL was finalized to achieve an absorbance of not more than 1.0.

Drug Solubility Study and Solution Stability

The pH-solubility profile of the drug was determined in triplicate at 37 ± 1 °C in aqueous media with a pH in the range of 1–6.8 using the shake-flask method. The drug was added to the 10 mL of the corresponding buffer solution until a saturated solution was formed. Saturated solutions were kept in a shaker maintained at 37 ± 1 °C for 24 h. After 24 h, each solution was filtered (0.45-µ nylon syringe filter, Millipore), followed by dilution using the same buffer solution, and the concentration was

Table 3. Case Study: Composition of Optimized Formulation

Components	Function	Value (mg)
Intragranular		
Metformin Hydrochloride	Drug substance	50
Povidone K 30	Binder	15
Lactose Monohydrate	Diluent	181.25
Purified water	Solvent	q.s.
Extragranular		
Colloidal Silicon Dioxide	Glidant	1.25
Magnesium Stearate	Lubricant	2.5
Subcoating		
Hypromellose – 5 CPS	Film former	7.5
Purified water	Solvent	q.s.
Controlled-release polymer coating:		
Ethyl cellulose – 10 CPS	Release controlling polymer	16.22
Hypromellose – 5 CPS	Pore former and film former	19.7
Triethyl Citrate	Plasticizer	2.7
Isopropyl Alcohol	Solvent	q.s.
Purified water	Solvent	q,s,
Film Coating		
Opadry Premix	Film former with color	8.88
Purified water	Solvent	q.s.
Film coated tablet weight		305

CPS: Centipoise; q. s.: quantity sufficient

determined using UV spectrophotometry. Mean drug solubility was 199, 167, 250, and 200 mg/mL in the 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate, and purified water, respectively. The stability of the standard solution in each medium at 37 ± 1 °C was checked for up to 72 h.

Sink Condition and Dissolution Medium

The drug has pH-independent, high solubility, and the sink condition can be maintained in 500 mL, allowing 3 times the unit dose (150 mg) to be sufficiently dissolved. The drug solution with each medium was found stable for up to 72 h. Considering the solubility data, any medium can be taken forward as a dissolution medium. As the drug has pH-independent solubility, water was preferred as the dissolution medium, which was also proven to have discriminatory capacity, as discussed in the later sections.

A standard calibration curve was prepared in purified water with the drug concentration ranging from 2–12 µg/mL. The linear relationship between the drug concentration and absorbance makes water suitable for determining the drug concentration by measuring the absorbance. To obtain the drug concentration within the linear calibration range during dissolution analysis, the dilution factor was adjusted to achieve a final concentration of 10 µg/mL.

Dissolution Apparatus and Agitation Speed

The dissolution apparatus was evaluated by conducting the dissolution test with the optimized formulation using a basket apparatus at 100 rpm and paddle apparatus at 50, 75, and 100 rpm. The dissolution data are presented in Table 4 and Figure 2.

Both apparatus were found feasible and showed uniform drug release. Floating or sticking of the tablet was not observed in the case of the paddle, so a sinker was not required. Although the agitation speed increased with the paddle, the release rate was similar, which could be due to the design of the drug product by the reservoir system. The discriminatory capability of the method can be reduced by increasing the agitation speed; hence, a paddle at 50 rpm and a basket with 100 rpm was considered appropriate for comparison.

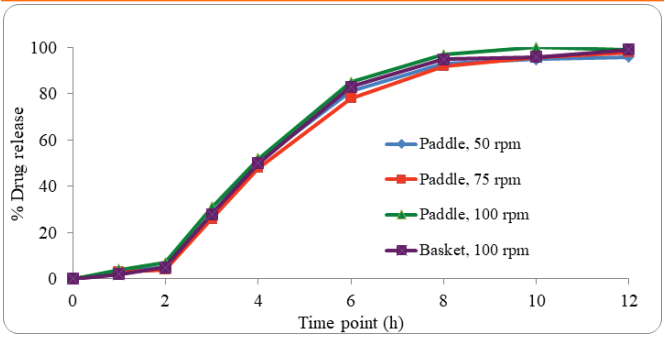

Figure 2. Dissolution profiles (evaluation of test apparatus).

Evaluation of Discriminatory Power

The discriminatory power was evaluated by preparing the different formulations with meaningful changes in the composition like polymer ratio, coating weight build-up, and changes in the manufacturing process like coating spray rate. Dissolution profiles of the formulation with these changes were compared with the dissolution profile of the optimized formulation through f_1 and f_2 calculation. The difference in dissolution profiles is not only measured through these calculations, but also based on the overall dissolution profile. The reason for this is that the f_1 and f_2 values are driven by multiple time points, which may not be necessary to show discrimination. Sometimes, the data can be evaluated by identifying differences at particular time points that are critical to controlling the in vivo performance (i.e., part of the acceptance criteria).

Table 4. Case Study: Dissolution of Optimized Formulation

Time Point (h)	USP Apparatus 2, 50 rpm	USP Apparatus 2, 75 rpm	USP Apparatus 2, 100 rpm	USP Apparatus 1, 100 rpm
0	0	0	0	0
1	3 (1 – 4)	3 (2 – 5)	4 (3 – 7)	2 (1 – 5)
2	5 (3 – 8)	4 (3 – 7)	7 (6 – 10)	5 (4 – 8)
3	28 (23 – 31)	26 (24 – 29)	31 (28 – 35)	28 (25 – 31)
4	51 (46 – 54)	48 (46 – 51)	52 (47 – 56)	50 (48 – 53)
6	81 (75 – 83)	78 (76 – 81)	85 (84 – 88)	83 (81 – 85)
8	93 (90 – 95)	92 (89 – 94)	97 (95 – 100)	95 (91 – 99)
10	95 (93 – 98)	96 (94 – 99)	100 (98 – 102)	96 (94 – 99)
12	96 (95 – 99)	98 (97 – 100)	99 (97 – 101)	99 (99 – 102)

Values are mean (range), n = 12. Dissolution medium was 500 mL of water.
USP: United States Pharmacopeia.

To evaluate the discriminatory power of the dissolution test methods (paddle apparatus at 50 rpm versus basket apparatus at 100 rpm), three formulations trials were developed by changing formulation variables (formulation #2 and #3) or process variables (formulation #4). Formulation trial #2 was manufactured by changing the release-controlling polymer-to-pore former ratio (ethylcellulose: hypromellose) from 42:51 to 39:54 and keeping the coating weight build-up, other components, and process parameters constant with the optimized formulation. Formulation trial #3 was manufactured by keeping the same coating composition and process parameters but increasing the CR polymer coating weight build-up from 15% to 17% w/w. Formulation trial #4 was manufactured by keeping the composition same and only increasing the spray rate to 10–16 g/min from the optimized spray rate of 5–8 g/min, which affects the film property.

Results and Discussion

The results are presented in Table 5 and Figure 3. Both dissolution methods successfully discriminated the slight changes in polymer-to-pore former ratio (Fig. 3A and 3B), polymer coating weight build-up (Fig. 3C and 3D), and polymer spray rate (Fig. 3E and 3F). Although f_2 values were above 50, there were differences in the release at some early and middle time points.

Although both the dissolution methods are discriminatory and equally feasible, the paddle apparatus method is comparatively more discriminatory than the basket apparatus. Thus, the preferred dissolution method for metformin hydrochloride ER tablets is USP apparatus 2 (paddle) at 50 rpm with 500 mL of purified water (37 ± 0.5 °C).

If the optimized formulation (#1) is the same as that used in the clinical or BE study and no in vitro-in vivo

Table 5. Case Study: Dissolution of Optimized Formulation (#1) vs. Formulation Trials[a]

Time Point (h)	Formulation #1	Formulation #2	Formulation #3	Formulation #4
USP Apparatus 2, 50 rpm				
0	0	0	0	0
1	3 (1–4)	5 (2–7)	0	8 (6–11)
2	5 (3–8)	13 (10–15)	2 (1–4)	14 (11–16)
3	28 (23–31)	37 (34–39)	17 (14–21)	42 (38–45)
4	51 (46–54)	68 (66–71)	40 (36–42)	59 (56–62)
6	81 (75–83)	87 (86–91)	77 (76–81)	89 (86–91)
8	93 (90–95)	97 (94–99)	92 (89–95)	99 (96–101)
10	95 (93–98)	99 (97–101)	93 (90–99)	100 (98–101)
12	96 (95–99)	100 (99–102)	96 (92–100)	102 (99–104)
f_1	Ref	32	17	28
f_2	Ref	51	58	52
USP Apparatus 1, 100 rpm				
0	0	0	0	0
1	2 (1–5)	3 (2–3)	1 (0–3)	6 (3–8)
2	5 (4–8)	11 (8–13)	3 (1–6)	12 (10–13)
3	28 (25–31)	34 (30–36)	18 (16–23)	37 (35–39)
4	50 (48–53)	65 (61–67)	39 (35–44)	56 (53–59)
6	83 (81–85)	88 (83–90)	79 (74–82)	89 (83–90)
8	95 (91–99)	99 (98–101)	94 (90–96)	101 (98–101)
10	96 (94–99)	100 (99–102)	99 (98–102)	100 (99–102)
12	99 (99–102)	99 (98–102)	100 (99–103)	101 (98–102)
f_1	Ref	26	15	21
f_2	Ref	55	60	59

Values are mean (range), n = 12. Dissolution medium was 500 mL of water.
USP: United States Pharmacopeia.

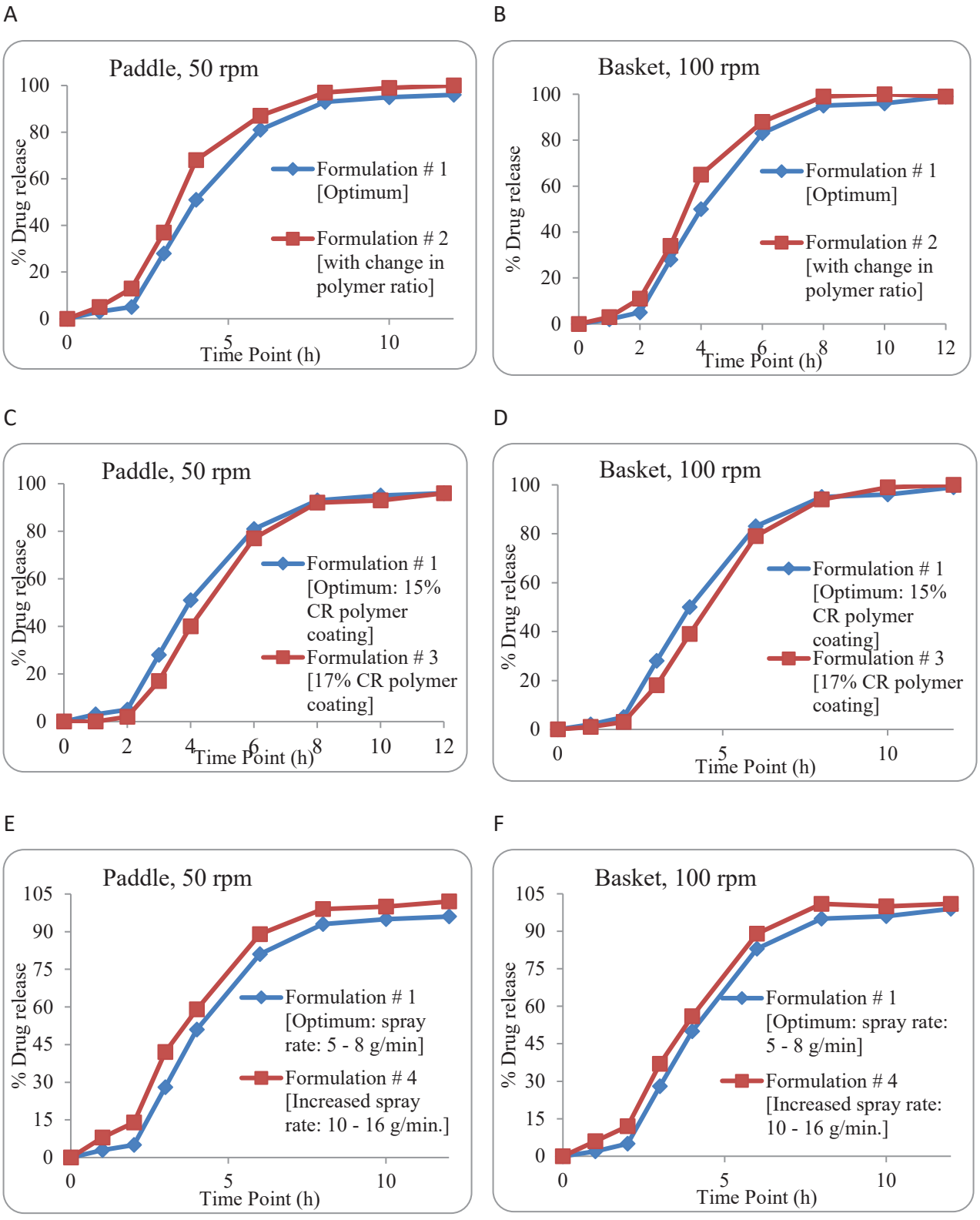

Figure 3. Dissolution of formulations with changes in polymer ratio (A and B), CR polymer coating weight build-up (C and D), and coating spray rate (E and F) using apparatus 2 (A, C, E) and apparatus 3 (B, D, F).

correlation (IVIVC) is established, then the final dissolution specification for the commercial life of the product can be proposed as given in Table 6. The same acceptance criteria can be applied in the American and European markets.

If the dissolution profiles of formulation #1 and #4 (see Table 5) are compared with the derived specifications (Table 6), then the batches are out of specification. This indicates that the dissolution method is capable of discriminating batches with acceptable and non-acceptable release characteristics.

Table 6. Case Study: Derived Specifications for the Optimized Formulation

Time Point (h)	Mean Drug Release (%)	Proposed Acceptance Criteria	
		Option 1	Option 2
1	3	--	--
2	9	NMT 20%	--
3	28	--	NLT 18%, NMT 38%
4	51	NLT 41%, NMT 61%	NLT 41%, NMT 61%
6	81	--	--
8	93	NLT 80%	NLT 80%
10	95	--	--
12	96	--	--

NLT: not less than; NMT: not more than.

SUMMARY

This review showcases the importance of the dissolution test and the specifications for oral solid dosage forms, including a concise summary of regulatory requirements and expectations in the US and Europe. The discussion on dissolution method development, including a case study, provides handy guidance to academics, research scholars, and industry scientists to develop a dissolution method for any new or generic solid oral dosage form.

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