dx.doi.org/10.14227/DT200213P6

Dissolution Testing of a Controlled-Release Capsule Formulation: Challenges and Solutions Using a Semi-Automated Dissolution System

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ABSTRACT

A controlled-release formulation was developed using enteric-coated beads in a hard gelatin capsule shell. This formulation requires two-stage dissolution testing at low and neutral pH. Because of high toxicity and limited stability of the active pharmaceutical ingredient in aqueous solution at room temperature, it is preferable to limit the analyst's contact with the sample solutions during testing, and aliquots from the dissolution vessel need to be quickly filtered and refrigerated immediately after sampling. To meet these challenges, a semi-automated dissolution method was developed and validated. Dissolution samples are withdrawn and filtered into vials in the HPLC sample compartment where the temperature is controlled at 4 °C. A fast HPLC method was developed with a 3-min run per injection, enabling analysis of the samples within a very short time after collection, thereby decreasing the sample storage time and potential for degradation. An evaluation was also conducted for comparison of serial and parallel operation of two dissolution baths for the two-stage testing. Serial operation was chosen for this method and applied with a medium-exchange technique, which is safe, robust, easy to perform, compliant with USP, and gives enhanced productivity.

INTRODUCTION

Enteric coating is a widely used technique for controlled-release oral formulation of pharmaceutical products, specifically for delayed release (*1*). The formulation purposely limits drug release in the stomach, but facilitates release in the neutral environment of the intestine. It enables protection of the drug from the acidic gastric fluid to prevent possible degradation, as well as protection of the stomach from the drug to avoid possible irritation and adverse effects. The enteric materials are usually applied to substrates like tablets, pellets, or beads. The coated pellets and beads are further filled into a capsule shell (*2*–*5*).

During development of an oncology drug at Bristol-Myers Squibb, the technology of coating on beads was applied to make a controlled-release capsule formulation. The physiochemical properties of this drug posed significant challenges for the formulation development, especially its instability in various conditions including (1) in an aqueous acidic environment,(2) during the process of granulation, and (3) when in contact with enteric coating materials. To overcome these challenges, the enteric-coated beads were developed with multiple different coating layers. This formulation uses sugar spheres as the core substrate. The first coating layer on the sphere is a mixture of the drug and excipient. The second layer coating is an Opadry film that prevents drug from contacting the next layer, the final enteric coating. After the final enteric coating is applied, the beads are filled into a hard gelatin capsule shell (Figure 1). The various dosage strengths of the capsules are made using different fill weights.

Evaluation of enteric-coated beads has been performed in both gastric and intestinal media (*5*, *6*). A two-stage dissolution test is specified in *USP* General Chapter <711> Dissolution (*7*), in which the integrity of the enteric coating is determined in an acidic environment and the drug release is measured in a neutral environment. The test can be performed using either medium-addition or medium-exchange methods; both start with an acid stage in 0.1 N hydrochloric acid for two hours and follow with a buffer stage in phosphate buffer at pH 6.8 for 45 min or a specific time as needed for the individual drug product. The quality of the dosage form is ensured by meeting *USP* accep-

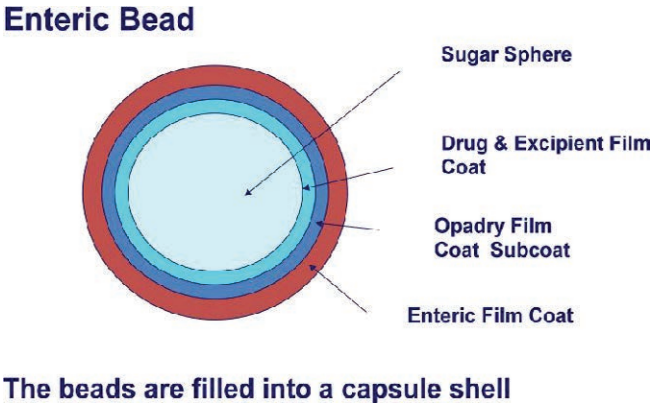

Figure 1. Enteric-coated beads for controlled-release formulation.

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tance criteria for the acid stage when the amount released is limited to 10% or less of the labeled content, as well as for the buffer stage when each unit releases not less than Q + 5% as determined for the design of the dosage form.

Medium addition or medium exchange both require unconventional operational procedures that are not required in the dissolution test for immediate-release and extended-release dosage forms. For the medium-addition approach, a designated amount of concentrated phosphate buffer needs to be added to the dissolution vessel to neutralize the medium to the target pH before the buffer stage starts. The operations of adding the buffer and adjusting the pH need to be completed within 5 min. For the medium-exchange approach, the acid medium is drained after two hours, and a full amount of pH 6.8 buffer is added to the same vessel for the buffer stage. The dosage unit should be undisturbed during the medium change. Alternatively, the vessel containing the acid could be removed and replaced with another vessel containing the buffer, and the dosage unit transferred to the new vessel.

Manually performing the two-stage dissolution test is labor intensive and requires well-trained analysts with a good level of experience. For instance, 5 min is a very tight time period in which to complete the medium addition, pH adjustment, and pH confirmation for six vessels. Also, both medium-addition and medium-exchange approaches require the buffer medium to be preheated and equilibrated to 37 ± 0.5 °C. Zhao and co-workers (*8*) described a manually operated two-stage dissolution method using medium addition and USP Apparatus 2 (paddle), in which the surfactant Tween 80 was also included in the media to enhance solubility of the drug in the buffer stage. However, for testing of the oncology drug in our study, two additional challenges were encountered with manual operation. (1) It is preferable to limit the analyst's contact with the sample solutions during sampling and final washing because of the high cytotoxicity of this drug compound. (2) The dissolution aliquots need to be quickly filtered and refrigerated immediately after sampling due to limited stability of the API in aqueous solution at room temperature.

Automated or semi-automated dissolution systems have been widely available and used in the industry for improvement of productivity with regulatory agency acceptance and 21 CFR Part 11 compliance. Unfortunately, they are not specifically designed for automation of the two-stage dissolution of delayed-release formulations and may face challenges for special types of samples and testing requirements. Fully automated systems all have the capability to perform multiple tasks without analyst attendance, including medium preparation and delivery to vessel, automated dosage-form introduction, automated sampling, filtering, sample collection, vessel washing, and a variety of analytical finish options, such as online photometric analysis and on- or offline HPLC (*9–11*). However, some of them simply cannot be used for two-stage dissolution because they only can prepare (preheating and degassing), hold, and deliver a single type of medium. Other systems may be capable of automatic medium addition and replacement, but they may have a limitation when collecting samples if the sample storage rack cannot be temperature controlled. Therefore, these fully automated systems were not suitable choices for dissolution testing of the controlled-release capsule formulation in this study because of the refrigeration requirement for the sample solutions.

A semi-automated dissolution system is usually a combination of a dissolution bath, an autosampler, and a fraction collector. It has most of the capabilities that the fully automated systems have, except for medium preparation and vessel washing after testing. Many autosamplers are on the market and can be used in combination with devices made by the same or different vendors. Integrated semi-automated dissolution systems are also commercially available with online or offline detection. However, none of the semi-automated systems can perform the complete medium exchange, and none of the systems have a temperature-controlled sample storage rack on their fraction collection station to reduce drug degradation.

A two-stage dissolution method was developed in this lab using the Waters Alliance Dissolution System (Alliance D) and semi-automation for the testing of controlled-release enteric-coated beads in the capsule formulation. This method uses USP Apparatus 1 (basket) and the medium-exchange approach. The Alliance D controls the dissolution baths, withdraws sample aliquots, filters and transfers the samples directly into sealed vials in its sample compartment, and queues under controlled temperature. A fast HPLC method was developed to analyze the samples within a very short time after collection. A Distek Ez-Fill 4500 medium preparation station and a Distek VIP 4400 vessel washer were also applied to the dissolution test to further improve productivity of the testing and reduce analyst contact with the sample solutions. In this paper, the challenges, solutions, and outcome related to the development and validation of the two-stage dissolution method for this special application are described.

MATERIALS AND METHODS

Materials

Both 0.1 N hydrochloric acid and pH 6.8 potassium phosphate buffer were Chata CHEM+NECT ready-to-use dissolution media and were supplied by Chata Biosystems, LLC (Fort Collins, CO). Acrodisc 25-mm syringe filters (1.0-µm glass fiber, non-directional for automation system, and 0.4-µm PTFE membrane filters) were purchased from Waters (Milford, MA). Deionized water (DI-water) was prepared from a Milli-Q water filtration system from EMD Millipore (Billerica, MA). Acetonitrile and methanol used for the study were both HPLC grade from Sigma-Aldrich (St. Louis, MO). Tris buffer pH 7.0 was prepared using

Trizma Pre-set crystals from Sigma-Aldrich (St. Louis, MO). HPLC sample vials with pre-slit Teflon septa caps were purchased from VWR (Radnor, PA).

Samples

The delayed-release formulation studied is composed of enteric-coated beads in hard gelatin capsules. Three dosage strengths of the capsules (2.0, 5.0, and 10 mg) were made using the same beads with different fill weights in the capsule shell. The active pharmaceutical ingredient (API) in the formulation is a BCS Class 3 compound**.**

Semi-Automation System

Four types of semi-automation devices were used for the dissolution test. All of them are GMP-compliant with documented IQ/OQ/PQ records:

1) Dissolution medium preparation station Ez-Fill 4500 (Distek, North Brunswick, NJ). This system degasses, preheats to 37 °C, and dispenses the medium in 90 sec for each vessel.
2) Two dissolution baths VK7000 (VanKel, Cary, NC).
3) Waters Alliance dissolution system, 2695D (Waters, Milford MA). The Alliance 2695D includes two modules: a Waters transfer module (WTM) and an HPLC separation module. It also controls the two dissolution baths. The WTM operates six syringes and withdraws aliquots from the six vessels simultaneously. The data processing and reporting were performed by Waters Empower Chromatography software.
4) Vessel washer VIP 4400 (Distek, North Brunswick, NJ) for post-run vessel washing. It can drain a vessel in 10 sec and wash six vessels using three cycles within 5 min.

Dissolution Method

The two-stage dissolution method developed for the enteric-coated beads in capsule formulation consists of a two-hour acid stage dissolution in 0.1 N HCl with one sampling time point at the end, and a one-hour buffer-stage dissolution in pH 6.8 phosphate buffer with five sampling time points. The medium is changed by the analyst from the acid to the buffer after the first stage has been completed. The dissolution parameters listed in Table 1 are for manual operation. When performed semi-automatically, the dissolution aliquots are withdrawn from the dissolution bath and filtered by the WTM. A non-directional glass fiber filter is utilized, and 1 mL is transferred into the HPLC vials that were pre-capped and stored in the HPLC sample compartment. The autosampler flush volume for the WTM is 12.5 mL. The samples are kept at 4 °C in the sample compartment when queuing for injection to prevent further sample degradation.

Online HPLC Method Finish

A fast HPLC method was developed using the Alliance 2695D for determination of the drug concentration in the dissolution samples. This method uses a Phenomenex Gemini C18 column, 50 mm × 4.6 mm, 5 µm, at 25 °C. A gradient starts with 65% mobile phase A (10% acetonitrile in 5 mM Tris buffer pH 7.0) and 35% mobile phase B (90% acetonitrile in 5 mM Tris buffer pH 7.0) with a flow rate of 2 mL/min and changes to 15% A and 85% B over 2 min. After 2 min, the gradient returns to 65% A and 35% B for 1 min at a flow rate of 3 mL/min to wash and equilibrate the column. The diluent for the reference standard solutions is acetonitrile. The injection volume is 10 µL. The UV detection wavelength is 240 nm. The total run time is 3 min. The retention time of the API is 1.1 min.

RESULTS AND DISCUSSION

Modes of Semi-Automated Operation

As the Alliance 2695D is able to control up to two dissolution baths and samples using 12 lines, it is possible to have two different semi-automation schemes to conduct the two-stage dissolution test, serial and parallel (Figure 2). Both operations start with the Ez-Fill and finish with an online HPLC test and vessel wash. The major difference between the two operations is the usage of the two baths.

Table 1. Two-Stage Dissolution Method for Controlled-Release Enteric-Coated Beads in a Capsule Formulation

Acid Stage		Buffer stage	
Dissolution Apparatus:	USP Apparatus 1 (Basket)	Dissolution Apparatus:	USP Apparatus 1 (Basket)
Basket Size:	40 mesh	Basket Size:	40 mesh
Rotation Speed:	100 rpm	Rotation Speed:	100 rpm
Medium I:	0.1 N HCl	Medium II:	0.05M KH_2PO_4, pH 6.80 ± 0.05
Medium Volume:	1000 mL	Medium Volume:	1000 mL
Medium Temperature:	37.0 ± 0.5 °C	Medium Temperature:	37.0 ± 0.5 °C
Sampling Timepoints:	120 min	Sampling Timepoints:	10, 20, 30, 45, 60 min
Sampling Volume:	5 mL	Sampling Volume:	5 mL
Sample Filter:	0.45 µm, PTFE membrane	Sample Filter:	0.45 µm, PTFE membrane

Conditions for the manual method are provided here; differences when using the semi-automated method are described in the text

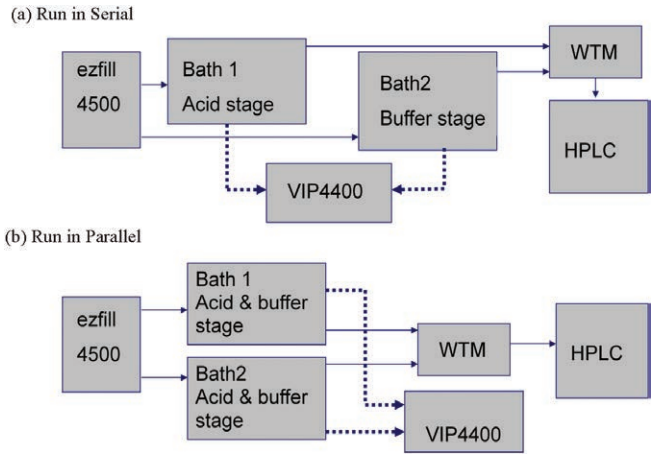


Figure 2. Schemes of semi-automated operation for the two-stage dissolution method. The two baths can be used either in serial or in parallel. The serial scheme can meet the USP requirement for the two-stage dissolution as well as improve productivity.

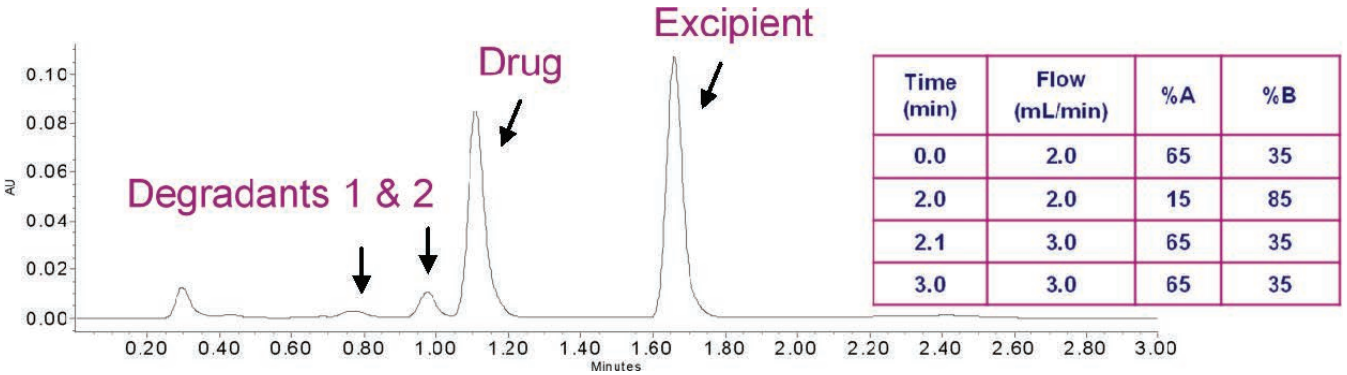
During development, the medium-change procedure was selected over the medium addition. This was based on consideration of the tight 5-min timeslot required by USP for completion of the medium addition and pH adjustment and confirmation for all vessels, which could be a burden during dissolution operation. In contrast, the medium exchange with the use of baskets to hold the capsule provides greater operational flexibility and especially allows the use of a second dissolution bath to prepare the medium for the buffer stage.

When operating in serial mode, Bath 1 is designated for the acid stage and Bath 2 is for the buffer stage. The system performs testing for one sample set (six dosage units) at a time, and starts in Bath 1. When the system is ready, a signal from the Alliance 2695D triggers the start of the HPLC run as well as the dissolution run. Because the first aliquot would not be withdrawn until 2 h later, the HPLC module can complete the analysis of the blank and working standard solutions and stay on standby until the six acid samples are ready to inject. As the acid stage is in progress, Bath 2 is being prepared and filled with preheated and degassed medium. The baskets that hold the drug dosage units are removed from Bath 1 at the end of the acid stage and immediately transferred to Bath 2 to start the buffer stage without any delay. The HPLC continues to inject the queued samples; analyses for all aliquots from the sample set can be completed one hour after the buffer stage stops. In case more sample sets need to be tested, a new acid stage can start for the second sample set as soon as the HPLC run is completed because Bath 1 can be drained, washed, and prepared when waiting for the HPLC analysis. In this way, the time needed for the two-stage testing of two sets of the samples is about 8 h 20 min, but the analyst does not need to attend for the last two hours after moving the baskets to Bath 2 for the second sample set. This enables the analyst to complete the dissolution for two sets of samples within a daily working schedule.

When operating in parallel, each of the two baths is used for both acid and buffer stages for one sample set. In theory, two sample sets could be tested using this operation and started simultaneously. In this configuration, it is possible to complete the two-stage testing for two sets of the samples within 5 h 30 min including the time for the HPLC analyses. However, a problem occurs when changing the media. The system will take at least 15 min to clean and refill six vessels. This will exceed the 5 min required by USP for the gap between the two stages.

Analytical Method Finish

HPLC analysis was chosen over a UV spectrophotometric assay for the dissolution method finish. This was because the excipients in the formulation have UV absorbance in a similar wavelength range as the API, which will interfere with the quantification if online or offline UV is utilized. A fast gradient was developed to separate the excipients, API, and drug-related degradants, and thus overcome the excipient interference (Figure 3). The 3-min run



Time (min)	Flow (mL/min)	%A	%B
0.0	2.0	65	35
2.0	2.0	15	85
2.1	3.0	65	35
3.0	3.0	65	35

Figure 3. HPLC chromatogram of a typical dissolution sample measured using a fast gradient elution program and UV detection at 240 nm. The total peak areas of the drug and degradants 1 and 2 are quantified and summed to determine the total amount of drug released.

time per injection enables quick analysis of the samples after collection. This rapid analysis is enabled via the use of a 2 mL/min flow rate during the separation and a flow step to 3 mL/min during the re-equilibration to reduce the required re-equilibration time. As a result, the storage time of the post-dissolution samples and the potential for degradation are decreased. However, the drug compound is very unstable in aqueous solution, and so even though the sample storage time is shortened and the storage temperature is controlled to 4 °C, degradation does still occur in the vessel during the dissolution test. Two drug-related degradants were confirmed using mass spectrometry, so a procedure to account for this was established in the Empower (chromatographic data system) method for peak integration and calculation. The peak areas of the drug and related degradants were summed and the total was used for quantification of the drug released. As the degradants have similar UV spectra as the API, a correction factor is not needed for the quantification. The Alliance 2695D can be applied to either online or offline finish.

Validation of the Semi-Automated Dissolution Method

The semi-automated dissolution method was validated per requirements of *USP* General Chapter <1092> (*12*). With respect to the use of the method for early drug development, the validation focused on parameters of HPLC analysis, filter evaluation, flush volume justification, sample carryover, and equivalency to manual operation.

HPLC Validation

The specificity was evaluated by assessing the interference from capsule shell and excipients at the 2-mg and 10-mg dosage levels. The results show no interferences >2.0% in comparison with working standard solutions.

The linearity was tested for seven points from 0.5% of the 2-mg level to 140% of the 10-mg level. The coefficient of determination (R^2) was 0.9999, and the *y*-intercept was -0.08% of the target concentration at the 2-mg level.

The accuracy was evaluated with three spiked samples with the presence of capsule shell and excipients at 100% of the target concentration in the buffer stage for the 2- and 10-mg dosages. The mean percent recovery in the pH 6.8 buffer was 101.4% with 1.40% RSD for the 2-mg level and 100.4% with 0.72% RSD for the 10-mg level. Similar spiked samples were made in the acid medium but containing only 5% of the target concentration of API. The lower concentration was used since extensive drug release was not expected in the acid medium, and so the validation was performed at a lower level that is relevant to the analysis. The mean percent recovery in the acid was 83.7% with 2.28% RSD for the 2-mg level and 83.8% with 1.62% RSD for the 10-mg level. This was within the acceptance criterion of ±20%, which is appropriate for the measurement at the expected low levels in the acid medium.

The precision was determined for both the 2- and 10-mg levels using six replicate injections. The RSDs of the total peak areas were less than 1.3% for all the working standard solutions and the samples in the buffer. For the samples in acid, however, the RSD was 8.8% for the 2-mg level and 9.6% for the 10-mg level.

The stability of the sample solutions stored for 24 h at 4 °C was assessed. The recoveries of the working standard solutions and the samples in the buffer were all within 100.0 ± 2.0%. The API in 0.1 N HCl was very unstable. Close to 30% degradation was detected for a 0.1 mg/mL solution stored at ambient temperature for 6 h.

Filter Evaluation

The PTFE membrane filter used for the manual dissolution test is not suitable for the semi-automation because the 2695D requires a bidirectional filter with less resistance. A 1.0-µm glass fiber, non-directional filter specially designed for the 2695D system was utilized instead and validated. The filter was tested in both directions for the filtration of the working standard solution and the samples in acid and buffer, all at the concentration of the 2-mg level. The recoveries of all the filtered solutions were compared with those of the unfiltered solutions. All results were within 100.0 ± 1.0%.

Flush Volume

The flush volume was studied to determine the minimum volume required to thoroughly flush the WTM in the 2695D system sample lines for each time point before sampling. Evaluation was performed for 5, 10, and 12.5 mL for the buffer-stage sampling. Results show that a suitable volume is 12.5 mL (See Figure 4). The system actually flushed 12.5 mL and dispensed a 1-mL aliquot into an HPLC sample vial for analysis.

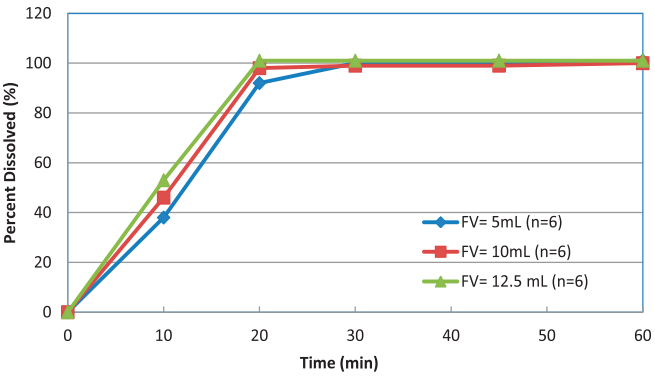


Figure 4. Dissolution profiles of the 10-mg dosage of the controlled-release enteric-coated beads in capsule formulation in the buffer stage. A flush volume of 12.5 mL was selected for the Alliance 2695D. The selected flush volume is greater than the vendor suggested volume 7.5 mL.

Sample Carryover

Two studies were performed to evaluate the possible carryover of the drug and excipient from run to run and to determine the required washing: (1) WTM post-run washing cycle to clean up the sampling syringe, the dispenser needle, and transfer line; and (2) VIP 4400 vessel washing cycle to remove possible residue. For the WTM study, a post-run washing cycle using 15 mL of DI-water and 15 mL of methanol/water (50/50) was sufficient. For the VIP 4400 study, DI-water at room temperature was used as the washing reagent. Three DI-water wash cycles of 250 mL each were necessary to clean each vessel. Each evaluation was conducted with a null sample test after a dissolution run. The null test results showed that the carryovers were all less than 0.5%.

Manual and 2695D Equivalency

Dissolution was performed for both 2- and 10-mg capsules using the semi-automated method as well as manual sampling at each time point with offline HPLC finish. The drug percent of label dissolved in the acid stage was less than 1% for both manual and automated sampling. The differences of the percent of label dissolved in the pH 6.8 phosphate buffer between the manual and automated sampling were <3% at the 10-min time point and <1% at 20, 30, 45, and 60 min (See Figure 5).

Method Application

The method was successfully applied to the testing of 2-, 5-, and 10-mg capsules for formulation development, an IND stability study, and clinical release. The 5-mg dosage was initially developed but not used for IND stability and clinical studies. However, the method was considered valid for testing of the 5-mg dosage because the 5-mg dosage used the same enteric-coated beads and capsule

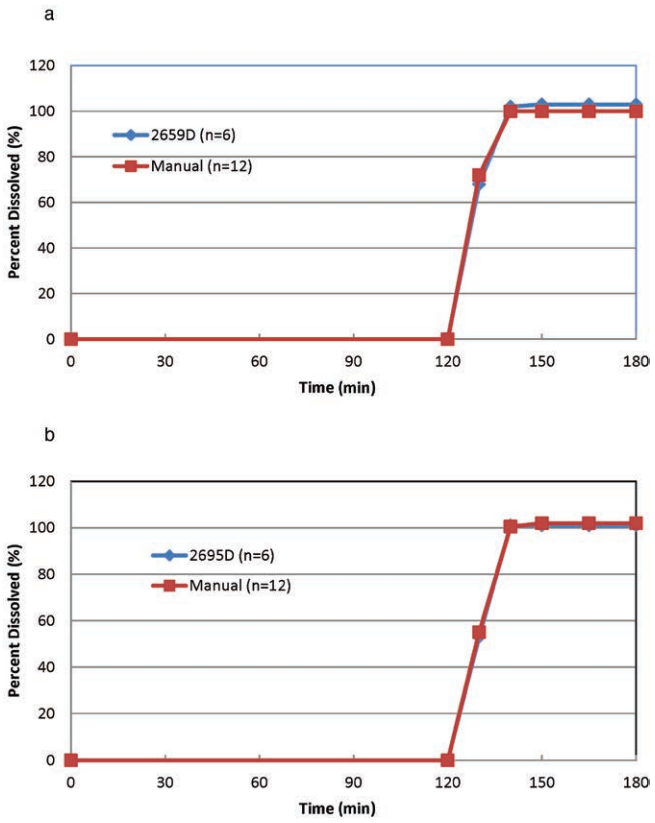


Figure 5. Comparison of dissolution profiles of the dosage controlled-release enteric-coated beads in capsule using semi-automated Alliance 2695D versus manual sampling, (a) 2-mg dosage; (b) 10-mg dosage.

Table 2. Dissolution Results for Stability and Clinical Samples of the 2- and 10-mg Controlled-Release Enteric-Coated Beads in a Capsule Formulation Generated Using the Semi-Automated Two-Stage Dissolution Method

Sample	Timepoint (min)	Acid stage	Buffer stage				
		120	10	20	30	45	60
2-mg stability initial	% Released[1]	0	70	99	100	100	100
	STDEV[2]	0	8.6	2.2	2.3	2.3	2.3
2-mg stability	% Released[1]	0	74	104	104	105	105
3 month/25C60%RH	STDEV[2]	0	9.2	3.8	3.3	3.1	3.5
10-mg stability initial	% Released[1]	0	54	100	101	101	101
	STDEV[2]	0	10.2	1.4	1.3	1.3	1.3
10-mg stability	% Released[1]	0	53	99	101	101	102
3 month/25C60%RH	STDEV[2]	0	4.2	2.6	2.4	2.1	2.3
10-mg clinical batch	% Released[1]	1	64	97	98	98	98
	STDEV[2]	0	3.3	1.8	1.5	1.9	1.6

[1] *The % released for each sample at each timepoint is the average of 6 dosage units.*
[2] *STDEV is the standard deviation of % release for the measurements in 6 vessels at each timepoint.*

shell as for the 2- and 10-mg dosages but with only a different fill weight. The 5-mg dosage was bracketed by the validation using the 2- and 10-mg dosages. The results shown in Table 2 for the 2- and 10-mg dosages indicate that high-quality analytical data was achieved using this method, which is suitable for development support. The method proved to be rugged, practical, and easy to operate over a period of several months during development of this drug candidate.

CONCLUSION

The semi-automated two-stage dissolution method developed for the controlled-release enteric-coated beads in a capsule formulation is a practical solution to meet all challenges in the development and testing of this formulation. The method utilized the medium-exchange approach, with semi-automated preheat, degas, dispense, post-run wash, and sample storage under controlled temperature. The method was validated, is compliant with USP, and is equivalent with the manual dissolution. Use of the semi-automated method doubled the productivity, improved the sample stability, and reduced the potential for analyst contact with the toxic drug solution. The operation of the system in a serial mode was beneficial to this study.

To further improve the productivity and simplify the semi-automated two-stage dissolution method, several considerations can be explored in future work: (1) Test the medium-addition approach for parallel operation. It may be possible to narrow the time gap between the two stages to less than 5 min by eliminating the vessel draining and decreasing the refill volume, as the medium-addition approach need not remove the acid, but only needs to add 250 mL of concentrated phosphate buffer with confirmation of the pH. (2) Work with the vendor to improve the control software of the Alliance 2695 D so that more flexibility can be achieved to set up more than two runs with the two baths and to coordinate more overlapping of the HPLC injections. (3) Develop an even faster HPLC method to further decrease the current 3 min/injection run time to match the dissolution sampling speed and time points. It would be ideal if the WTM of the Alliance D could be applied to an Acquity system, as the current HPLC method can be easily scaled down to a very fast VHPLC method on an Acquity with 90 sec/injection, which could make it possible for timely analysis of the dissolution aliquots.

ACKNOWLEDGMENT

The authors wish to thank Ruben Lozano and Steve Klohr for helpful comments and review of this article. Discussions with Gary Wiley on the formulation and method development are greatly appreciated.

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