A Flexible Automated Dissolution Testing System for Use with Either USP Apparatus 1 or USP Apparatus 2

Jeanette D. Dunkle,[1] Daniel J. Gleason,[1] and Gerard C. Hokanson[1,2]

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INTRODUCTION

Dissolution testing of solid oral dosage forms is required by a variety of official compendia (1,2) for both initial analytical release and shelf-life stability testing. For some products this *in vitro* test may mimic the *in vivo* process of drug dissolution after oral administration of the drug product to patients (3). With the widespread acceptance of routine dissolution testing within the pharmaceutical industry, various automated procedures have been developed (4–11). Complete automation has been achieved by the Zymark Corporation, whose system is capable of filling test vessels, introducing dosage units, analyzing samples, emptying and rinsing the vessels, and then repeating the cycle several times. However, the Zymark system as purchased in late 1986 was capable of performing dissolution analysis using only USP Apparatus 2, with only UV sample analysis available on-line. The shortest sampling interval achievable was 15 min. Although adequate to test a large number of pharmaceutical samples, additional system flexibility was desired.

Beginning with the automated system as purchased from Zymark, capabilities were expanded to accomplish (i) reduction of the sampling interval for six test vessels to 10 min to generate more detailed dissolution profiles; (ii) on-line HPLC as well as UV analysis; and (iii) utilization of both USP Apparatus 1 (rotating baskets) and Apparatus 2 (rotating paddles). In this report, the steps necessary to achieve these development goals and the development rationale guiding this work are described.

MATERIALS AND METHODS

Materials

The tablets analyzed were samples of products under development at Parke-Davis at the time of this work. Dissolution and chromatographic data are presented for investigational samples of propranolol hydrochloride tablets USP and quinapril hydrochloride tablets (Accupril, Parke-Davis) obtained in-house. Dissolution calibrator tablets and standards were obtained from the United States Pharmacopeial Convention, Inc.

Instrumentation

The robotic system used was a Zymate II automated dissolution testing system (Zymark Corporation, Hopkinton, MA). The system was also equipped with an analytical instrument interface, two power and event controllers, an HPLC injector station, and a Vanderkamp VK 6000 six-spindle dissolution tester (VanKel Industries, Inc.).

Chromatographic Analysis

Ultraviolet measurements were recorded using a Hewlett-Packard 8451A spectrophotometer which ran a Zymark-supplied program allowing the spectrophotometer to accept data from the system controller. HPLC analysis was performed using either a Brownlee CN (5-μm, 4 mm × 3-cm) or a Zorbax CN (3-μm, 6 mm × 4-cm) column, an ABI 783 UV/VIS detector, and an ABI series 400 pump. Data were collected simultaneously on a Hewlett–Packard 3393A computing integrator and Beckman LIMS running Peak-Pro software using a Hewlett–Packard 1000 computer. All solvents, buffers, and reagents used were HPLC grade.

RESULTS AND DISCUSSION

Profiled Dissolution Testing

During the development of oral dosage forms, the rate of drug release *in vitro* is a critical parameter in judging the performance of experimental formulations. In order to generate dissolution rate information to evaluate the potential correlation between *in vitro* and *in vivo* results, drug release at several sampling points during the test must be measured. Examination of the dissolution profile at short time intervals (e.g., 5–10 min) also provides the best characterization of dissolution properties throughout a stability program. As an added benefit, more meaningful product specifications for eventual use in quality assurance can be established if dissolution profiles are monitored throughout development.

As purchased, the automated dissolution system was capable of sampling each of six test vessels at no less than 15-min intervals. To provide 10-min sampling, the frequency of filter replacement was reduced, the sample flow was reversed back through the sampling line to the vessel (to dislodge any particulates adhering to the filter), and only one UV reading per sample was recorded. While reducing the number of filters used during the run increases the potential for sample carryover from one vessel to the next, no significant (greater than 1%) sample contamination has been observed during validation runs. The lack of product adsorption onto the filter tips is also validated as each new product is introduced onto the system.

On-Line HPLC Sample Analysis

Dissolution sample analysis is typically performed using simple spectrophotometric measurements whenever possi-

[1] Analytical Development Department, Parke-Davis Pharmaceutical Research, Warner-Lambert Company, Morris Plains, New Jersey 07950.
[2] To whom correspondence should be addressed.

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ble. However, when greater method selectivity is required, due to excipient interferences or the weak UV absorption of the drug, HPLC sample analysis is preferred. The Zymate II dissolution system accommodated HPLC analysis for immediate-release products only through sample storage and off-line testing. Off-line analysis, however, presents several disadvantages, including potential degradation of the analyte and considerable delay in obtaining final results. The availability of numerous commercial HPLC columns with both a high sample capacity and short chromatographic run times has made on-line analysis of dissolution samples feasible. To accomplish on-line HPLC analysis with the Zymate II dissolution testing system, a chromatographic pump, injector station, detector, and data handling equipment were added to the benchtop layout. The sampling line which extended from the robot "hand" to the spectrophotometer was reconnected to the inlet port of the loop injector and a new line added to connect the outlet of the injector to the inlet of the spectrophotometer flow cell. This setup permits either HPLC or UV sample analysis (or both if desirable) without modification of the benchtop. In addition, with this setup the same dissolution software programs are operative in both UV and HPLC applications.

To facilitate inspection of HPLC data, the chromatographic run time was configured to encompass all injections from a six-unit dissolution test. For a typical 30-min dissolution test with 10-min sampling intervals, a total of 18 sample injections is contained in the same chromatogram. Using this format, the analyst can visually examine the relative dissolution profile at a glance by comparing the relative peak heights over time, without having to page through separate chromatograms. Figure 1 shows a representative chromatogram for a dissolution trial (reduced to three samples for clarity of presentation). An example of a chromatogram in which system precision is assessed with a standard preparation using the same chromatographic approach is shown in Fig. 2.

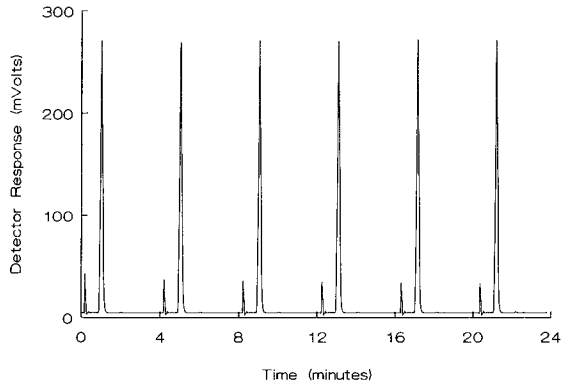

Fig. 2. Representative chromatogram for testing HPLC system suitability parameters.

Dissolution Analysis with USP Apparatus 1 (Rotating Baskets)

The final development goal was the utilization of USP Apparatus 1 (rotating baskets). Automation of dissolution procedures using USP Apparatus 2 (rotating paddles) has been accomplished in a number of laboratories. The use of the rotating-basket apparatus presents two additional challenges to automation: (i) using the basket apparatus described in the USP, attachment of the basket to the stainless-steel shaft cannot effectively be performed robotically; and (ii) assuming that baskets could be attached, independent start times for each test vessel would be difficult.

Several attempts to reliably attach the standard (USP) wire-mesh basket to the conventional stainless-steel shaft using the robot were unsuccessful. An alternative basket attachment procedure utilizing a magnetic mechanism has been reported (4). However, this modified apparatus includes coated magnets fitted to both the basket and the shaft, resulting in an enlargement of the apparatus which may alter the fluid flow dynamics within the test vessel when compared with the standard USP apparatus. Therefore an alternative attachment scheme was desired.

The start time for a dissolution test using the rotating paddle test apparatus is the moment at which the dosage unit

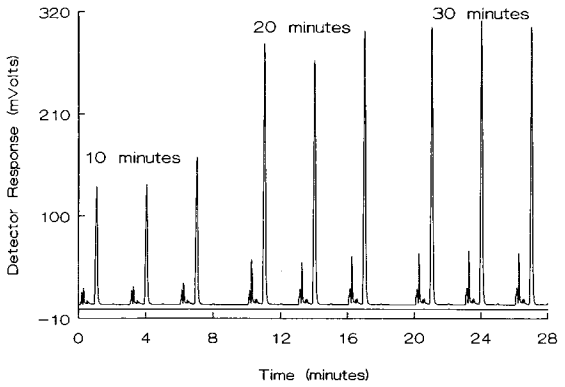

Fig. 1. Representative chromatogram for a set of three dissolution samples at three time points.

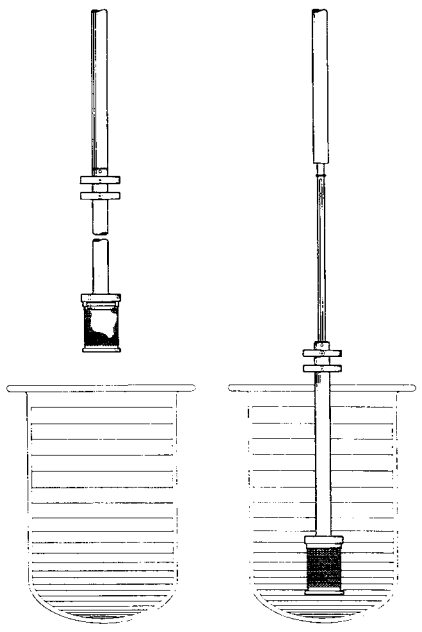

Fig. 3. Schematic diagram of the modified stainless-steel shaft for use with the rotating-basket apparatus.

Table I. Comparative Dissolution Results Obtained Using USP Apparatus 2 (Rotating Paddle Apparatus) with Manual and Robotic UV Sample Analysis: Results for Propranolol Hydrochloride Tablets USP

	Results (%)	
Time (min)	Manual	Robotic
10	67	67
20	92	92
30	100 (3.6)[a]	100 (3.6)[a]

[a] Percentage relative standard deviation in parentheses (n = 12).

Table III. Comparative Dissolution Results Obtained Using the Modified USP Apparatus 1 (Rotating-Basket Apparatus) with Off-Line (Manual Sampling) and On-Line (Robotic) HPLC Sample Analysis: Results for Accupril Tablets

	Results (%)	
Time (min)	Manual	Robotic
10	74	78
20	94	94
30	95 (1.5)[a]	96 (1.7)[a]

[a] Percentage relative standard deviation in parentheses (n = 12).

is dropped into the media. Automated lowering of the rotating basket containing the dosage unit into the medium is more difficult. The dissolution bath used in this study can be modified to raise or lower a set of six basket/shaft assemblies simultaneously into the test medium. However, the USP guidelines allow only ±2% tolerance in the stated sampling times. With a single sampling device, i.e., the robotic arm with the sampling hand attached, automated sampling at short time intervals while still remaining within the ±2% limit is not possible.

To overcome the limitations of the existing basket apparatus and achieve independent start times for each sample, a modified basket shaft was designed. This shaft, depicted in Fig. 3, employs an inert O-ring to secure a standard USP wire mesh basket to the shaft. The shaft utilizes a telescoping mechanism to allow independent lowering of each shaft/basket combination into the medium at the start of the test. An O-ring is also used to support the movable portion of the shaft in the collapsed position. Using this improved shaft and the standard basket, the same timing sequence and on-line HPLC procedure developed for Apparatus 2 (paddles) could also be used for Apparatus 1.

The modified shafts used for these studies were in-house prototypes. The shaft design has been licensed to the Zymark Corporation for commercial development. The prototype shafts were employed to calibrate the robotic system for basket use (see below) and have been successfully used for an extended period of time with the O-rings exhibiting no sign of wear.

System Validation

To accomplish system validation, three criteria had to be met: (i) the system must conform to all standard requirements for dissolution test systems, (ii) dissolution results using the automated system must be in close agreement with results obtained by manual testing, and (iii) all HPLC methods employed must be validated in the standard manner. To realize the first two of these objectives, the complete robotic system was validated by performing our in-house calibration procedure, including use of USP calibrator tablets (Prednisolone and Salicylic Acid) with both paddle and basket assemblies, and by performing a series of comparison studies using actual products. Using the modified robotic dissolution system described above, all specifications have routinely been met.

As each new product is tested for the first time on the automated system, a side-by-side test is performed comparing results obtained robotically with those obtained using standard manual sampling procedures. Representative results for comparative testing are shown in Tables I–III. These data demonstrate that the modified robotic system is capable of generating results which agree well with those obtained manually.

Table II. Comparative Dissolution Results Obtained Using USP Apparatus 2 (Rotating-Paddle Apparatus) with Off-Line (Manual Sampling) and On-Line (Robotic) HPLC Sample Analysis: Results for Propranolol Hydrochloride Tablets USP

	Results (%)	
Time (min)	Manual	Robotic
10	90	89
20	97	98
30	97 (5.2)[a]	99 (4.6)[a]

[a] Percentage relative standard deviation in parentheses (n = 12).

CONCLUSIONS

The Zymate II automated dissolution testing system has been modified to perform fully automated analysis with maximum system flexibility. As modified, the system can perform dissolution analysis at 10-min time intervals, generating profiled dissolution data for interpretation. The system can also analyze samples using either UV or on-line HPLC methods and can perform testing with either Apparatus 1 or Apparatus 2 (baskets or paddles) with a minimum of changeover time. Using the modified system, detailed information regarding the dissolution properties of new products can be obtained without the expenditure of significant analyst time. As a result of flexible system automation, nearly any sample received in a lab for analysis may now be tested for dissolution properties concurrently with other required analysis, reducing the overall sample turnaround time while maximizing immediate feedback of test results to the analyst.

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