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Short Communication

Validating an automated dissolution method for a tablet containing both sustained and immediate release active components*

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Keywords: *Multi-Bath Dissolution Testing System; validation; automation; dissolution rate system; diode-array spectrophotometry; sustained release.*

Introduction

Dissolution testing of a tablet formulation containing one sustained release and one fast release component required automation to allow periodic sampling over 24 h and high sample throughput. A Hewlett–Packard Multi-Bath Dissolution Testing System® (MBDS), in conjunction with USP Apparatus II, was considered for this purpose, particularly because of its potential for high throughput with sustained release products. The MBDS can operate up to four dissolution apparatuses simultaneously and generate a final report, including graphics, at the end of the run. However, the system can only be used with analytes with appropriate spectral properties because it operates with a diode-array spectrophotometer. The purpose of this work was to determine the applicability of multicomponent diode-array spectrophotometry to the formulation in question, and the extent to which the resulting procedure could be operated in compliance with GMP/GLP requirements for automated systems (21 CFR 211.68). Recently published clarifications of regulatory positions on this subject [1–3] were considered. The applicability of the methodology to the formulation was assessed from the quality of data, the ruggedness of the method and a comparison against an independent method. A protocol was devised to test and document the performance of the MBDS and dissolution apparatuses. The protocol utilized all of the MBDS software driven diagnostics as well as a number of independent checks and documentation routines.

Experimental

Equipment

Multi-Bath Dissolution Testing System (Hewlett–Packard, Palo Alto, CA) consisted of: four eight-port valve units (Model HP89079A); four peristaltic pumps (Model HP89052B); channel controller (Model HP89078A); diode-array spectrophotometer, single beam, 2 nm resolution, 190–820 nm (Model HP8452A) with multicell transport unit (Model HP89075C) for four 1 mm QS quartz flow cells; personal computer, Vectra QS/20 Model 46 with 42 MB hard drive, 20 MHz-80386 1 MB system memory, 4 MB memory expansion (Model HP312), math coprocessor, Intel (part no. 80387-20), colour monitor, VGA (Model HP491), mouse (Model HP471), printer, Paintjet (Model HP532), and tape drive (part no. D2045A). Connecting tubing was 1/32 in. i.d. Teflon. Software consisted of: Multi-Bath Dissolution Testing Software rev. 2.00 (Model HP89551A) (Hewlett–Packard); MS-DOS rev. 4.0 (Model HP491) (Hewlett–Packard); Microsoft Windows rev. 3.0 (Microsoft, Redmond, WA); Tiffany Plus rev. 1.5N (Anderson Consulting and Software, North Bonneville, WA); and EZ-Tape (Microsoft).

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Spectral overlays for illustration were acquired with UV–vis General Scanning Software rev. 3.00 (Model HP89531A) (Hewlett–Packard).

Dissolution Apparatuses — DissoRate8 (Scientific Instruments and Technology, Englishtown, NJ) conformed to USP Apparatus II and consisted of four units. Each unit provided programmable print outs of bath temperature and paddle speed. Vessel probes were constructed of 1/16 in. i.d. Teflon tubing, and were constantly immersed throughout run at the prescribed USP sampling position. Filters were not required in this application because the formulation did not produce particulates. Paddles were Teflon coated.

External calibration equipment consisted of: a NIST certified mercury thermometer, 0–50°C, readable to 0.1°C; model no. 2100-3 (W. Kessler, Westbury, NY), and a NIST certified hand held tachometer, max. error 0.05%, cat. no. 05-028-23 (Fisher Scientific, Pittsburgh, PA).

Samples and media

Samples consisted of one lot of an experimental tablet formulation providing sustained release of 240 mg of drug A over 24 h and fast release of 10 mg of drug B over 1 h. Simulated gastric fluid was prepared as described in USP XXII except without the addition of enzymes (12 g sodium chloride and 42 ml concentrated hydrochloric acid diluted to 6 l with distilled water). It was used without degassing except as required for ruggedness testing where ultrasound and vacuum were applied for 30 min prior to use.

Configuration of the system

Each USP dissolution apparatus contained eight vessels, six for test samples, one for blank media and one for control solution. The sample probe in each vessel connected to an eight port valve. Each valve had a single line passing through a peristaltic pump to its own flow through cell in the spectrophotometer. The stream went to waste from the cell. Cells moved into and out of the light path by means of a cell transport unit. One to four dissolution apparatuses could be used with the MBDS during a run, but all had to operate under the same method.

Method

The method was created through dialogue with the MBDS software. The parameters were set as follows. Bath temperature = 37°C. Paddles speed = 50 rpm. Media = 900 ml SGN without enzymes. Wavelength interval = 210–280 nm. Pump time = 70 s. Sampling intervals = 1, 3, 6, 12, 18 and 24 h. Data type = absorbance every 2 nm over the entire wavelength interval. Calculation method = least squares fit of the standard spectra to the spectrum of the measured sample, integration time = 1.0 s. Type of volume correction = 'correct for lost volume'. Volume per sample = volume dispensed (5–10 ml) in 70 s (pump time). Report units = % dissolved.

Validation and Documentation Procedures

Assay for analytes by diode-array spectrophotometry

The fast releasing drug B, which is present at a lower level in the formulation, dissolves in 900 ml of media within 1 h, while the sustained release drug A, at more than a 20 fold higher level, dissolves slowly over 24 h. Theoretically, by the first monitoring point at 1 h, 100% of drug B would be in solution. The expected differences in concentrations of the two drugs over the course of the dissolution test were considered in the following work. Absorption in the UV region and independence of standards were demonstrated by acquiring spectra for each drug by itself in media. The concentrations represented the point in the dissolution test where 50% of A and 100% of B would be dissolved. Addition of absorbances was demonstrated by combining equal volumes of these two solutions and measuring absorbances at wavelengths where both drugs absorb (222 and 246 nm). Linearity of absorbance with concentration was tested with individual solutions of drugs A and B in media, representing a range wherein 10–100% of the respective drug would be dissolved. The accuracy of the assay, as measured through the MBDS, was determined with mixtures of known concentrations of drugs A and B in media. These concentrations represented points at which 20, 40, 80 and 100% of drug A would be in solution along with 100% of drug B. The concentration of each analyte found by assay was compared to the known concentration to evaluate accuracy. Finally, potential interference from excipients was evaluated by performing a dissolution test with a placebo tablet and acquiring the spectrum of the media at the 24 h sampling interval.

Ruggedness testing

A series of dissolution tests on the tablet lot was conducted by varying one parameter at a time, as shown in Table 1, for temperature, paddle speed, media composition, media degassing and computation method.

Comparison against an independent dissolution test

A dissolution testing system involving robotic sample collection and liquid chromatographic analysis was used for comparison to the MBDS system. The type of dissolution apparatus, test conditions, tablet lot and sampling intervals were the same for both systems.

Protocol for validation of equipment performance

The MBDS offered numerous software driven diagnostic tests to check the operational status of the system and displayed the results on screen, but not in hard copy. Screen printing through the Tiffany software provided the hard copies required for documentation, but annotation by hand was required to include additional key information. Some of the MBDS software driven diagnostics required infrequent application, while others were performed just prior to and during the course of a run. A semi-annual diagnostic test checked the integrity of the program by processing an internal set of raw data. A validation test of the valve system was run monthly to check for contamination resulting from obstructions causing variation in flow from channel to channel. The following MBDS diagnostic tests were conducted just prior to a run to check: (1) operational status of valves, pumps, and cell transport unit; (2) agreement of actual volume dispensed within the pump time with the value in the method; (3) adequacy of the flow rate to allow sample reading within the pump time; and (4) compliance with spectrophotometer dark current, intensity and stability specifications. Upon entering the run mode, the response of the MBDS to a control solution containing known concentrations of each analyte was checked. The media test was also performed at this point to check for contamination in the vessels or lines by sampling and scanning, in turn, each of the six test vessels in the bath against blank media in the seventh vessel.

Aside from the software controlled validation tests, a number of other checks were performed to ensure that the system was functioning correctly. Results were documented by log entry. The dissolution apparatus was calibrated semi-annually according to USP procedures. The spectrophotometer was calibrated semi-annually for stray light, and wavelength and spectrophotometric accuracy and repeatability. Immediately before each run paddle speed and media temperature were checked against a calibrated tachometer and thermometer, respectively. All plumbing connections and positions of flow cells were checked. Size of flow cells were checked against that specified by the method. Sufficient spectrophotometer warm up time was confirmed. The method was printed out and compared to that of an authentic reference copy to assure that no changes had been made. Raw data files were protected from overwriting at the conclusion of the run. Accumulated data were periodically transferred from hard disk to tape storage in order to preserve data and clear the disk.

The MBDS software was tested by determining its reponse to changes in interdependent variables (minimum cycle time, pumping time), entry of incompatible parameter values (sampling intervals, minimum cycle time), or incorrect information (control solution concentration). Program controlled timed events (pumping time, tablet drop time) were measured against an external clock.

Table 1
Ruggedness testing of the dissolution method involving variation in bath temperature, paddle speed, media composition and mode of calculation

Parameter	Standard method	Variation
Bath temperature	37°C	25°C; 45°C
Paddle speed	50 rpm	25 rpm; 75 rpm
Media composition	USP SGN (no enzymes)	Low HCl; No NaCl
Media degassing	No	Yes
Computation method	Absorbance with least squares	First derivative with maximum likelihood

Table 2
Additive absorbance of drug A and drug B in SGN at 222 and 246 nm

Wavelength	Absorbance				
	Soln 1*	Soln 2†	Soln 3‡	Adjusted sum of 1 and 2§	Per cent difference‖
222	0.01614	0.02928	0.02321	0.02271	2.2
246	0.00746	0.00537	0.00615	0.00642	4.2

*Soln 1 = 0.134 mg A ml^{-1} or 50% of the label content (240 mg A) dissolved in 900 ml of SGN.
†Soln 2 = 0.013 mg B ml^{-1} or 117% of the label content (10 mg B) dissolved in 900 ml of SGN.
‡Soln 3 prepared by mixing equal volumes of solutions 1 and 2.
§Adjusted sum = $(Abs_{\lambda soln\,1} + Abs_{\lambda soln\,2})/2$.
‖Per cent difference = $(Abs_{\lambda sum} - Abs_{\lambda soln\,3}) \times 100/Abs_{\lambda sum}$.

Results and Discussion

The spectra for analytes A and B, which are shown in Fig. 1, indicated that absorption and spectral differences in the region of 210–280 nm were adequate for multicomponent diode-array analysis. A value of 2.6 for independence of standards (1.0 = no spectral difference) was calculated through the MBDS software. Absorbances were shown to be additive to within ~5% as shown in Table 2. Regression analysis for three standards of drug A, covering a concentration range of 0.0300–0.254 mg ml^{-1}, resulted in values of: slope = 0.369 (SE = 2.19×10^{-3}), intercept = 1.810×10^{-3} (SE = 3.77×10^{-4}), and $r = 0.9999$. Three standards of drug B, covering a range of 0.001–0.012 mg ml^{-1}, resulted in values of: slope = 1.43 (SE = 2.231×10^{-2}), intercept = 3.794×10^{-4} (SE = 1.86×10^{-4}), and $r = 0.9998$. These results indicated that linearity and zero intercept were satisfactory for each analyte. At the end of a 24 h dissolution test, the placebo tablet produced a clear solution with no significant absorption over the analytical wavelength range, thereby showing that the excipients did not interfere in the test. Results for the analysis of mixtures of A and B in media agreed to within ±5% of the known concentrations (Table 3).

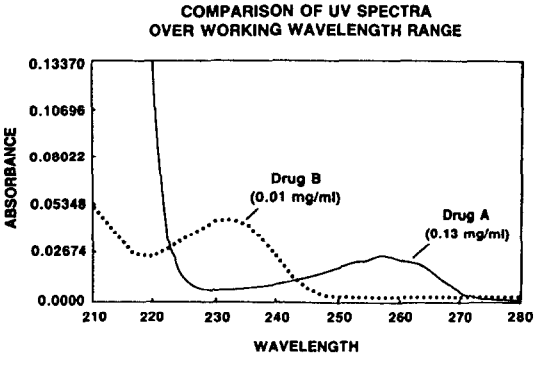

Figure 1
Individual solutions of drug A (---) at 0.13 mg ml^{-1} and drug B (●●●) at 0.01 mg ml^{-1}. These levels represent 50% of label of drug A and 100% of label of drug B dissolved in 900 ml of dissolution media (SGN, no enzymes).

Table 3
Analysis of mixtures of drug A and drug B using the MBDS

Soln	Nominal % of label potency*		Per cent recovery†	
	Drug A	Drug B	Drug A	Drug B
1	20	100	104	104
2	40	100	102	102
3	80	100	101	99
4	100	100	100	98

*Label potency = 240 mg drug A and 10 mg drug B per tablet. Concentration represents per cent of label potency dissolved in 900 ml of SGN.
†Per cent recovery = (Found Conc./Prepared Conc.) × 100.

Ruggedness testing demonstrated that within the ranges of the parameters tested, dissolution rates were only affected by a wide variation in temperature. Per cent dissolved values of drug A at the 12 h point were 48, 58 and 72% at 30, 37 and 45°C, respectively. Comparison of results obtained by the MBDS method versus those acquired by robotic sample collection with liquid chromatographic analysis are shown in Fig. 2. The dissolution rate curves, which represented an average of six tablets in each case, were essentially superimposable, thereby indicating that there was no significant difference in results by the two procedures.

The program responded appropriately to changes in interdependent run parameters (minimum cycle time, pump time), and incompatible or incorrect input values. Timed events measured against an external clock were in agreement with programmed values.

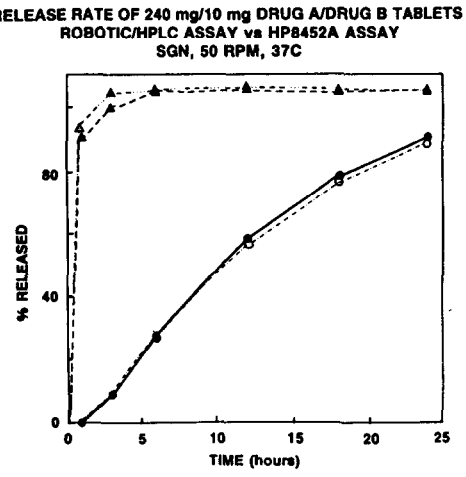

Figure 2
Release rate results for a batch of tablets (240 mg/10 mg, drug A/drug B) were obtained by both the MBDS and an alternative procedure which used a robot for sample collection with off-line analysis by HPLC. Drug A: robot/HPLC (○); drug A: MBDS (●); drug B; robot/HPLC (△); drug B: MBDS (▲).

Conclusions

MBDS technology can be applied to a complex drug delivery system in a manner that is consistent with many, although not all, GMP/GLP requirements for validation. Tests for UV absorbance, independence of standards, addition of absorbances, linearity, accuracy, ruggedness and comparison to an independent method can adequately demonstrate the applicability of multicomponent diode-array analysis to a dosage formulation. Following a protocol, such as the one used here, can fulfil many of the requirements for testing and documenting equipment performance. The addition of screen printing capabilities and a tape drive enables greater compliance with requirements for documentation, safe storage and ready retrieval of data. However, software validation is the one area where the user cannot adequately demonstrate GMP/GLP compliance. This is due to the proprietary nature of commercial software and its development prior to the industry's response to current regulations.

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[2] R.F. Tetzlaff, *Pharm. Technol.* **16**, 60–72 (1992).
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