



Comparative Study of Manual Dissolution with On-line UV and Fiber Optical probe Automated Dissolution Systems

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INTRODUCTION

Purpose

To compare the reliability and reproducibility of manual and automated dissolution-UV methods.

Two automated dissolution configurations were included in this study:

- Flow through UV configuration
- Fibre optic UV configuration

Automated dissolution has become increasingly popular in the R & D laboratory mainly due to the ability to collect rapid real time data giving a complete dissolution profile. However, automated dissolution-UV does suffer from disadvantages of potential interferences caused by insoluble excipients.

METHODOLOGY

Acetaminophen extended release 650mg caplet (Tylenol™) was used for this comparative dissolution study. The USP method was used as the guide for the dissolution procedure. Dissolution tests were carried out using VK 7000 USP Apparatus 2 at 50 rpm and sampling time points at 10, 20, 30, 45, 60, 120, 180, 240 and 300 min at 37°C ± 0.5°C using simulated gastric fluid (without gastric enzymes).

Flow through UV dissolution was carried out on a Cary 50 system with 90-second rinse time, 60-second purge time and in-line filtration with 10 µm full flow filters. 1 mm gap probes were employed for fiber optic experiments with Cary 50 spectrophotometer coupled with a multiplexer.

For Cary 50 system, online filtration, carry-over, robustness and system interference were also performed. To eliminate the effects of variabilities between caplets, in the flow through UV system, additional samples were taken manually for off-line UV determination.

The Cary 50 system employed the use of single beam pulsed Xenon lamp using 80 pulses per second with avoid delays required for warming up of the lamp. Sampling time was 1 minute for UV spectrum accumulation at 278 nm with a 1mm path length.

RESULTS AND DISCUSSION

Extended release Acetaminophen was selected as the model because the dissolution profile presented a suitable challenge for the required comparative study. In addition, a disintegrating type tablet is generally more problematic for fiber-optic type dissolution systems because the presence of insoluble excipients, which flow both through and around the flow cell, may lead to light scattering together with reduced and variable light absorbance readings.¹

The results from data collected using automated dissolution systems using manual UV detection, flow through UV detection and two types of UV fiber optic detection systems are shown in tables 1-5 and in Figure 1. In Table 1 manual dissolution was carried out without the use of an automated system. However, data in Tables 2 and 3 shows data for samples taken from the same experiment. UV samples were measured both manually offline and online with the Cary 50 automated flow through UV detection system.

Table 1—Manual Sampling on a standard UV spectrometer

Vessel #	Dissolution Release (%)									
	10	20	30	45	60	120	180	240	300	300
1	23.8	26.2	41.1	47.2	72.9	90.1	96.2	99.0	98.2	98.0
2	45.8	51.9	92.6	95.1	78.9	97.3	99.2	98.2	98.8	98.8
3	49.9	51.9	99.0	95.1	68.8	91.8	99.2	100.4	100.7	100.7
4	58.2	56.4	81.1	88.0	73.7	91.3	99.1	101.1	101.0	101.0
5	52.8	59.8	82.1	89.0	76.1	91.8	96.4	97.4	97.3	97.3
6	52.2	58.2	81.1	78.4	77.0	94.4	97.6	98.1	97.2	97.2
Mean	43.2	50.2	81.3	82.6	74.2	92.6	97.8	99.3	99.3	99.3
SD	1.2	1.4	1.7	1.1	1.2	1.9	1.6	1.1	1.1	1.1
%RSD	2.8	2.8	2.1	1.3	1.6	2.1	1.7	1.1	1.1	1.1
MIN	49.8	51.9	99.0	95.1	68.8	91.8	99.2	97.6	97.3	97.3
MAX	52.8	59.8	82.1	78.4	77.0	94.4	99.1	101.1	101.0	101.0

Data for Simultaneous manual and flow through sampling during a single experiment is shown below (table 2 & 3).

Table 2—Manual Sampling on a standard UV spectrometer (simultaneous with automated flow through UV detection Table 3)

Vessel #	Dissolution Release (%)									
	10	20	30	45	60	120	180	240	300	300
1	23.2	26.8	46.4	51.0	74.0	90.9	96.2	100.0	100.0	100.7
2	51.2	58.8	92.3	92.3	74.0	90.9	96.8	97.7	97.8	97.8
3	41.8	51.0	99.8	91.4	68.8	91.8	99.2	98.1	97.6	97.6
4	51.8	58.8	82.1	87.7	72.4	92.2	97.2	98.6	99.8	99.8
5	52.8	56.1	80.0	86.7	72.0	90.7	97.8	98.1	98.1	98.1
6	52.4	57.3	81.8	80.0	70.0	91.9	97.8	98.0	98.4	98.4
Mean	41.9	52.8	82.2	80.3	72.3	90.9	97.9	99.1	99.7	99.7
SD	1.2	1.2	1.4	1.1	1.0	1.6	1.4	1.1	1.1	1.1
%RSD	2.9	2.3	1.7	1.4	1.4	1.8	1.6	1.1	1.1	1.1
MIN	41.9	51.0	99.8	91.4	68.8	91.8	99.2	98.1	97.6	97.6
MAX	51.2	58.8	86.4	74.0	74.0	90.9	96.2	100.0	100.0	100.7

Table 3—Automated sampling on a Cary-50 flow through UV autosampler (simultaneous with manual UV detection Table 2)

Vessel #	Dissolution Release (%)									
	10	20	30	45	60	120	180	240	300	300
1	23.9	26.2	46.4	51.7	74.7	91.5	98.9	99.7	99.9	99.9
2	51.2	58.2	92.3	92.1	73.7	90.2	96.2	96.2	97.4	97.4
3	41.8	51.0	99.8	91.8	68.8	91.8	99.2	99.9	99.9	99.9
4	51.8	58.4	82.0	87.7	72.4	92.2	97.2	97.7	98.1	98.1
5	52.8	56.1	80.0	86.4	72.0	90.7	97.8	97.4	98	98
6	51.8	57.7	80.0	80.4	70.0	91.4	97.8	98.0	97.4	97.4
Mean	41.8	51.8	81.3	81.9	72.8	90.3	97.9	97.3	98.0	98.0
SD	1.1	1.1	1.4	1.1	1.0	1.6	1.4	1.1	1.1	1.1
%RSD	2.6	2.1	1.7	1.3	1.4	1.8	1.6	1.1	1.1	1.1
MIN	41.9	51.0	99.8	91.4	68.8	91.8	99.2	99.9	99.9	99.9
MAX	51.2	58.8	86.4	74.0	74.0	90.9	96.2	99.7	99.7	99.9

Automated Dissolution using Fiber optic probes

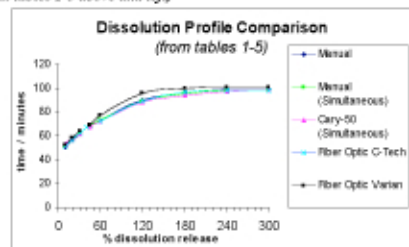
Table 4—Data collected on a Fiber-Optic C-Tech automatic dissolution system

Vessel #	Dissolution Release (%)									
	10	20	30	45	60	120	180	240	300	300
1	45.4	54.1	92.4	95.7	78.2	93.9	97.8	98.4	97.3	97.3
2	51.2	56.4	90.8	95.1	73.9	94.2	99.3	98.1	98.8	98.8
3	52.5	58.8	82.6	87.0	72.8	91.9	97.8	97.7	97.8	97.8
4	51.7	58.7	82.7	79.3	70.3	91.9	97.8	98.0	98	98
5	51.4	56.4	81.0	80.2	72.0	90.4	98.8	100.1	100.4	100.4
6	52.2	58.8	81.0	80.2	73.3	90.3	97.2	97.7	97.8	97.8
Mean	50	55.9	82.1	87.0	72.7	90.9	98.9	98.3	98	98
SD	1.4	1.6	1.1	1.0	1.0	1.6	1.4	1.1	1.1	1.1
%RSD	2.8	2.7	1.3	1.2	1.4	1.8	1.6	1.1	1.1	1.1
MIN	45.4	54.1	92.4	95.7	70	90.9	97.8	98.1	98.8	98.8
MAX	51.7	58.7	82.8	79.3	73.3	91.9	98	100.1	100.4	100.4

Table 5—Data collected on an Optic Varian automatic dissolution system

Vessel #	Dissolution Release (%)									
	10	20	30	45	60	120	180	240	300	300
1	23.8	26.2	45.0	47.0	78.1	97.7	100.2	101.1	101.1	101.1
2	51.8	57.4	87.1	87.4	75.4	92.2	98.0	98.4	100.1	100.1
3	52.0	58.6	87.7	87.8	75.2	92.4	98.8	101.1	101.1	101.1
4	51.9	58.8	82.1	82.0	74.0	91.1	101.2	101.2	101.2	101.2
5	52.1	52.1	80.2	74.0	66.1	91.2	101.2	101.2	101.2	101.2
6	48.7	56.1	81.3	80.2	76.7	91.9	98.6	100.1	98.8	98.8
Mean	52.2	58.6	84.4	82.0	77.9	96.8	100.2	100.8	101.1	101.1
SD	1.9	2.1	2.3	2.1	1.8	2.1	1.4	1.4	1.4	1.4
%RSD	3.6	3.6	2.8	2.6	2.3	2.2	1.4	1.4	1.4	1.4
MIN	48.7	56.1	81.3	80.2	74.0	91.9	98.6	98.6	98.8	98.8
MAX	55.1	62.1	90.2	74	86.1	101.2	101.2	101.2	101.2	101.2

Figure 1—Profile comparison of data collected using both manual UV sampling and automatic flow through UV sampling and two systems using fiber optic sampling systems (data shown in tables 1-5 above and left)



Very similar dissolution profiles were obtained for all three methods with dissolution profiles that showed less than 80% release up to 60 minutes and completion of dissolution at around 240 minutes. The RSD for manual off-line UV sampling, automatic flow through UV sampling and fiber optic methods were 4.1, 4.9, 2.2 and 5.0 % at 60 minutes and 1.4, 1.4, 1.5 and 1.4 % at 240 minutes, respectively. These results satisfy the criteria recommended by the FDA for Dissolution Testing of Immediate Release Solid Oral Dosage Forms,² where it is recommended that for profile comparisons, RSD of early time points should not exceed 20% and for later time points the RSD should not exceed 10%.

Similarity and difference factors were calculated (Table 6) using the following equations (Equations 1 and 2) as recommended by the FDA for Dissolution Testing of Immediate Release Solid Oral Dosage Forms.²

Equation 1: Difference factor (f1) to compare dissolution profiles.

$$f_1 = \left\{ \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right\} \times 100$$

Equation 2: Similarity factor (f2) to compare dissolution profiles.

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

n is the number of time points

R is the dissolution value of the reference t (pre-change) batch at time t,

T is the dissolution value of the test (post-change) batch at time t

Compared to the manual methods, the similarity factors were 88, 96 and 75 for flow through and fiber optic probe methods, respectively. The difference factors were 2, 1 and 3 respectively for the two methods. These results also satisfy the recommended criteria, (50 ≤ f2 ≤ 100 and 0 ≤ f1 ≤ 15), suggesting acceptable results are obtained using these automated dissolution systems.

Table 6—Comparison of data for three automated dissolution systems.

Time (min)	f1 (Manual)	f2 (Cary 50)	f2 (C-Tech)	f2 (Varian)
10	21.2	53.6	52.0	52.1
20	36.9	98.0	37.0	38.0
30	61.2	81.0	62.1	64.4
45	67.6	67.6	67.8	68.0
60	73.3	71.8	72.7	72.9
120	89.0	88.1	88.8	89.0
180	97.0	98.5	98.7	100.3
240	99.1	97.1	98.2	100.3
300	99.1	98.0	98.0	100.1
Similarity Factor (f2)	98	94	75	
Difference Factor (f1)	2	1	3	

*This reading was taken at 40 minutes

Rt: the mean dissolution value of the manual sampling sample at time t

T1: the mean dissolution value of the sample from Cary 50 at time t

T2: the mean dissolution value of the sample from Fiber Optic-C Tech.

T3: the mean dissolution value of the sample from Fiber Optic-Varian

Carry Over and System Interference

The Cary-50 transfers samples from the dissolution vessel to the UV cell and then back to the dissolution system. The possibility of carry-over from one run or time point, to another has been investigated by measuring the UV absorbance of subsequent 100% API and placebo solutions.

Between each step the system was rinsed with the dissolution medium and a UV measurement was taken. At the same time it was also possible to determine system interference by comparing the online and off line (manual) UV measurements.

Table 7—Carry over data for Automatic sampling on a Cary-50 flow through UV autosampler

Step #	Sample Type	Manual UV (Abs)	Automated UV (Abs)	Difference (Abs)
1	100% API	1.9132	1.9111	0.0022
2	Dissolution Medium	0.0083	0.0069	-0.0016
3	100% API	1.9080	1.9089	0.0009
4	Dissolution Medium	0.0082	0.0081	0.0001

The results in Table 7 shows insignificant differences between the manual and automatic sampling systems therefore showing no significant API or medium constituents interfere with the sampling results between the time points.

Online Filtration

For many dissolution methods it is preferable to filter the sample before measurements are taken.

With the Cary-50 instrument, it is possible to use Vankel Full flow inline filters to reduce insoluble particle interference.

Samples were taken using a 100% API solution in a vessel. Then automated UV readings were measured for the same samples with and without Vankel 10µm full flow filter attached to the stainless steel cannulas, refer to Table 8.

Table 8—Online filtration for sampling on a Cary-50 using a flow through UV autosampler

Vessel #	UV (with filter)	UV (without filter)	% recovery
1	99.1	98.2	98.1
2	99.1	98.2	98.1
3	99.1	98.2	98.1
4	99.1	98.2	98.1
5	99.1	98.2	98.1
6	99.1	98.2	98.1
Mean	99.1	98.2	98.1
SD	0.1	0.1	0.1
%RSD	0.1	0.1	0.1
MIN	98.9	98.0	98.0
MAX	99.1	98.2	98.1