Assessment of Multiple Sampling Techniques and Their Impact on Dissolution Results Using the Hanson Dissolution Tester with Autoplus™

TELEDYNE HANSON
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Application Note: H-AN-002

Ashvin Patel, Ph.D.

Background: Sample Collection for Dissolution Test

Typical dissolution apparatus consists of six to 14 vessels, with or without an autosampler installed. During the dissolution test, the sample is withdrawn at predetermined time intervals and the collected sample evaluated against a standard solution of known concentration. This evaluation is performed using an appropriate analytical technique, such as high-performance liquid chromatography or UV spectroscopy. The most common sample withdrawal technique involves removing a fixed volume, which may or may not be replaced with an equal amount. The sampling procedure may be performed by autosamplers, in which case it is very important to rinse the sampling tubes prior to collecting samples for analysis. Some autosamplers are designed to hold rinsed solution for a brief period prior to sample collection. Once the sample has been removed, the rinsed solution is returned to the vessel.

Image 1: Images of Hanson Dissolutin Testers with Autosamplers

Experimental

Multiple experiments were performed at the Teledyne Hanson Analytical Research Center in Chestnut Ridge, NY, to evaluate different sampling techniques and their impact on results. The tests were conducted during February 2022 to March 2022, using commercially available acetaminophen tablets, USP, Lot # P119534, expiration date: 03/2022, purchased from a retail pharmacy in the United States.

The dissolution test was performed using a current, approved USP monograph. The secondary reference standard was purchased from the Sigma-Aldrich® brand of Millipore Sigma, United States. A dissolution medium of pH 5.8 phosphate buffer was prepared as described in the current USP monograph, and using chemicals purchased from Sigma-Aldrich.

A quantity of 900 mL of dissolution medium was transferred into six dissolution vessels. Once the temperature of the dissolution medium reached the required temperature of 37.0° ± 0.5 °C, the test was begun at a speed of 50 RPMs using Apparatus II (paddles). One tablet was used in each vessel and the experiment was repeated multiple times to examine the four sampling techniques shown below.

Techniques Tested

1. Manual sampling, no replacement at 5, 10, 15, 20, and 30 time points.
2. Automated Sampling, no replacement at 5, 10, 15, 20, and 30 time points.
3. Automated sampling, replacement at 5, 10, 15, 20, and 30 time points.
4. Use of a retrieval reservoir assembly*, no replacement at 5, 10, 15, 20, and 30 time points.

* The retrieval reservoir assembly is used to temporarily hold the sample during the sampling process.

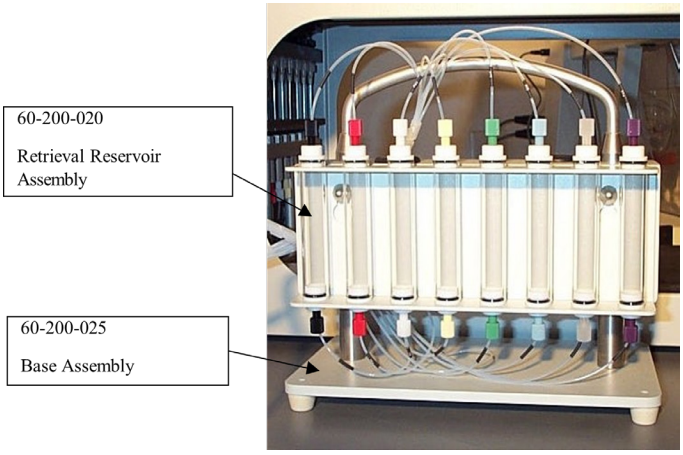

Image 2: Retrieval Reservoir Assembly

The retrieval reservoir is an optional Teledyne Hanson AutoPlus™ Maximizer™ accessory that enables the return of sample and rinse volumes back to the dissolution vessel(s) in multi-bath applications. This method will accommodate two dissolution baths with media replacement or three baths without media replacement. The rinse volume from the dissolution vessels is collected and dispensed, via the sample path, to the retrieval reservoir, where it is held temporarily. After a predefined sample volume is collected from the dissolution vessels, detected and or dispensed into the multi-fill collection rack, sample and rinse volume (plus an air purge) from the retrieval reservoir is dispensed back to the dissolution vessels.

For this study, the following protocol was used:

- The collected solutions were filtered using a 45 µ, 25 mm nylon syringe filter, prior to analysis.
- A reference standard solution of a known 0.01 mg/mL concentration was prepared in the same dissolution medium.
- The sample solution was diluted 10 times to obtain an appropriate absorbance reading at the 243 nm wavelength using a 10 mm path length of quartz cells.
- All samples were analyzed using a Shimadzu UV-1800 spectrophotometer.

Results

Sampling Time Minutes	% Dissolved corrected for volume Manual sampling							
	Vessel - 1	Vessel - 2	Vessel - 3	Vessel - 4	Vessel - 5	Vessel - 6	Average	%RSD
0	0	0	0	0	0	0	0	0
5	31.86	31.50	30.13	31.73	31.06	29.43	30.95	2.9
10	69.87	68.17	70.34	67.72	68.98	67.97	68.84	1.4
15	89.28	90.94	90.67	89.81	87.32	90.08	89.68	1.3
20	95.10	94.17	92.95	94.24	94.59	95.83	94.48	0.9
30	96.99	96.02	95.28	96.17	96.13	97.15	96.29	0.7

Table 1: Sampling Technique #1 Results

Sampling Time Minutes	Automated sampling 10 mL replacement % Dissolved amount of Acetaminiphen							
	Vessel - 1	Vessel - 2	Vessel - 3	Vessel - 4	Vessel - 5	Vessel - 6	Average	%RSD
0	0	0	0	0	0	0	0	0
5	28.49	31.85	28.20	30.08	30.95	30.21	29.96	4.3
10	67.95	65.75	65.48	63.73	63.20	64.39	65.08	2.4
15	91.04	90.54	91.57	92.66	90.77	91.14	91.29	0.8
20	92.05	92.21	92.30	91.80	91.99	93.03	92.23	0.4
30	95.39	95.76	96.93	95.52	96.57	96.95	96.19	0.7

Table 2: Sampling Technique #2 Results

Sampling Time Minutes	Automated sampling, no replacement % Dissolved amount of Acetaminophen							
	Vessel - 1	Vessel - 2	Vessel - 3	Vessel - 4	Vessel - 5	Vessel - 6	Average	%RSD
0	0	0	0	0	0	0	0	0
5	29.86	30.69	33.17	27.07	30.60	30.14	30.26	5.9
10	77.74	77.23	75.74	70.86	74.00	79.24	75.80	3.6
15	89.04	87.06	87.19	87.13	87.87	91.76	88.34	1.9
20	91.29	90.49	89.11	87.87	88.62	91.96	89.89	1.6
30	92.50	91.47	90.27	93.79	90.28	97.97	92.71	2.9

Table 3: Sampling Technique #3 Results

Sampling Time Minutes	Automate+ Retrival. No replacement % Dissolved amount of Acetaminophen							
	Vessel - 1	Vessel - 2	Vessel - 3	Vessel - 4	Vessel - 5	Vessel - 6	Average	%RSD
0	0	0	0	0	0	0	0	0
5	31.98	31.79	30.07	30.72	32.92	31.09	31.43	3.0
10	79.95	75.15	81.60	73.93	70.38	76.24	76.21	4.9
15	90.01	96.04	97.99	92.65	81.64	84.42	90.46	6.5
20	96.22	94.83	95.87	95.15	94.75	94.25	95.18	0.7
30	95.80	95.01	96.02	94.90	94.93	94.18	95.14	0.6

Table 4: Sampling Technique #4 Results

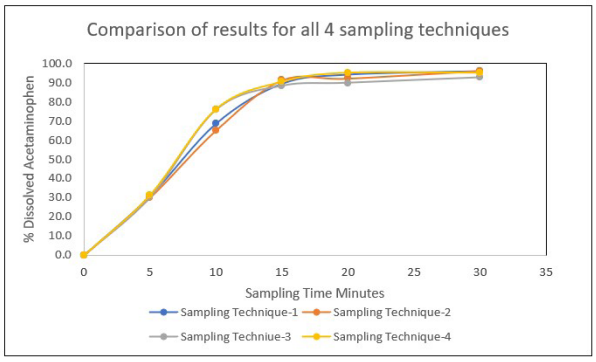

Image 3: A graphic comparison of the average percentage dissolved acetaminophen using the four different sampling techniques tested.

Discussion

Results from this study indicate that the sampling techniques tested had no significant impact on percentage dissolved acetaminophen results. Additionally, whether the solution is withdrawn and replaced or not replaced also had no impact on final results. When 4 mL of dissolution medium was temporarily removed from the vessel just prior to sampling and then returned to the vessels after the sampling, no significant impact on final results was observed. The following observations should be noted:

- Users should ensure the proper calculation is used (according to the sample technique) to obtain percent dissolved data. Specifically, the dilution effect should be considered when an amount is removed from the dissolution vessel and then replaced.
- When configuring a sampling technique that uses an autosampler, the tubing length and the volume needed to replace the solution in tubes should be considered. A 4 mL retrieval volume was used in this study.
- The limits for percentage dissolved acetaminophen per tablet according to USP monograph is Not Less Than (NLT) Q=80%. This requirement was met for all samples in this study.

Conclusion

Based on the data obtained from this study, it can be concluded that the dissolution apparatus tested produces accurate and robust data following the USP monograph. Any of the sample collection techniques examined in this study can be used during the dissolution profile testing (or single time-point testing). Data obtained from this study was consistent with Teledyne Hanson's autosampler platform using the formulas appropriate to the sampling technique used.

When compared to single time-point or extended-release drug product sampling at longer time points, immediate-release drug products are more susceptible to variability during sample collection at early time points. Consequently, analytical results for immediate release drug products are affected by day-to-day, batch-to-batch and analyst-to-analyst variations. Any of the sampling techniques examined in this study can easily be adapted to any currently approved dissolution test method. It should be noted that prior to revising an existing sampling technique, a cross-over study including the two methods should be performed.

This study was conducted at the Teledyne Hanson Analytical Research Center in accordance with all applicable in-house standard operating procedures and prepared in compliance with the U.S. Food and Drug Administration's Good Manufacturing Practice requirements. These facilities are available to assist in the development of customer protocols.

Teledyne Hanson
9810 Variel Ave, Chatsworth, California, 91311 USA
Phone: (818) 882-7266

TELEDYNE HANSON
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