

A Look at Cleaning Effectiveness in Automated Dissolution Systems

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ABSTRACT

Cleaning in any Good Manufacturing Practice (GMP) laboratory is an important aspect of the analytical experiment. The laboratory must ensure the equipment does not contain residual active pharmaceutical ingredients (APIs) or impurities that may affect the outcome of any current or future experiments. While this is standard practice for GMP manufacturing operations, common laboratory equipment is often held to less stringent standards. The potential manhours lost due to investigations for extraneous peaks and contamination can be significant and cause delays in releasing product.

Potential compliance issues related to ineffective cleaning are particularly important for dissolution instrumentation. Our laboratory has modeled the challenges of cleaning automated dissolution systems using representative soluble and poorly soluble APIs. Poorly soluble drugs often entail the use of surfactants in the dissolution media which also have a potential carryover issue. Using a manufacturing cleaning validation based approach, the study discussion presented will address the cleaning effectiveness for both sample and media considerations.

KEYWORDS: Automated dissolution, dissolution bath cleaning, poorly soluble drugs, surfactant

INTRODUCTION

Cleaning in any Good Manufacturing Practice (GMP) laboratory is an important aspect of the analytical experiment. The laboratory must ensure the equipment does not contain residual active pharmaceutical ingredients (APIs) or impurities that may affect the outcome of any current or future experiments (1, 2).

Common laboratory equipment is often held to less stringent standards than manufacturing equipment, and potential man hours lost due to investigations for extraneous peaks and contamination related to unclean equipment can be significant and cause delays in releasing product. For compliance, efficiency, and cost savings, effective cleaning investigations of critical laboratory equipment should be maintained. An example of critical laboratory equipment that can be affected by poor cleaning strategies is dissolution instrumentation. Dissolution instrumentation is critical for characterizing tablet performance (3). Failure to effectively clean the equipment can not only lead to erroneously high percent-dissolved results, it can also introduce unexpected

extraneous peak responses that require costly and time-consuming laboratory investigations. The laboratory must ascertain if the extraneous response came from the equipment or the product prior to proposing a solution. Unless the issue is systematic, the investigation will be challenged by definitively assigning instrument contamination as opposed to the possibility of super-potent, unit-dosage form.

Automated dissolution systems have become effective tools for improving drug testing throughput (4–30). The cleaning of dissolution vessels is seemingly straightforward, yet we have found in our laboratory that the cleaning of transfer lines is just as important, and sometimes insufficient in systems routinely testing a variety of APIs, dosage forms, and strengths. The challenge of using unattended systems in dissolution is that issues in cleaning are often not discovered until after data have been generated. System suitability criteria to run blank media through the system prior to analysis to demonstrate the absence of line contamination is commonly used with on-line UV analysis. This blank control assessment can hinder the efficiency of automated systems. In the literature applications cited, only Mathieu

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et al. suitably addressed the issue of cleaning (10). It is the authors' contention here that automated systems should be operated with cleaning investigations in mind. It is far better to add cleaning steps to the sample queue than to open investigations afterwards. To address this need, the challenge of cleaning automated dissolution systems in our laboratory was studied using representative soluble (biopharmaceutics classification system [BCS] class I and III) and poorly soluble and (BCS class II and IV) APIs (31).

MATERIALS AND METHODS

Materials

Except where noted, the chemicals used for this investigation were American Chemical Society (ACS) grade or better and purchased from MilliporeSigma (St. Louis, MO, USA). A sodium phosphate (pH 6.8) dissolution media was made from Dilut-it dissolution media concentrate from J.T. Baker/Avantor Performance Materials Holdings, S.A. (Gliwice, Poland). Sodium dodecyl sulfate (SDS) was Calbiochem OmniPur grade from EMD Millipore (Billerica, MA, USA). Itraconazole was purchased from Tokyo Chemical Industry (TCI) America Inc. (Portland, OR, USA). Labsan 230C citric acid cleaner was purchased from Sanitation Strategies LLC (Bend, OR, USA). Ritonavir was synthesized in house by AbbVie Inc. (North Chicago, IL, USA)

In-house swabbing procedures used cellulose support pads (AP10 024 00, MilliporeSigma, Burlington, MA, USA) for ritonavir, and Alpha sampling swabs (TX715, Texwipe, USA) for itraconazole and acetaminophen.

Automated Dissolution System

The automated dissolution system used for this investigation was an AT-70 from SOTAX (Westborough, MA, USA). The system was configured for United States Pharmacopoeia (USP) apparatus 2 paddle methods. The AT-70 was controlled by WinSOTAXplus Advanced Dissolution Software (version 2.57, SOTAX). The Xtend SAM sample manager (SOTAX) was directly coupled to an UltiMate 3000 high-performance liquid chromatography (HPLC) system (Thermo Fisher Scientific, Waltham, MA, USA) and controlled by Atlas Chromatography Data System (CDS) (version 9.00.00.10711, Thermo Fisher Scientific).

The dissolution methods used for this investigation were consistent with compendial procedures (32). The filters used for the dissolution samples were 0.45- μm GxP polyvinylidene difluoride (PVDF) (Acrodisc, Pall Corp., USA) for acetaminophen, 0.45- μm nylon for ritonavir (Pall Corp.), and 2.7- μm Whatman grade GF/D (GE Healthcare Life Sciences, USA) for itraconazole.

SOTAX AT 70 Cleaning Cycle

The AT-70 triggers the cleaning cycle immediately after the test run is completed. The cleaning cycle includes (1) removing filters from the filter station; (2) emptying vessels using the hemispheric valves on the bottom of the vessels; (3) removing sinkers, pellet cartridges, or undissolved dosage form simultaneously while the valves are opened; (4) removing baskets and collecting them in a cleaning reservoir; (5) power washing the inner vessel surface, shafts, and paddles using high speed rotation and pressurized deionized (DI) water; and (6) cleaning the circulation path using pressurized, DI water.

Design Approach

For our study, validated manufacturing cleaning methods were used for glass (vessel) and stainless steel (paddles). Swab recoveries were established for these surfaces using standard coupon recovery procedures (33). System transfer lines were investigated using rinse sampling (34).

RESULTS AND DISCUSSION

Cleaning Targets

Specific limits have not been established for dissolution apparatus as they are not directly used in the manufacturing of drug products. The industry has used cleaning limits based on 10 ppm for finished drug manufacture, 50–100 ppm for API manufacture or dose, and maximum allowable carryover (MAC) calculations (35–38). The idea behind GMP cleaning limits can be used as a justifiable detection benchmark for dissolution instruments. The difference for analytical equipment is method integrity, not patient risk. Patient safety is not the concern for analytical test equipment cleaning investigations. The cleaning investigation for analytical instrumentation is used to minimize the risk of carry-over and impurities that may affect the next test run.

Traditional Dissolution Cleaning Studies

Traditionally, dissolution laboratories have simply executed the test method, performed their standard cleaning procedures and then verified the bath was clean by measuring the response from blank media. A response of less than 1% of the dose was a typical acceptance criterion (39). For a response of greater than or equal to 1%, additional cleaning would be required.

Less Than 1% Response

A target response of less than 1% is suitable only if the next application of the system is known ahead of time. The benchmark assumes the system will be used for the same method again. This is a poor assumption in research and development (R&D) laboratories. R&D laboratories routinely schedule testing queues on their

dissolution equipment that comprise differing APIs as well as differing doses. Automated dissolution systems return their maximum return on investment (ROI) when executing a series of unattended methods. These systems require flexibility in sequencing differing drugs and dose levels. Thus, a 1% target of a 100-mg dose could pose a significant issue if the subsequent sample tested is of lower dosage strength (e.g., it becomes a 10% response of a 10-mg dose and 100% response for a 1-mg dose). Each laboratory should assess their cleaning need based on the potency of the drug products used.

Proposed Cleaning Target

Generally, a 1-mg dose is a representative lower objective for tablet strength in development. A 1% target of a 1-mg dose would be equivalent to a 0.1% response of a 10-mg dose and a 0.01% response for a 100-mg dose. Thus, targeting a 0.01% criterion for cleaning our test 100-mg study samples is a practical, universal goal to use to minimize method integrity issues for automated dissolution applications. To make this target more discriminating, the cleaning procedure should ensure a 0.01% target when using a 100-mg dose of a poorly soluble drug. Such challenges would present a worst-case scenario and justify an effective standard cleaning procedure to be used for all methods going forward on the automated system.

Although this assumption works well for a homogeneously dispersed residue on a vessel surface using a coupon approach, one should expect a heterogeneous contamination in transfer lines where threaded junctions may have build-up. Such a scenario would not be expected with homogeneous samples. Although it might be 1% of the 1-mg dose, such contamination is more likely to be detected in an early sampling timepoint. For a 100 mg drug that has only released 9 mg into 900 mL of medium, and when flowing that 0.01 mg/mL solution through a transfer line, such a heterogeneous contaminant is often found in the first passage of sample and leads to the suspect result we are trying to avoid. Such a scenario is never totally avoidable in any dissolution system. Our goal is to minimize its occurrence.

Automated Dissolution Cleaning

Automated dissolution equipment allows unattended removal of sinkers, pellet cartridges, and undissolved dosage form components at the completion of the run. The instrumentation then can apply vessel emptying and cleaning procedures. For the instrument used in this investigation, a series of 14 rotating power washers were

employed by programming of cleaning procedures for vessels and tubes. Pressurized cold and hot DI water can be used for vessel cleaning and rinsing dissolution media from the transfer lines. As illustrated in Figure 1, swab investigations for the dissolution vessels were executed by outlining the dimension of a standard cleaning coupon on the outside glass of each vessel and then swabbing the glass inside within these markings.



Figure 1. Illustration of swabbing the designated area dimension on glass dissolution vessels.

Target Drugs

For our investigations, acetaminophen was used to represent BCS class I and III drugs, ritonavir to represent a poorly soluble (BCS class IV) drug, and itraconazole to represent a known and challenging BCS class II drug. HPLC methods with practical detection limits in the range of 2–30 $\mu\text{g}/100\text{ cm}^3$ were used to quantitate the media samples.

Cleaning Study Methods

Preliminary studies indicated that even for BCS class I and III drugs, a simple post run cleaning procedure, as designed by the manufacturer, left drug residue at levels higher than our 0.01% criteria, or 1.1 $\mu\text{g}/\text{mL}$, in the media tested for 100-mg doses. To address this, an extra cleaning run was added to the end of the sample queue to rinse the bath, paddle, and transfer lines with additional media prior to the DI water cleaning cycles. In addition, two cleaning cycles were used after the media blanks. To challenge the effectiveness of this revised procedure, 100-mg doses of each study drug were run through their validated dissolution method with surface exposures ranging from 30 min to 4 h, based on the method routinely used for the tableted product. Next, the media blank was tested

using 10-, 15- and 20-min hold times prior to draining the media. To check the glass and paddle surfaces, swab studies were run. To challenge the cleaning of the transfer lines, a blank run was executed after swabbing to test the rinsed lines. The revised cleaning procedure used for this investigation is listed in Table 1.

Cleaning Study Results for Acetaminophen, Ritonavir, and Itraconazole

The results for acetaminophen and ritonavir are listed in Tables 2 and 3, respectively. Acetaminophen, being highly soluble, showed efficient cleaning as expected. In addition, ritonavir, as a poorly soluble drug, also showed efficient cleaning with the procedures used. The method surfactants functioned to keep the drug soluble enough to be rinsed out of the system. The concern remains: at what point does surfactant residue itself become an issue? Future work will explore this impact upon automated systems. For now, the authors propose that investigators use the minimum amount of surfactant needed in their dissolution methods. To date, our procedure has been suitable for media containing up to 1% SDS. The preliminary results for itraconazole, which is a poorly soluble drug using low-acid pH media rather than a surfactant media, were higher than desired (Table 4). Additional studies into cleaning methods for itraconazole and media ensued (Table 5).

Each cleaning investigation must assess the chemistry, solubility, and solution stability issues that a drug may present. Itraconazole is a challenging drug to clean due to its poor aqueous solubility. Considering this challenge, the levels reported in Tables 4 and 5 may be suitable. To ensure the proposed 0.01% target could be obtained with this drug, further testing was initiated. Because of itraconazole's solubility in acidic media, end of sequence media rinses with either 0.1 N HCl or acidic detergent (Labsan 230C) were tested (32). As with other BCS class II and IV drugs, cleaning improved in the presence of surfactant media.

Optimized Cleaning Method for Automated Dissolution

Given the vigorous vessel rinsing and the swabbing techniques employed in the swabbing studies, the data supports that carry-over issues, if present, are more likely to originate in the transfer lines than the dissolution vessel and paddle surfaces. In addition, BCS class II and IV compounds, when using surfactant media, did not pose a challenge to our cleaning investigation. This was attributed to the solubilizing and rinsability of the surfactants used. With these drugs being more soluble in

surfactant media, and because surfactant media residues are easier to liberate from material surfaces than simple aqueous media, there is less need to liberate these drugs from contact surfaces. In fact, our investigation showed that BCS class II and IV drugs in surfactant media can be rinsed away more easily than BCS class I and III drugs in simple aqueous media. Simple aqueous media does not inhibit the attraction of BCS class I and III drugs to surfaces. Except for itraconazole, the optimized cleaning sequence used at the end of the sample queue was effective at ensuring that the target of 0.01% of a 100-mg dose was achieved. This procedure was also challenged with an additional proprietary BCS class I and III and BCS class II and IV drugs. While the results confirmed the procedure met the 0.01% cleaning target for a 100-mg dose as well, the data is not presented here. Based on this investigation, the final optimized cleaning procedure only requires the Blank Media Method section of Table 1; i.e., four sample pulls totaling 400 mL of line flush and 16 min of flushing is reduced to only two sample pulls, totaling 200 mL of line flush and 8 min of flushing.

Additional Recommendations for Automated Dissolution Runs

The goal of this cleaning investigation was to minimize suspect result investigations. Two additional suggestions will assist in minimizing the time lost to examining suspect data. First, consider adding carryover standard spikes to methods when different drugs are being tested in the queue sequence. This enables the analyst to assign the identity and likely cause of a suspect peak that washed into the next method. Second, order sequence queues in the order of low to higher doses of the drug or drugs under investigations. This notion could also be expanded to cases where multiple actives are screened in an automated run. In those cases, the sequence should be optimized in order of weakest analytical signal (ultraviolet [UV] maxima) to strongest.

CONCLUSION

For the dissolution testing of BCS class I and III and BCS class II and IV drugs with surfactant media, suitable cleaning procedures have been developed that enable automated dissolution sequences with minimal risk of analyte carry-over. The cleaning benchmarks used were based on a 1% target for the lowest expected dose. This benchmark provided flexibility in the sequence queue. Cleaning procedures for the dissolution testing of BCS class II and IV drugs in the absence of surfactant media, such as itraconazole, should be investigated on an individual basis.

Table 1. Study Cleaning Procedures for SOTAX AT-70 Automated Dissolution System

Task	Procedure	Reasoning
Media Flush Before Sampling	100 mL	At 25 mL/min, this gives 4 min of line flush per pull
Blank Media Method	4 Sample Pulls	Totals 400 mL of line flush and 16 min of flushing
Default Cleaning Method	2 Cycles	Thorough rinsing of media with deionized water

Table 2. Acetaminophen Cleaning Study Results

Vessel	Media 10 Min	Media 15 Min	Swab Blank (Paddles)	Glass Surface	Blank Run 5 Min	Blank Run 10 Min	Blank Run 15 Min	Blank Run 20 Min
Blank	0.002	0.028	0.000	0.000	0.000	0.000	0.000	0.000
Blank	0.014	0.004	0.000	0.000	0.000	0.000	0.000	0.000
1	0.030	0.017	0.000	0.000	0.000	0.000	0.000	0.000
2	0.033	0.019	0.000	0.000	0.000	0.000	0.000	0.000
3	0.029	0.022	-	0.000	0.000	0.000	0.000	0.000
4	0.024	0.018	-	0.000	0.000	0.000	0.000	0.000
5	0.029	0.021	-	0.000	0.000	0.000	0.000	0.000
6	0.026	0.020	-	0.000	0.000	0.000	0.000	0.000
Average	0.028	0.019	0.000	0.000	0.000	0.000	0.000	0.000

Results adjusted to represent the impact (in µg/mL) to the next dissolution run

Table 3. Ritonavir Cleaning Study Results

Vessel	Media 10 Min	Media 15 Min	Media 20 Min	Media 25 Min	Paddles	Glass Surface	Blank Run 5 Min	Blank Run 10 Min	Blank Run 15 Min	Blank Run 20 Min
Blank	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.093	0.071	0.072	0.068	0.001	0.000	0.000	0.000	0.000	0.000
2	0.087	0.061	0.057	0.059	0.000	0.000	0.000	0.000	0.000	0.000
3	0.096	0.077	0.069	0.068	-	0.000	0.000	0.000	0.000	0.000
4	0.260	0.292	0.309	0.310	-	0.000	0.000	0.000	0.000	0.000
5	0.103	0.072	0.068	0.067	-	0.000	0.000	0.000	0.000	0.000
6	0.101	0.063	0.060	0.059	-	0.000	0.000	0.000	0.000	0.000
Average	0.123	0.106	0.106	0.105	0.000	0.000	0.000	0.000	0.000	0.000

Results adjusted to represent the impact (in µg/mL) to the next dissolution run

Table 4. Itraconazole Cleaning Study Results for Transfer Lines

Vessel	Cleaning Procedure					
	A	B	C	D	E	F
T1	0.40	0.10	0.04	0.03	0.05	0.00
T2	0.20	0.04	0.02	0.01	0.01	0.00
T3	0.40	0.13	0.06	0.03	0.02	0.00
T4	0.20	0.06	0.03	0.01	0.01	0.00
T5	0.20	0.06	0.02	0.01	0.02	0.01
T6	0.20	0.04	0.02	0.00	0.01	0.00
Average	0.27	0.07	0.03	0.02	0.02	0.00

Data expressed as % of a 100 mg itraconazole

A: Itraconazole with one cleaning program

B: Itraconazole with two 15-min infinity runs of 0.1N HCl and five cleaning programs

C: Itraconazole with two 50-min infinity runs of 0.1N HCl and five cleaning programs

D: Itraconazole with two 50-min infinity runs (0.1N HCl followed by 20% Labsan 230C) and five cleaning programs

E: Itraconazole with two 50-min infinity runs (0.1N HCl followed by 40% Labsan 230C) and five cleaning programs

F: Itraconazole with two 50-min infinity runs (0.1N HCl followed by 2.3% SDS) and five cleaning programs

Table 5. Itraconazole Cleaning Study Results for Glass and Paddle Surfaces

Vessel	Cleaning Procedure					
	A	B	C	D	E	F
Glass 1	4.30	0.14	0.07	0.12	0.02	0.02
Glass 2	1.60	0.08	0.29	0.06	1.07	0.02
Glass 3	6.80	0.09	0.25	0.05	0.02	0.04
Glass 4	5.20	0.10	0.11	0.05	0.01	0.03
Glass 5	0.70	0.00	29.70	0.13	1.52	0.04
Glass 6	0.80	0.53	0.04	0.08	0.02	0.04
Paddle	17.60	0.46	0.09	0.35	0.05	0.06
Average	5.29	0.20	4.36	0.12	0.39	0.04

Data expressed as % of 100 mg itraconazole

A: Itraconazole with one cleaning program

B: Itraconazole with two 15-min infinity runs of 0.1 N HCl and five cleaning programs

C: Itraconazole with two 50-min infinity runs of 0.1 N HCl and five cleaning programs

D: Itraconazole with two 50-min infinity runs (0.1 N HCl followed by 20% Labsan 230C) and five cleaning programs

E: Itraconazole with two 50-min infinity runs (0.1 N HCl followed by 40% Labsan 230C) and five cleaning programs

F: Itraconazole with two 50-min infinity runs (0.1 N HCl followed by 2.3% SDS) and five cleaning programs

The data not only confirm that surfactants in dissolution media help with cleaning residual components from the system but from our experience in using automated systems has us observing that it is easier to clean for BCS II/IV drug methods when using surfactants than experienced with traditional BCS class I and III drug method investigations. This again is attributed to the use of surfactants in the media. Finally, laboratories should not assume that instrumentation used with BCS I/III drug methods are easily cleansed using minimal default methods. Investigators should note that BCS I/III drugs can have affinity for transfer lines as well.

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CONFLICT OF INTEREST

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