Merits of Automated Sampling in Dissolution Testing

Technical Overview

Introduction

It is often said that there are four primary sources of potential error in any process, the so-called four Ms: Man, Method, Machine, and Materials. Any failure investigation must look at each of these four areas to understand its impact on the results. Performing dissolution methods is highly labor intensive, as well as extremely technique and time dependent.

This technical overview examines the typical dissolution workflow and how an automated sampling procedure can help eliminate many of the variables associated with out-of-specification (OOS) results.

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Dissolution Workflow

When laboratories evaluate the automation of the sample processing phase in a dissolution test, it is easy to see the benefit of improved throughput. Although there are significant gains in automating dissolution sample processing, immeasurable gains are realized through the absence of aberrant data due to analyst intervention. Additionally, analyst time may be spent on other analytical tasks.

The autosampler can be programmed with dissolution parameters that ensure the method is performed precisely and reproducibly. Administration privileges also ensure the integrity of the method that it is controlled and consistent with the current operating procedures for each product. Methods should only be created and modified by an analyst with the proper security level. At the beginning of each test, the analyst is prompted for specific product information to be linked with the analysis and ultimately, with a dissolution report.

Assuming the autosampler initiates the start of a method, the method parameters are downloaded to the dissolution apparatus. The volume of the media in each vessel is programmed, ensuring the sampling probes descend to the exact sample depth (midway between the top of the paddle or basket and the surface of the media). The autosampler measures the initial vessel temperatures and records them. For paddle methods, the dosage forms can be simultaneously dropped and the paddle rotation automatically started after the dosage form settles at the bottom of the vessel as required in harmonized pharmacopeial methods.

At designated timepoints, the sampling cannulas are simultaneously lowered, the sampling lines are primed, and the samples are collected. The sampling cannulas then raise, and any remaining media in the lines is purged back into the vessels. By removing the sampling cannula immediately after sampling, the hydrodynamic disturbance caused by resident dwelling sampling cannula is minimized. If the method requires media replacement, this is also easily accomplished through the autosampler. Preheated media can be accurately dispensed back into each vessel to maintain sink conditions.

A closer examination of each step reveals the true benefits of the dissolution autosampler.

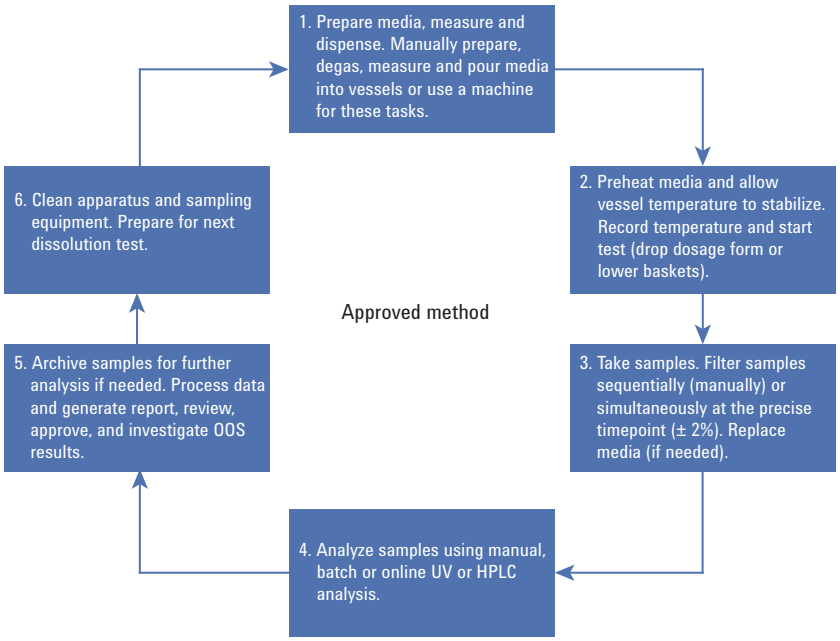

Figure 1. Dissolution workflow for a validated method.

Improved Accuracy

- Timing is a key component of the dissolution test from the moment a dosage form is introduced, until samples are pulled and filtered. Depending on your autosampler, it can either automatically lower the drive unit to the proper height to initiate a basket method, or automate dosage introduction when using paddles.

- The autosampler initiates the sampling sequence to collect the samples during the sampling window within ± 2% of the time the dosage form was introduced. Manual sampling is predicated on an analyst watching a clock, or being reminded by an alarm, then quickly sampling from each vessel at exactly the right time and at the correct position within the vessel.

- The filtration step is also included in the ± 2% timing step above because filtration essentially stops the dissolution process. Manually sampling followed by manual filtering introduces an additional time element for the dissolution process to continue. The autosampler can prime an exact amount of sample through the filter to condition it, ensuring the sample is accurately and consistently collected, and its integrity is not compromized by drug adsorbing onto the filter. This process may be accomplished using cannula filters, smaller porosity membrane filters, or both.

- Using an autosampler ensures that samples are collected and stored correctly. The sampling trays store samples from each timepoint in a defined location, depending on your autosampling firmware.

Improved Precision

- Errors due to pulling samples from improper and inconsistent locations within the vessel simply cannot be captured in a post-run investigation, challenging the variability of dissolution data. Once the event has happened, it is impossible to retrace unless it was observed and documented at the time by a trained analyst. An autosampler and dissolution apparatus with a movable manifold removes samples at the correct depth, based on the volume of media, and at the proper distance from the shaft and the vessel wall. This is especially important at early timepoints as analysts may be rushed due to the tight sampling window, and could withdraw samples erratically. Syringe pumps used in the workflow extract precise sample volumes from each vessel. Similarly, the media replacement feature uses the same syringe drive to replenish media withdrawn from the vessel. The closed loop system ensures volume accuracy and accurate sample volumes at each timepoint to reduce the variability in multiple timepoint calculations.

- Methods that require short intervals between timepoints are particularly difficult to handle manually. Even staggering the start does not help when methods call for small intervals, but an autosampler can simultaneously sample and filter in minutes.

- Establishing a cleaning procedure is critical to minimizing carryover from traces of product, excipients, and media that may require unique cleaning methods. Some autosamplers include a cleaning procedure that is automatically initiated at the end of a method. This dramatically improves instrument performance and reduces routine maintenance that may be required.

Enhanced Productivity

- Modified release products demand long drug release methods, which require the processing of samples outside of normal working hours. An autosampler can deposit the filtered samples directly into capped HPLC vials, protecting the integrity of the sample until it is relocated for analysis.

- Depending on your autosampler, it should offer additional features such as setting and documenting temperature, sample collection times, stir rates, filtration, and media replacement (if required), with a variety of data export options.

- Autosamplers typically store methods, minimizing the chance of error when programming a method. Restricted access to method and instrument changes also decreases the likelihood of setup or program errors.

The Agilent Autosampling Solution

With these facts in hand, you are now ready to choose an autosampler such as the Agilent 850-DS Dissolution Sampling Station. The 850-DS Dissolution Sampling Station is an integrated system that offers both automated filtering and sampling capabilities. The built-in rotary piston syringe pump, which saves valuable bench space and provides a combination of speed and accuracy, allows for a minimum of 2-minute sampling intervals. The autosampler also has the ability to handle surfactants (up to 5% SLS).

The optional built-in printer records the essential method parameters as well as document temperatures and timepoints. The integrated filter module option is located in the top of the instrument, and uses unique Whatman 8-channel filter plates by GE Healthcare to make changing filters between timepoints simple. In addition, filtration can be easily enabled or disabled for any method without disconnecting or adjusting sampling lines. This control is done via firmware when the method is initially created.

The 850-DS is also unique in its ability to handle a wide variety of sampling trays, from test tubes, to HPLC vials, and even 96-well plates. Methods that require smaller volumes will benefit from taking smaller sample sizes.

The aim of the 850-DS Dissolution Sampling Station is to account for the variability of dissolution methodology and provide a flexible instrument that meets a wide range of laboratory needs. To learn more about autosampling solutions from Agilent, visit www.agilent.com/lifesciences/850-DS.

Figure 2. Agilent 850-DS Dissolution Sampling Station with optional build-in filter module.

www.agilent.com/lifesciences/dissolution

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