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A Quality by Design (QbD) Aligned Approach to Developing a Robust Dissolution Method

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Introduction

Quality by Design (QbD) principles are being routinely applied to the pharmaceutical development process as numerous NDA and ANDA applicants have implemented this strategy, not only for drug development but also for analytical method development. This flexible knowledge based approach has proven ideal for analytical method development. However, it's full utilization for dissolution methods may break down some traditional thinking such as requiring speeds of 50, 75, 100 rpm and volumes of 500, 900, and 1000 mL. Applying the concept of a rugged design space through QbD principles, we have new opportunities for the development of more robust dissolution methods which may be more discriminatory and robust at non-traditional level settings of key instrument parameters. For example, for a given drug product a paddle speed of 65 rpm and/or a pH of 4.80 may provide a substantially more robust method than one which was restricted to the traditional settings of 50 rpm and pH 4.50.

The Analytical Target Profile (ATP) for the dissolution method is presented below. The ATP contains requirements for both Mean (average) performance and Robustness performance. The mean performance requirements are presented in Table 1. For each mean performance characteristic there is a corresponding method robustness (method repeatability) performance requirement. The requirement is that the method's performance in normal use will not violate the mean performance requirement given the expected total (±3σ) operating variation in the key method parameters around their final method setpoints. The expected total operating variations for the key method parameters included in this study are presented in Table 2.

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Analytical Target Profile	Means Performance Requirements
f2	Goal ≥ 60% Lower Acceptability Limit = 50%
15 Minute Release	Goal = 80% Lower Acceptability Limit = 70%
30 Minute Release	Goal = 90% Lower Acceptability Limit = 80%
45 Minute Release	Goal = 100% Lower Acceptability Limit = 90%

Table 1

Analytical Target Profile	Robust Performance Requirements
pH	± 0.10
Vessel Volume (mL)	± 10.0 mL
Paddle Speed (rpm)	± 5.0 rpm
Surfactant (%)	± 0.05%

Table 2

Experimental

The Fusion QbD Software Platform (S-Matrix Corporation, www.smatrix.com) was used for design, modeling, and reporting of experiment results. The experiment was carried out using a dissolution apparatus configured with paddles (Apparatus 2) and 1.0 liter vessels. Samples were drawn at Time = 0, 15, 30, 45, and 60 minutes and analyzed for API % Released by UHPLC.

Table 3 presents the four key dissolution parameters (study variables) included in this study along with their experimental ranges. The Fusion QbD software generated a 27-run statistical experimental design. The software can automatically construct the required dissolution testing sequences for the study in the Agilent OpenLAB Chromatography Data Software (CDS), including the required blank and standards injections. Once the chromatograms are processed in OpenLAB, the software can also automatically import the results and aggregate the data from the individual vessels used in each run (test replicates) into average release profiles, as shown in Figure 1. The software's Response Data Reduction wizard can then automatically derive curve fit metrics such as f1 and f2 from the profiles as analyzable responses, and also obtain specific time-point based responses such as the API % Released at the 15, 30, and 45 minute time points used in this analysis.

Name	Units	Range/Level(s)
pH	*	4.10 <= pH <= 4.90
Vessel Volume	mL	500 <= Vessel Volume <= 1,000
Paddle Speed	rpm	50 <= Paddle Speed <= 100
Surfactant	%	0.5 <= Surfactant <= 1.50

Table 3

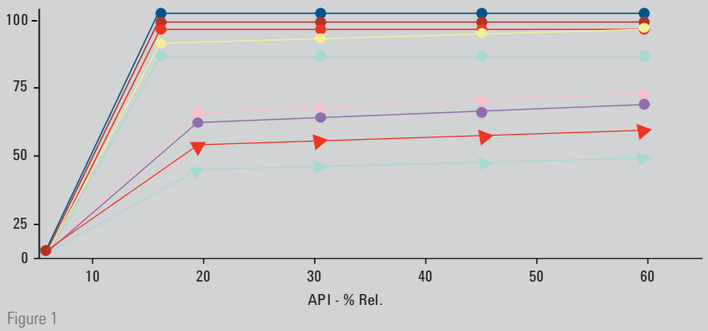

Figure 1

Mean (Average) Performance Analysis

The Fusion QbD software enables the user to search for a "best method" by assigning performance goals to the responses using the models (equations) it automatically derives from the experimental data. The user can set a specific type of numerical goal for each response (Minimize – a smaller result is better, Maximize – a larger result is better, or Target – a specific value is desired). The user can also set minimum acceptability limits on the responses. The software then evaluates thousands of possible methods within the combined experimental ranges of the study parameters (variables) and determines the level setting combination which best meets all performance goals at once. The result shown in Table 4.A was obtained for a search which included the full experimental ranges of the study variables. The corresponding goals, and the predicted results for the analyzed responses, are presented in Table 4.B.

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Variable	Level Setting
pH	4.70
Vessel Volume	625
Paddle Speed	50
Surfactant	1.1

Table 4.A

Response	Goal	Predicted Result
API - f2	Maximize	65.25
API - Y-Mean at X = 15	80.0	82.63
API - Y-Mean at X = 30	90.0	89.96
API - Y-Mean at X = 45	Maximize	98.38

Table 4.B

Figure 2.A is a graph of predicted mean performance for the experimental ranges of Vessel Volume (X axis) and Paddle Speed (Y axis) when pH = 4.70 and Surfactant = 1.1%. Note that the software associates a color with each response and uses the color to shade the region of the graph where methods fail to meet the minimum performance requirement for the response. The dark line of a given color demarcating the unshaded and shaded regions is therefore the performance acceptability limit for the associated response – this is termed the edge of failure in the QbD lexicon. Figure 2.B is the same graph but with pH = 4.50. Comparing these graphs shows the reduction in the unshaded region resulting from setting the pH to its traditional level.

Note that these are graphs of predicted mean performance, and individual results will normally deviate about the mean. These graphs were therefore generated using restricted acceptability limit settings for each response to shift predicted mean performance away from the absolute acceptability limits associated with the responses. These restricted and absolute limits are presented in Table 5.

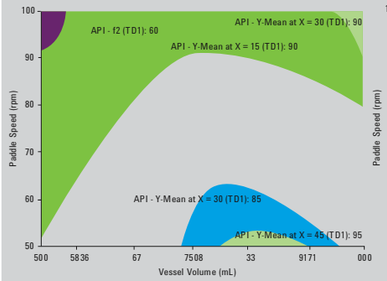

Figure 2.A

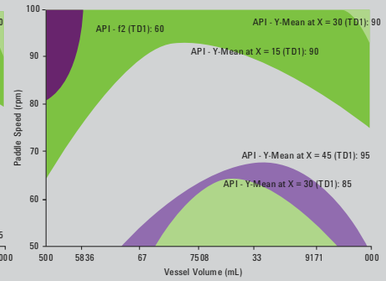

Figure 2.B

Response	Restricted Acceptability Limit	Absolute Acceptability Limit	Tolerance Limit Delta
API - f2	60.00	50.00	10.00
API - Y-Mean at X = 15	75.0	70.00	5.00
API - Y-Mean at X = 30	85.0	80.00	5.00
API - Y-Mean at X = 45	95.00	90.00	5.00

Table 5

Robustness Analysis

Once it is determined that methods can be identified which meet all restricted mean performance requirements, we then must determine if a portion of the unshaded region in the graphs contains methods that fail robustness – i.e., methods that can yield failed results due to expected variation in the instrument parameters during normal use. Monte Carlo simulation is used for the robustness analysis. To execute this analysis the user first defines the maximum expected operating variation (±3σ) for each study variable during normal use. These values are defined for the study parameters in Table 2. The user then defines the numerical distance of the restricted edge of failure to the absolute edge of failure for each response – this defines the method's maximum allowable ±3σ variation limits about the predicted mean response. The numerical distance is termed the Tolerance Limit Delta. Table 5 presents the Tolerance Limit Delta settings for the responses included in this analysis.

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Table 6 presents the Final Design Space and the Proven Acceptable Ranges (PARs) for the study parameters determined using the Fusion QbD software's graphical analysis and visualization toolset. Figure 2 presents the 4D Trellis graphs associated with this result.

Name	Lower Bound	Upper Bound	Method Setpoint
pH	4.60	4.80	4.70
Vessel Volume	615	635	625
Paddle Speed	50	60	55
Surfactant	1.05	1.15	1.10

Table 6

Figure 3 presents the 4D Trellis of graphs corresponding to the PARS in Table 6. Note that the PARs for pH and Vessel Volume are represented in Figure 3 by the black rectangle common to all graphs. Note also that the 4D trellis series of graphs also represents the PARs for Paddle Speed and Surfactant. The graph series in Figure 3 therefore visualizes the Final Design Space and PARs for all four study parameters simultaneously. The use of a graphical visualization tool is critically important, as it showed that a target pH of 4.50 could not support the establishment of a robust design space across the required PARs for all variables. However, changing the target pH to 4.70 enabled the robust design space goal to be achieved.

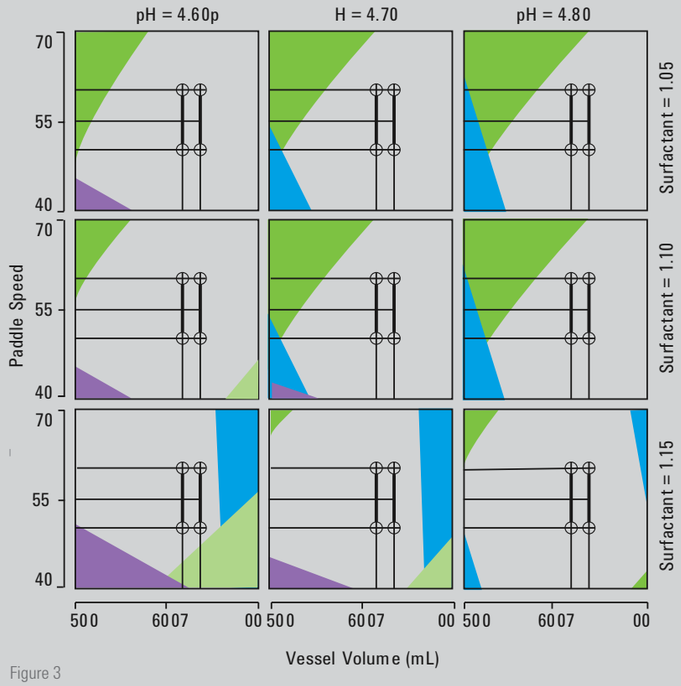

Figure 3

Conclusions

Formal experimental design, also known as Design of Experiments (DOE), is required in order to efficiently investigate multiple important parameters in combination, and model all the effects of the study parameters within their joint study ranges, including interaction effects. This modeling is key to characterization of the mean performance and also the relative robustness of given candidate methods. The QbD-aligned approach integrated within the Fusion QbD software therefore enabled the identification of a method meeting all performance requirements, and the establishment and visualization of the robust Final Design Space and PARs for the four study variables.

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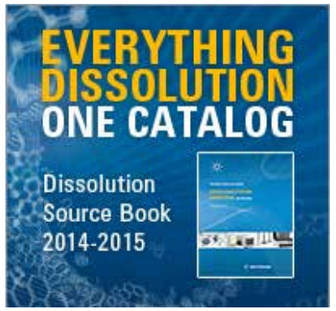

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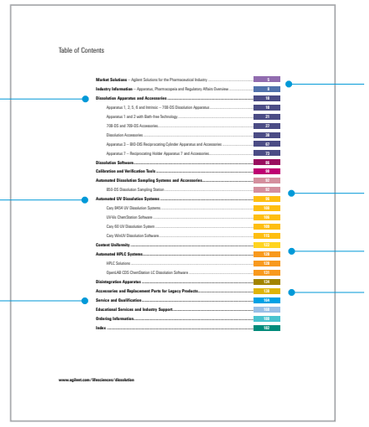
Table of Contents

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Tips and Tricks to Improve Your Dissolution Testing

Dissolution Method Cleaning Validation

Dissolution has its share of labor intensive tasks. One important responsibility of any analyst is to perform a proper cleanup and turnaround of the system for the next test. Additionally, a key component of an automated method is a validated cleaning method. This ensures the sample integrity for each test as well as serving to extend the life of the instrumentation.

Depending on the exact method, media or product formulation characteristics, a specific cleaning procedure should be validated for each dissolution method. It's critical to execute this procedure as soon as possible after the test has completed. Abrasives or bleach-based solutions should not be used for cleaning – an appropriate solvent should be determined for the specific product and material of the system components that contact the media.

A simple cleaning validation may consist of the following steps:

1. Execute dissolution test
2. Perform system cleaning procedure
3. Execute dissolution test with no product – blank media in vessels
4. Ensure < 1% response of active component in the blank (typically acceptable)
5. If carryover response is ≥ 1%, modify cleaning method and repeat

Some items should also be examined periodically for wear, deformation or corrosion. It's beneficial to implement a preventative maintenance schedule and replace certain components such as sample tubing, needles and valves to keep the system performing at a high level. Sticky residues, surfactant-based media, non-water soluble constituents or any other difficult to clean elements may require a more extensive process involving multiple solutions, elevated temperatures or both. Some suggested cleaning solutions include hot water, water with alcohol up to 30% and repeated cycles which should always be followed by a purified water rinse and purging of the sample lines.

In summary, remember that a good understanding of the product, media and instrumentation can help to develop the proper cleaning technique. Validated procedures are necessary for each method – not simply an apparatus or automated system. Prompt execution combined with a sound procedure goes a long way in ensuring the integrity of the dissolution results while serving to protect the investment in the dissolution system.

An automated cleaning cycle can be added to any dissolution test when using Agilent's 850-DS Sampling Station. Parameters can be customized based on specific cleaning requirements.

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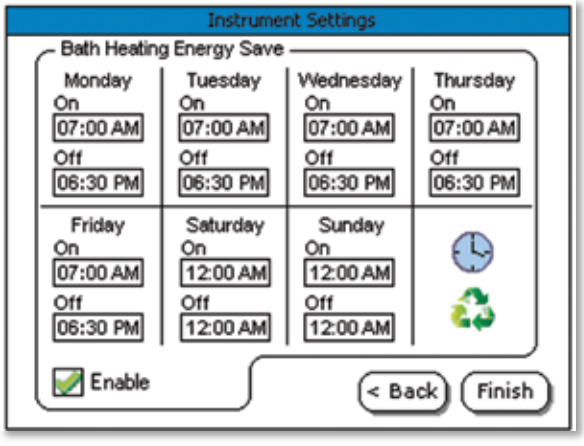
A variety of evaporation covers, including the newly designed split cover for easy removal, are available for the 708-DS and 709-DS Dissolution Apparatus.

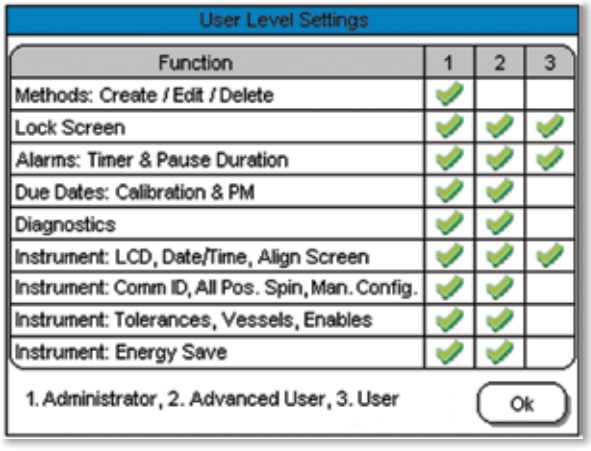
Agilent's 708-DS Dissolution Apparatus – The Same... but Different

Here are some of the recently implemented improvements to the 708-DS and its accessories:

- **Split evaporation covers** – easily remove your evaporation covers for cleaning without detaching the paddle or basket shaft.
- **Heater/Circulator Energy Save** – program on/off times for your 708-DS heater to minimize power use; simply enter the desired schedule and the water bath can be ready when you are.
- **Certificates of Conformance (COC)** – all paddle and basket shafts include an individual certificate documenting all critical measurements in accordance with the ASTM E2503-07 mechanical calibration guidelines.
- **Increased method storage** – store up to 40 dissolution methods in the 708-DS and 709-DS firmware.
- **Manual sampling bracket** – take advantage of the motorized sampling manifold and stored depth settings to ensure repeatability even if you're not using an automated sampling system.
- **User access levels** – regulate access and limit entry errors to your 708-DS and 709-DS firmware settings by placing the instrument in a restricted mode so only certain functions can be executed.



Heater/Circulator Energy Save – Program on/off times for your 708-DS heater/circulator to minimize power use; simply enter the desired schedule to ready your apparatus for use.



User access levels – Control access and eliminate entry errors by placing the 708-DS in a specific mode that prohibits the execution of certain functions.

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