Introduction

Quality by Design (QbD) has proven an ideal methodology for analytical method development. Its full utilization for dissolution methods may break down traditional thinking such as limiting speed to 50, 75, and 100 rpm or volumes to 500, 900, and 1000 mL. This article presents QbD aligned development of a dissolution method which is more discriminatory and robust at non-traditional level settings of key instrument parameters.

Table 1 summarizes the Analytical Target Profile (ATP) for the dissolution method. The table presents the four key dissolution parameters (study variables) included in this study, their experimental ranges, and their expected total (±3σ) operating variations in routine use. The ATP also summarizes the critical Mean (average) performance and Robustness performance requirements for the method – each mean performance goal has the associated robustness requirement that method performance will not violate the associated Acceptability Limit given the combined variations in the method study parameters which will occur in routine use.

Table 1

STUDY PARAMETERS		
Study Variable	**Study Range**	**Expected ±3σ Variation**
pH	4.10 <= pH <= 4.90	±0.10
Vessel Volume (mL)	500 <= Vessel Volume <= 1,000	±10.0
Paddle Speed (rpm)	50 <= Paddle Speed <= 100	±5.0
Surfactant (%)	0.5 <= Surfactant <= 1.50	±0.05
PERFORMANCE REQUIREMENTS		
Response	**Mean Performance Goal**	**Lower Acceptability Limit**
f2	≥ 60%	50%
15 Minute Release	80%	70%
30 Minute Release	90%	80%
45 Minute Release	100%	90%

Experimental

The Fusion QbD Software Platform (S-Matrix Corporation, www.smatrix.com) was used for experiment design generation and testing automation on the Agilent OpenLAB Chromatography Data Software (CDS), data modeling, and QbD results reporting. 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.

Fusion QbD automatically constructs the required dissolution testing sequences in OpenLAB, including required blank and standards injections. The software can also import the processed chromatogram results and aggregate the data from the individual vessels used in each trial (test replicates) into average release profiles, derive curve fit metrics such as f1 and f2 from the profiles as analyzable responses, and obtains responses at user specified time points such as % Released at 15, 30, and 45 minutes.

Mean (Average) Performance Analysis

Automated data modeling provides a mean performance prediction equation (mean response model) for each analyzed response data set. For proposed settings of the study parameters the mean response model directly predicts the expected mean (average) result for the response. The software uses these models to search for a “best method” – one that simultaneously meets all user specified performance goals for the responses. The user can also set not-to-exceed acceptability limits for each response (referred to as ***edges of failure*** in the QbD lexicon). Since individual results for a given response will normally vary about the mean, the search is done using ***restricted*** acceptability limits to shift the required mean result away from the ***absolute*** acceptability limit defined for the response. Table 2 presents the method obtained from this search along with the restricted acceptability limits used in the search and the corresponding predicted result for each response.

Table 2

Study Variable	Search Answer Level Setting
pH	4.7
Vessel Volume	625
Paddle Speed	50
Surfactant	1.1

Response	Restricted Acceptability Limit	Predicted Result
API - f2	≥60	65
API - Y-Mean at X = 15	75	83
API - Y-Mean at X = 30	85	90
API - Y-Mean at X = 45	≥95	98

Figure 1.A is a graph of predicted mean performance for the study 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 1.B is the same graph but with pH = 4.50. Comparing these two graphs shows the reduction in the unshaded region resulting from changing the pH to its traditional level. The preliminary design space is reduced much further when the pH is set to 4.40, the lower limit of its expected variation in normal use.

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. The numerical distance of the restricted edge of failure to the absolute edge of failure for each response is termed the ***Tolerance Limit Delta***. Table 3 presents the Tolerance Limit Delta values for the responses used in the mean performance analysis, and also in the graphs presented in Figures 1.A and 1.B.

Figure 1.A

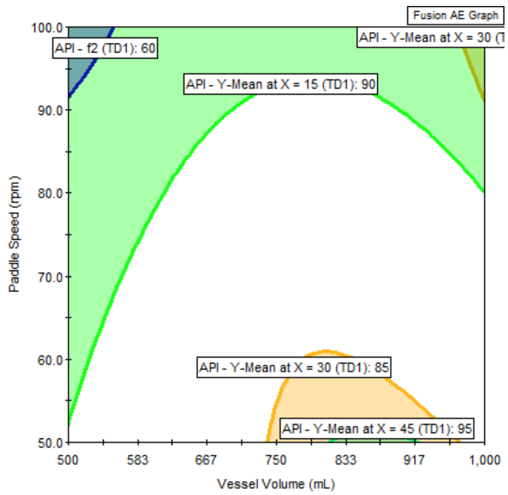


Figure 1.B

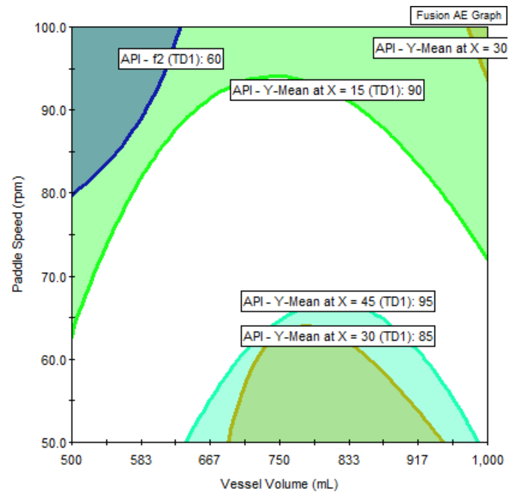


Table 3

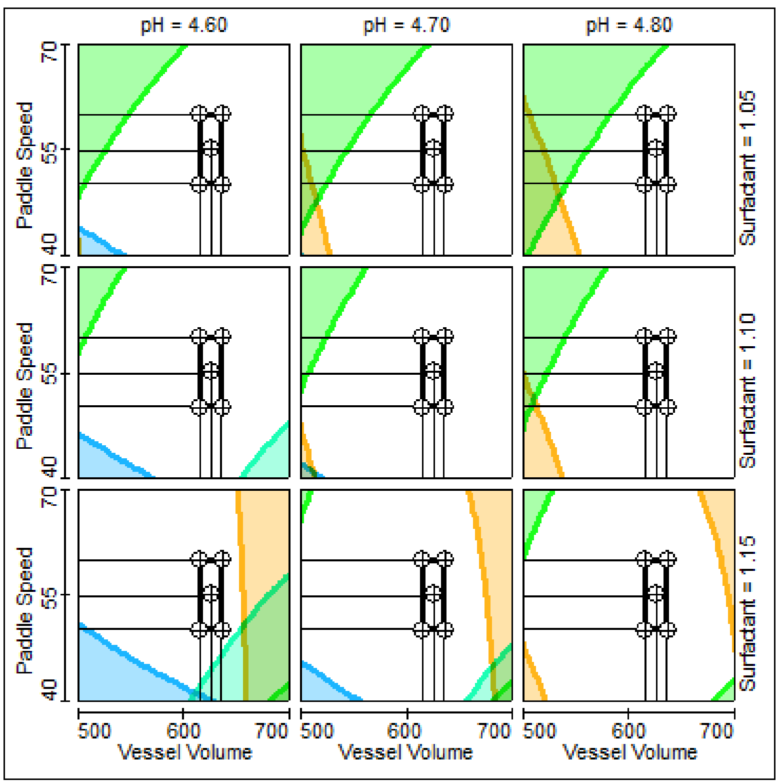
Response	Restricted Acceptability Limit	Absolute Acceptability Limit	Tolerance Limit Delta
API - f2	60.00	50.00	10.00
API - Y-Mean at X = 15	75.00	70.00	5.00
API - Y-Mean at X = 30	85.00	80.00	5.00
API - Y-Mean at X = 45	95.00	90.00	5.00

Robustness Analysis

Once it is determined that one or more methods can be identified which meet all restricted mean performance requirements, a ***preliminary*** design space for mean performance is established using the restricted acceptability limits. It must then be determined if any methods exist within this design space which can fail robustness – i.e., the method will sometimes provide unacceptable results due to expected variation in the study parameters during routine use. The software uses Monte Carlo simulation analysis for this determination, incorporating user input expected operating variation for the study variables (the ±3σ variations presented in Table 1) to generate models which can predict a method's robustness performance for each response.

Figure 2 is 4-variable (4D) Trellis graph series showing the ***Final Design Space*** and ***Proven Acceptable Ranges*** (PARs) for the study parameters determined using Fusion QbD's graphical analysis and visualization feature, which also displays the results in tabulated form (not shown). As with the previous graphs, the software associates a color with each mean response to shade the regions of the graph where methods fail to meet the minimum performance requirements for the response and demarcate the QbD edge of failure for the response.

Figure 2



The PARs for Paddle Speed and Vessel Volume are represented in Figure 2 by the black rectangle common to all nine trellis graphs. Note that the trellis series also represents the PARs for pH (±0.1) and Surfactant (±0.05). The graph series in Figure 2 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 enables the robust design space goal to be achieved.

Conclusions

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

- http://www.smatrix.com/fusion_product_development.html

References

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