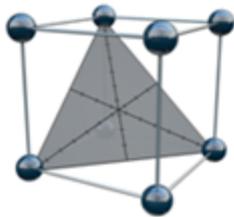


Dissolution Method Development with Fusion QbD

Fusion QbD

Quality by Design Software System

WINDOWS®



S-Matrix®

S-Matrix, the S-Matrix logo, and Fusion QbD are either registered trademarks or trademarks of S-Matrix Corporation in the United States and/or other countries. Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Protected by a U.S. Patents. Patents pending in the U.S. and other countries. © 1995-2014 S-Matrix Corporation. All rights reserved. Made in the USA.

S-Matrix Corporation
1594 Myrtle Avenue
Eureka, CA 95501
USA

Phone: 707-441-0404

URL: www.smatrix.com

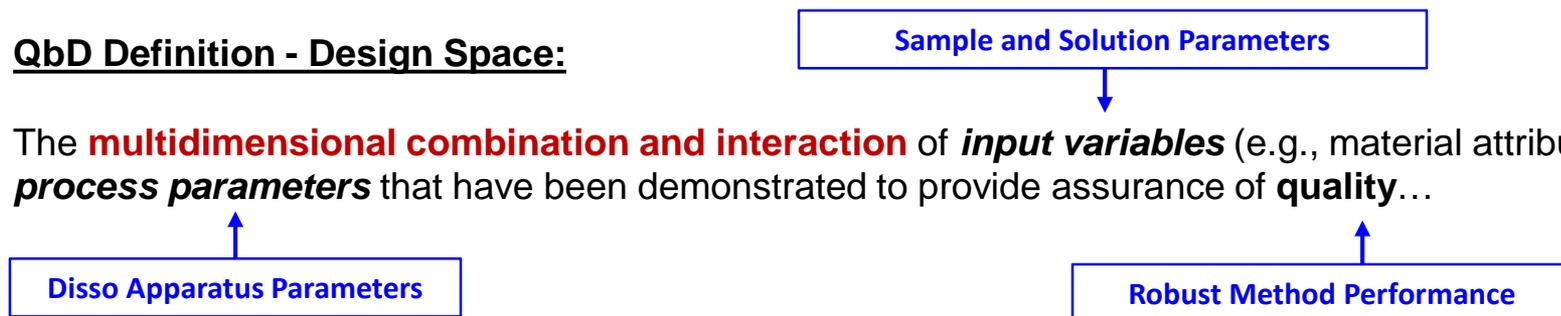
QbD Guidances Mapped to Dissolution Method Dev.

QbD Approach – should provide accurate quantitative knowledge of how all critical solution and apparatus parameters affect all critical method performance characteristics, independently and in combination.

QbD Result – robust methods which meet all critical performance requirements.

QbD Definition - Design Space:

The **multidimensional combination and interaction** of *input variables* (e.g., material attributes) and *process parameters* that have been demonstrated to provide assurance of **quality**...



QbD Definition - Formal Experimental Design:

A structured, organized method for **determining the relationship between factors** affecting a *process* and the *output of that process*. Also known as "Design of Experiments".



Critical to QbD – Knowledge of Factor Interactions

Note the Key Phrases in the previous slide:

Design Space: ... multidimensional combination and interaction ...

Formal Experimental Design: ... determining the relationship between factors ...

It is now well understood that **interactions can greatly affect**:

- ◆ Mean (Average) Method Performance
- ◆ Method Robustness Performance

Therefore –

the guidances stress **STUDYING VARIABLES IN COMBINATION**

because it is **THE ONLY WAY** to understand and characterize **interactions!**

Before QbD – Standard Approach Was OFAT

OFAT = One Factor At a Time

OFAT Approach: Study one factor (variable) such as pH while holding all other factors constant.

Once “best” pH is identified, hold it constant and select a second variable for study, and so on ...

- The Problems:
- 1 – **no knowledge of interactions**
 - 2 – **no robustness characterization**
 - 3 – **sub-optimal results**
 - 4 – **not aligned with regulatory expectations**

OFAT versus DOE – Study Efficiency

OFAT

3 levels of pH

3 levels of Vessel Volume

3 levels of Paddle Speed

3 levels of Disintegrant

$3 \times 3 \times 3 \times 3 = 81$ possible combinations

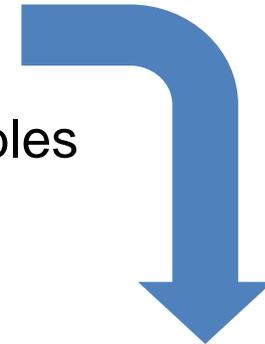
DOE

Fusion QbD Design = **23 runs**

~ 3x efficiency.

Fusion QbD – Simple Experiment Setup

Just enter your study variables and their study ranges or specific study levels



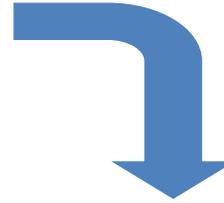
Name	Units	Type	Level Settings
pH	"	Discrete Numeric	Level 1: 5.00 Level 2: 6.00 Level 3: 7.00
State <input checked="" type="radio"/> Variable <input type="radio"/> Constant		No. of Levels: 3	

Name	Units	Type	Lower Bound	Upper Bound
Vessel Volume	mL	Continuous	600	1,000
State <input checked="" type="radio"/> Variable <input type="radio"/> Constant				

Name	Units	Type	Lower Bound	Upper Bound
Paddle Speed	rpm	Continuous	60	100
State <input checked="" type="radio"/> Variable <input type="radio"/> Constant				

Name	Units	Type	Lower Bound	Upper Bound
Disintegrant	grams	Continuous	4.0	12.0
State <input checked="" type="radio"/> Variable <input type="radio"/> Constant				

Generate the Experimental Design



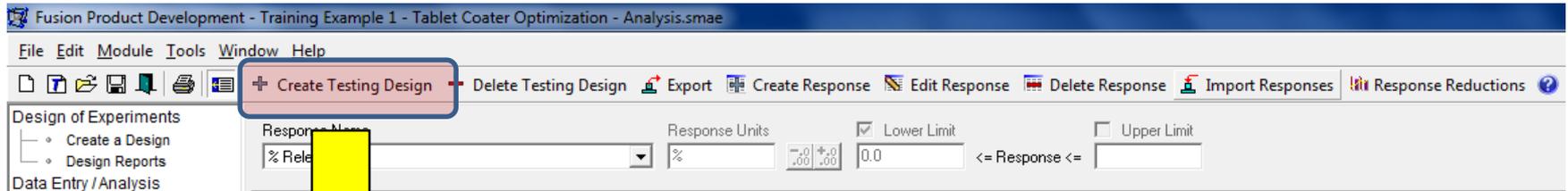
Fusion QbD

Automatically selects the most efficient design based on the your selected parameters and type of study – screening or optimization.

Automatically includes repeat runs for error checking.

	Run No.	pH	Vessel Volume	Paddle Speed	Disintergrant
1	1	5	600	60	12
2	2	5	600	100	12
3	3	5	800	100	4
4	4	7	1000	60	4
5	5	5	1000	100	4
6	6	7	1000	60	8
7	7	7	600	60	12
8	8	7	1000	80	4
9	9	6	800	100	4
10	10	7	1000	100	12
11	11	7	600	80	4
12	12	6	600	60	4
13	13	5	1000	60	12
14	14	7	1000	100	12
15	15	5	1000	60	4
16	16	7	600	100	4
17	17	7	1000	100	4
18	18	5	600	100	8
19	19	6	800	80	8
20	20	7	800	60	4
21	21	6	800	60	4
22	22	6	800	80	8
23	23	5	800	100	12
24	24	6	600	60	12
25	25	5	600	100	12
26	26	5	1000	60	12
27	27	7	600	60	4

Creates Dissolution Testing Designs for LC



Create Testing Design

Testing Design Name: Dissolution Testing (TD2) Testing Design Type: Time Series

Reference Standards: Reference Standard Runs: 0 Replication Scheme: No. of Preparation Repeats: 1, No. of Test Repeats per Preparation: 3

Sampling Rate: Uniform (selected) Variable (unselected)

Uniform: No. of Measurements: 4 per Hour Total Time Period: 1 Hours Start time at 0.0 (checked) Update

Measurement	Time Point (Minutes)
1	0.0
2	15.0
3	30.0
4	45.0
5	60.0

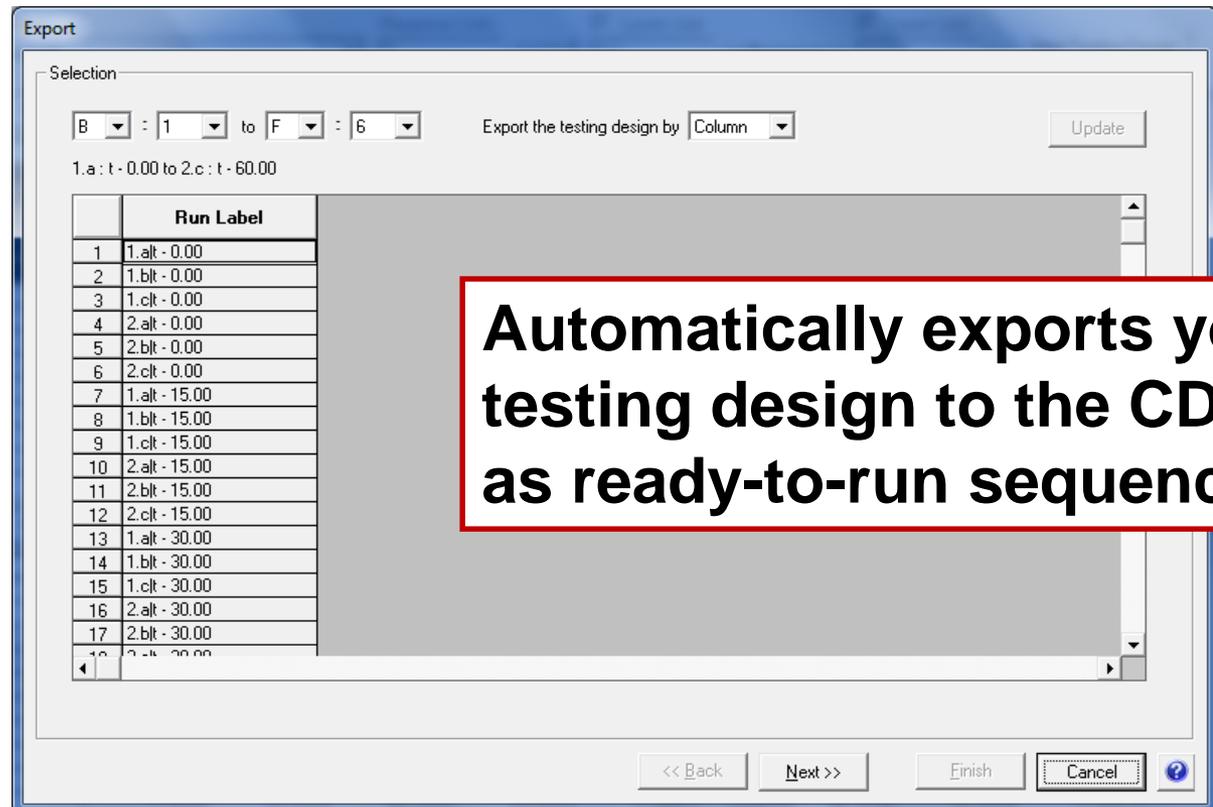
The settings are valid.

Back Finish Cancel

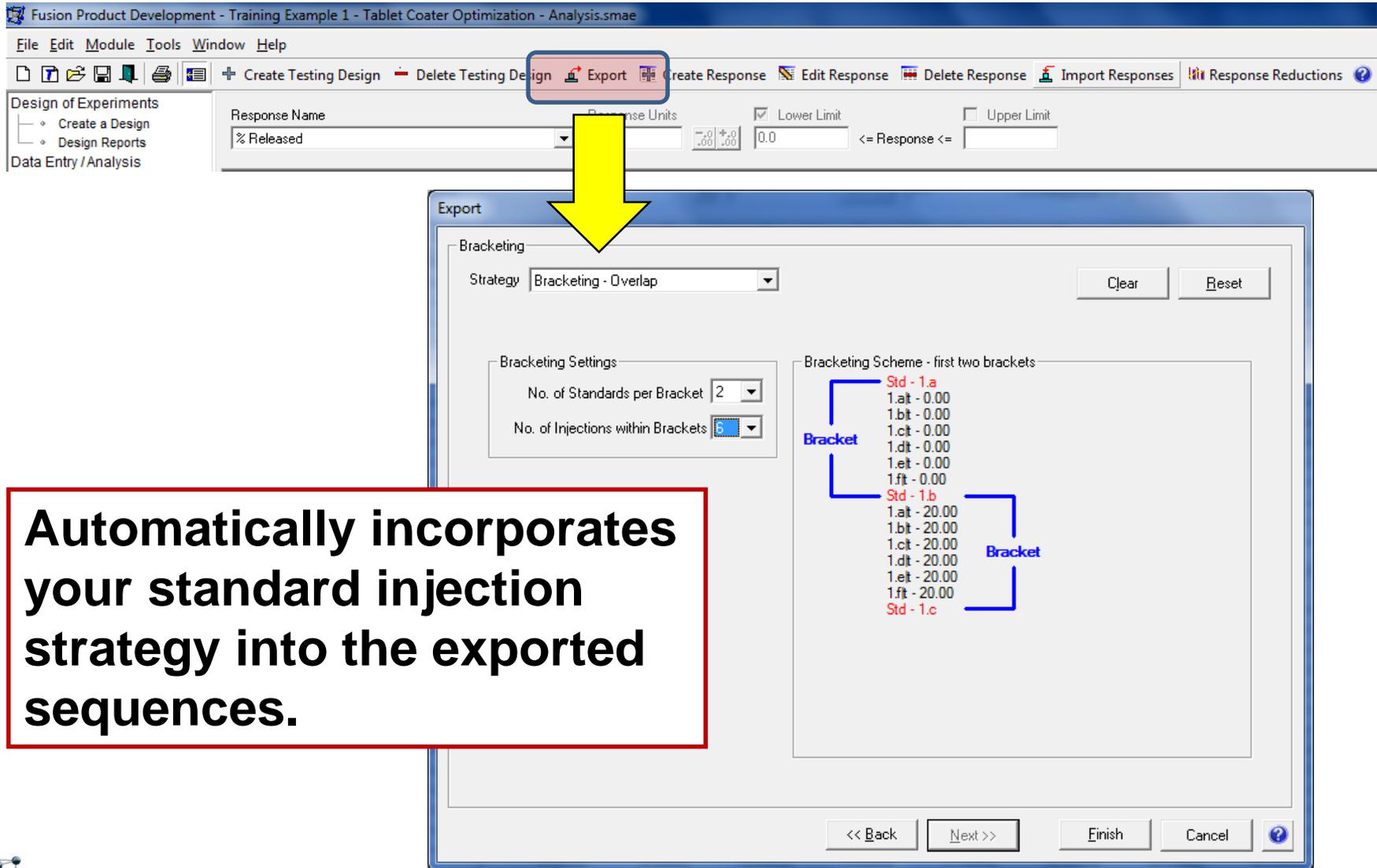
Fusion QbD supports:

- Uniform or variable sampling plans
- Multiple sample preparation repeats
- Multiple test repeats at each time point
- Internal test standard data

Exports Testing Designs to CDS



Adds Standard Injections



Fusion Product Development - Training Example 1 - Tablet Coater Optimization - Analysis.smae

File Edit Module Tools Window Help

Create Testing Design Delete Testing Design Export Create Response Edit Response Delete Response Import Responses Response Reductions

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

Response Name: % Released

Response Units: %

Lower Limit: 0.0

Upper Limit:

Export

Bracketing

Strategy: Bracketing - Overlap

Clear Reset

Bracketing Settings

No. of Standards per Bracket: 2

No. of Injections within Brackets: 5

Bracketing Scheme - first two brackets

Std - 1.a

1.at - 0.00

1.bt - 0.00

1.ct - 0.00

1.dt - 0.00

1.et - 0.00

1.ft - 0.00

Std - 1.b

1.at - 20.00

1.bt - 20.00

1.ct - 20.00

1.dt - 20.00

1.et - 20.00

1.ft - 20.00

Std - 1.c

Bracket

Bracket

<< Back Next >> Finish Cancel ?

Automatically incorporates your standard injection strategy into the exported sequences.

Imports Dissolution Chromatogram Results

Fusion Product Development - FPD - Dissolution Demo File - Analysis - May 2014.smae

File Edit Activity Tools Window Help

Create Testing Design Delete Testing Design Create Response Edit Response Delete Response Response Reductions Export Import Responses

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry**
- Data Analysis

Best Answer Searches

- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics

- Single Response Series
- Multiple Response Series

Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

Response Name: API - % Released
Response Units: %
Lower Limit: 0.0
Upper Limit: 105.0
View Testing Design

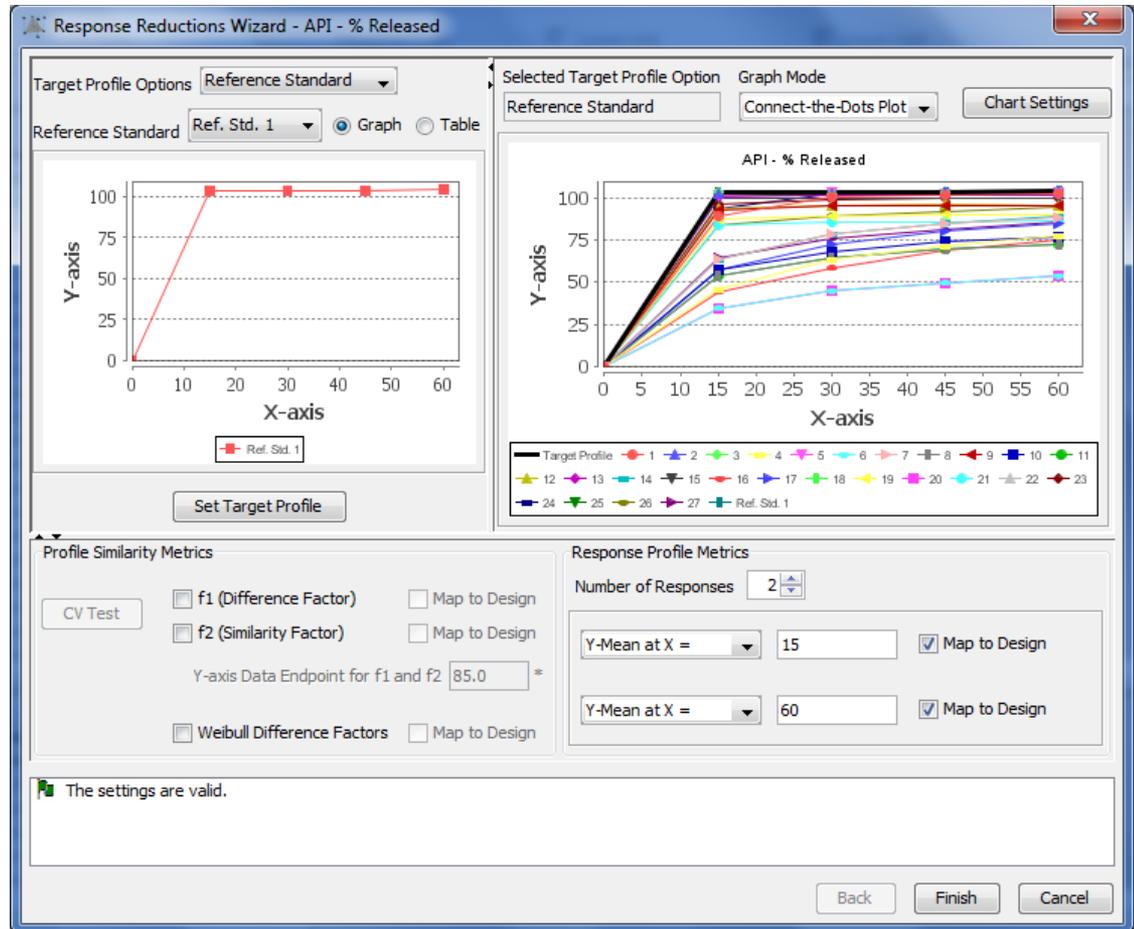
	A Run No.	B t - 0.00	C t - 15.00	D t - 30.00	E t - 45.00	F t - 60.00
1	1.a	0.00	93.00	99.00	100.00	101.00
2	1.b	0.00	81.00	101.00	103.00	103.00
3	1.c	0.00	94.00	101.00	102.00	103.00
4	2.a	0.00	104.00	104.00	103.00	103.00
5	2.b	0.00	102.00	102.00	103.00	103.00
6	2.c	0.00	101.00	101.00	103.00	103.00
7	3.a	0.00	102.00	102.00	103.00	103.00
8	3.b	0.00	103.00	102.00	103.00	103.00
9	3.c	0.00	104.00	103.00	103.00	103.00
10	4.a	0.00	45.00	63.00	77.00	87.00
11	4.b	0.00	47.00	66.00	77.00	87.00
12	4.c	0.00	45.00	61.00	77.00	87.00
13	5.a	0.00	100.00	101.00	103.00	103.00
14	5.b	0.00	103.00	103.00	103.00	103.00
15	5.c	0.00	101.00	104.00	103.00	103.00
16	6.a	0.00	36.00	45.00	50.00	53.00
17	6.b	0.00	34.00	45.00	50.00	55.00
18	6.c	0.00	34.00	44.00	49.00	53.00
19	7.a	0.00	64.00	79.00	86.00	90.00
20	7.b	0.00	63.00	78.00	84.00	87.00
21	7.c	0.00	63.00	77.00	84.00	87.00

Automatically imports all results from the dissolution testing chromatograms.

Converts Raw Chromatogram Results into Profiles

Fusion QbD Automatically:

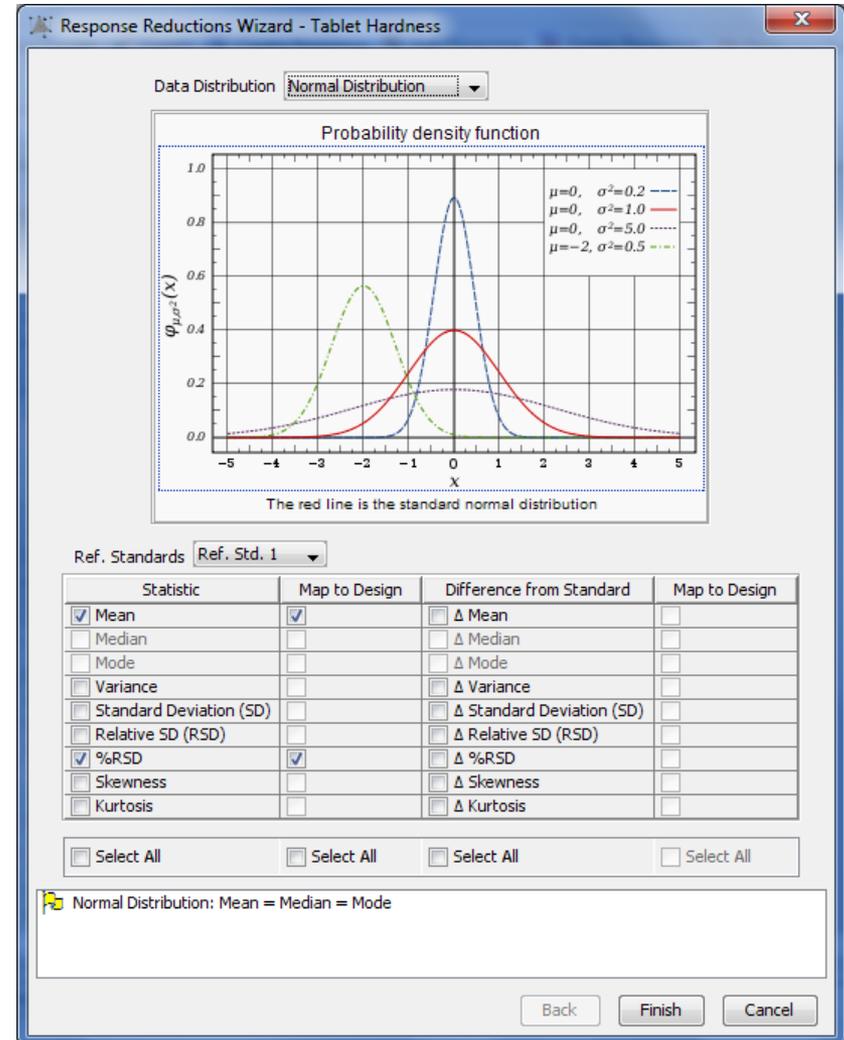
- handles repeat injections at each time point
- computes average profiles
- computes f1 & f2 curve fit metrics
- computes additional profile response metrics
- Maps all computed responses to the experimental design for instant data analysis



You Can Add Results From Any Other Tests

Fusion QbD Automatically:

- handles test repeat data
- handles non-normal data
 - Log-normal
 - Exponential
 - Gamma
 - Weibull
- computes descriptive statistics based responses
- computes differences of all statistics from a reference standard
- Maps all responses to the experimental design for analysis



One-click Analysis & Modeling with Full Reporting

Fusion Product Development - FPD - Dissolution Demo File - Analysis - May 2014.smae

File Edit Activity Tools Window Help

Analyze Data Import Images Custom Model Builder

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry
- Data Analysis

Best Answer Searches

- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics

- Single Response Series
- Multiple Response Series

Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

Response Data

API - % Released - Y-Mean at X = 15 (TD1) View All Reports

Analysis Reports

- Summary Report
- Summary Report
- Experimental Error Analysis
- Regression Analysis
- Residuals Table & Plots
- Transformation Analysis Table & Plot
- Extra Sum of Squares Statistics
- Coefficients Table and Models
- Mean Effects Pareto Ranking Table & Plot

Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: May 27, 2014 3:58:24 PM PDT [GMT-07:00]

S-Matrix®

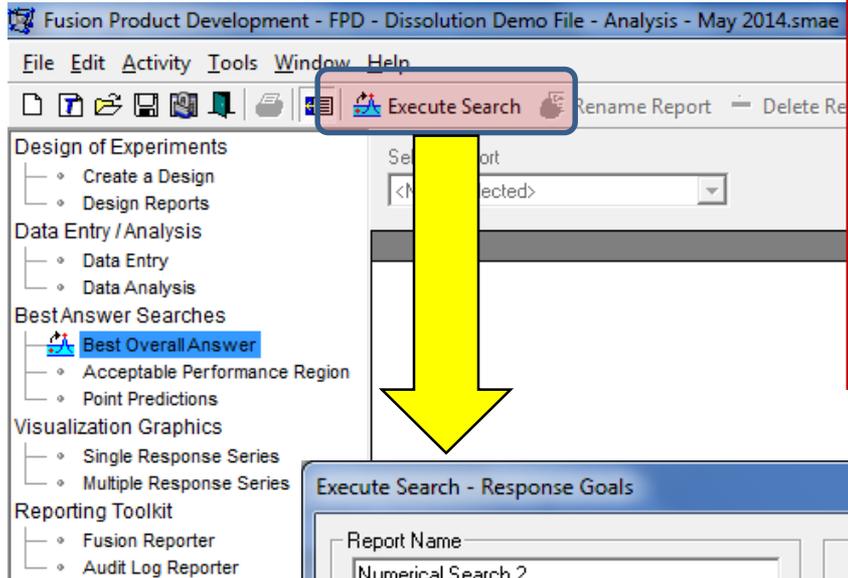
Analysis Summary Report: API - % Released - Y-Mean at X = 15 (TD1)

Model Sufficiency Chart

Fusion AE Graph

Statistic	Value
MSR	0.9537
MSE	0.0110
MS-LOF	0.0100
MS-PE	0.0188
0.0902 (ST - MS-LOF)	0.0902
0.0296 (ST - MSR)	0.0296

Best Overall Answer Search



Easily enter performance goals for each analyzed and modeled dissolution method performance characteristic.

Execute Search - Response Goals

Report Name: Numerical Search 2

Model Prediction Error C.I. for Report: \pm 2 Sigma

	Response Name	Goal	Lower Bound	Upper Bound	Relative Rank
<input checked="" type="checkbox"/>	API - % Released - Y-Mean at X = 15 (TD1)	Target	60.00	80.00	1
<input checked="" type="checkbox"/>	API - % Released - Y-Mean at X = 60 (TD1)	Maximize	90.00	100.00	1

Validation Status: Your settings are valid.

Buttons: Modify Search Region..., Restore Defaults, <<Back, Finish, Cancel, ?

Finds Best Performing Method

The screenshot displays the Fusion Product Development software interface. The title bar reads "Fusion Product Development - Dissolution Demo File - Analysis - June 2014.smae". The menu bar includes "File", "Edit", "Activity", "Tools", "Window", and "Help". The toolbar contains icons for "Execute Search", "Rename Report", "Delete Report", "RS Robustness Simulator", "Export", and "Import Images".

The left sidebar shows a navigation tree with categories: "Design of Experiments", "Data Entry / Analysis", "Best Answer Searches", "Visualization Graphics", and "Reporting Toolkit". Under "Best Answer Searches", "Best Overall Answer" is selected.

The main content area shows the results for "Numerical Search 1". A text box contains the following information:

Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: June 1, 2014 5:42:39 PM

Below this is the section "Numerical Answer Search" with a sub-section "Answer #1" and "Variable Settings".

Variable	Level Setting
pH	6.51
Vessel Volume	603
Paddle Speed	100
Disintegrant	12.0

Below the variable settings is the section "Predicted Results" with a table:

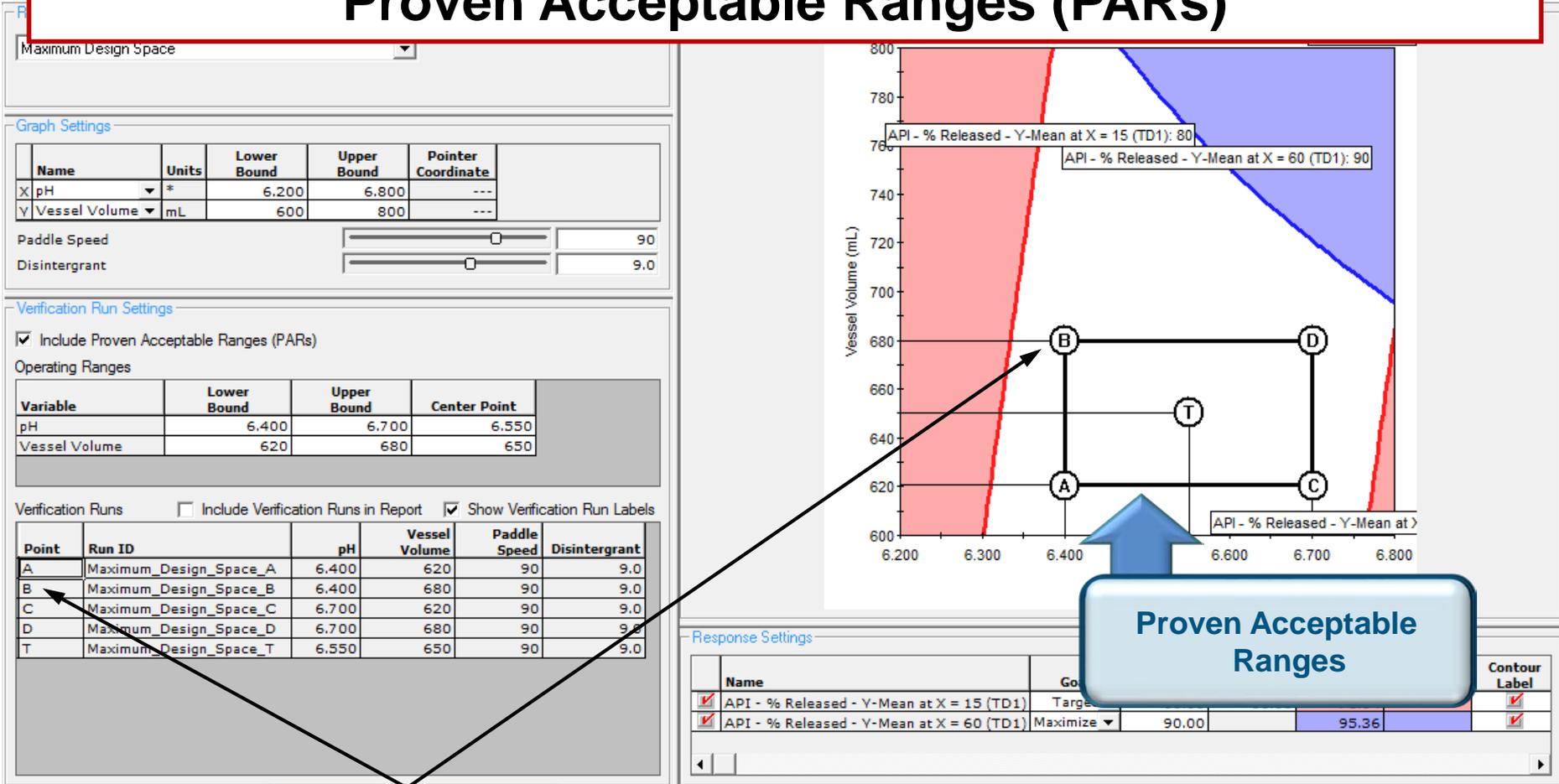
Response	Goal	Predicted Result	Desirability	-2 Sigma Conf. Limit	+2 Sigma Conf. Limit
API - % Released - Y-Mean at X = 15 (TD1)	70.00	69.89	0.9893	56.43	83.36
API - % Released - Y-Mean at X = 60 (TD1)	Maximize	100.88	1.0000	95.77	102.61

A red-bordered box highlights the following text:

Automatically identifies the best achievable method in terms of simultaneously meeting all analyzed and modeled performance characteristics.

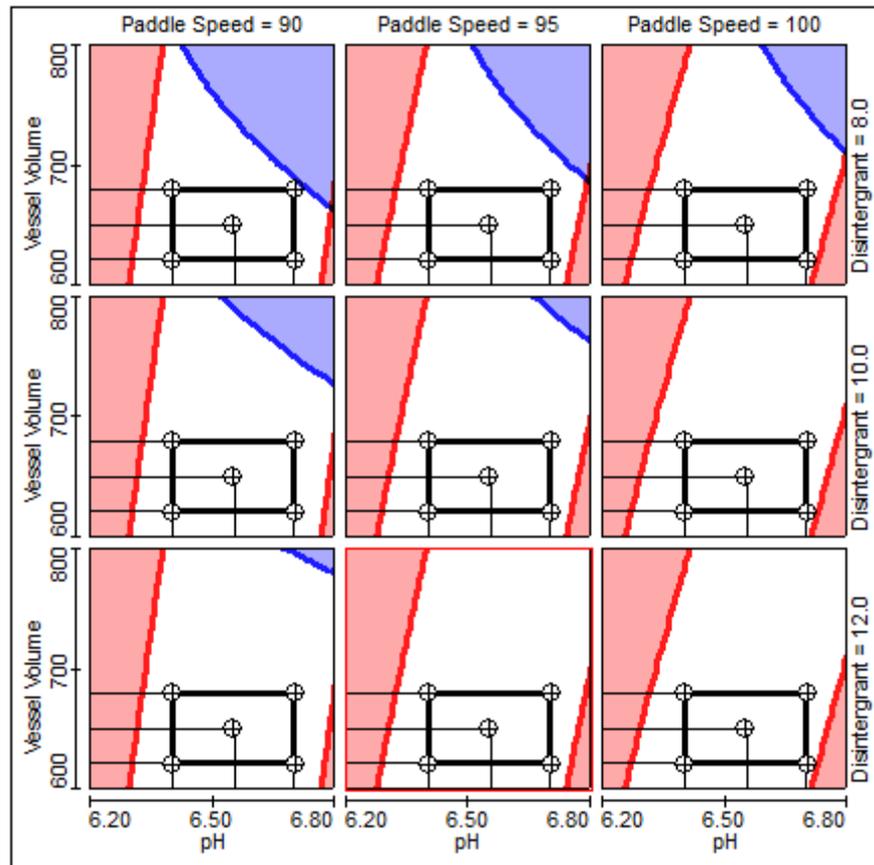
Visualizes Your Design Space & PARs

Graphically Explore and Visualize the Design Space & Proven Acceptable Ranges (PARs)



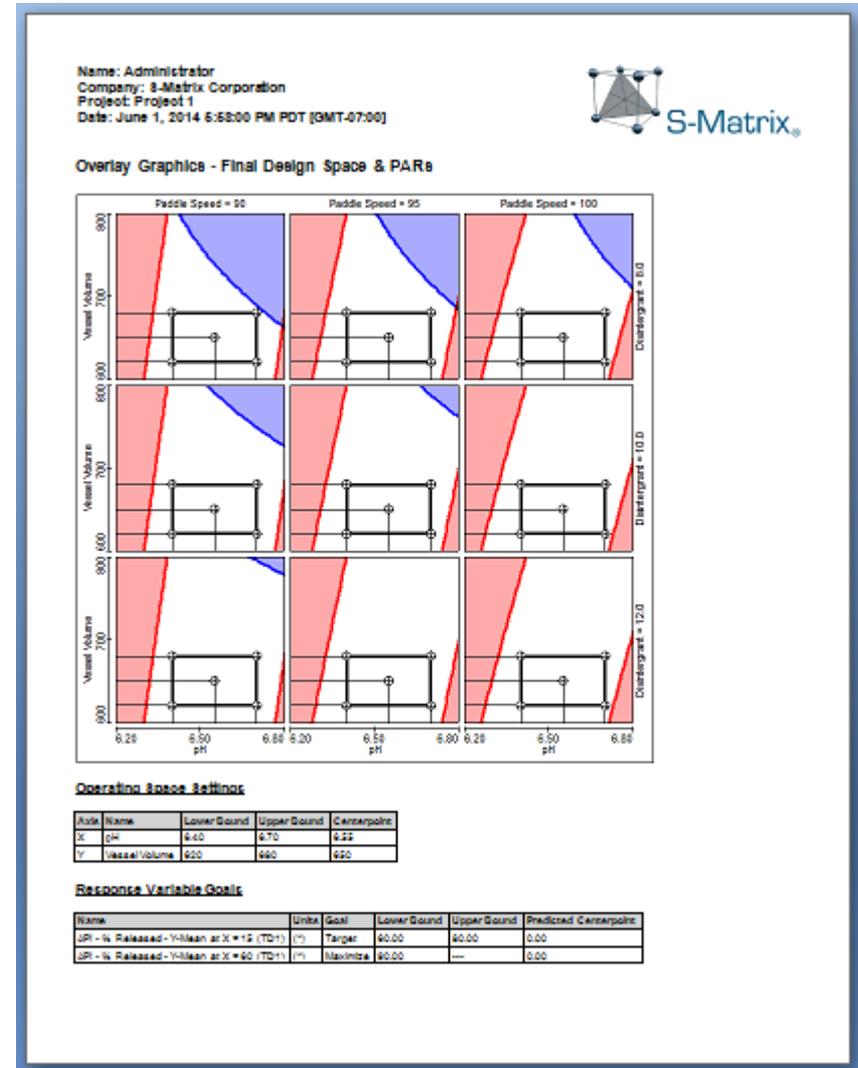
Visualizes Your Design Space & PARs

Create a Trellis Graph Series to Visualize the Design Space & PARs for Multiple Parameters



Creates Complete Final Reports With All Required Content and Graphs Which Can be Output in Multiple Document Formats – e.g.

- MS Word
- PDF
- HTML



Fusion QbD vs. Competitors – Critical QbD Features

Critical QbD Capability

Fusion QbD

Competitors

Study Parameter Flexibility



Automated DOE Experimenting



Advanced Modeling Capabilities



Fully Integrated Robustness



Complete QbD Reporting



Supports All Install Environments



Supports Full Part 11 Compliance



Conclusions

The Fusion QbD Approach:

- ✓ **Greatly accelerates successful method development through:**
 - **Automation**
 - **Statistically valid experimentation**
 - **Novel data treatments**
- ✓ **Provides quantitative knowledge of all critical parameter effects**
- ✓ **Enables establishing Design Space for both:**
 - **Mean Performance (setpoint optimization)**
 - **Process Robustness (operating space)**
- ✓ **Required time for the work is dramatically reduced**
- ✓ **Success promotes further use of QbD!**