Functional Data Explorer adds a new dimension to Sequential Experimental Design

Martin Owen
martin.owen.insight@gmail.com

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The Leicester School of Pharmacy
(Faculty of Health and Life Sciences)

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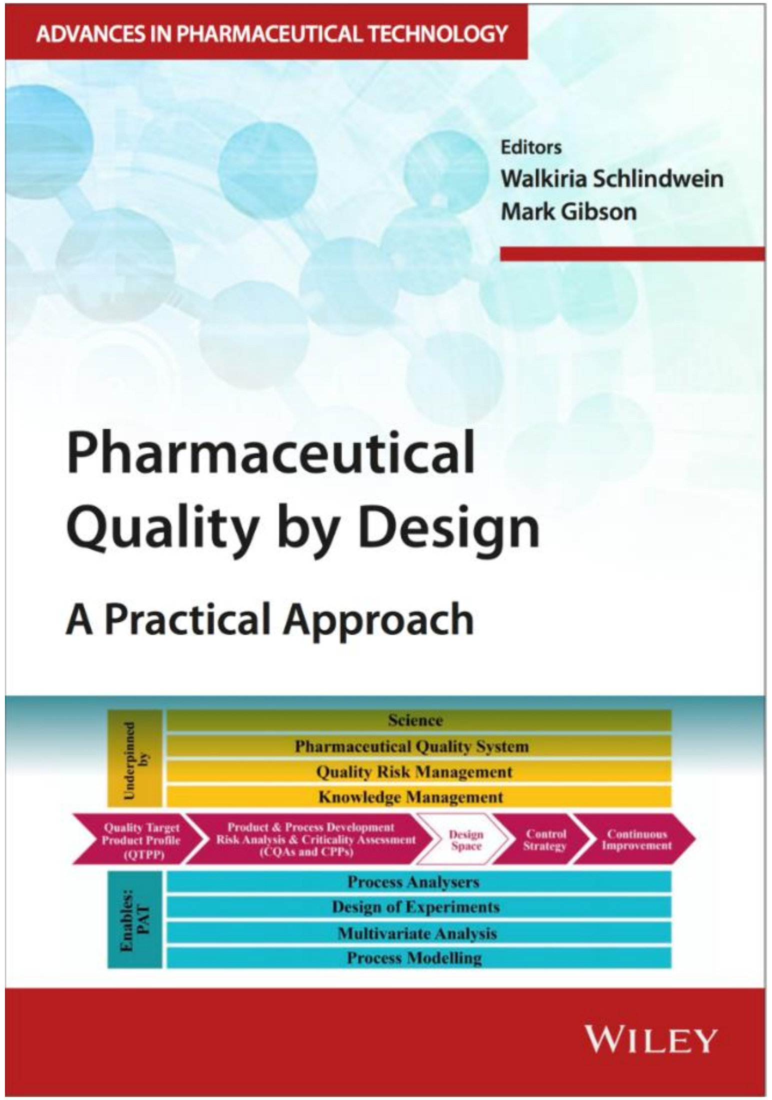
What is 'Quality by Design?'

"A **systematic** approach to development that begins with predefined objectives and emphasizes **product and process understanding** and process control, **based on sound science** and quality **risk management**." (ICH Q8)



Quality by Design overview

Quality Target Product Profile (QTPP)	Therapeutic aim Content Uniformity (Toxicity, Stability….)
Design selection	Determine the potential Critical to Quality Attributes (CQA) Determine formulation Determine method: Process conditions Analytical method
Risk Assessed Control Strategy	Perform detailed risk assessment and confirm CQAs Link material attributes and process parameters to CQAs Design and implement a control strategy Identify Critical Process Parameters (CPP) Develop Design Space(s) In-line controls, specifications etc Verification and scale-up, technical transfers
Lifecycle Management	Manage product lifecycle, including continuous improvement

Piroxicam (Drug substance/Kollidon VA64(polymer)

Quality Target Product Profile (QTPP)

Design selection

Risk Assessed Control Strategy

Lifecycle Management

Quality Target Product Profile

Active pharmaceutical ingredient (API) content uniformly distributed within a polymer matrix

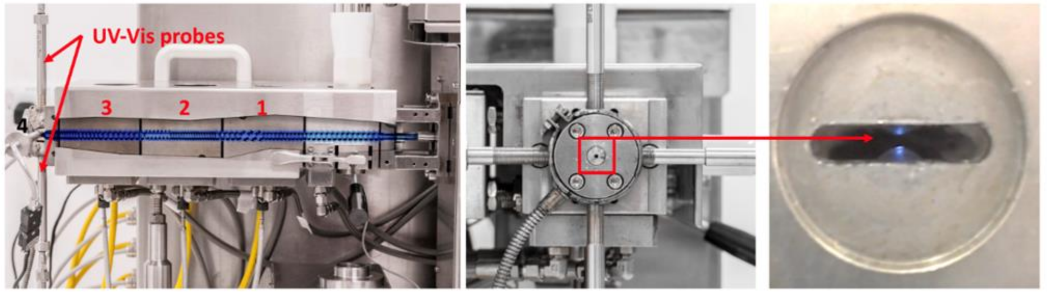
Design Selection

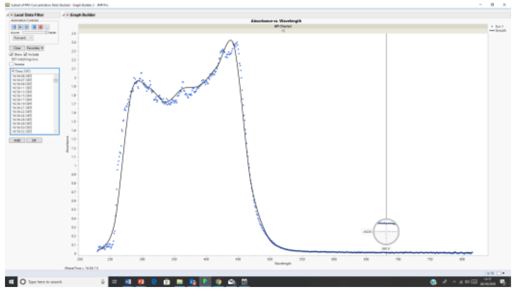
Hot melt extrusion

Nano 16
Hot-melt extruder

Process Analytical Technology

- **In-line UVvis Spectrometer**





Produces spectra every two seconds

Aims and risks

Quality Target Product Profile (QTPP)

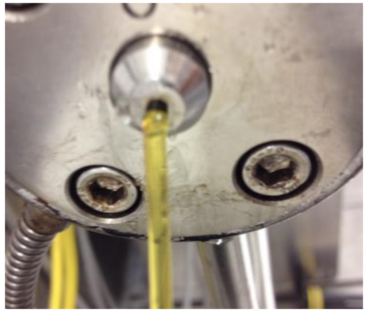
Design selection

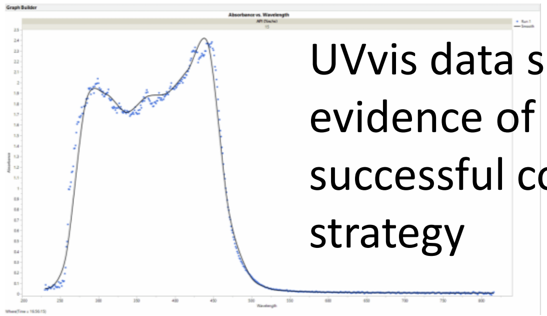
Risk Assessed Control Strategy

Lifecycle Management

Desired outcome

Active Pharmaceutical Ingredient uniformly dissolved in polymer matrix

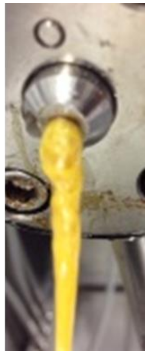




UVvis data shows evidence of a successful control strategy

Potential failure modes

Saturation: compromises content uniformity and bioavailability



Bubbles: compromises content uniformity

Change of colour: indicates possible impurity formation and degradation of API

DoE Strategy

Quality Target Product Profile (QTPP)

Design selection

Risk Assessed Control Strategy

Lifecycle Management

Potential Critical Process Parameters

- **API Concentration (%w/w) :** Too high leads to oversaturation
- **Temperature :** Potential degradation
- **Screw speed :** High mechanical energy aids solubility, but may cause possible degradation
- **Solid feed rate:** May cause bubbles if extruder fill level is too low

Sequential Experimental Design

- **Screening Design** to gain process understanding
- **Robustness Design** to verify control strategy

UVvis Spectra

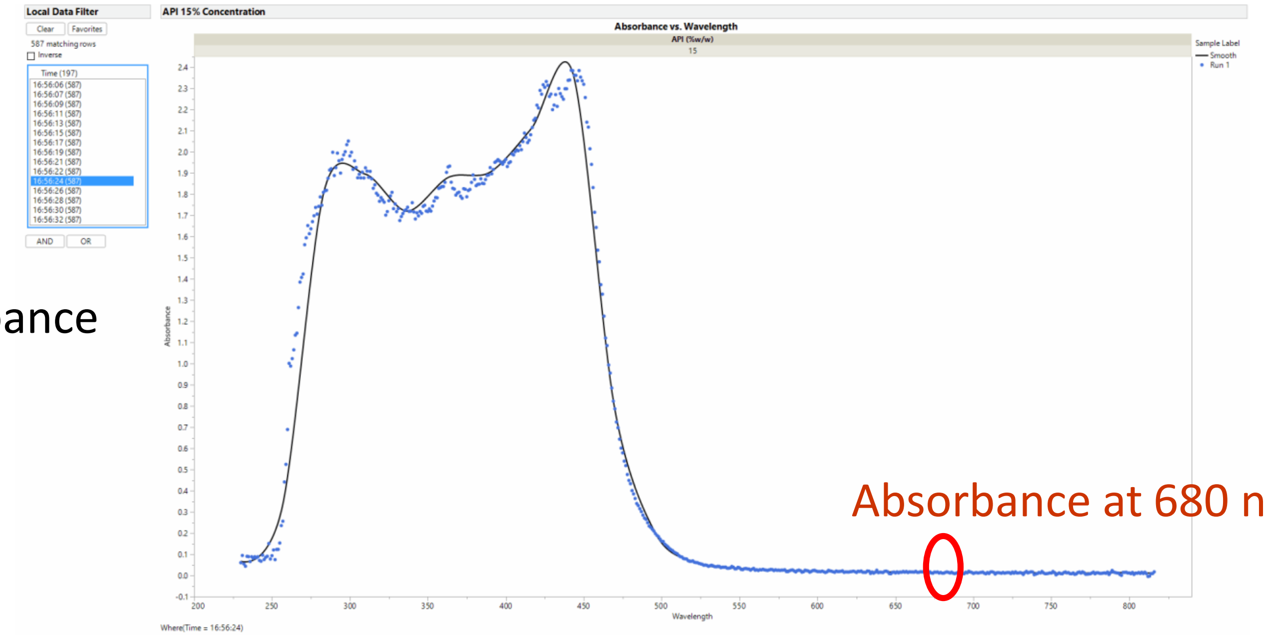
Data collected every 2 seconds over 6 min period (180) across wavelength range 230-816 (586)

>100,000 data-points per run

ColVisTec
Inline Process Monitoring

Functional data can be defined as data that are recorded over a continuous domain, where a set of measurements form a curve or image. Here the domain is wavelength and the sets of measurements are defined by an ID variable.

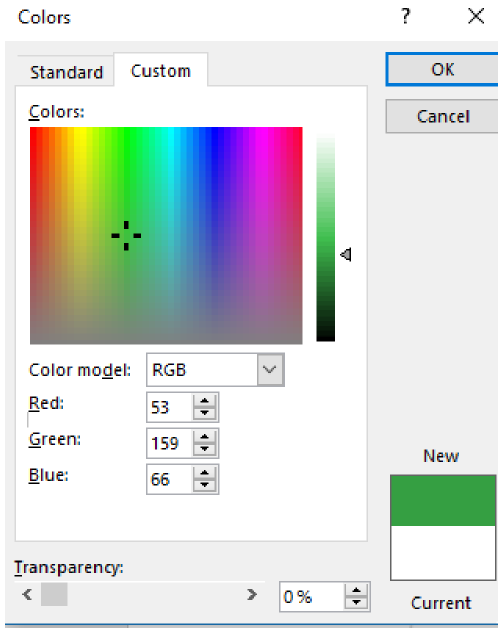
Absorbance



Absorbance at 680 nm

Wavelength

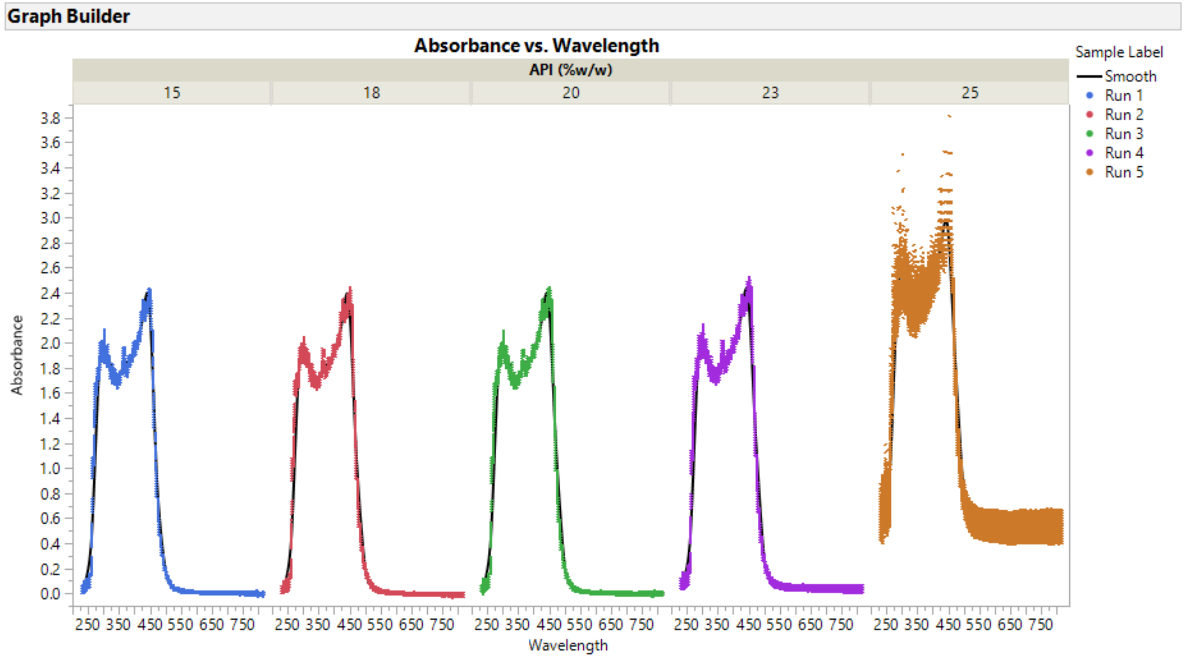
CIELAB Color space
L* lightness
a* green-red component
b* blue-yellow component

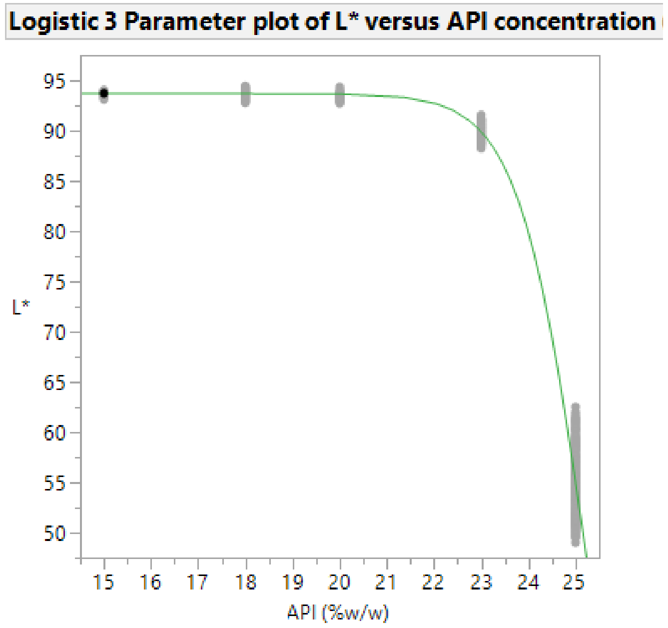


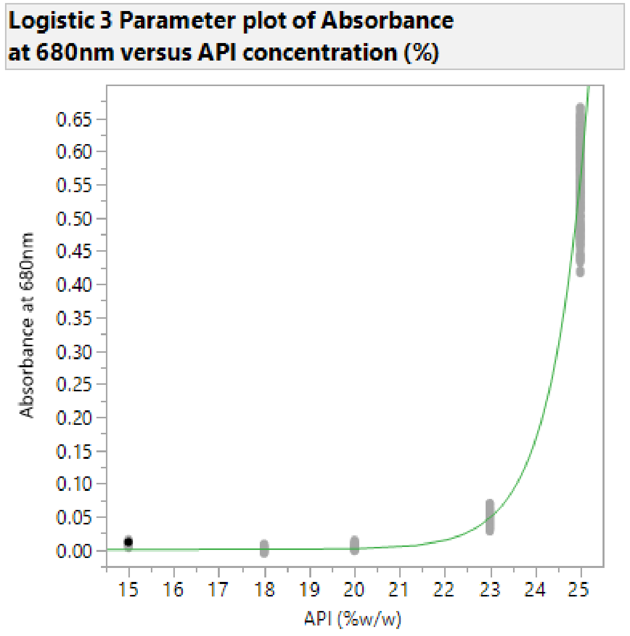
The Functional Data Explorer platform enables the exploration and analysis of functional data

5 level Concentration Experiment

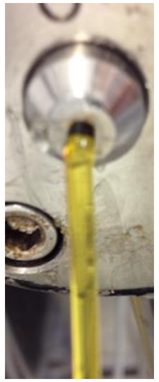
(API 15-25%, Other factors held at (140 ^{0}C, 200 rpm, 7 g/min)







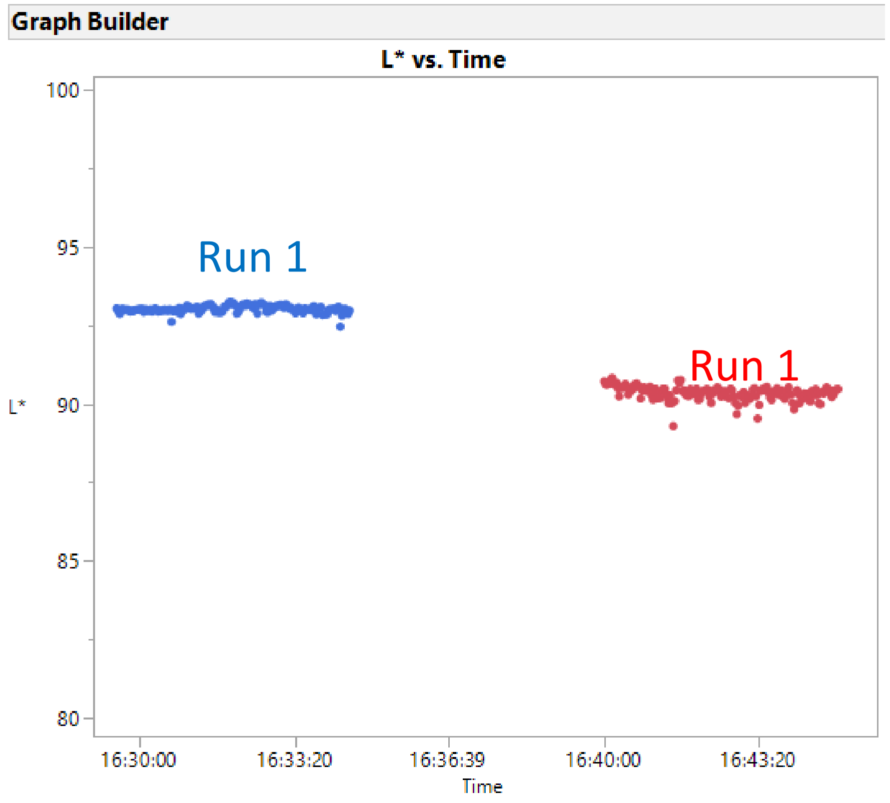
the darkest black at $L^* = 0$,
the brightest white at $L^* = 100$.



Absorbance changes and increase in variability due to scattering effects in translucent material

Logistic 3P plots suggest “edge of failure” is at around API Concentration of approximately 21%

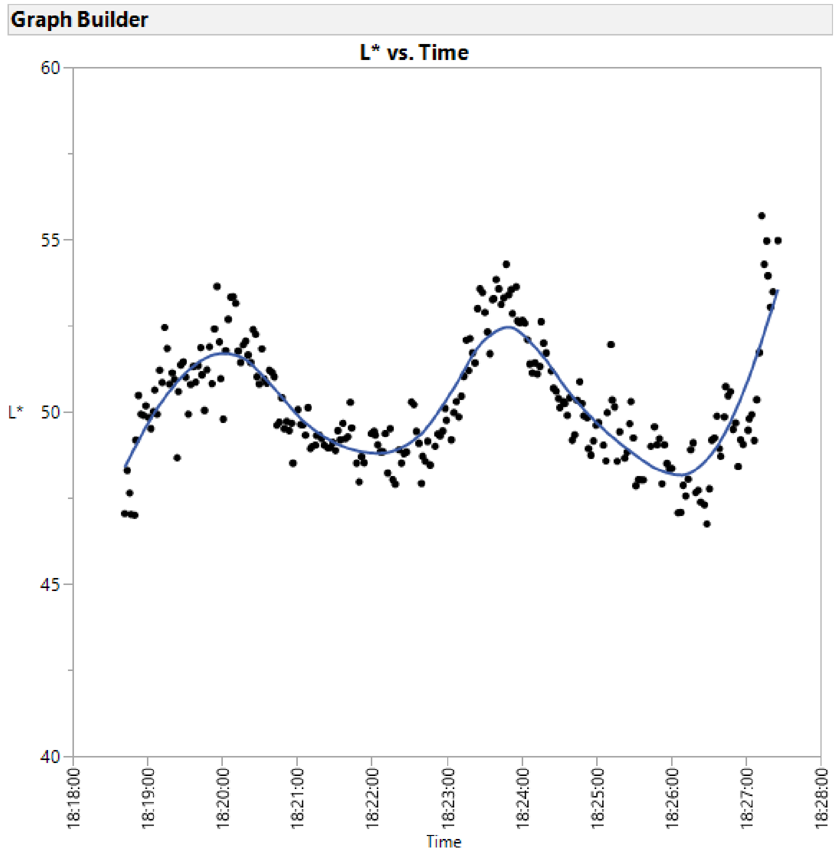
Has the system reached steady state for each run?



Conditions are set for each run and attainment of steady state is assessed by measuring the L* value.

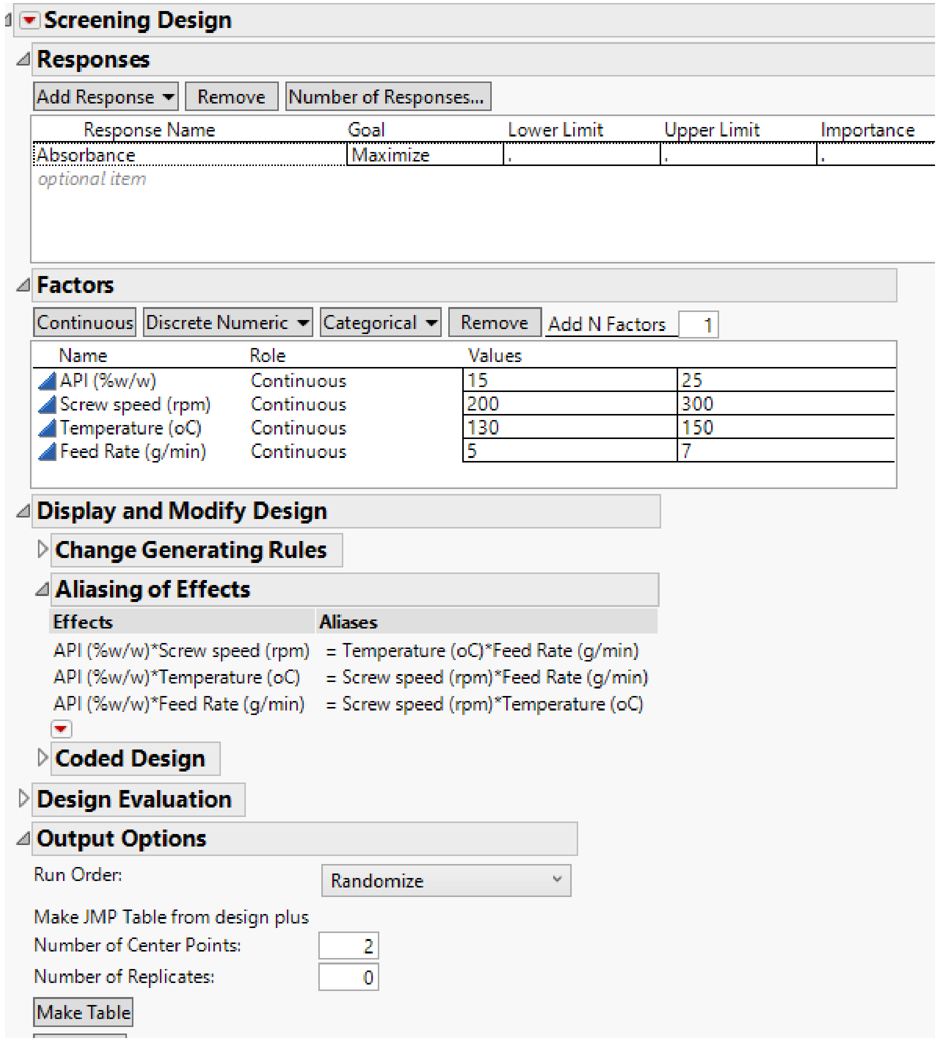
The system is held under steady state for about 5 mins and the data collected over this period is analysed.

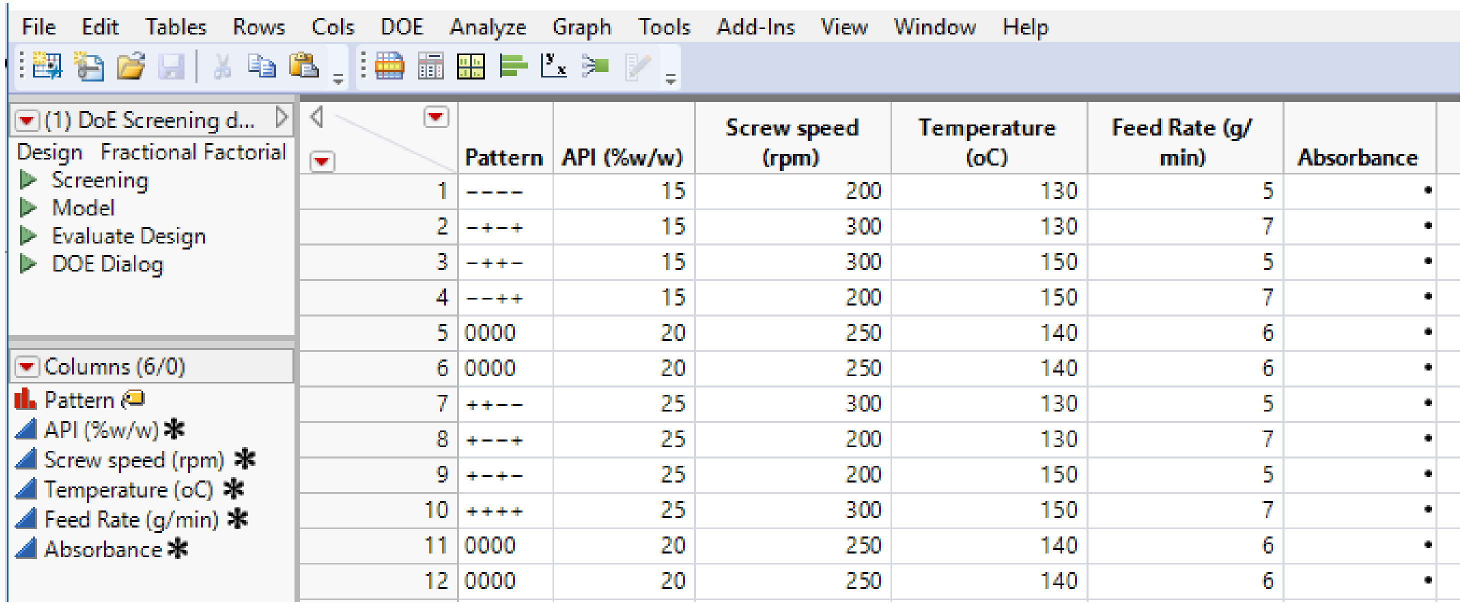
The conditions are reset for the new run and the sequence repeated until data on all runs has been acquired



Note that if scattering occurs then it is harder to judge when steady state is occurring.

Screening design

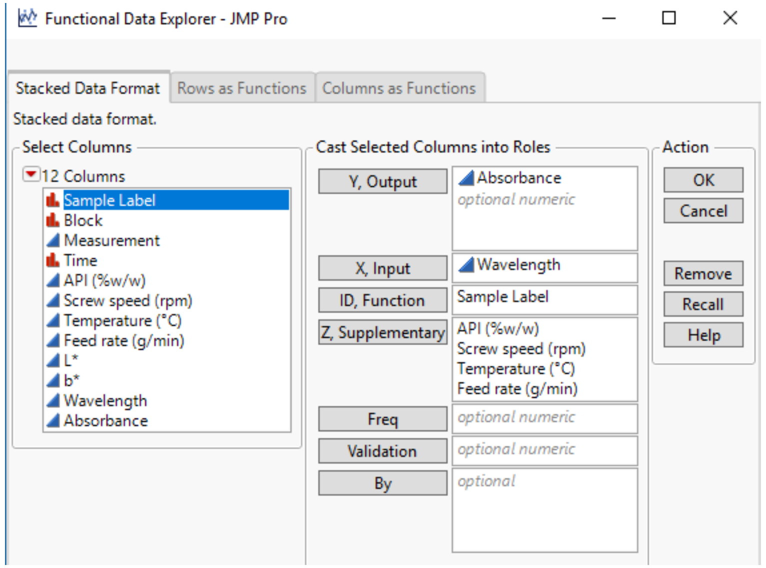


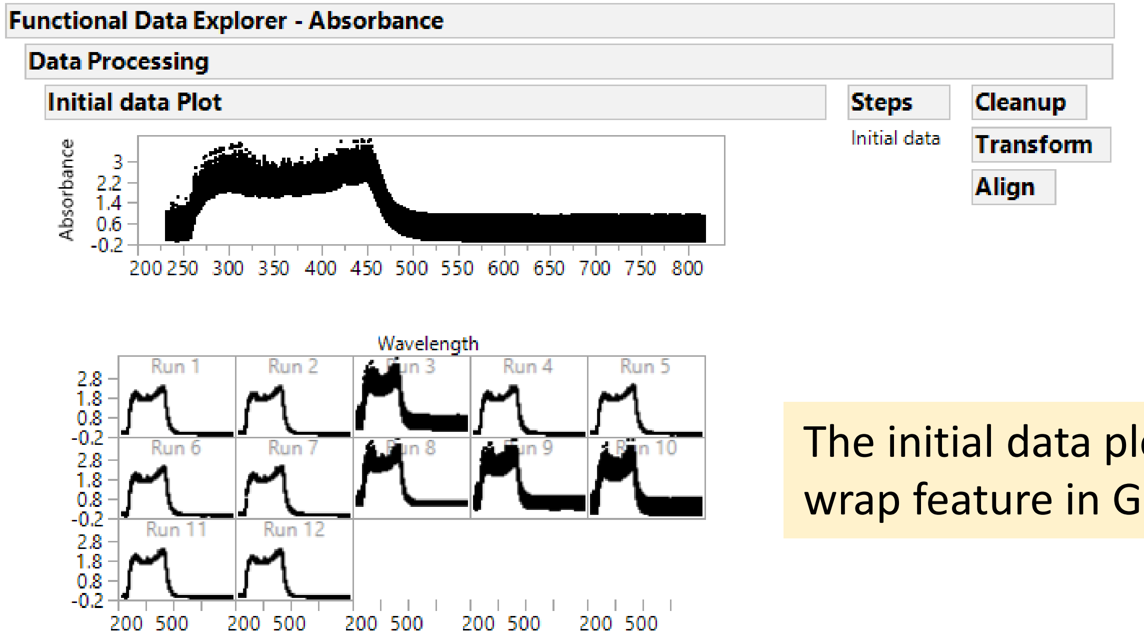


	Pattern	API (%w/w)	Screw speed (rpm)	Temperature (oC)	Feed Rate (g/min)	Absorbance
1	−−−−	15	200	130	5	•
2	−+−+	15	300	130	7	•
3	−++−	15	300	150	5	•
4	−−++	15	200	150	7	•
5	0000	20	250	140	6	•
6	0000	20	250	140	6	•
7	++−−	25	300	130	5	•
8	+−−+	25	200	130	7	•
9	+−+−	25	200	150	5	•
10	++++	25	300	150	7	•
11	0000	20	250	140	6	•
12	0000	20	250	140	6	•

Other screening platforms
(e.g Custom Design) are available…

Functional Data Explorer - FDE

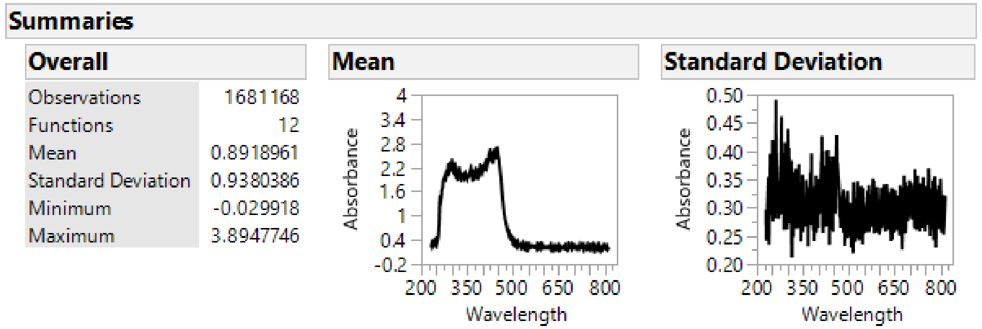




The initial data plot is equivalent to the wrap feature in Graph Builder

The Functional Data Explorer (FDE) platform can be used as an exploratory data analysis tool

In JMP14.2 use **Z Supplementary** to assign the DoE factors for a secondary analysis

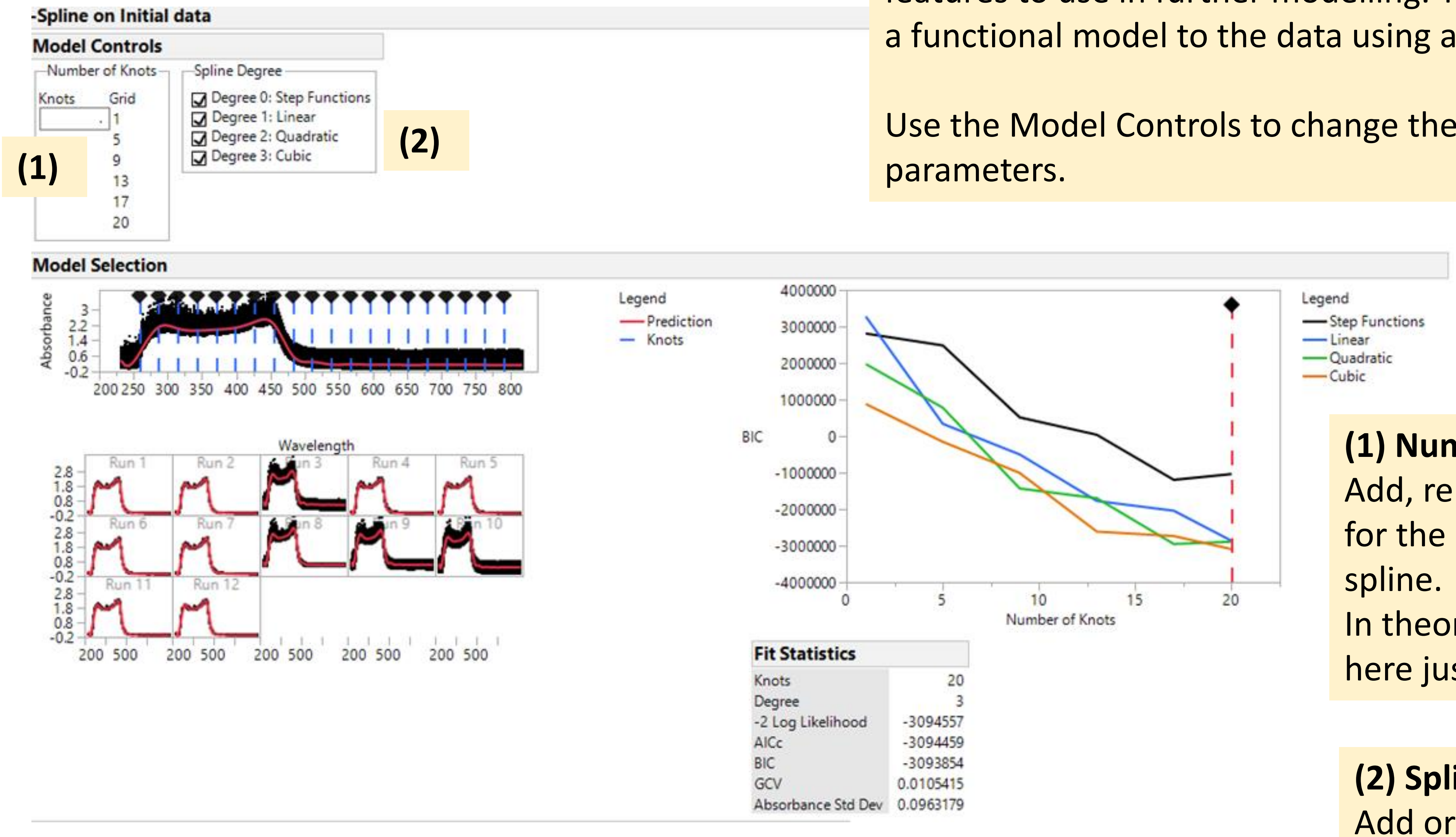


The summary shows the average spectrum and the standard deviation at each wavelength

B-spline surrogate model

The FDE platform is takes many functional processes (that might be associated with a scalar response) and extracts key features to use in further modelling. This is done by first fitting a functional model to the data using a B-spline.

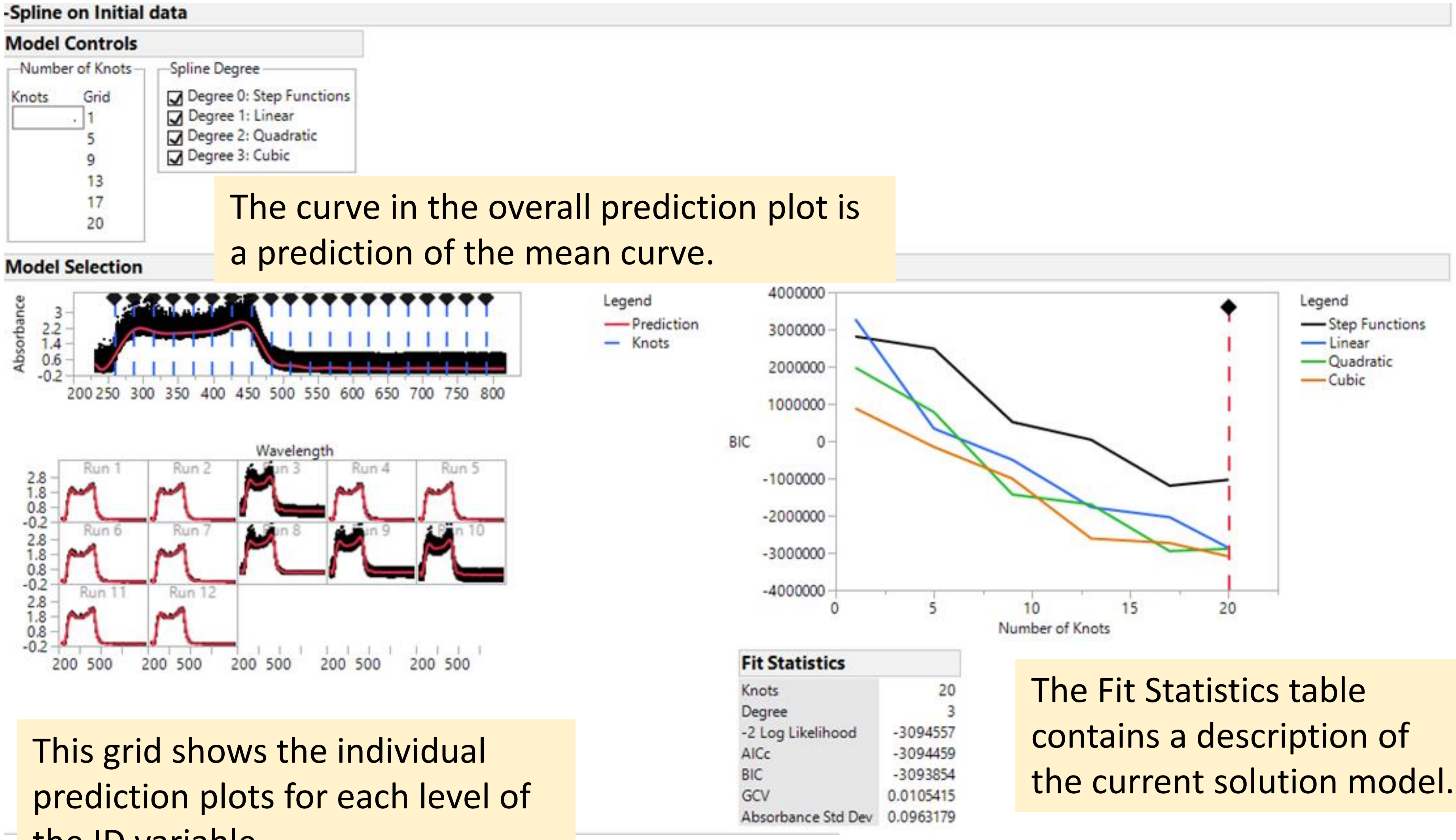
Use the Model Controls to change the solution path plot parameters.



(1) Number of Knots
Add, remove, or specify a range for the number of knots in each spline.
In theory could fit 586 knots, but here just 20 knots are fitted

(2) Spline Degree
Add or remove spline degree fits from the Model Selection report.

B-spline surrogate model



The curve in the overall prediction plot is a prediction of the mean curve.

This grid shows the individual prediction plots for each level of the ID variable

The Fit Statistics table contains a description of the current solution model.

B-spline surrogate model

The Bayesian Information Criterion (BIC) is the default fitting criterion
The prediction plots show the raw data and prediction curves that correspond to the current model. For spline models, the default model selected is the degree of spline with the best fit

-Spline on Initial data

Model Controls

Number of Knots

Knots	Grid
	1
	5
	9
	13
	17
	20

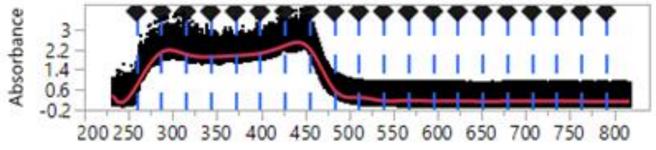
Spline Degree

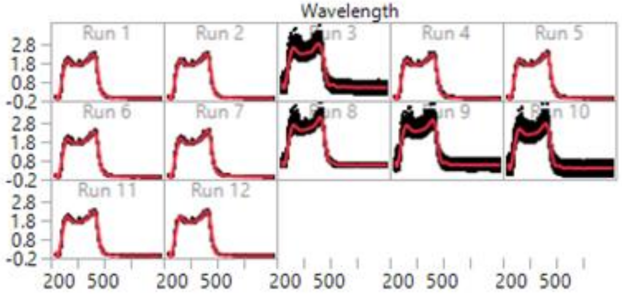
- ☑ Degree 0: Step Functions
- ☑ Degree 1: Linear
- ☑ Degree 2: Quadratic
- ☑ Degree 3: Cubic

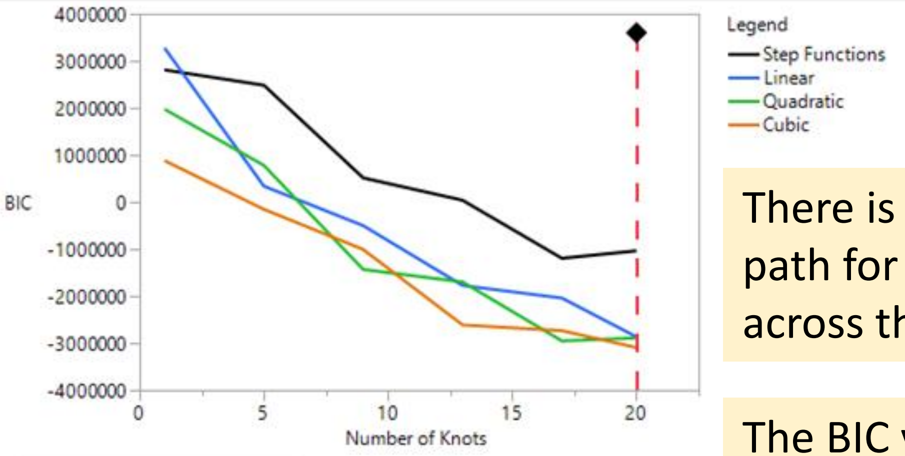
The solution path plot shows a model selection criterion plotted over values of a model parameter

The overall prediction plot

Model Selection







There is a separate curve in the solution path for each spline degree plotted across the defined number of knots

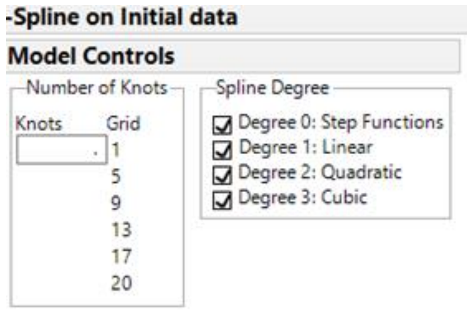
The BIC values are levelling off suggesting that adding further knots will not add much improvement

Fit Statistics

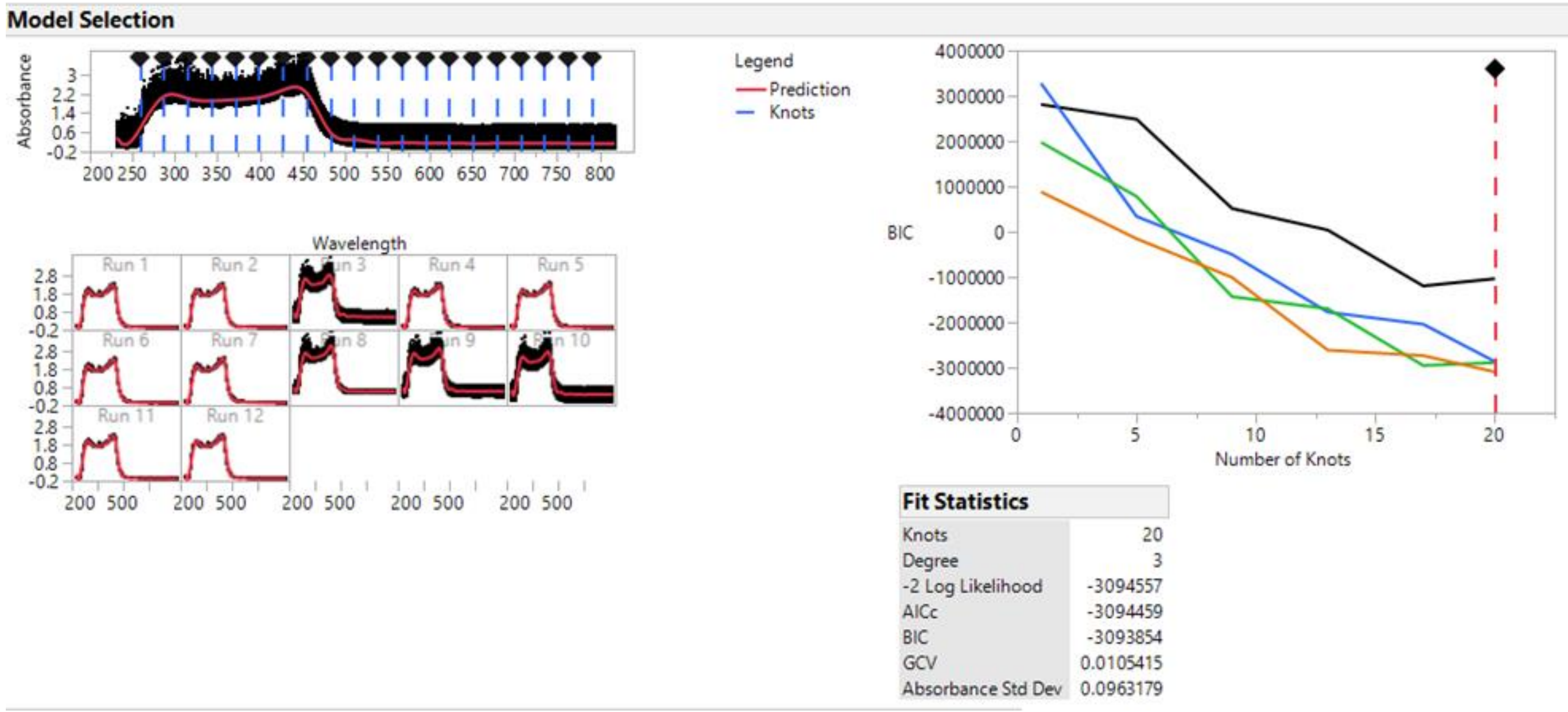
Knots	20
Degree	3
-2 Log Likelihood	-3094557
AICc	-3094459
BIC	-3093854
GCV	0.0105415
Absorbance Std Dev	0.0963179

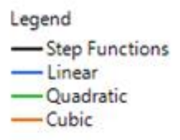
The grid of individual prediction plots for each level of the ID variable

B-spline surrogate model



The overall prediction plot also displays the location of the knots. The location of the knots can be changed by dragging the blue slider bars to different locations. Update the model reports according to the new knot locations by clicking the **Update Models** button. To reset the knots to their default locations, click the **Reset Knots** button.



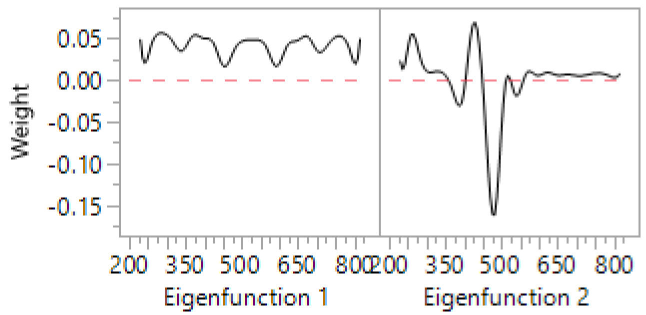


The current solution is designated by the dotted vertical line in the solution path plot. By default, the slider is placed at the number of knots corresponds to the model that has the smallest model selection criterion value

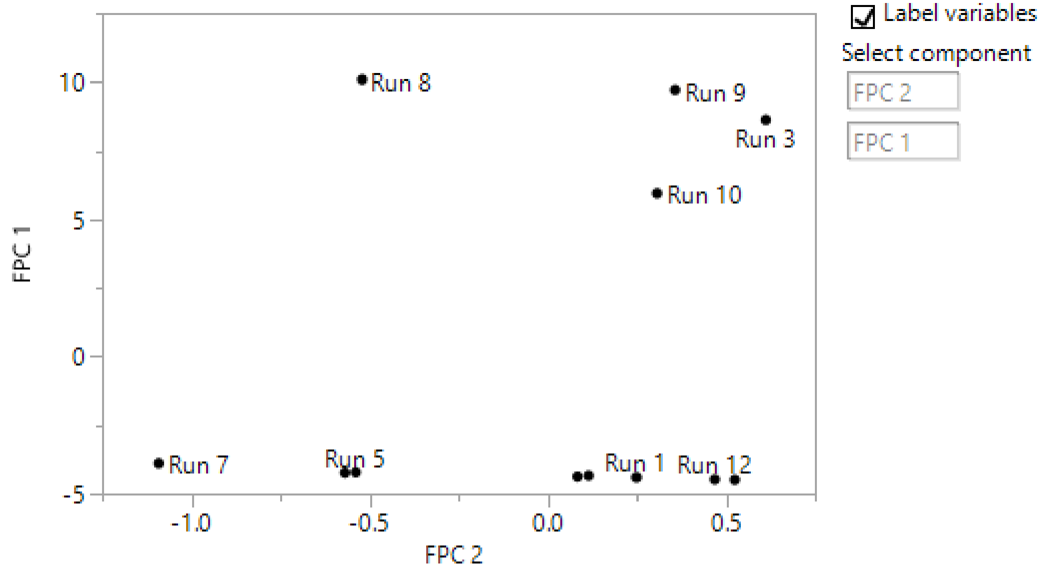
Principle component analysis

Functional PCA

FPC	Eigenvalue	20 40 60 80	Percent	Cumulative
1	34.221		98.9%	98.9%
2	0.310		0.9%	99.8%



Score Plot



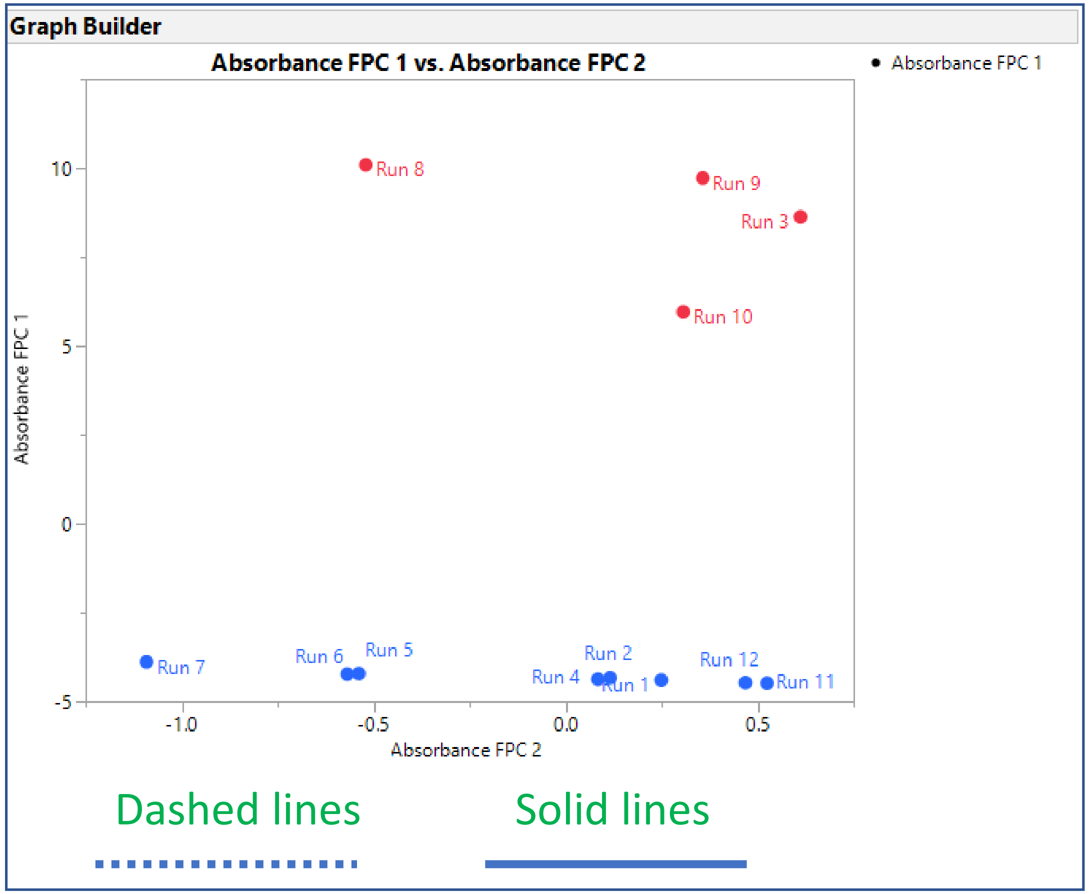
When a model is fitted, functional principal components analysis (functional PCA) is automatically performed on the surrogate model

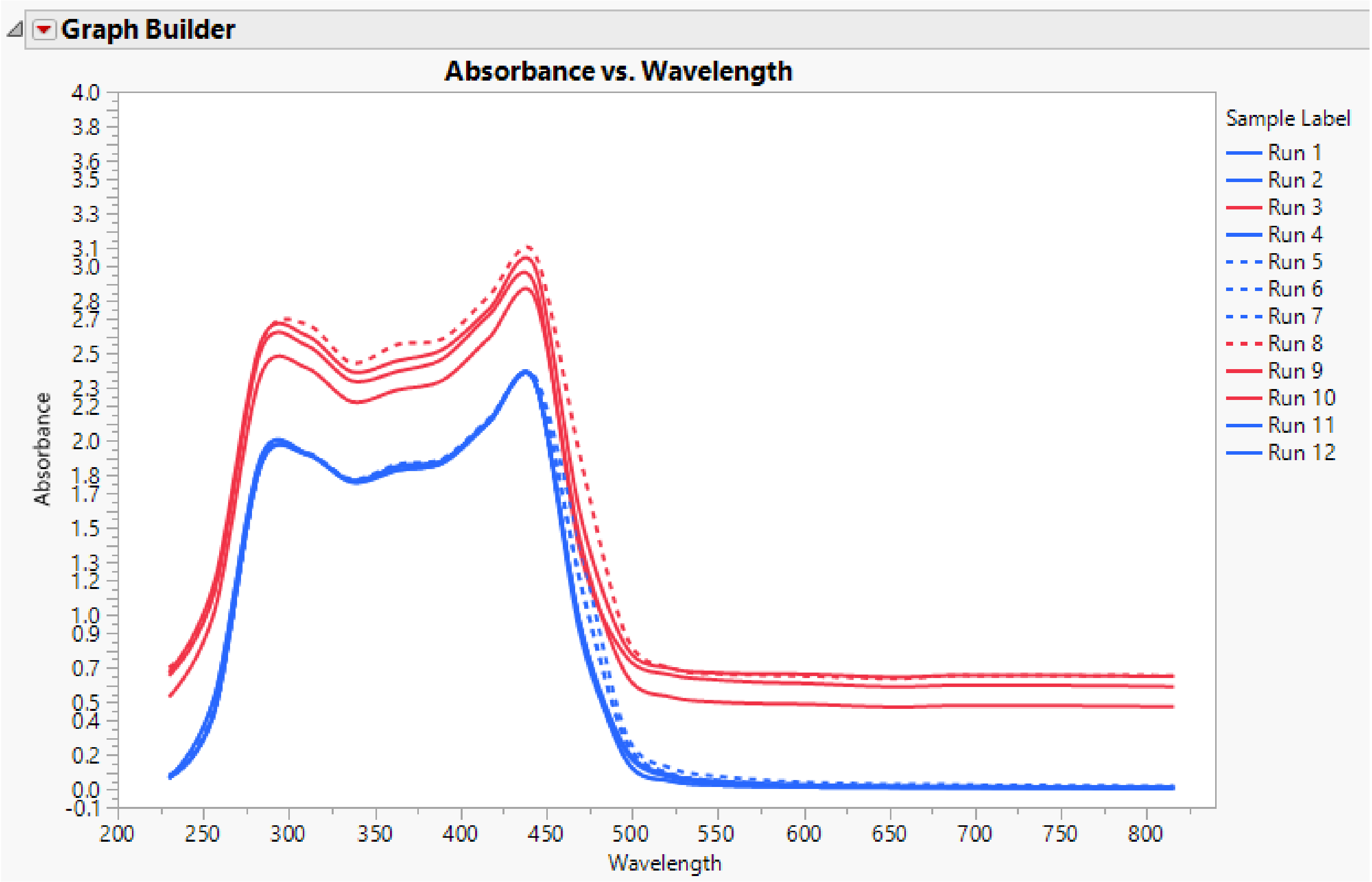
The Functional PCA report lists the eigenvalues that correspond to each functional principal component (FPC) in order from largest to smallest. The percent of variation accounted for by each FPC and the cumulative percent is listed and shown in a bar chart.

- Two functional principle components shown here describe 99.8% of the variation
- Eigenfunction 1 shows that for high values of FPC1, the spectra will be higher than the mean
- Eigenfunction 2 shows the absorbance in the 450nm region determine the values of FPC2

Results from the functional PCA, such as the functional principal component (FPC) scores for each run, are saved and used for feature extraction and analysis in another modelling platform.

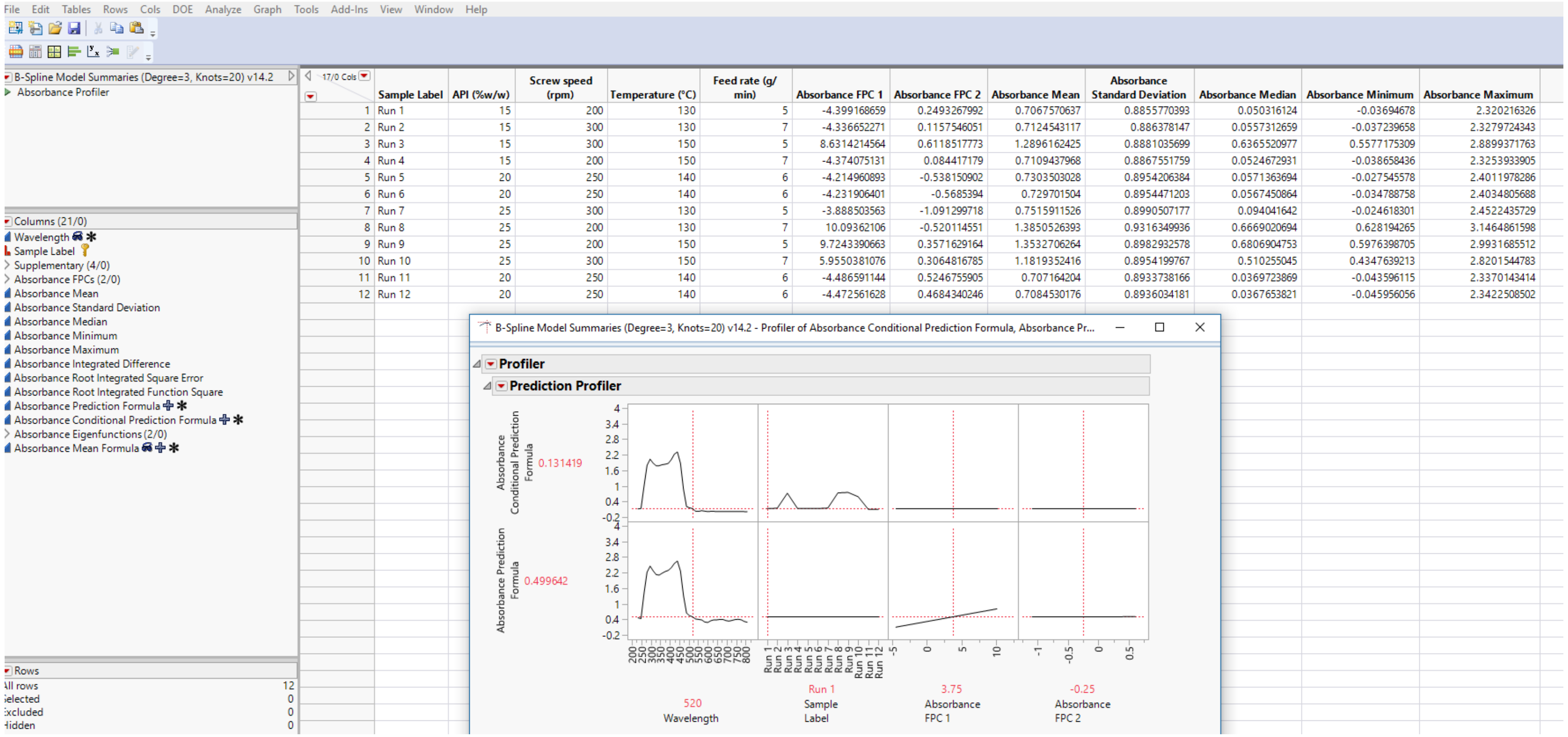
Relating the principle components to the spectra





- For high values of FPC1 the spectra are shifted upwards
- For low values of FPC2 the spectra are shifted to the right.

Model the FPC against the Absorbance spectra and see how the profile changes as the FPC change



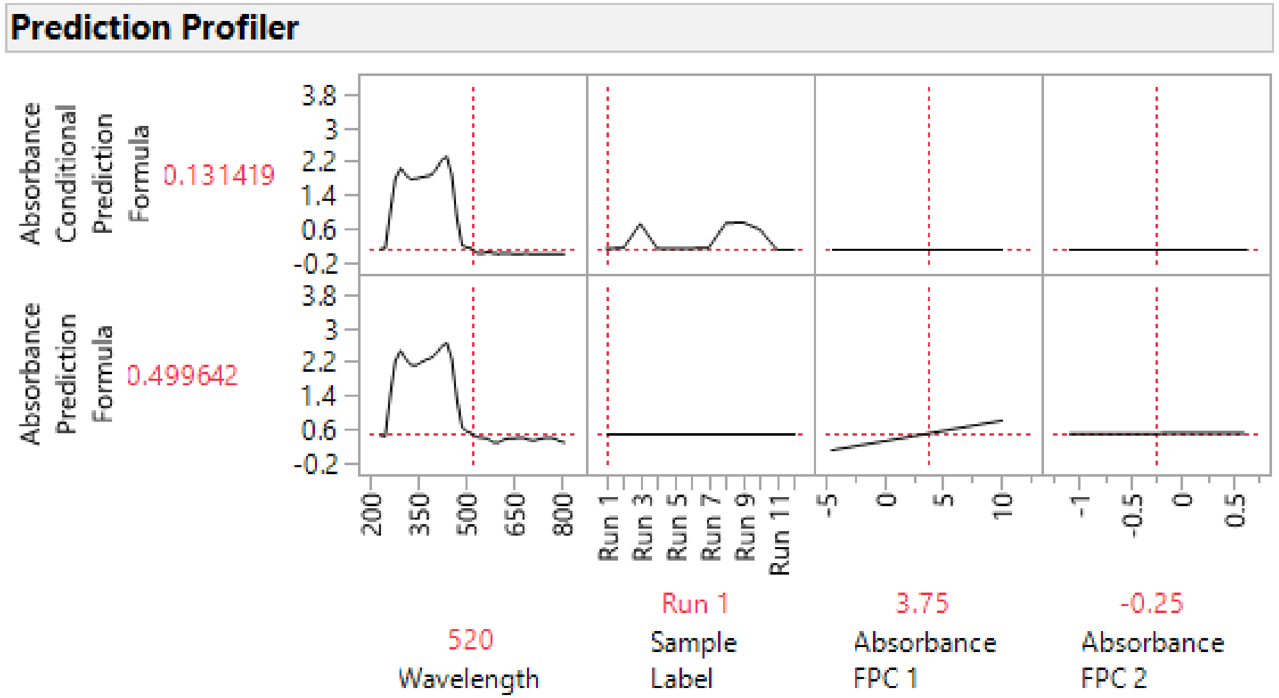
	Sample Label	API (%w/w)	Screw speed (rpm)	Temperature (°C)	Feed rate (g/min)	Absorbance FPC 1	Absorbance FPC 2	Absorbance Mean	Absorbance Standard Deviation	Absorbance Median	Absorbance Minimum	Absorbance Maximum
1	Run 1	15	200	130	5	-4.399168659	0.2493267992	0.7067570637	0.8855770393	0.050316124	-0.03694678	2.320216326
2	Run 2	15	300	130	7	-4.336652271	0.1157546051	0.7124543117	0.886378147	0.0557312659	-0.037239658	2.3279724343
3	Run 3	15	300	150	5	8.6314214564	0.6118517773	1.2896162425	0.8881035699	0.6365520977	0.5577175309	2.8899371763
4	Run 4	15	200	150	7	-4.374075131	0.084417179	0.7109437968	0.8867551759	0.0524672931	-0.038658436	2.3253933905
5	Run 5	20	250	140	6	-4.214960893	-0.538150902	0.7303503028	0.8954206384	0.0571363694	-0.027545578	2.4011978286
6	Run 6	20	250	140	6	-4.231906401	-0.5685394	0.729701504	0.8954471203	0.0567450864	-0.034788758	2.4034805688
7	Run 7	25	300	130	5	-3.888503563	-1.091299718	0.7515911526	0.8990507177	0.094041642	-0.024618301	2.4522435729
8	Run 8	25	200	130	7	10.09362106	-0.520114551	1.3850526393	0.9316349936	0.6669020694	0.628194265	3.1464861598
9	Run 9	25	200	150	5	9.7243390663	0.3571629164	1.3532706264	0.8982932578	0.6806904753	0.5976398705	2.9931685512
10	Run 10	25	300	150	7	5.9550381076	0.3064816785	1.1819352416	0.8954199767	0.510255045	0.4347639213	2.8201544783
11	Run 11	20	250	140	6	-4.486591144	0.5246755905	0.707164204	0.8933738166	0.0369723869	-0.043596115	2.3370143414
12	Run 12	20	250	140	6	-4.472561628	0.4684340246	0.7084530176	0.8936034181	0.0367653821	-0.045956056	2.3422508502

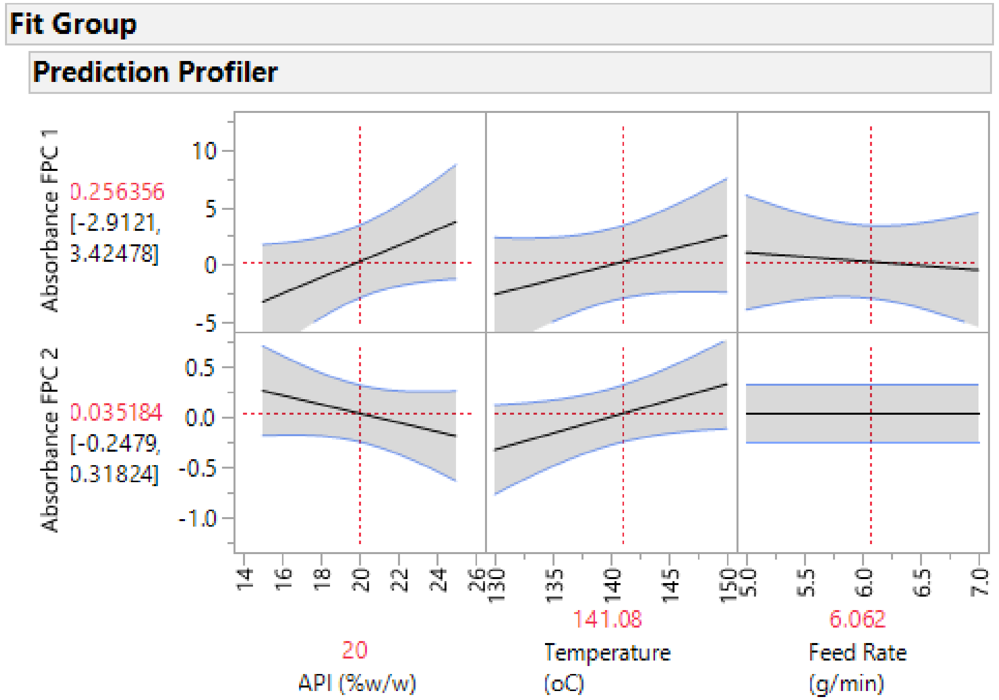
- The Absorbance Conditional Prediction Formula is used to reconstruct the spectrum for each run using the Eigen function formulae and the mean formulae

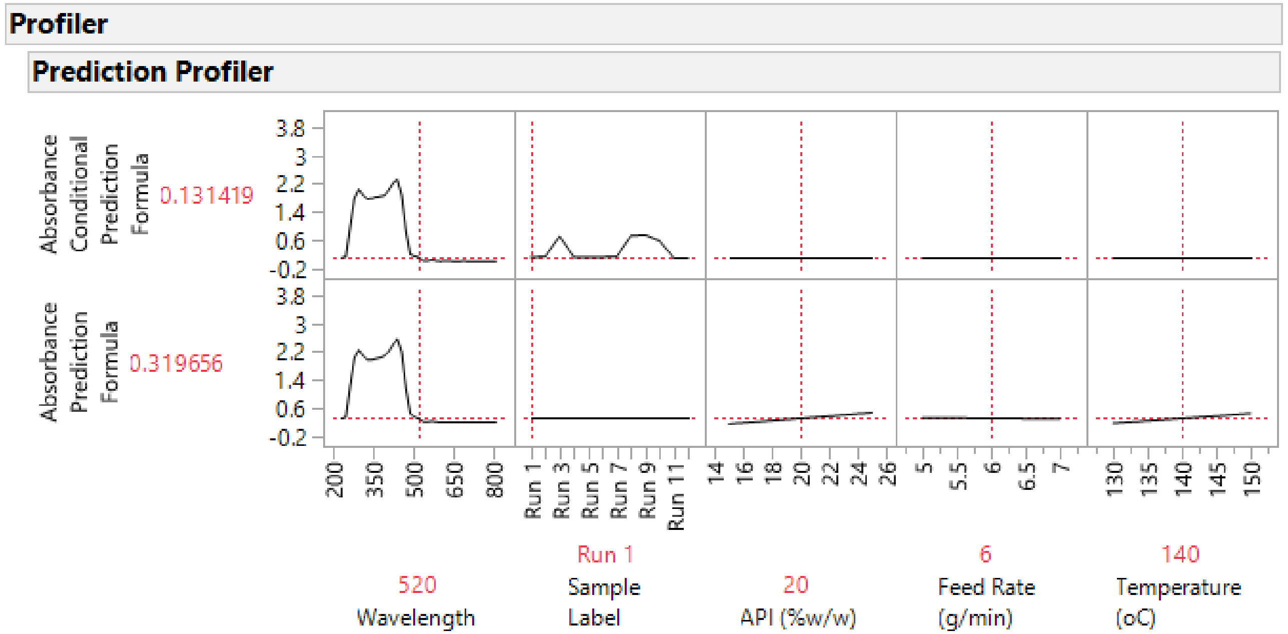
The Prediction Profiler shows

- the spectrum for each run
- the impact of each Functional Principle Component

- Now we need to create the profiler with the DoE factors
- Use Stepwise Forward selection Fit model to model the impact of DoE factors on the functional principle components



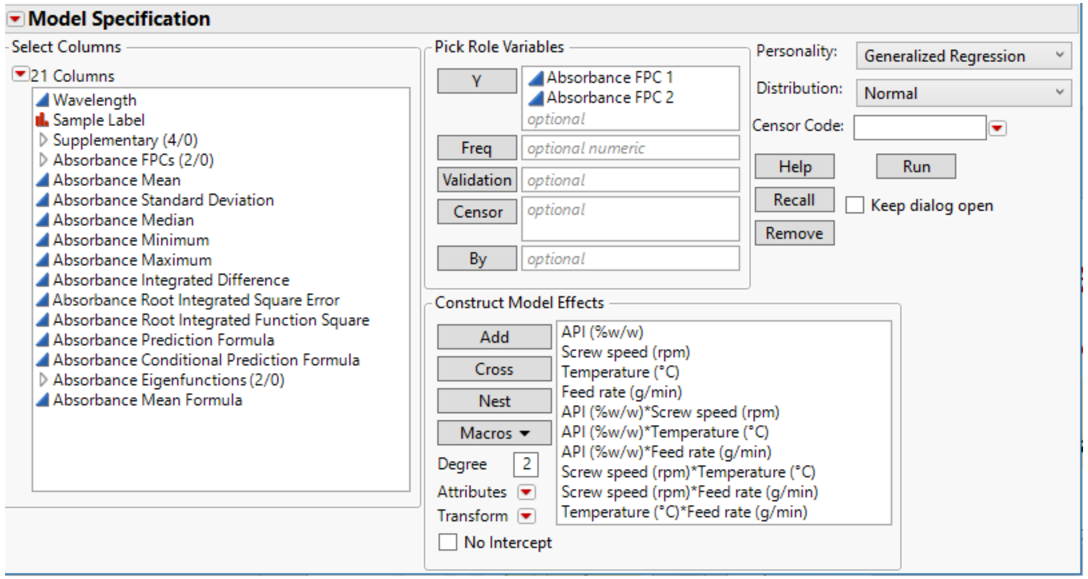


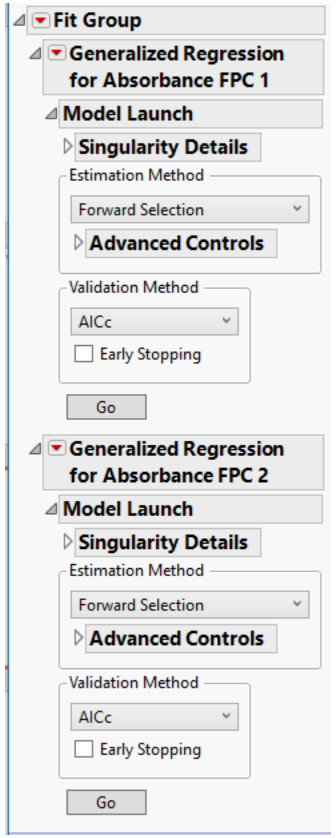


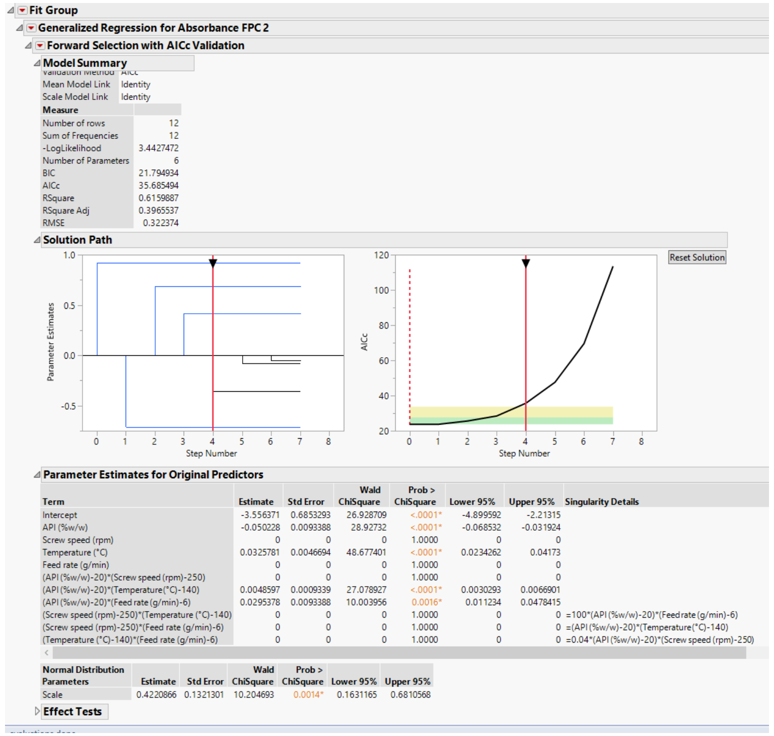
With high temperatures AND low concentration , with low feed rate gives bubbles and scattering effects shifts baseline to higher absorbance

With some manipulation of the formulas it is possible to produce a prediction profiler of DoE factors against the spectra profile

In JMPv14.2, Gen Reg offers new features to handle the DoE results





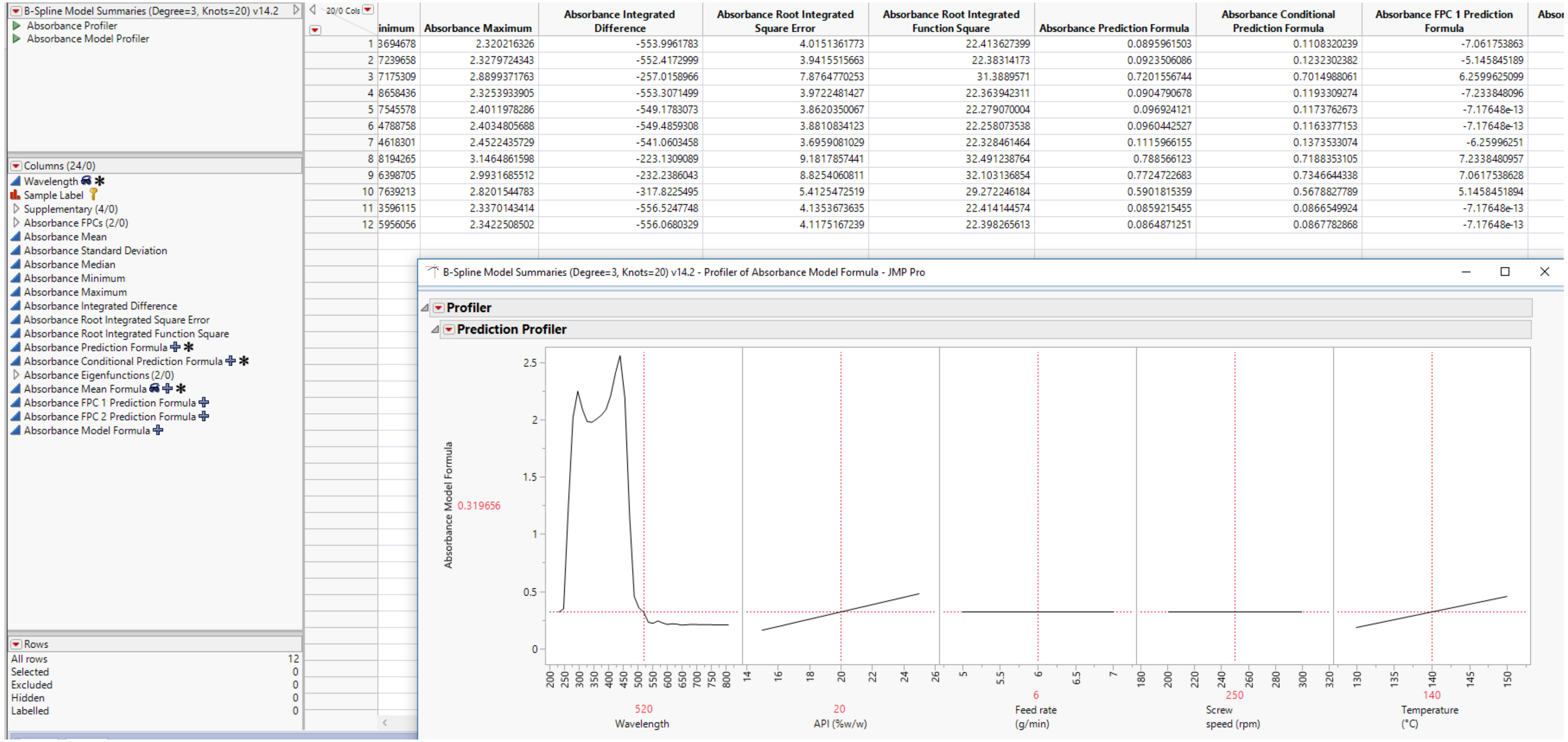


- Model the FPC1 and FPC2 as responses and construct the model effects using the DoE factors supplied as supplementary variables

Use Generalised Regression forward selection in this second stage to analyse the DoE

Save Functional Predictive Formula. This creates a JMP column formula that ties up the eigen function with the principle component scores

Modelling the absorbance spectra using the DoE factors



	inimum	Absorbance Maximum	Absorbance Integrated Difference	Absorbance Root Integrated Square Error	Absorbance Root Integrated Function Square	Absorbance Prediction Formula	Absorbance Conditional Prediction Formula	Absorbance FPC 1 Prediction Formula	Absor
1	3694678	2.320216326	-553.9961783	4.0151361773	22.413627399	0.0895961503	0.1108320239	-7.061753863	
2	7239658	2.3279724343	-552.4172999	3.9415515663	22.38314173	0.0923506086	0.1232302382	-5.145845189	
3	7175309	2.8899371763	-257.0158966	7.8764770253	31.3889571	0.7201556744	0.7014988061	6.2599625099	
4	8658436	2.3253933905	-553.3071499	3.9722481427	22.363942311	0.0904790678	0.1193309274	-7.233848096	
5	7545578	2.4011978286	-549.1783073	3.8620350067	22.279070004	0.096924121	0.1173762673	-7.17648e-13	
6	4788758	2.4034805688	-549.4859308	3.8810834123	22.258073538	0.0960442527	0.1163377153	-7.17648e-13	
7	4618301	2.4522435729	-541.0603458	3.6959081029	22.328461464	0.1115966155	0.1373533074	-6.25996251	
8	8194265	3.1464861598	-223.1309089	9.1817857441	32.491238764	0.788566123	0.7188353105	7.2338480957	
9	6398705	2.9931685512	-232.2386043	8.8254060811	32.103136854	0.7724722683	0.7346644338	7.0617538628	
10	7639213	2.8201544783	-317.8225495	5.4125472519	29.272246184	0.5901815359	0.5678827789	5.1458451894	
11	3596115	2.3370143414	-556.5247748	4.1353673635	22.414144574	0.0859215455	0.0866549924	-7.17648e-13	
12	5956056	2.3422508502	-556.0680329	4.1175167239	22.398265613	0.0864871251	0.0867782868	-7.17648e-13	

A script is added to the data table and the Profiler now shows how the spectra curve changes as a result of “turning the knobs on the DoE”

Workflow for analysing repeated measures for functional response DoE

- Design your DoE
- Execute the DoE runs and get the measurements
- Store in a table
- Load into the Functional Data Explorer platform, along with the DoE factors as supplementary variables
- Fit Functional Data Explorer models (e.g. B splines)
- Save summaries to new table
- Analyse the FPC scores as if regular DoE responses
- Save Functional Prediction Formulae from General Regression platform
- Use the Profiler to see impact of DoE factors on the Absorbance spectra

Robustness design

Robustness design - JMP Pro

File Edit Tables Rows Cols DOE Analyze Graph Tools Add-Ins View Window Help

Robustness design

Columns (5/0)

Rows

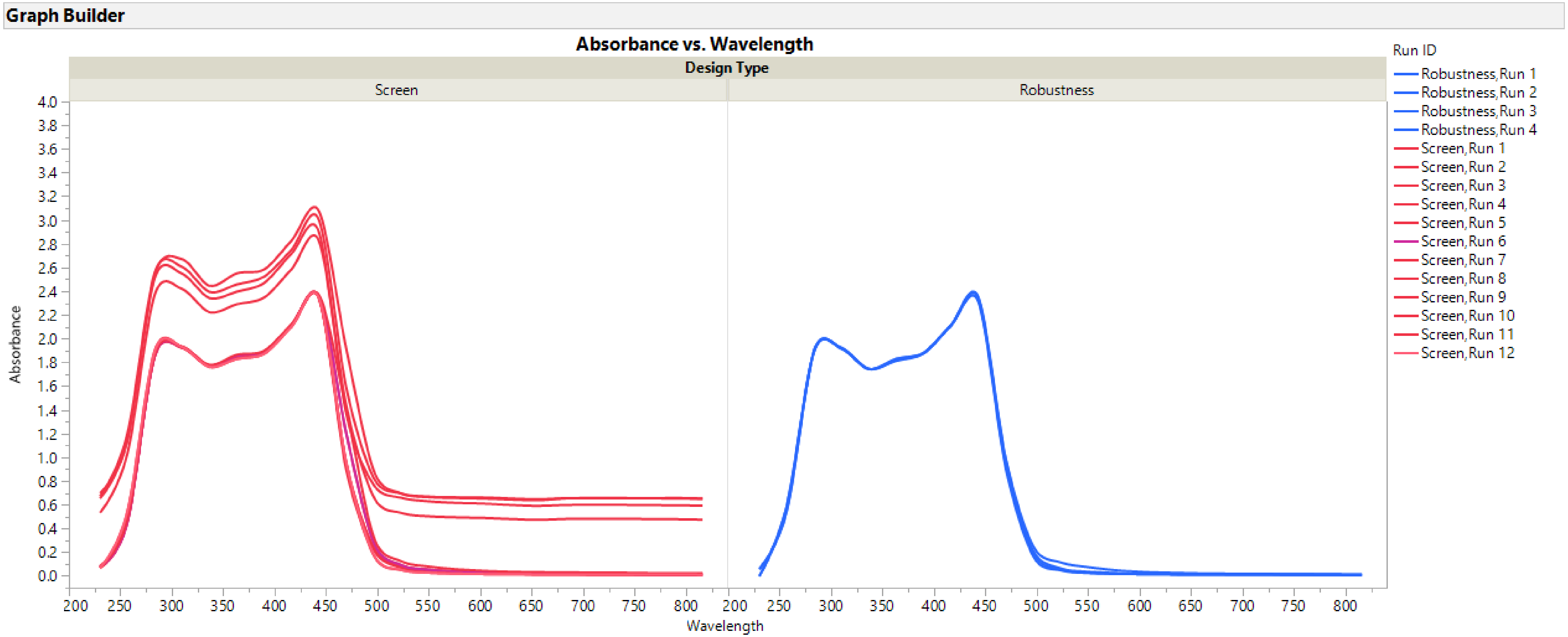
All rows	4
Selected	0
Excluded	0
Hidden	0
Labelled	0

	API (%w/w)	Screw speed(rpm)	Temperature (oC)	Feed rate (g/min)	Absorbance
1	17	200	140	5	•
2	17	300	140	5	•
3	17	200	140	10	•
4	17	300	140	10	•

The purpose of the Robustness design is to assess whether we can use the information gained in the Screening design to show the process is in control

Note that the API concentration and Temperature are held constant for all the runs.
The range for the Feed rate has been extended.

Process understanding   Process control



the runs in Screening design gave different spectra, and the process was inconsistent over the combination of factor settings investigated

In contrast, the runs in Robustness design gave consistent output over the combination of factor settings investigated. No scattering due to bubbles or oversaturation was observed

After action review

Knowing what we know now…

- What worked well
- What might we have done differently?
  - Choice of factors and ranges
  - Design
  - Method of statistical analysis

Moving forward

- What do we know?
- What don’t we know?
- What is the risk of not knowing?

Quality by Design overview

Quality Target Product Profile (QTPP)

Therapeutic aim
Content Uniformity
(Toxicity, Stability….)

Design selection

Determine the potential critical to quality attributes (CQA)
Determine formulation
Determine method:
  Process conditions
  Analytical method

Risk Assessed Control Strategy

Perform detailed risk assessment and confirm CQAs
Link material attributes and process parameters to CQAs
Design and implement a control strategy
  Identify critical process parameters (CPP)
  Develop Design Space(s)
  In-line controls, specifications etc
  Verification and scale-up, technical transfers

Lifecycle Management

Manage product lifecycle, including continuous improvement

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  The Gateway

  Leicester LE1 9BH
- Mariana Palmeria Bezerra
- Juan Carlos Zelaya Almeida