Determination of Water Content in Tablets

In This Tutorial You Will Learn How To

- Generate a Reduced Combinatorial Design (RCD) using the Design Wizard
- Analyze DOE data using the Analysis Wizard
- Investigate how RCD can be used to accomplish a representative subset selection of experiments taken from a larger pool of theoretically possible experiments
- Understand how such data can be used to confirm if the alternative measurement method can replace the conventional analytical method

Background

One typical objective of multivariate calibration is to replace a target or reference analytical method, which may be time-consuming and laborious, with an alternative measurement technique, often spectroscopic in nature, which should be fast, precise, and preferably also non-destructive to the analyzed samples. To ensure robustness is built in to the development of a calibration model it is recommended to include simultaneous changes to the concentrations of the constituents and the settings of occurring process and/or matrix factors, an ideal application for DOE. Because applications of DOE in multivariate calibration easily involve many factors at many levels the novel Reduced Combinatorial Designs (RCDs) represent a viable alternative for reducing the number of experiments required, yet still providing results that are reliable and have a faithful interpretation. Below, we will review an application of RCD in a multivariate calibration study investigating the usability of microwave resonance spectroscopy for determining water content in tablets.

Data

The example dataset is taken from the Master's Thesis "Microwave spectroscopy – Matrix effects and interferences for water determinations in pharmaceutical formulations", written by Halldis S. Thoroddsen. The objective of the investigation was to explore methods for determination of water content in solid pharmaceutical formulations (tablets). The reference method was the classical Karl-Fischer titration method and the alternative method was microwave spectroscopy.

Responses

To be able to compare the outcome of the reference method with the outcome of the alternative method two responses were specified:

- The first response was water content as determined using the reference method (Karl Fischer).
- The second response was the microwave signal of water.

The details of the two responses are given below.

Responses

	Name	Abbreviation	Units	Condition	Objective	Min	Target	Max
1	**KF water content**	KFw	%	Observed	Predicted			
2	**Microwave response**	Mic		Observed	Predicted			

Factors

The following factors were defined:

- type of drug substance (active pharmaceutical ingredient, API);
- particle size of filler (small/medium/large); 57 / 115 / 228 µm
- tablet size (small/large); 150 / 235 mm3
- tablet hardness, encoded as tensile strength (low, medium, high); 1 / 2 / 3 MPa
- moisture level, represented as four different chamber climates for conditioning the tablets; 5 / 10 / 55 / 75 %

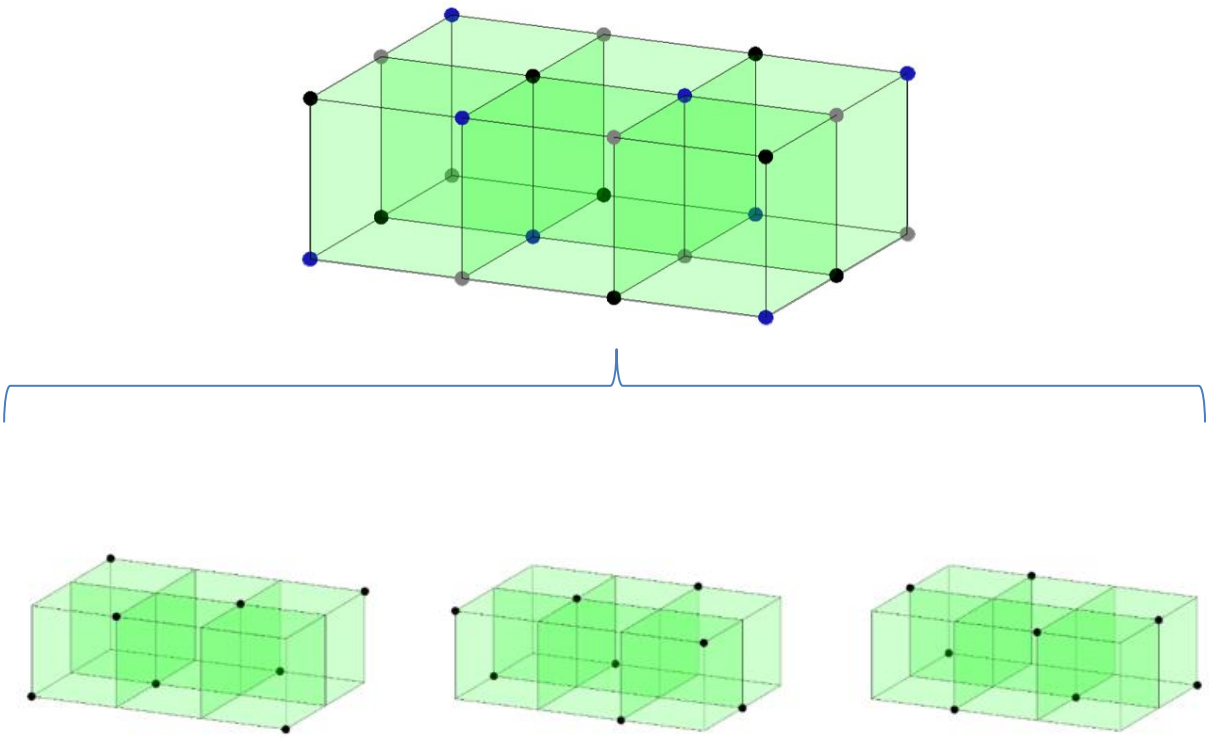
Factors

	Name	Abbreviation	Units	Type	Settings
1	**API**	API		Qualitative	Paracetamol; Propranolol
2	**Filler**	Fil	µm	Multilevel	57; 115; 228
3	**Tablet Size**	Size	mm3	Quantitative	150 to 235
4	**Tensile Strength**	Str	MPa	Multilevel	1; 2; 3
5	**Moisture Level**	Moi	%	Multilevel	5; 10; 55; 75
+	*Add...*				

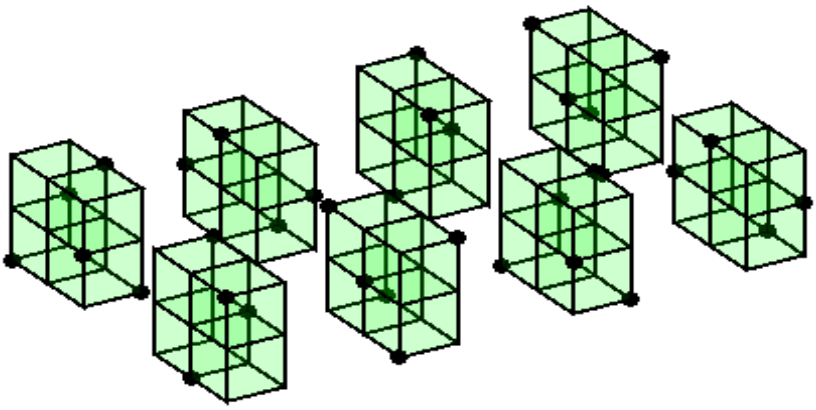
Experimental protocol

The reduced combinatorial design (RCD) is an algorithmic design, which generates a reduced design. The RCD is generated from a strict combinatorial perspective striving for a balanced coverage of all factor settings. The algorithm selecting the design runs treats qualitative and quantitative multilevel factors equally.

Let us consider an example in which there is 24 (4*3*2) possible factor combinations. Using RCD these 24 factor combinations can be partitioned as 24 = 8 + 8 + 8 equivalent design sets. Each such design set can be run standalone.

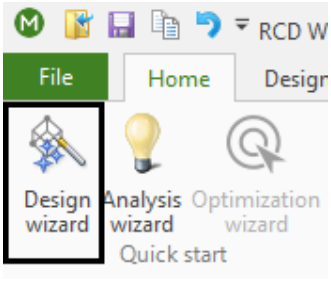


Now, returning to the microwave spectroscopy example, the total number of factor combinations is 144 (2*3*2*3*4). As will be discussed in more detail below, RCD was used to select a quarter fraction consisting of 36 experiments. The actual quarter fraction that was used in the calibration example is shown below. In addition to the 36 experiments, the investigators decided to augment the quarter fraction by adding 12 replicated experiments. Thus, in total, the final design contained 48 experiments.

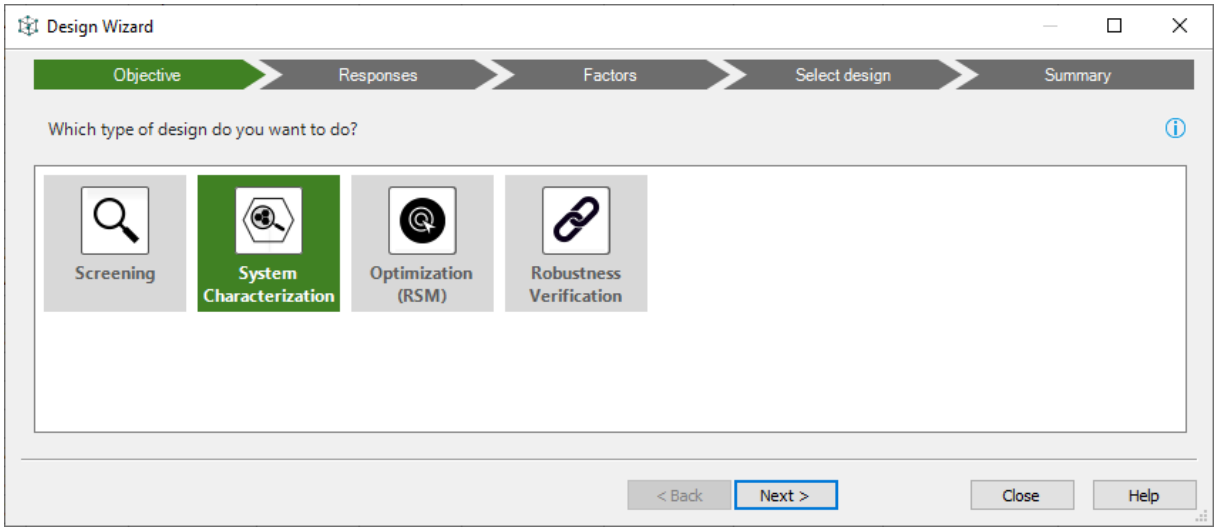


Creating the Reduced Combinatorial Design

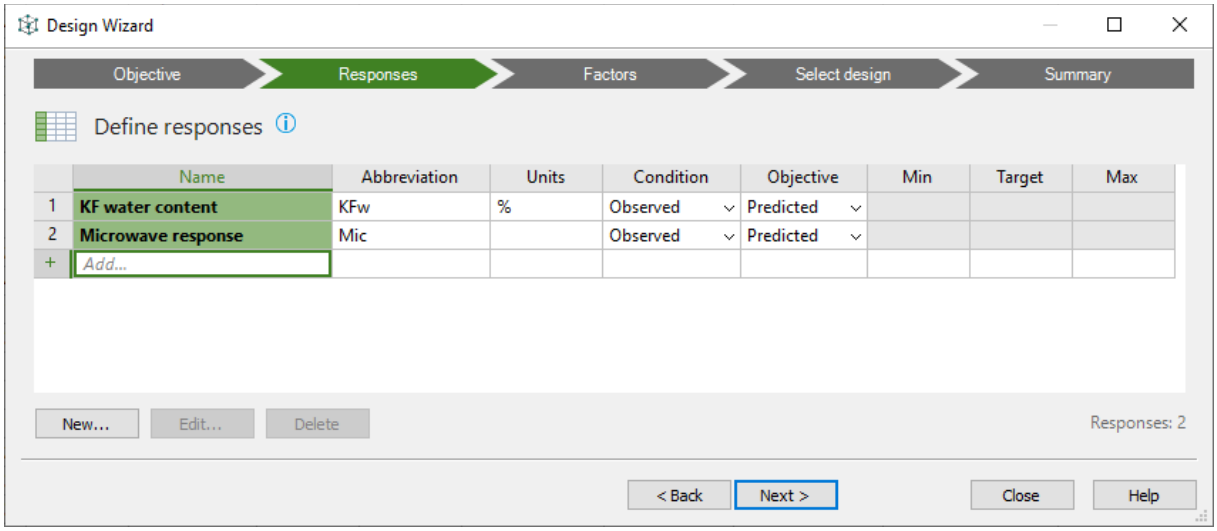
The first step is to create a MODDE project and reproduce the experimental design that was used. Use the Design Wizard to help you set up the design.



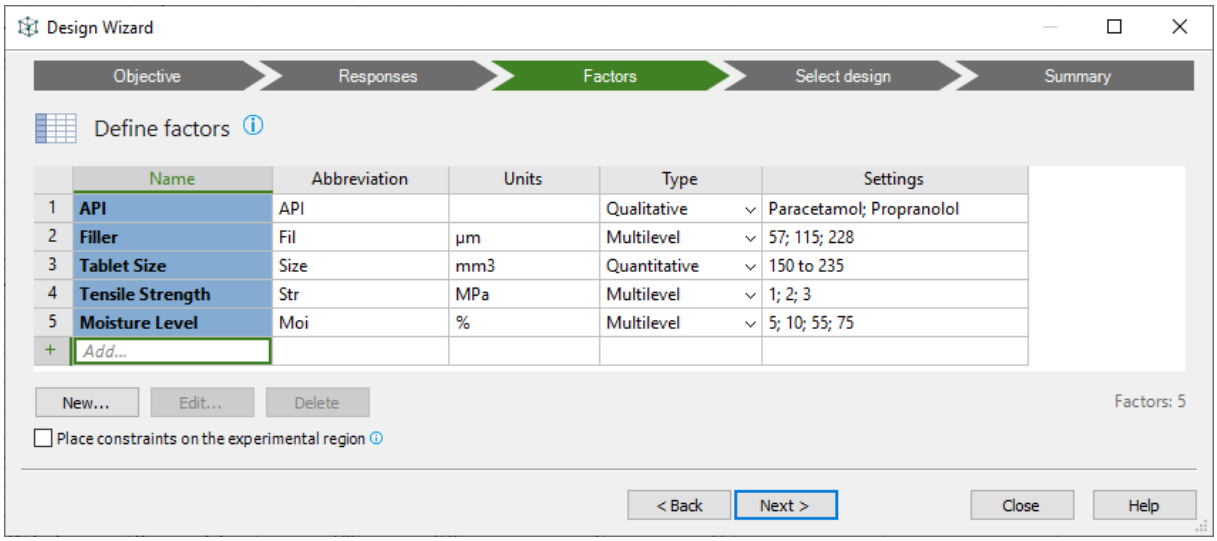
Select System Characterization. Click Next.



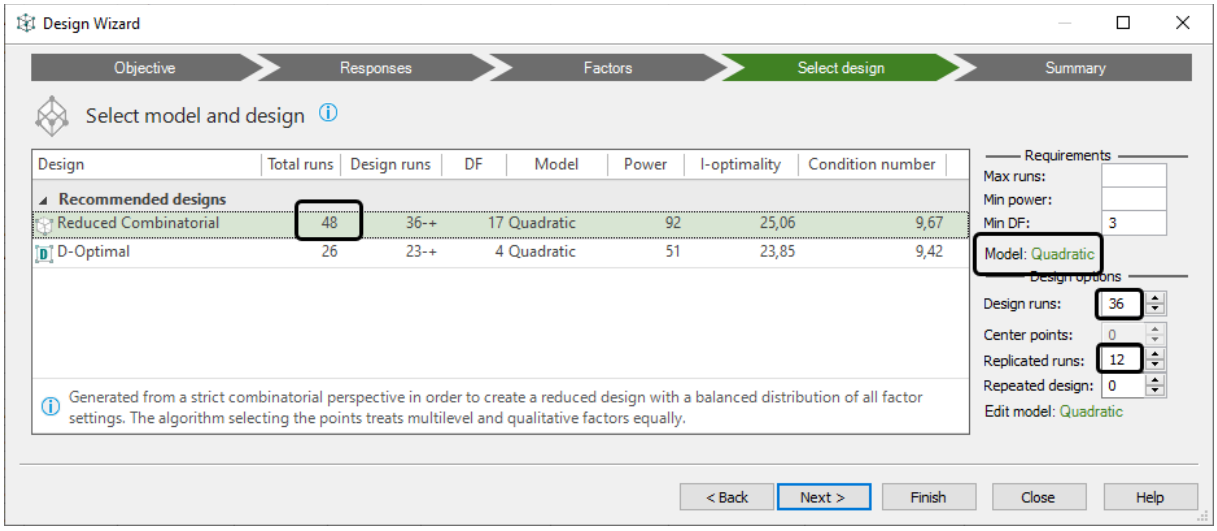
On the responses page, define the two responses as seen in the screenshot below. When done, click Next.



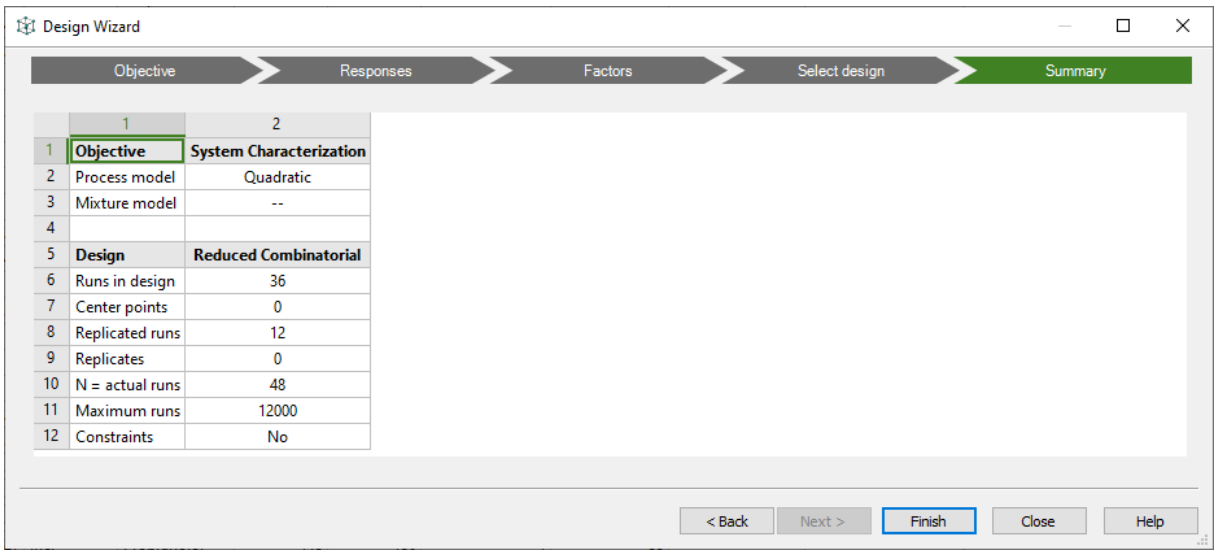
On the factors page, define the five factors as seen in the screenshot below. When done, click Next.



Select the Reduced Combinatorial design. Set the number of design runs = 36 and number replicated runs = 12. Verify that the number of Total runs = 48. Verify that a quadratic model is selected. Click Next.



On the final Summary page you can review your selections and settings, which should look like the screenshot below. Click Finish to exit the Design Wizard.

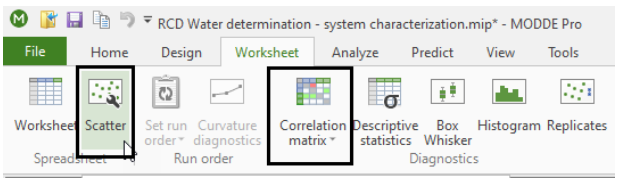


Upon exiting the Design Wizard a preliminary worksheet with 48 rows is created. Open the file *RCD Water Content.XLS* and copy | paste the data into your worksheet. Your resulting worksheet should be identical to the data seen in the screenshot below.

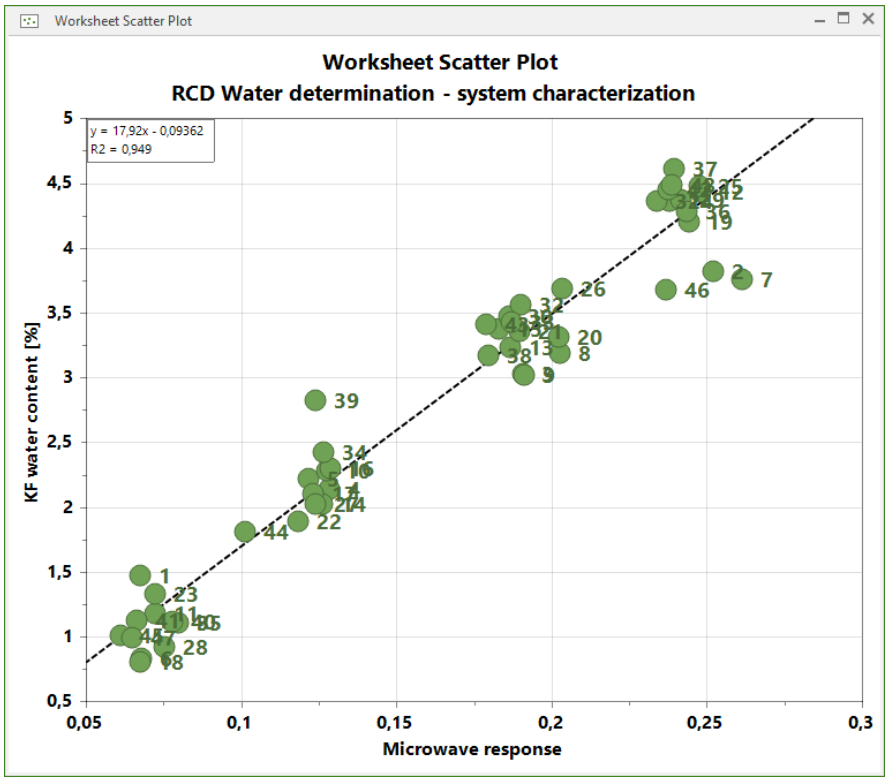
Worksheet

	1	2	3	4	5	6	7	8	9	10	11
	Exp No	Exp Name	Run Order	Incl/Excl	API	Filler	Tablet Size	Tensile Strength	Moisture Level	KF water content	Microwave response
1	1	N1	47	Incl	Paracetamol	57	150	1	5	1,47	0,0674
2	2	N2	1	Incl	Propranolol	57	150	1	75	3,82	0,2519
3	3	N3	35	Incl	Paracetamol	115	150	1	55	3,03	0,1909
4	4	N4	20	Incl	Propranolol	115	150	1	10	2,14	0,1282
5	5	N5	2	Incl	Paracetamol	228	150	1	10	2,22	0,1216
6	6	N6	29	Incl	Propranolol	228	150	1	5	0,83	0,068
7	7	N7	25	Incl	Paracetamol	57	235	1	75	3,76	0,2615
8	8	N8	30	Incl	Propranolol	57	235	1	55	3,19	0,2025
9	9	N9	22	Incl	Paracetamol	115	235	1	55	3,02	0,1913
10	10	N10	45	Incl	Propranolol	115	235	1	10	2,28	0,1276
11	11	N11	32	Incl	Paracetamol	228	235	1	5	1,18	0,0723
12	12	N12	33	Incl	Propranolol	228	235	1	75	4,43	0,2479
13	13	N13	17	Incl	Paracetamol	115	150	1	55	3,23	0,1867
14	14	N14	13	Incl	Propranolol	115	150	1	10	2,02	0,1262
15	15	N15	21	Incl	Paracetamol	115	235	1	55	3,38	0,1828
16	16	N16	4	Incl	Propranolol	115	235	1	10	2,3	0,1286
17	17	N17	42	Incl	Paracetamol	57	150	2	10	2,1	0,123
18	18	N18	10	Incl	Propranolol	57	150	2	5	0,81	0,0673
19	19	N19	8	Incl	Paracetamol	115	150	2	75	4,2	0,2442
20	20	N20	23	Incl	Propranolol	115	150	2	55	3,31	0,2022
21	21	N21	7	Incl	Paracetamol	228	150	2	55	3,36	0,1896
22	22	N22	19	Incl	Propranolol	228	150	2	10	1,89	0,1182
23	23	N23	26	Incl	Paracetamol	57	235	2	5	1,33	0,0721
24	24	N24	14	Incl	Propranolol	57	235	2	75	4,36	0,2378
25	25	N25	48	Incl	Paracetamol	115	235	2	75	4,48	0,2478
26	26	N26	12	Incl	Propranolol	115	235	2	55	3,69	0,2033
27	27	N27	39	Incl	Paracetamol	228	235	2	10	2,02	0,1238
28	28	N28	31	Incl	Propranolol	228	235	2	5	0,92	0,0751
29	29	N29	40	Incl	Paracetamol	115	150	2	75	4,37	0,2418
30	30	N30	11	Incl	Propranolol	115	150	2	55	3,47	0,1862
31	31	N31	44	Incl	Paracetamol	115	235	2	75	4,36	0,2337
32	32	N32	6	Incl	Propranolol	115	235	2	55	3,56	0,1899
33	33	N33	41	Incl	Paracetamol	57	150	3	55	3,43	0,1871
34	34	N34	38	Incl	Propranolol	57	150	3	10	2,42	0,1265
35	35	N35	15	Incl	Paracetamol	115	150	3	5	1,11	0,0798
36	36	N36	5	Incl	Propranolol	115	150	3	75	4,28	0,2434
37	37	N37	46	Incl	Paracetamol	228	150	3	75	4,61	0,2395
38	38	N38	24	Incl	Propranolol	228	150	3	55	3,17	0,1798
39	39	N39	9	Incl	Paracetamol	57	235	3	10	2,82	0,1239
40	40	N40	18	Incl	Propranolol	57	235	3	5	1,12	0,0778
41	41	N41	34	Incl	Paracetamol	115	235	3	5	1,13	0,0665
42	42	N42	16	Incl	Propranolol	115	235	3	75	4,45	0,2375
43	43	N43	37	Incl	Paracetamol	228	235	3	55	3,41	0,1788
44	44	N44	28	Incl	Propranolol	228	235	3	10	1,81	0,1011
45	45	N45	43	Incl	Paracetamol	115	150	3	5	1,01	0,0611
46	46	N46	3	Incl	Propranolol	115	150	3	75	3,68	0,2368
47	47	N47	27	Incl	Paracetamol	115	235	3	5	0,99	0,065
48	48	N48	36	Incl	Propranolol	115	235	3	75	4,49	0,2386

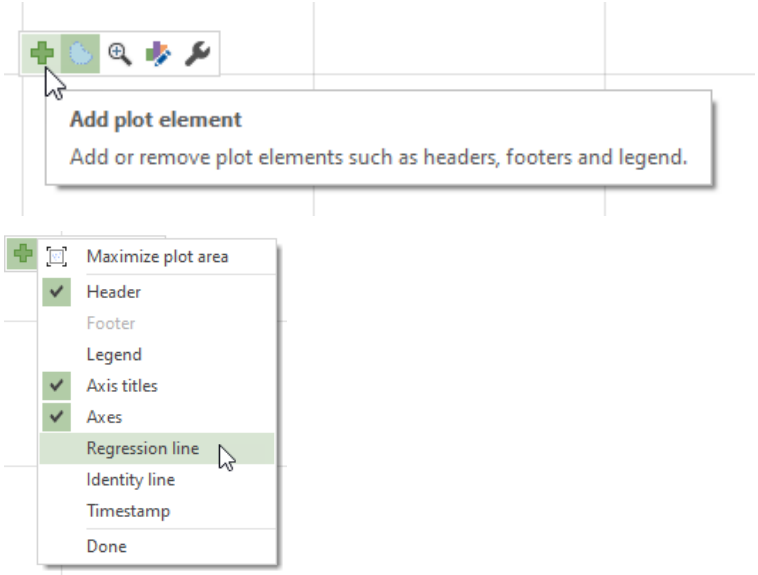
It is essential that the two responses are highly correlated; otherwise the alternative measurement method cannot be used to replace the reference method (Karl Fischer titration). We can use Scatter plots of the data or the correlation matrix to understand how correlated the two responses are.



Here we show results of using the scatter plot tool. The two responses show a strong correlation with an R2 ≈ 0.95. The scatter plot also shows that we have a clustered distribution of the response data, but none of the two responses have any tendency for tailing or skewed data distribution.



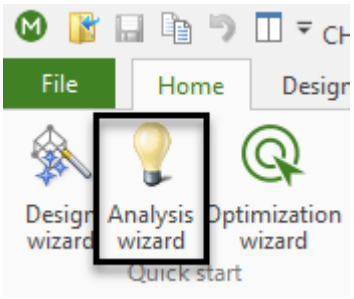
TIP: In order to visualize the regression line, you have to click in the plot and select Add plot element followed by selecting Regression line.



Analyzing the Data

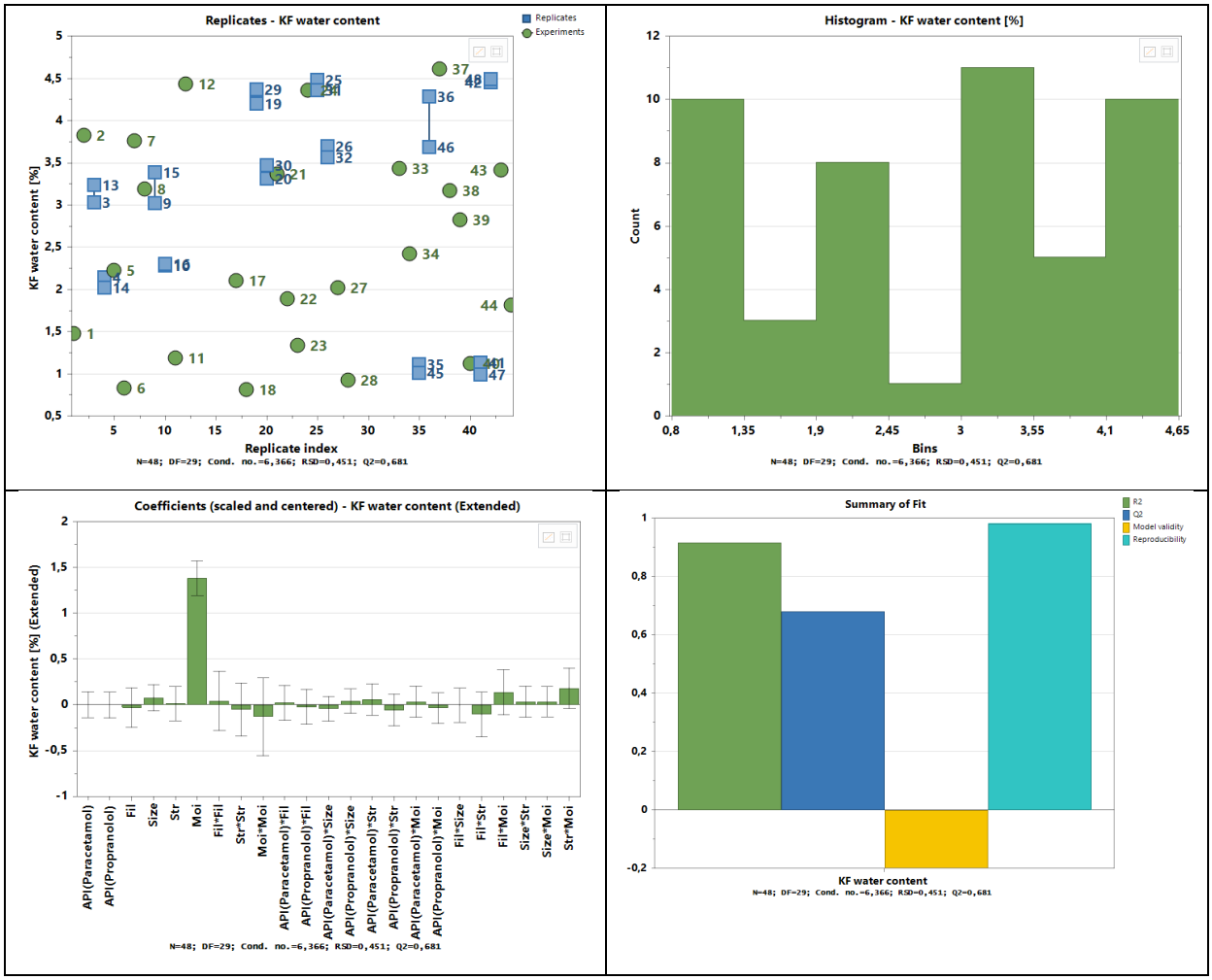
Use the Analysis Wizard to model the two responses.

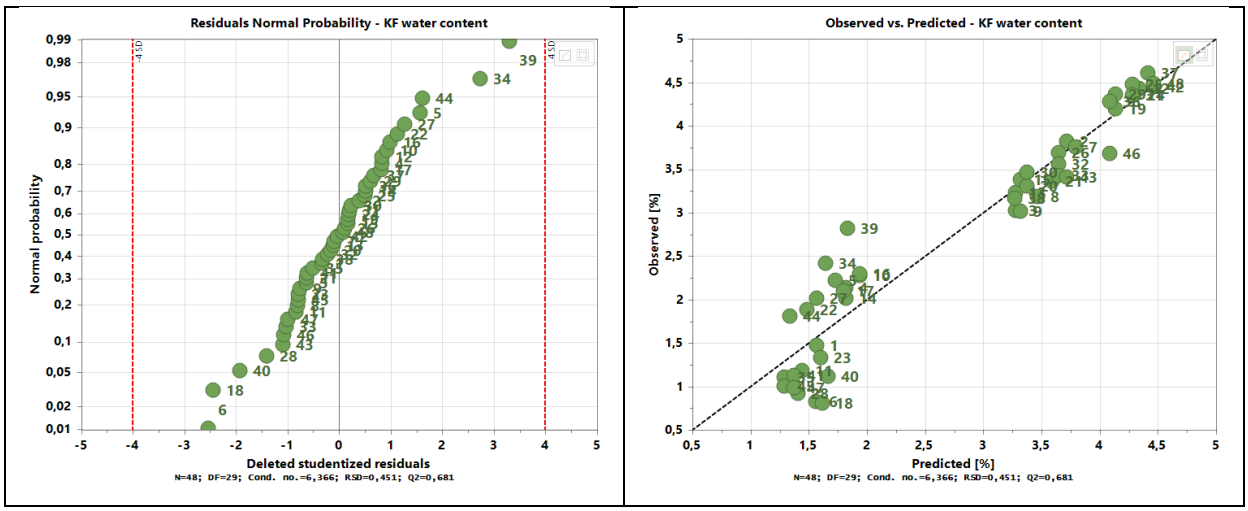
We here present the results for one response at a time.



KF Water Content

The plots of the Analysis Wizard arising from calculating the quadratic model are seen below.

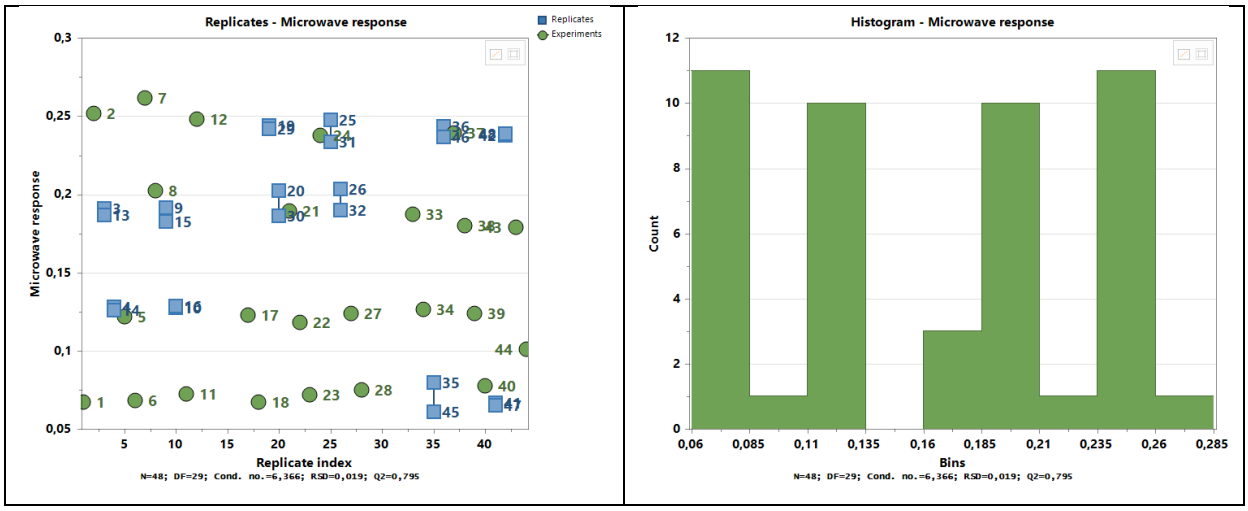


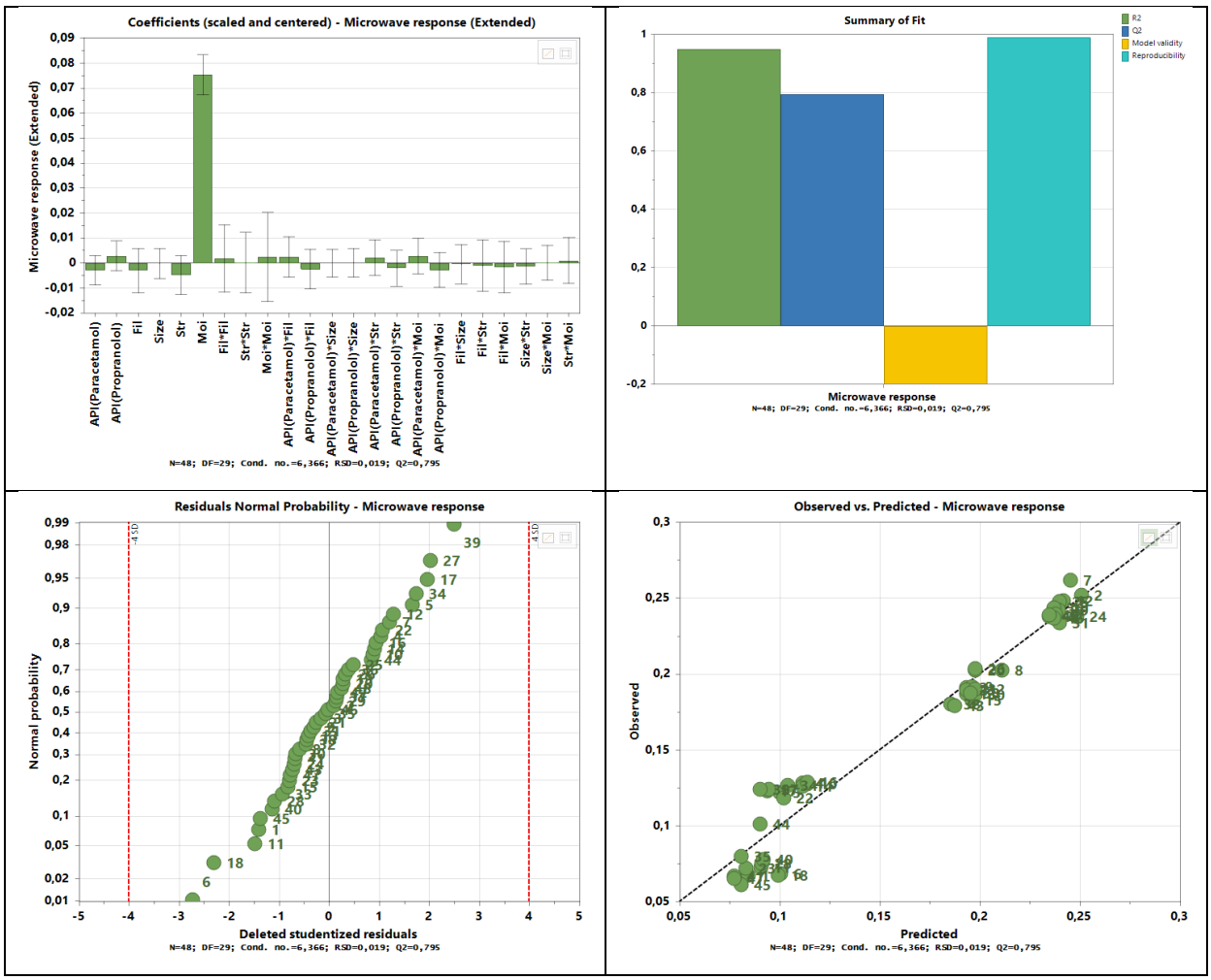


The replicate plot shows there is very small variability among the replicates. Because there is one dozen replicates, the pooled replicate error will be very small and this means that the Model Validity statistic will be low, or even negative. This is more of a cosmetic issue rather than a real practical problem. The histogram plot indicates that the response does not need a transformation and can be analyzed using the untransformed metric. According to the coefficient plot, Moisture is the factor having the strongest impact on the response. The summary of fit plot, the normal probability plot of residuals, and the observed versus predicted plot all point to a very good model for the KF water content response.

Microwave Response

The plots of the Analysis Wizard arising from calculating the quadratic model are seen below.





The replicate plot shows there is very small variability among the replicates. Because there is one dozen replicates, the pooled replicate error will be very small and this means that the Model Validity statistic will be low, or even negative. This is more of a cosmetic issue rather than a real practical problem. The histogram plot indicates that the response does not need a transformation and can be analyzed using the untransformed metric. According to the coefficient plot, Moisture is the factor having the strongest impact on the response. The summary of fit plot, the normal probability plot of residuals, and the observed versus predicted plot all point to a very good model for the Microwave response.

Discussion and Conclusions

In this application to determine water content in tablets using an alternative method (microwave spectroscopy), a necessary condition is that both responses are highly correlated. In this case both responses are indeed highly correlated with an R2 ≈ 0.95. This insight is so to say the fundament of the whole application. Beyond this insight, it is still recommended to pursue all the steps in the Analysis Wizard, to verify that underlying data are of high quality (small replicate errors), to uncover which factors mainly influence the two responses, and to chase experimental outliers. This is means that in the coefficient plots you are more looking at the profiles of the coefficients rather than trying to fine-tune each regression model.

The main conclusion is that the alternative method for measuring water content in tablets (microwave spectroscopy) can be used to replace the traditional method (Karl Fischer titration). Moisture level is the most important factor to influence the two responses. This is according to expectation since different tablet conditioning climates were used to deliberately induce different water content in the tablets. An important observation is that both methods have not detected any significant effect of the interfering factors suggesting a robust calibration method. From a methodological point of view a complementary insight is that the approach to use a reduced combinatorial design works very well in the context of multivariate calibration. The reduced design gave reliable results with lower time consumption and cost of analysis as compared to the full factorial design in 144 runs.