Quality by Design approach for an in situ gelling microemulsion of Lorazepam via intranasal route

This research paper applies the concept of Quality by Design in the development, optimization and evaluation of Lorazepam loaded microemulsion containing ion responsive in situ gelator gellan gum and carbopol 934. Design of experiments (DoE) methodology is implemented in order to evaluate the effect of the independent variables on the responses.

The factors (independent variables) examined are: X_1 = oil to surfactant/cosurfactant ratio and X_2 = concentration of gellan gum (% w/v). All the factors are continuous. The responses (dependent variables) examined are: Y_1 = in vitro drug release (%) and Y_2 = viscosity at physiological pH (Pa·s). The applied DoE method is 3^2 full factorial design.

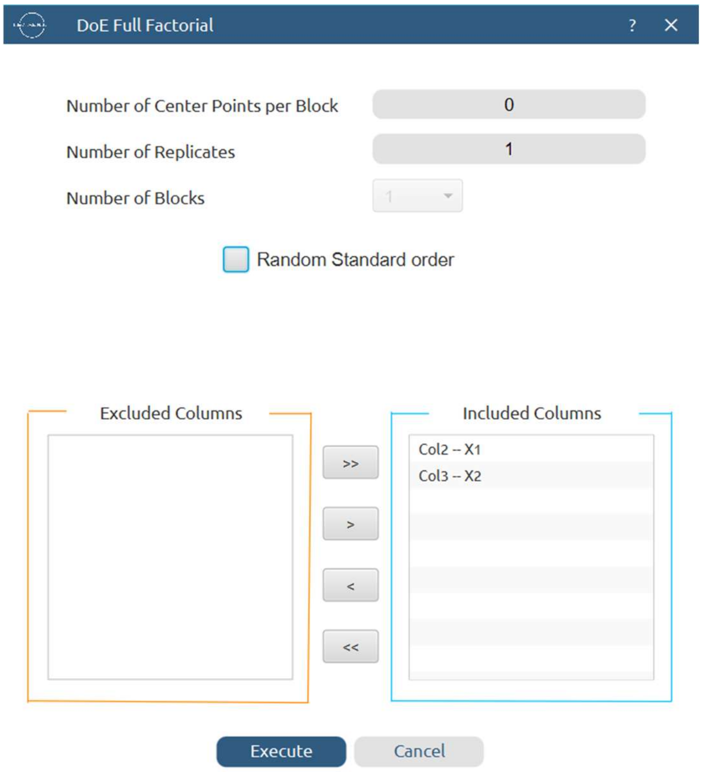
Isalos version used: 2.0.6

Scientific article: https://www.sciencedirect.com/science/article/pii/S0928493117308020

Step 1: Full Factorial Design

In the first tab named "Action" define the factors in the column headers and fill each column with the low and high levels of the corresponding factors. This tab can be renamed "Full Factorial". Afterwards, apply the full factorial method: *DOE → Factorial → Full Factorial*

	Col1	Col2 (D)	Col3 (D)
User Header	User Row ID	X1	X2
1		0.1	0.1
2		0.2	0.2
3		0.3	0.3

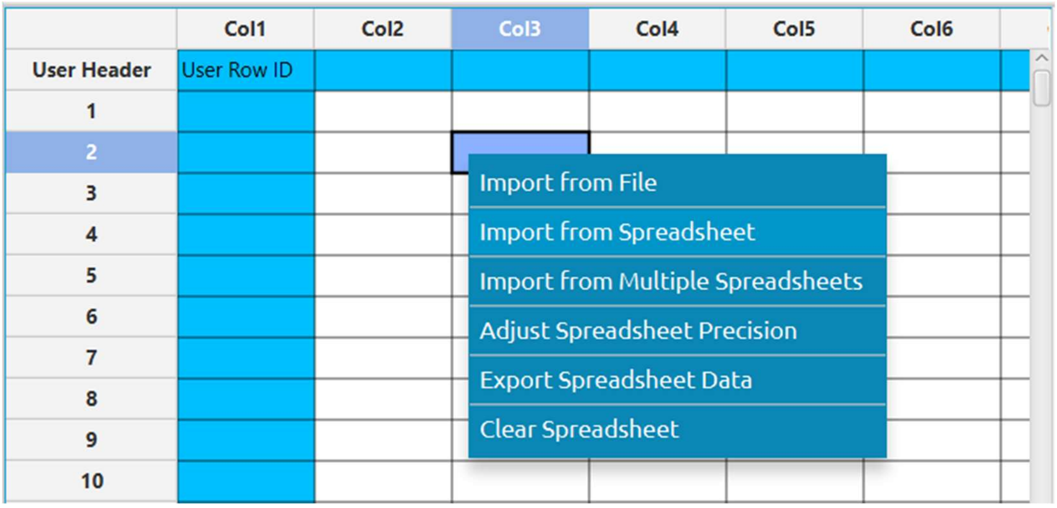


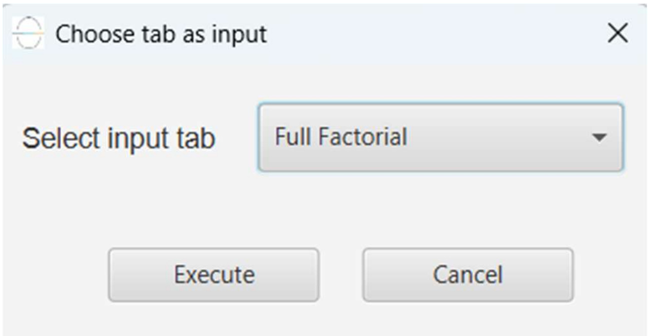
Results (right spreadsheet):

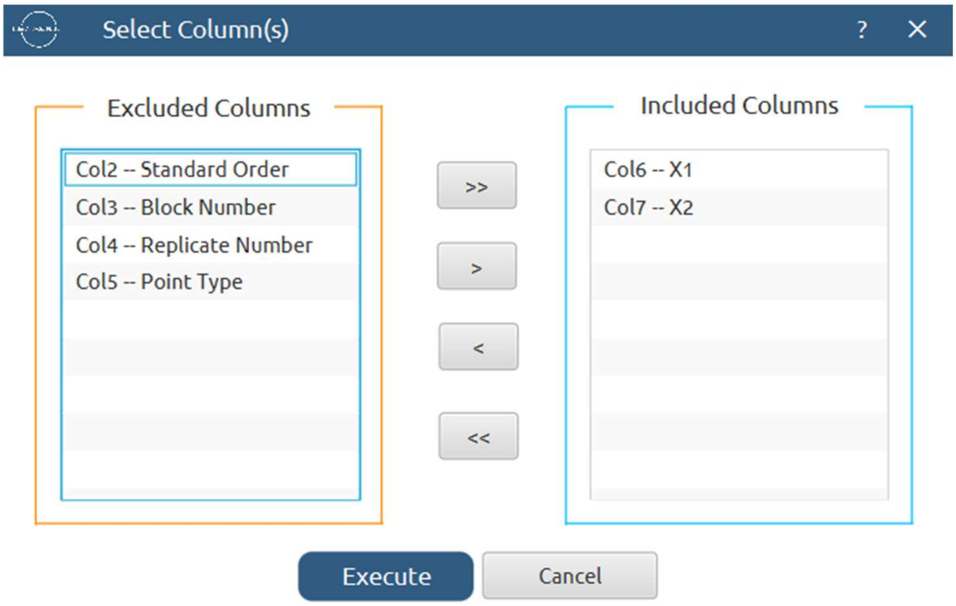
	Col2 (I)	Col3 (S)	Col4 (S)	Col5 (S)	Col6 (D)	Col7 (D)
User Header	Standard Order	Block Number	Replicate Number	Point Type	X1	X2
1	1	Block: 1	Replicate: 1	Design Point	0.1	0.1
2	2	Block: 1	Replicate: 1	Design Point	0.2	0.1
3	3	Block: 1	Replicate: 1	Design Point	0.3	0.1
4	4	Block: 1	Replicate: 1	Design Point	0.1	0.2
5	5	Block: 1	Replicate: 1	Design Point	0.2	0.2
6	6	Block: 1	Replicate: 1	Design Point	0.3	0.2
7	7	Block: 1	Replicate: 1	Design Point	0.1	0.3
8	8	Block: 1	Replicate: 1	Design Point	0.2	0.3
9	9	Block: 1	Replicate: 1	Design Point	0.3	0.3

Step 2: Factor isolation

Create a new tab named “Factors” and import the results from the “Full Factorial” spreadsheet by right clicking on the left spreadsheet. Then, select only the factor columns to be transferred to the right spreadsheet: *Data Transformation → Data Manipulation → Select Column(s)*







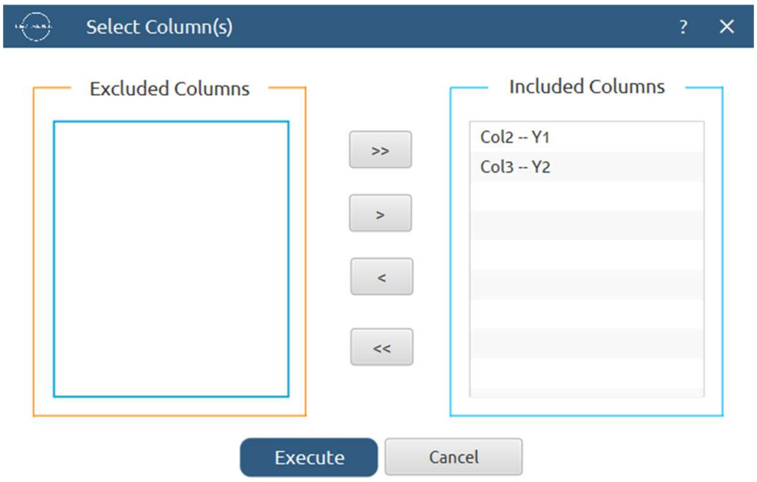
Results:

	Col1	Col2 (D)	Col3 (D)
User Header	User Row ID	X1	X2
1		0.1	0.1
2		0.2	0.1
3		0.3	0.1
4		0.1	0.2
5		0.2	0.2
6		0.3	0.2
7		0.1	0.3
8		0.2	0.3
9		0.3	0.3

Step 3: Definition of response variables

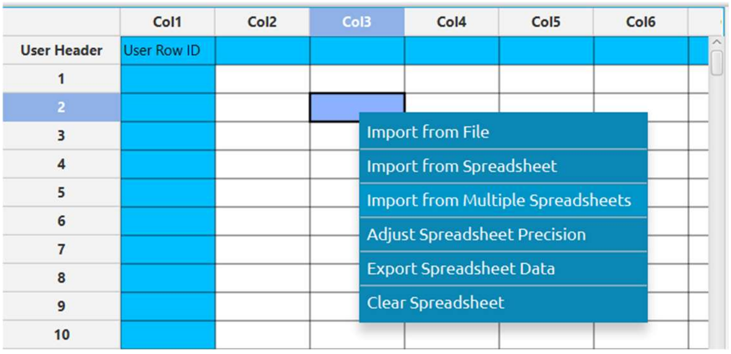
Create a new tab named "Responses" and define the responses in the column headers. Fill each column with the values of the corresponding responses that were observed and make sure the values follow the order of the experiments as given by the full factorial design. Then, select all columns to be transferred to the right spreadsheet: *Data Transformation → Data Manipulation → Select Column(s)*

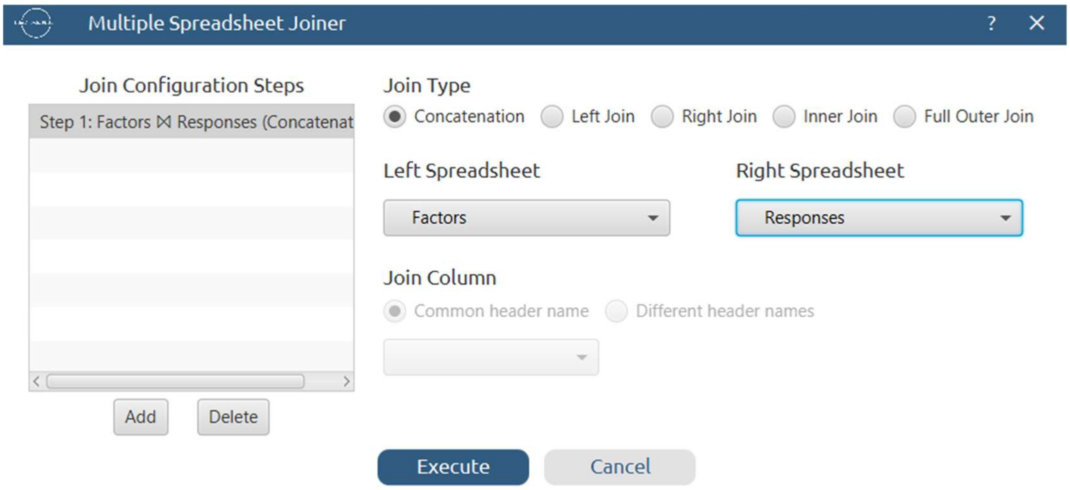
	Col1	Col2 (D)	Col3 (D)
User Header	User Row ID	Y1	Y2
1		97.32	470.248
2		94.47	391.517
3		89.02	348.227
4		91.87	576.101
5		87.42	484.726
6		80.85	408.57
7		88.75	648.117
8		81.98	586.212
9		74.48	510.41

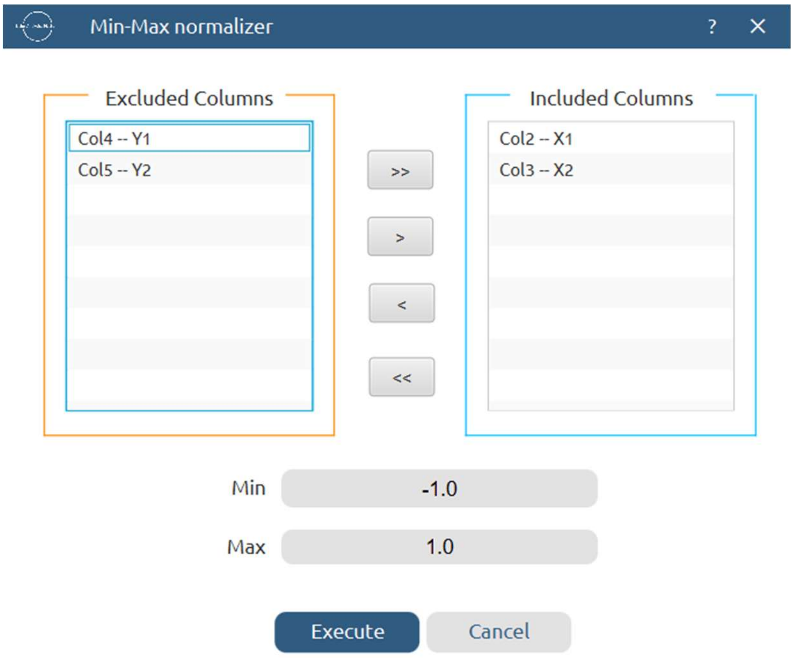


Step 4: Normalization

Create a new tab named "Normalized data" and import the results from the "Factors" and "Responses" spreadsheets. Afterwards, normalize the factor columns to take values in the range [-1, 1]: *Data Transformation → Normalizers → Min-Max*







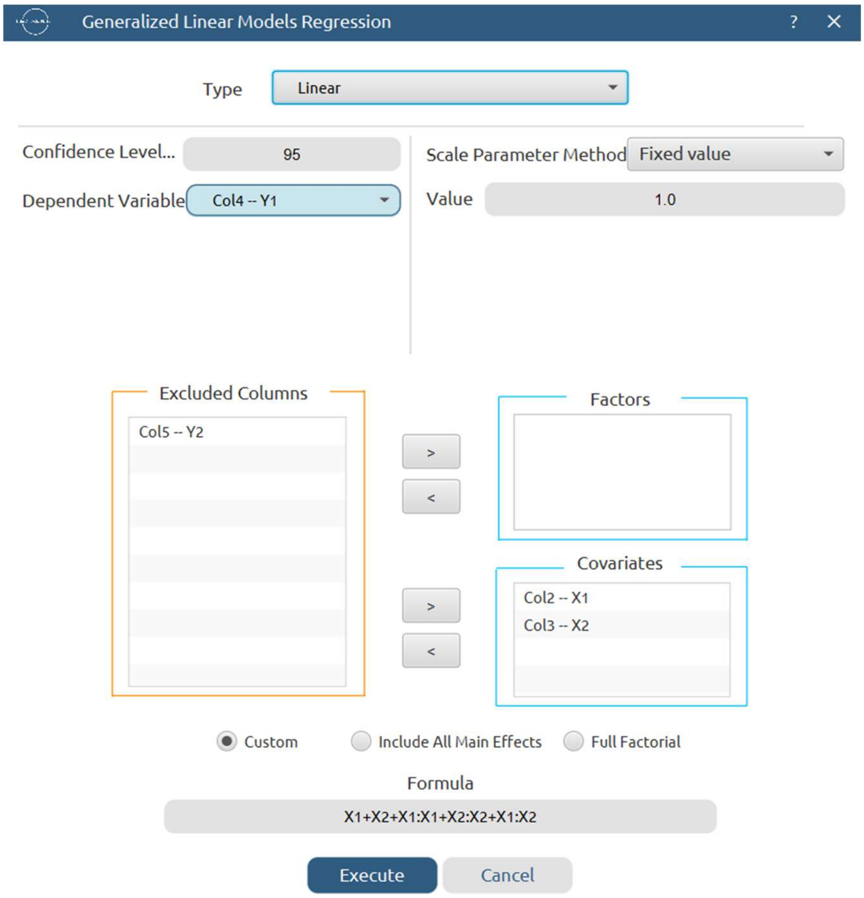
Results:

	Col1	Col2 (D)	Col3 (D)	Col4 (D)	Col5 (D)
User Header	User Row ID	X1	X2	Y1	Y2
1		-1.0	-1.0	97.32	470.248
2		0E-7	-1.0	94.47	391.517
3		1.0	-1.0	89.02	348.227
4		-1.0	0E-7	91.87	576.101
5		0E-7	0E-7	87.42	484.726
6		1.0	0E-7	80.85	408.57
7		-1.0	1.0	88.75	648.117
8		0E-7	1.0	81.98	586.212
9		1.0	1.0	74.48	510.41

Step 5: Regression

The goal here is to produce a regression equation that includes main effects, two-factor interactions and quadratic effects for Y_1: $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}{X_1}^2 + b_{22}{X_2}^2$

Create a new tab named "Regression – Y1" and import the results from the spreadsheet "Normalized data". Afterwards, fit a generalized linear model to the data: *Analytics → Regression → Statistical fitting → Generalized Linear Models*



Results:

Y1	Prediction
97.32	97.4063889
94.47	94.2088889
89.02	89.1947222
91.87	92.0088889
87.42	87.3188889
80.85	80.8122222
88.75	88.5247222
81.98	82.3422222
74.48	74.3430556

Goodness of Fit	
	Value
Deviance	0.3378194
Scaled Deviance	0.3378194
Pearson Chi-Square	0.3378194
Scaled Pearson Chi-Square	0.3378194
Log Likelihood	-8.4393565
Akaike's Information Criterion (AIC)	28.8787130
Finite Sample Corrected AIC (AICC)	70.8787130
Bayesian Information Criterion (BIC)	30.0620605
Consistent AIC (CAIC)	36.0620605

Parameter Estimates							
Variable	Coefficient	Std. Error	Lower CI	Upper CI	Test Statistic	df	p-value
intercept	87.3188889	0.7453560	85.8580180	88.7797598	13724.2590422	1	0.0
X1	-5.5983333	0.4082483	-6.3984853	-4.7981814	188.0480167	1	0.0
X2	-5.9333333	0.4082483	-6.7334853	-5.1331814	211.2266667	1	0.0
X1*X2	-1.4925000	0.5	-2.4724820	-0.5125180	8.9102250	1	0.0028358
X1*X1	-0.9083333	0.7071068	-2.2942372	0.4775705	1.6501389	1	0.1989400
X2*X2	0.9566667	0.7071068	-0.4292372	2.3425705	1.8304222	1	0.1760777

Repeat this step for the second response variable, Y_2. Results:

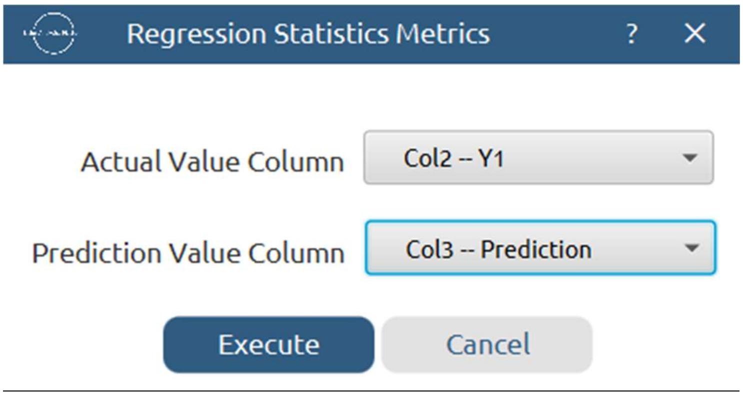
Y2	Prediction
470.248	472.6613889
391.517	399.2458889
348.227	338.0847222
576.101	563.0512222
484.726	485.7142222
408.57	420.6315556
648.117	658.7533889
586.212	577.4948889
510.41	508.4907222

Goodness of Fit	
	Value
Deviance	677.9847954
Scaled Deviance	677.9847954
Pearson Chi-Square	677.9847954
Scaled Pearson Chi-Square	677.9847954
Log Likelihood	-347.2628445
Akaike's Information Criterion (AIC)	706.5256890
Finite Sample Corrected AIC (AICC)	748.5256890
Bayesian Information Criterion (BIC)	707.7090365
Consistent AIC (CAIC)	713.7090365

Parameter Estimates							
Variable	Coefficient	Std. Error	Lower CI	Upper CI	Test Statistic	df	p-value
intercept	485.7142222	0.7453560	484.2533513	487.1750931	424652.9502041	1	0.0
X1	-71.2098333	0.4082483	-72.0099853	-70.4096814	30425.0421802	1	0.0
X2	89.1245000	0.4082483	88.3243481	89.9246519	47659.0590015	1	0.0
X1*X2	-3.9215000	0.5	-4.9014820	-2.9415180	61.5126490	1	0E-7
X1*X1	6.1271667	0.7071068	4.7412628	7.5130705	75.0843427	1	0.0
X2*X2	2.6561667	0.7071068	1.2702628	4.0420705	14.1104427	1	0.0001724

Step 6: Regression Metrics

Create a tab named "Metrics – Y1" and import the results from the spreadsheet "Regression – Y1". Then, produce the regression metrics for the Y_1 regression equation: *Statistics → Model Metrics → Regression Metrics*



Results:

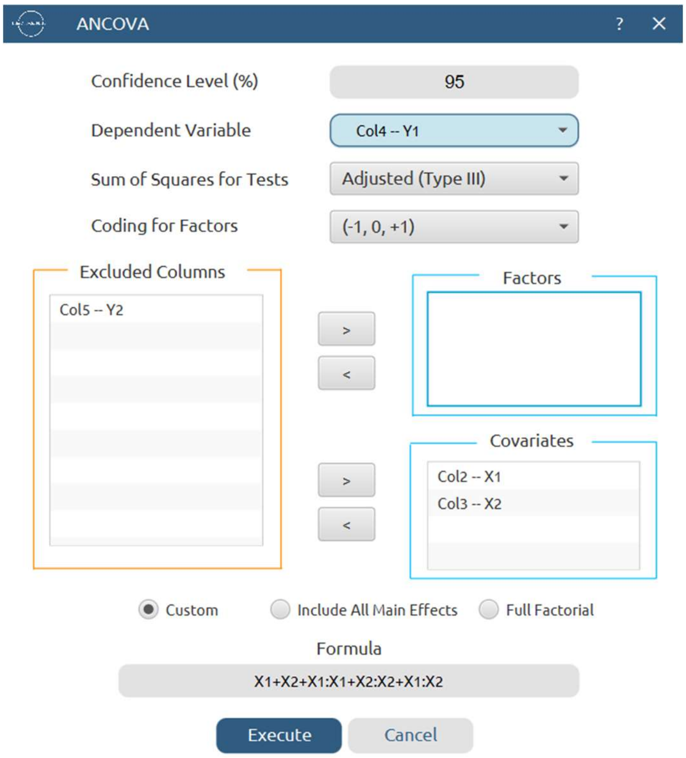
	Col1	Col2 (D)	Col3 (D)	Col4 (D)	Col5 (D)
User Header	User Row ID	Mean Squared Error	Root Mean Squared Error	Mean Absolute Error	R Squared
1		0.0375355	0.1937408	0.1693827	0.9991801

Repeat this step for the second response variable, Y_2. Results:

	Col1	Col2 (D)	Col3 (D)	Col4 (D)	Col5 (D)
User Header	User Row ID	Mean Squared Error	Root Mean Squared Error	Mean Absolute Error	R Squared
1		75.3316439	8.6793804	7.5174321	0.9914084

Step 7: Analysis of Covariance

Create a new tab named "ANCOVA – Y1" and import the results from the spreadsheet "Normalized data". Afterwards perform analysis of covariance for Y_1: *Statistics → Analysis of (Co)Variance → ANCOVA*



Results:

	Col1	Col2 (S)	Col3 (I)	Col4 (D)	Col5 (D)	Col6 (D)	Col7 (D)
User Header	User Row ID	Source	DF	Adj SS	Adj MS	F-Value	P-Value
1		X1	1	188.0480167	188.0480167	1669.9573079	0.0000322
2		X2	1	211.2266667	211.2266667	1875.7949266	0.0000271
3		X1*X1	1	1.6501389	1.6501389	14.6540312	0.0314017
4		X2*X2	1	1.8304222	1.8304222	16.2550343	0.0274342
5		X1*X2	1	8.9102250	8.9102250	79.1271060	0.0029962
6		Error	3	0.3378194	0.1126065		
7		Total	8	412.0032889			

Repeat this step for the second response variable, Y_2. Results:

	Col1	Col2 (S)	Col3 (I)	Col4 (D)	Col5 (D)	Col6 (D)	Col7 (D)
User Header	User Row ID	Source	DF	Adj SS	Adj MS	F-Value	P-Value
1		X1	1	30425.0421802	30425.0421802	134.6270995	0.0013749
2		X2	1	47659.0590015	47659.0590015	210.8855213	0.0007080
3		X1*X1	1	75.0843427	75.0843427	0.3322391	0.6047462
4		X2*X2	1	14.1104427	14.1104427	0.0624370	0.8188181
5		X1*X2	1	61.5126490	61.5126490	0.2721860	0.6379384
6		Error	3	677.9847954	225.9949318		
7		Total	8	78912.7934116			

References

(1) Shah, V.; Sharma, M.; Pandya, R.; Parikh, R. K.; Bharatiya, B.; Shukla, A.; Tsai, H.-C. Quality by Design Approach for an in Situ Gelling Microemulsion of Lorazepam via Intranasal Route. *Materials Science and Engineering: C* **2017**, *75*, 1231–1241. https://doi.org/10.1016/j.msec.2017.03.002.