EUROPE DISCOVERY SUMMIT

Definitive Screening Design and Advanced Predictive Modelling as Useful Tools in Product Development

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Introduction

Pharmaceutical formulation development might be quite challenging, especially for solid dosage forms, having in mind that most of active substances are difficult to process or dissolve, and there are many process steps and functional components that need to be included to solve all the issues that appear along the way.

At the beginning of development, it is important to recognize what are the most important factors for responses of interest, out of many potential factors. For that purpose, screening experimental designs are often used as a starting tool. Definitive screening designs are often described as most appropriate for experimentation with four or more factors. On the other hand, when there are also available results of experiments that are not part of a specific design, it is important to have tools such as more advanced predictive modelling techniques, that could help in getting valuable insights from these types of data (1, 2, 3).

The aim of this work was to apply different analytical techniques in evaluating effects of input factors on characteristics of tablets and active substance release profile. Main challenge was to find balance between factors that contribute to tablet mechanical resistance, and factors that enable quick active substance dissolution important for product in-vivo performance.

Materials and methods

Active substance belongs to BCS class I/III. Tablets were produced by wet granulation.
Data analysis was performed by using software JMP® Pro version 17 (JMP Statistical Discovery LLC, USA).
Definitive screening design with 6 factors on three levels: amount of binder, disintegrant, lubricant and glidant, compression force and tableting speed and 13 runs was used as screening DoE. Following responses were monitored: disintegration, hardness, friability, 15 min dissolution, 30 min dissolution. Data were analyzed by using Fit definitive screening and Model screening platform. 14th run was produced to evaluate predictive ability of obtained models. For further exploration of impact of factors on hardness, extended set including 13 more experimental runs was used. The Model Screening platform was used to run multiple predictive modeling platforms from one launch window and assemble summaries from the different methods. The best performing model was launched as an individual platform for further refinement and analysis. Dissolution profile was tested by using 900 ml of Phosphate buffer at 37 °C, and paddle apparatus at speed of 50 rpm at time points 15 and 30 minutes.

Results and discussion

Visual data exploration

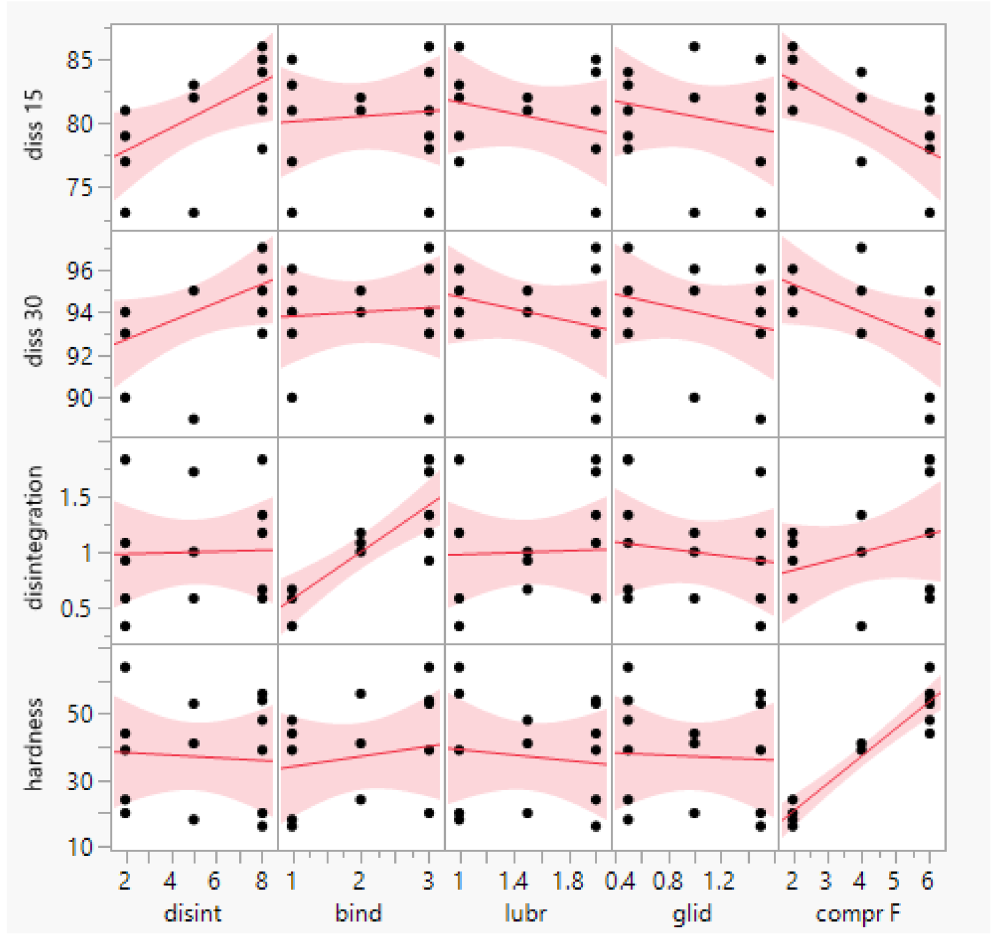


Figure 1. Scatterplot matrix provides quick assessment of relationships between multiple variables simultaneously

Fit definitive screening

Factor most significant for hardness is compression force. Factors most significant for dissolution are amount of disintegrant and compression force.

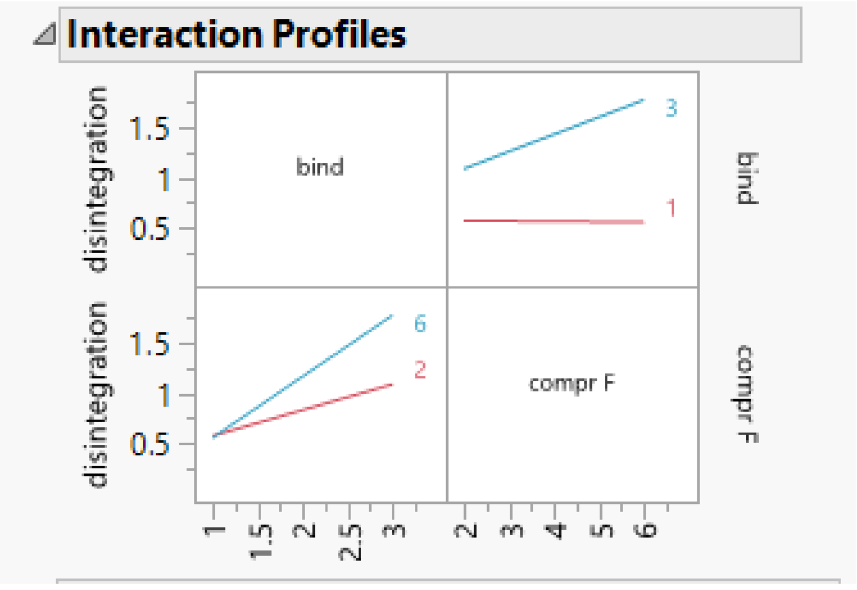
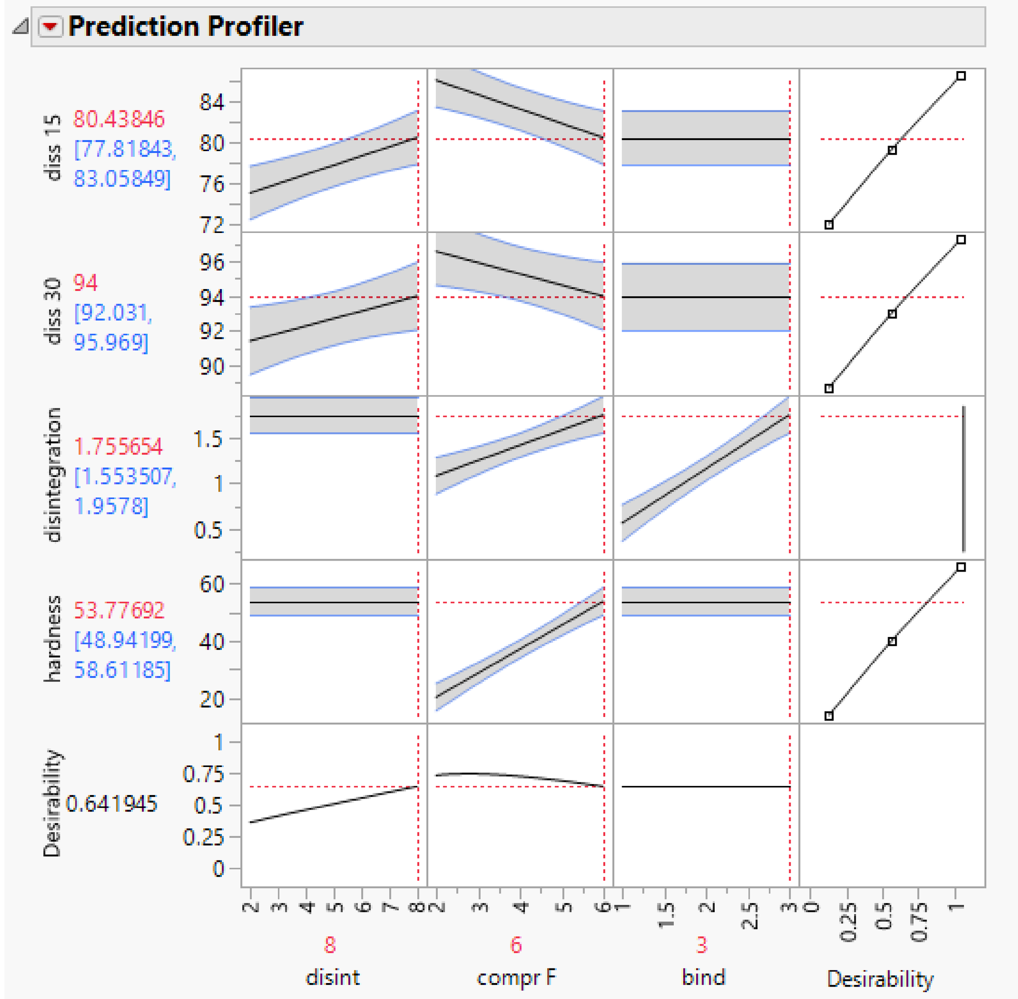


Figure 2. Interaction exists for binder amount - compression force for disintegration;

but disintegration is not relevant IPC for indicating dissolution outcome.



prediction for run 14

Real results
diss 15 78%
diss 30 93%
disintegration 1.83 min
hardness 54 N

Figure 3. Relatively good prediction for Test run 14

Model screening - Dissolution 15 min

Training

Method	N	Sum Freq	RSquare	RASE
Neural Boosted	8	8.0000	0.9204	1.0360
Fit Least Squares	13	13.0000	0.8821	1.9888
Fit Stepwise	13	13.0000	0.8617	1.4632
Support Vector Machines	13	13.0000	0.8130	1.7013
Generalized Regression Lasso	14	13.0000	0.6284	2.3982
Boosted Tree	13	13.0000	0.5975	2.4961
Bootstrap Forest	13	13.0000	0.5067	2.7632
K Nearest Neighbors	13	13.0000	-0.081	4.0899

Figure 4. Fit Least squares best model is reduced, factors similar as in DSD model (left) ; Neural boosted (right)

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	80.538462	0.536889	150.01	<.0001*
disint(2,8)	2.7	0.612148	4.41	0.0031*
bind(1,3)	0.4	0.612148	0.65	0.5343
lubr(1,2)	-1.1	0.612148	-1.80	0.1154
glid(0.5,1.5)	-1	0.612148	-1.63	0.1464
compr F(2,6)	-2.8	0.612148	-4.57	0.0026*

Model NTanH(3)NBoost(20)

Training – diss 15

Measures	Value
RSquare	0.9861324
RASE	0.4888758
Mean Abs Dev	0.3916217
-LogLikelihood	5.6263344
SSE	1.9119967
Sum Freq	8

Validation – diss 15

Measures	Value
RSquare	0.9851928
RASE	0.3690883
Mean Abs Dev	0.2885034
-LogLikelihood	2.1110958
SSE	0.6811309
Sum Freq	5

Conclusions

By using combination of different analytical tools, valuable insights were obtained regarding effect of formulation and process factors on tablet characteristics.

Optimal settings were defined to maximize dissolution. More experimental runs might be needed to explore potential effect of lubricant level on dissolution and tablet hardness.

References

1.Kovačević J, Kovačević A., Miletić T., Đuriš J., Ibrić S., 2022. Data mining techniques applied in the analysis of historical data. Arh. farm.; 72: 701 – 715

2. Mihajlovic T, Ibric S, Mladenovic A. Application of design of experiments and multilayer perceptron neural network in the optimization of spray drying process. Drying Tech. 2011; 29:1638-1647.

3. JMP documentation

Visual Data Exploring and Fit Definitive Screening Graphs

Results and discussion

Visual data exploration

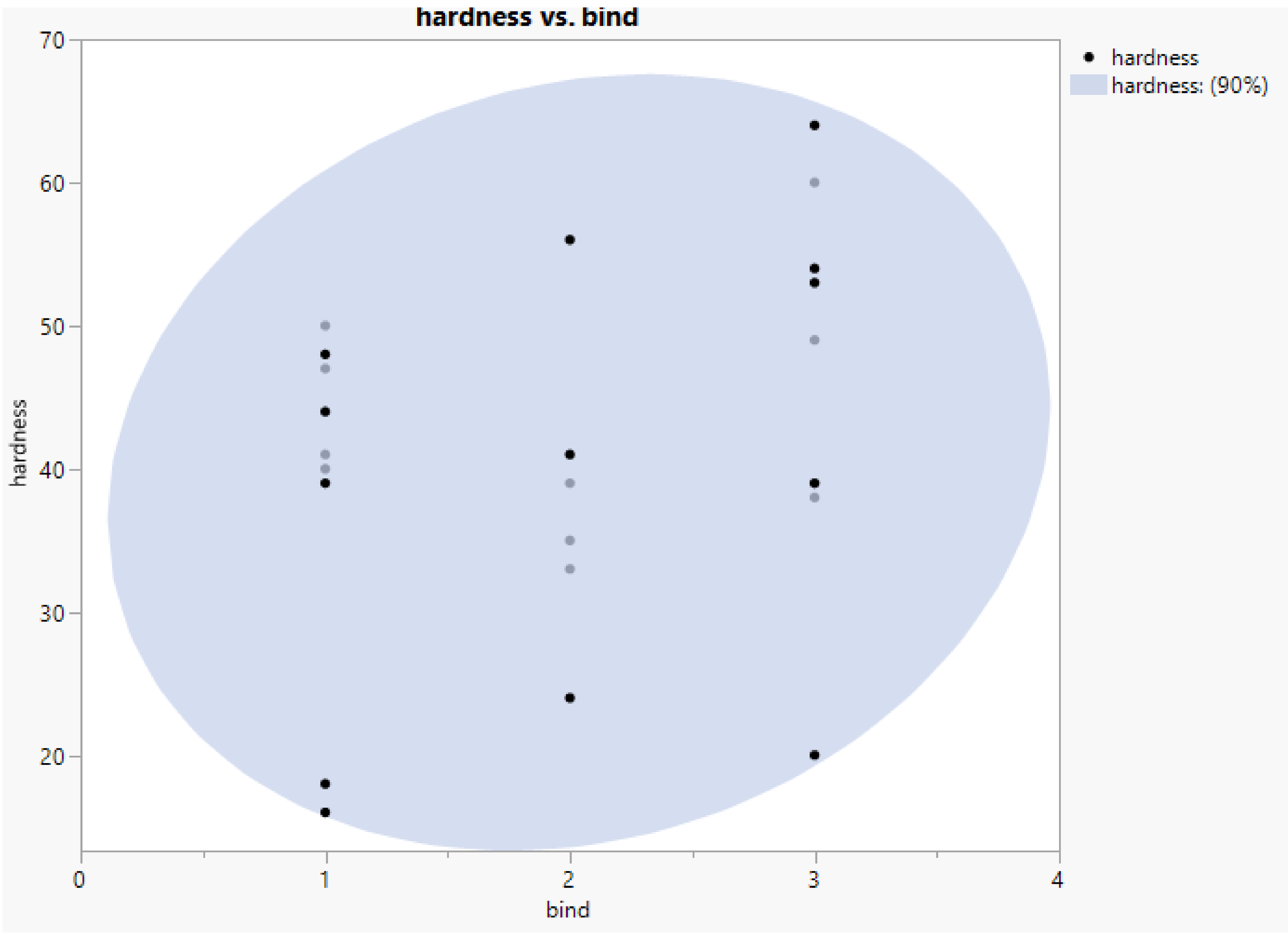


Figure 5. Bivariate normal density elipse obtained on larger dataset confirms tendency for increase of hardness when increasing binder level, effect not visible in DSD model

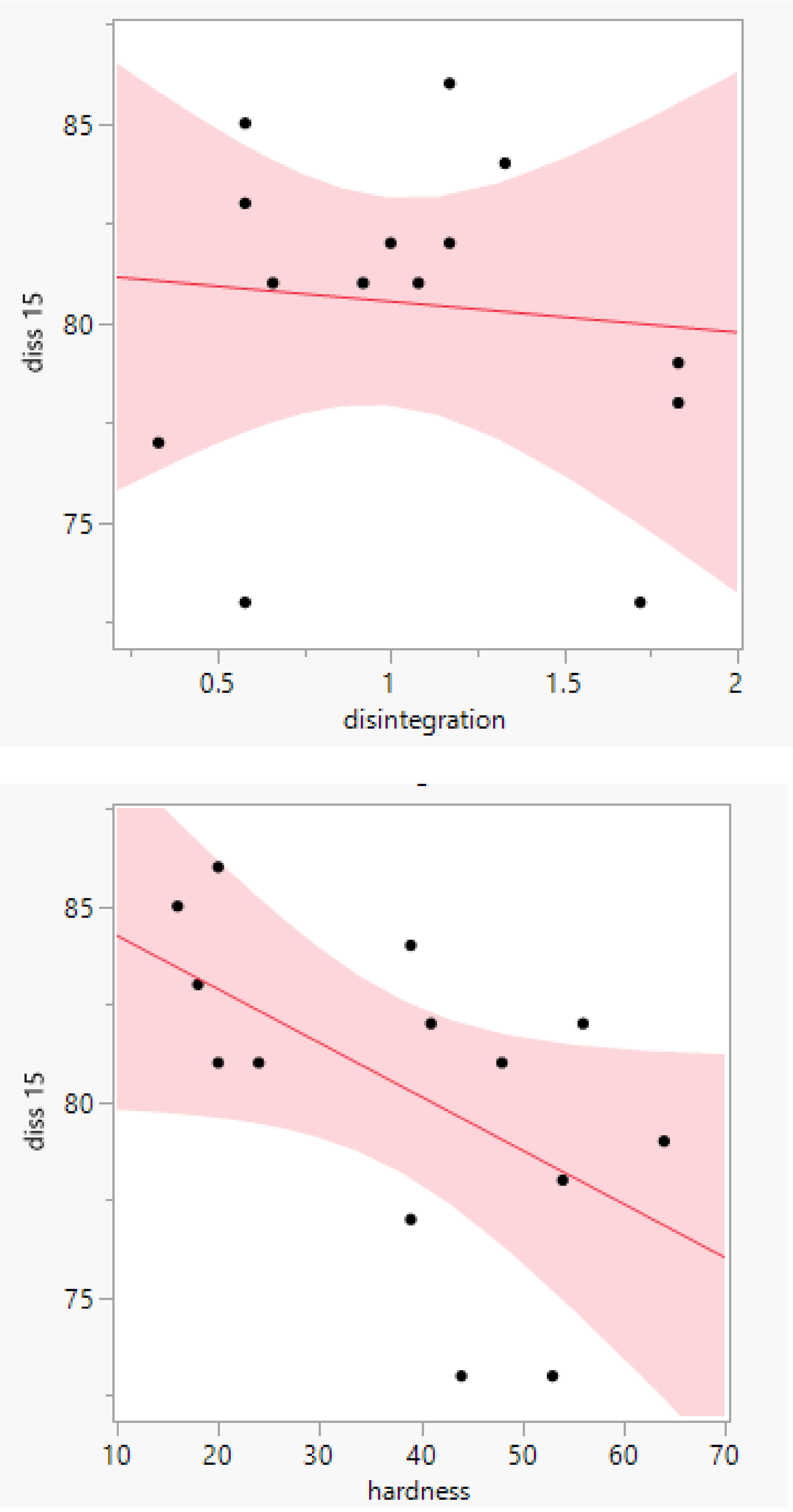


Figure 6. Scatterplot matrix revealed nature of relationships between tablet IPC tests and dissolution

Fit definitive screening

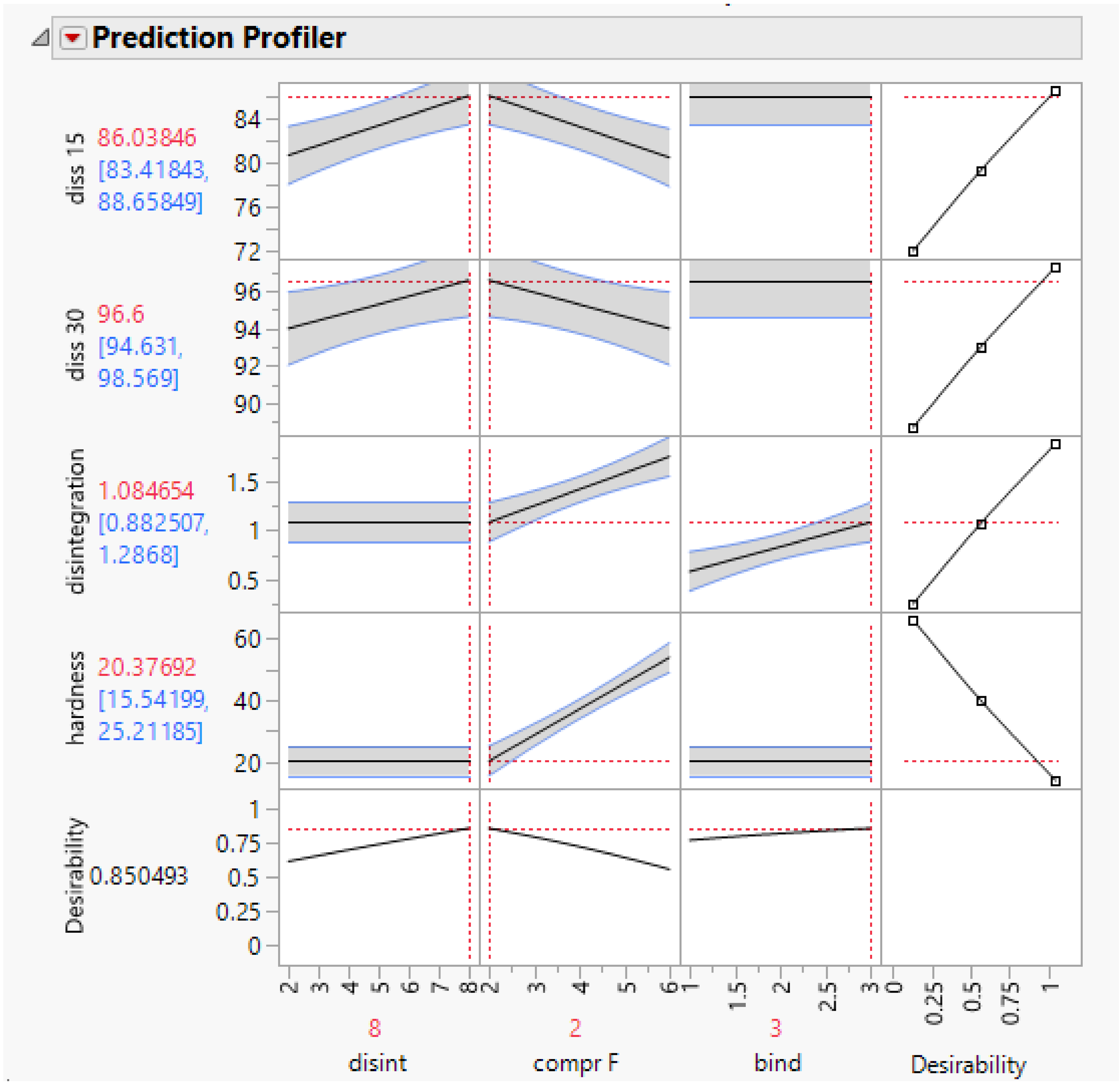


Figure 7. Prediction profiler enables simultaneous optimization for all responses by maximization of desirability

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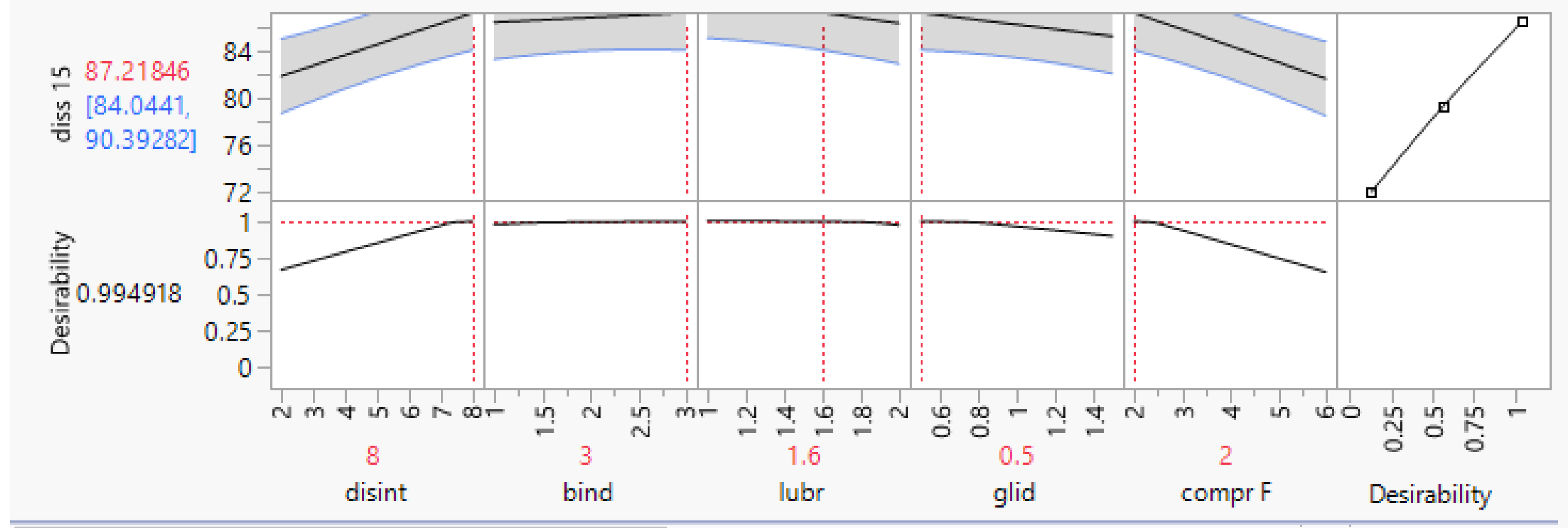
Model Screening Graphs

Model screening
Dissolution 15 min

Parameter Estimates Fit Least squares

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	80.538462	0.536889	150.01	<.0001*
disint(2,8)	2.7	0.612148	4.41	0.0031*
bind(1,3)	0.4	0.612148	0.65	0.5343
lubr(1,2)	-1.1	0.612148	-1.80	0.1154
glid(0.5,1.5)	-1	0.612148	-1.63	0.1464
compr F(2,6)	-2.8	0.612148	-4.57	0.0026*

Prediction Profiler Fit Least squares



Prediction Profiler Neural boosted

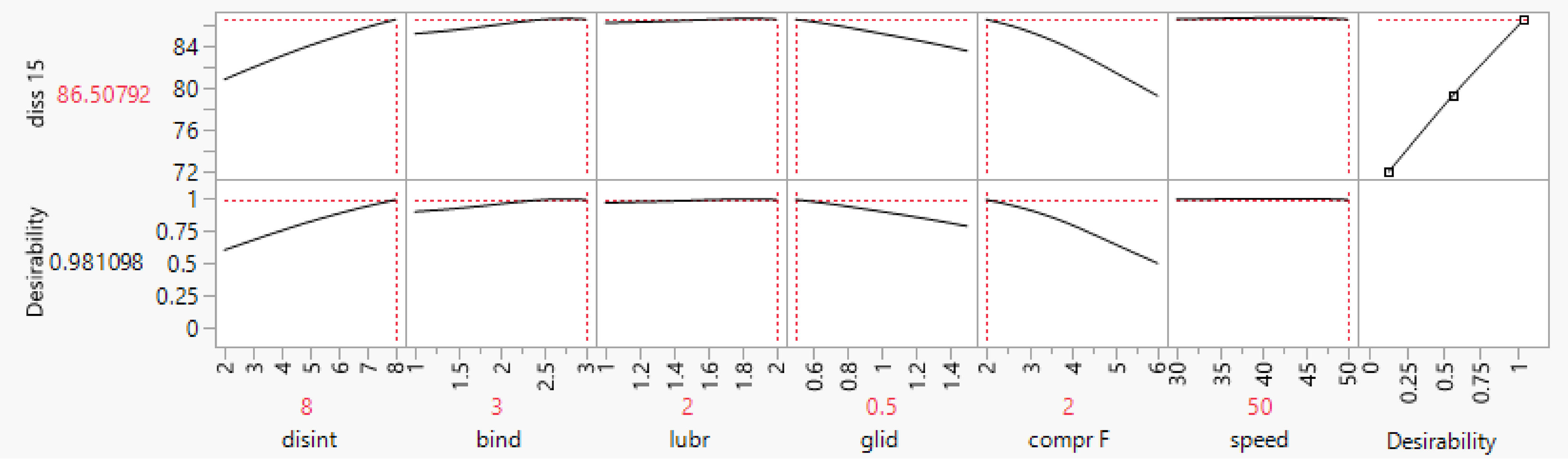


Figure 8. Fit Least squares optimal settings for dissolution 15, indicates that by increasing lubricant level above 1.6% decrease in dissolution is possible; Neural boosted predicts similar as DSD

Training Hardness

Method	Details	N	Sum Freq	RSquare	RASE
Fit Least Squares	2FI Quad	26	26.0000	0.9594	4.483
Fit Stepwise	2FI Quad	26	26.0000	0.9380	3.075
Neural Boosted		17	17.0000	0.9188	3.587
Support Vector Machines		26	26.0000	0.9130	3.641
Boosted Tree		27	27.0000	0.9125	3.669
Fit Least Squares		26	26.0000	0.8966	4.644
Generalized Regression Lasso		27	26.0000	0.8960	3.982
Fit Stepwise		26	26.0000	0.8585	4.644
Bootstrap Forest		27	27.0000	0.8397	4.967
Generalized Regression Lasso	2FI Quad	27	26.0000	0.8001	5.520
K Nearest Neighbors		27	27.0000	0.1304	11.568

Summary of Fit

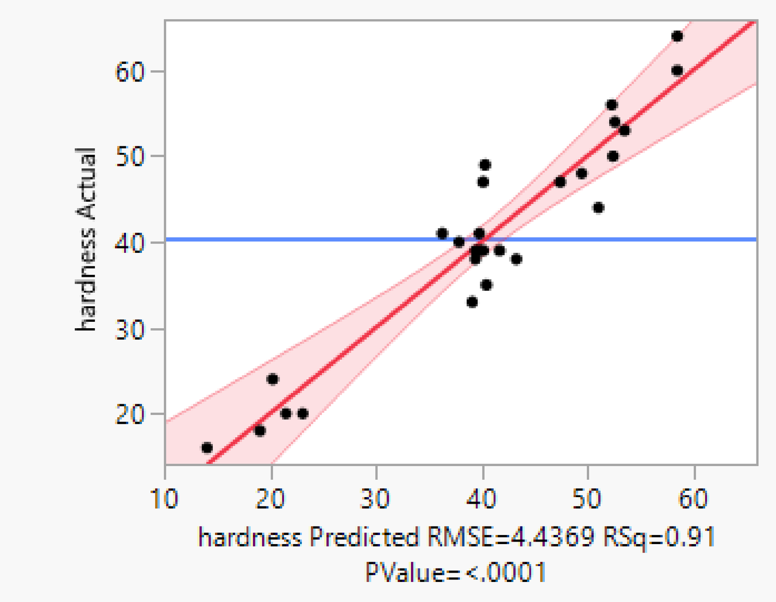
RSquare	0.905233
RSquare Adj	0.876803
Root Mean Square Error	4.436915
Mean of Response	40.44444
Observations (or Sum Wgts)	27

Model screening: Best model for hardness Fit least squares 2 reduced

Scaled Estimates Fit Least squares

Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	39.804101	1.237702	32.16	<.0001*
disint(2,8)	-1.631232	0.97345	-1.68	0.1094
bind(1,3)	2.2280759	0.973095	2.29	0.0330*
lubr(1,2)	-1.321924	0.973095	-1.36	0.1894
glid(0.5,1.5)	-0.35946	0.983549	-0.37	0.7186
compr F(2,6)	16.695128	1.243233	13.43	<.0001*
compr F*compr F	-3.508972	1.759573	-1.99	0.0599

Actual by Predicted Plot



hardness

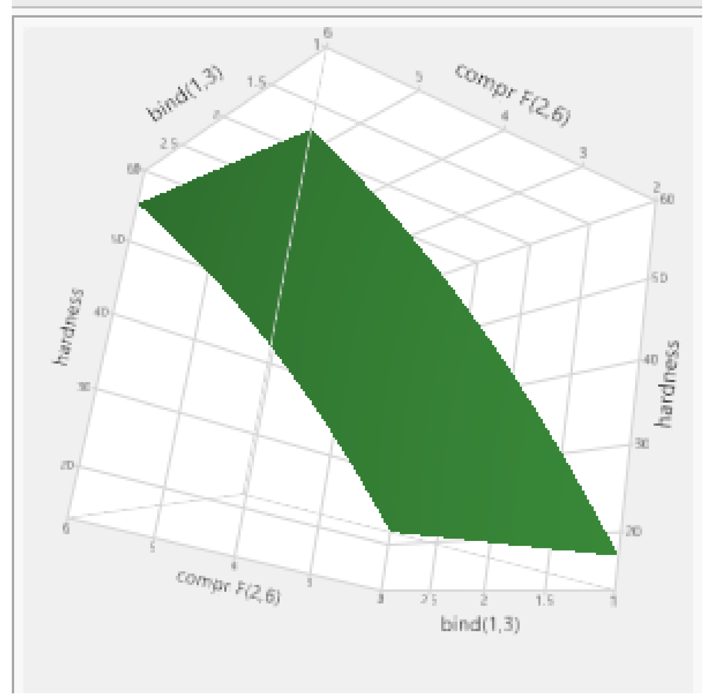
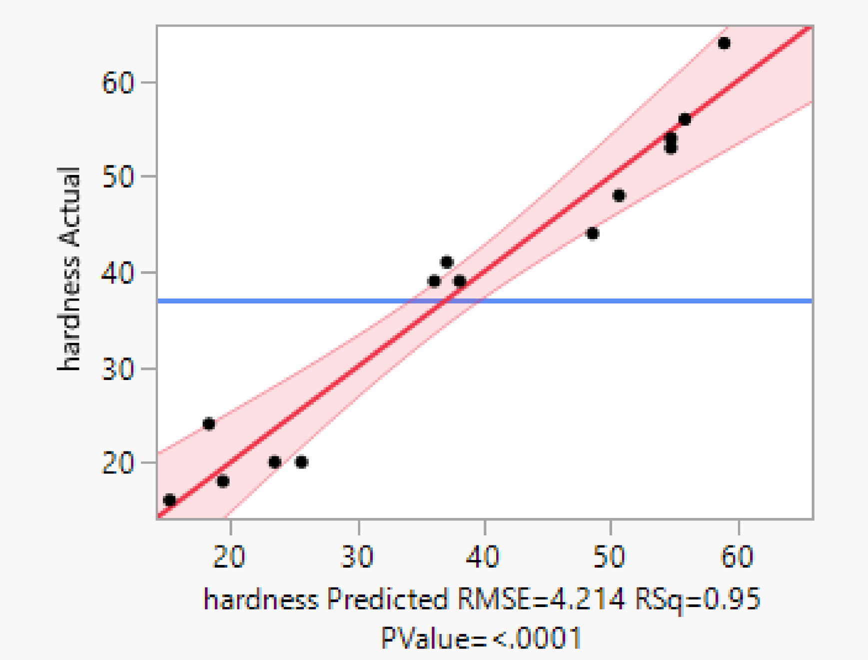


Figure 9. Best model for hardness Fit least squares is reduced, binder is significant factor (not visible in DSD fit), without negative impact on dissolution, could contribute to hardness and minimize risk for capping and friability, effect of compression force is slightly quadratic

Training Hardness

Method	N	Sum Freq	RSquare	RASE
Neural Boosted	8	8.0000	0.9999	0.158
Fit Least Squares	13	13.0000	0.9571	4.698
Fit Stepwise	13	13.0000	0.9483	3.506
Support Vector Machines	13	13.0000	0.9294	4.097
Generalized Regression Lasso	14	13.0000	0.8702	5.554
Boosted Tree	13	13.0000	0.8464	6.042
Bootstrap Forest	13	13.0000	0.8040	6.825
K Nearest Neighbors	13	13.0000	0.1383	14.309

Actual by Predicted Plot



Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	37.076923	1.168764	31.72	<.0001*
bind(1,3)	3.1	1.332596	2.33	0.0450*
lubr(1,2)	-2.1	1.332596	-1.58	0.1495
compr F(2,6)	16.7	1.332596	12.53	<.0001*

Scaled Estimates Fit Least squares

Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	37.076923	1.168764	31.72	<.0001*
bind(1,3)	3.1	1.332596	2.33	0.0450*
lubr(1,2)	-2.1	1.332596	-1.58	0.1495
compr F(2,6)	16.7	1.332596	12.53	<.0001*

Figure 10. Even with smaller dataset, best model (reduced) for hardness Fit least squares, binder is significant factor (not visible in DSD fit), there is indication here too, that lubricant might have slightly negative effect