Scientists dreamt of it, OMARS made it

Unveil the power of small data

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Summary

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Challenge: combine formulation & process factors for tabletting

3 formulation factors

6 process factors

Combination of quantitative and qualitative factors

50 responses to analyze

12 responses for optimization

Screening + optimization single design

Aim: reduce timing (<= 27 runs)

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Input parameters (factors)

9 factors

Stage	Factor	Coded name	Range	Levels	Category
Formulation	Croscarmellose repartition (%)	X1	2.5-5	3	Quant
	PVP (%)	X4	3-7	3	Quant
	MCC/mannitol ratio (%)	X5	15.5-35.5	3	Quant
Process	Total mixing time (min) (Granulation)	X2	2-6	3	Quant
	Water (%) (Granulation)	X3	18.2-38.5	3	Quant
	Impeller speed (rpm) (Granulation)	X7	350-600	2	Quant
	Calibration speed (rpm) (Sizing)	X6	1050-1550	3	Quant
	Grid size (µm) (Sizing)	X9	1016-1575	2	Quant
	Mixing method (Final mixing+lubrification)	X8	1 step/2 steps	2	Qual

50 Responses, focus on 12

Response	Coded name	Sense	Bound
Carr index 0 tap	Y6	Minimize	<20
Flodex disc (mm)	Y8	Minimize	<10
PSD < 150 µm (%)	Y9	Target	20-50
Extenso slope 100mg (Mpa/kN)	Y11	Minimize	
Extenso asymptote 100mg (N)	Y12	Maximize	>120
Min desag (sec) 2,2 Mpa	Y26	Maximize	>120
Mean disso 15 min 2,2 MPa (%)	Y28	Target	77
RSD disso 15 min (%) 2,2 Mpa	Y29	Minimize	
Mean disso 20 min 2,2 MPa (%)	Y30	Target	82
RSD disso 20 min (%) 2,2 Mpa	Y31	Minimize	
Mean disso 30 min (%) 2,2 Mpa	Y32	Target	90
RSD disso 30 min 2,2 MPa (%)	Y33	Minimize	

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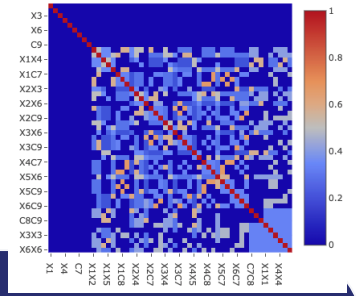
PVP: Polyvinylpyrrolidone , MCC: Microcrystalline cellulose, PSD: Particle Size Distribution, RSD: Relative Standard Deviation, Quant: Quantitative, Qual: Qualitative

Choosing the experimental design



Traditional approach

Formulation experiment ~ 15-17 runs
+
Process experiment ~ 30 runs

Total of 45-47 runs

versus

OMARS approach

Formulation & process experiment at the same time

Total of 24 runs

Extra benefits of using OMARS designs:

1. Orthogonality properties (among main effects, and between main and second-order effects)
2. Prioritization on most important effects indicated by the scientists (main and interaction effects)
3. Low correlations (between most important effects)
4. Sufficient power (for most important effects)
5. Good projections properties (fit a large variety of effects combinations, despite being super-saturated)

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The challenges in data modeling

51 potential effects in a second-order effects model → 2^{51} = 2.25 10^{15} possible models!

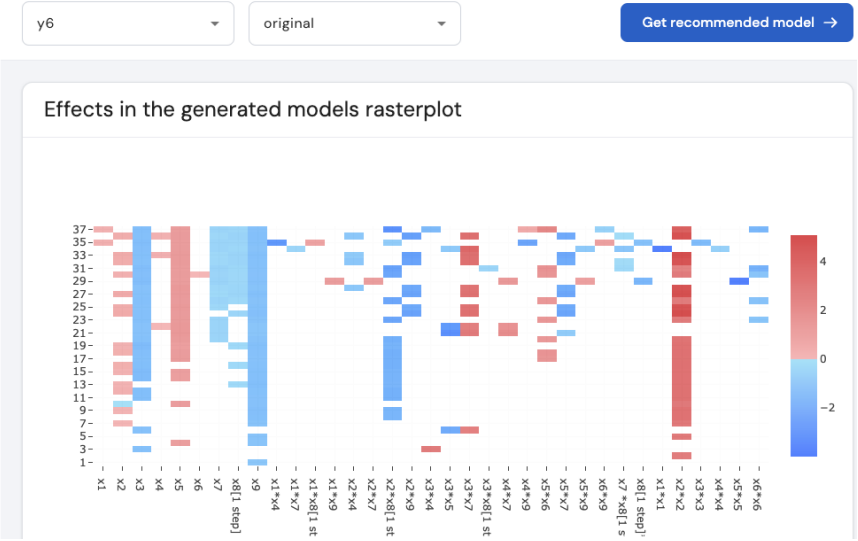
Two independent analyses:

- Using JMP and AICc-based Forward / Backward selection
- Using EFFEX and all-subsets model selection and model filtering

Methods identified same significant main effects and different second-order effects

All subset selection identifies the best models and reveals the most influential effects

Modeling was done together with scientists



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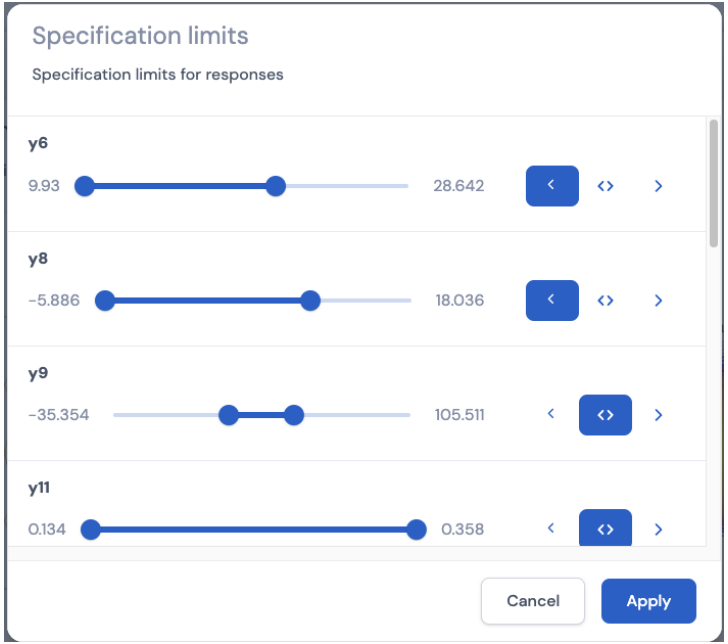
Multi-response optimization



12 different responses with different optimization senses: minimization, maximization, and in interval

Two approaches:

- Using JMP and desirability
- Using EFFEX and probability of success

Objective: explore the region you want in the knowledge space to find a design space, and additionally compare different sets of operating conditions

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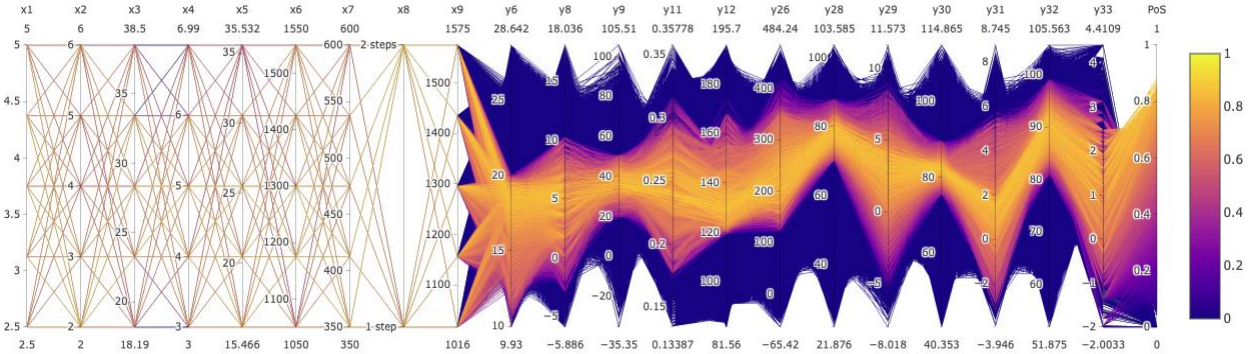
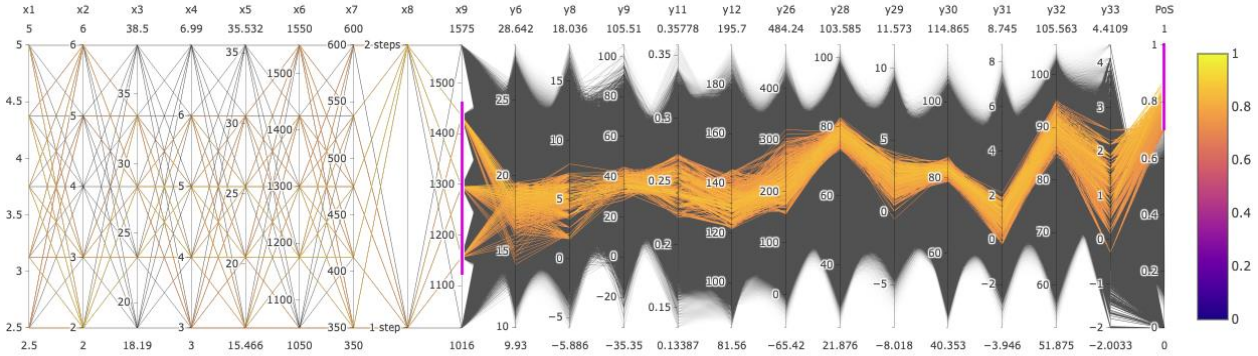
Multi-response optimization

Design space determination using a graphical interface

Results from JMP/EFFEX were similar





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Conclusions

Collaboration between scientists and statisticians is crucial to :

- Select the design in accordance with project's thoughtful risk endorsement,
- Then to identify meaningful models and determine the final optimal settings

Business impacts were:

- API saving: 9,5kg
- Project time saving: 4 months → Answered to project acceleration target

Optimization of formulation and process simultaneously → increased agility and flexibility of Drug Product development

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Thank you!

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