Exploiting Statistical Experiment Design to Accelerate Pharmaceutical R&D

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Maximizing this educational opportunity

Welcome everyone! To make the most from this webinar:

- Attendees on mute
- Chat addressed afterward
- Send further questions to mark@statease.com

PS: Presentation posted to www.statease.com/webinars/

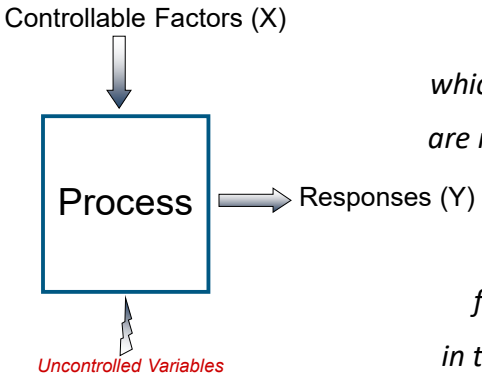
Please press the raise-hand button if you are with me.

The WIIFM (What's in it for me)

- Learn how multicomponent and multifactor design-of-experiment (DOE) tools empower experimenters to quickly converge on the quality by design (QbD) "sweet" spot—ingredient and factor settings that meet all specifications at minimal cost.
- Engineers, chemists and scientists working on drug development will do well by attending this briefing on DOEs for process screening and characterization, response surface methods (RSM) for process optimization (e.g., manufacturing of generics), and mixture design for optimal formulation (e.g., active pharmaceutical ingredients-APIs).

Whether you are new or experienced at doing DOE,
this talk is for you and your organization's bottom line!

DOE Works on Any Process



DOE is:

"A series of tests, in which purposeful changes are made to input factors, to identify causes for significant changes in the output responses."

Multi-Factorial (VS OFAT)
(life from accelerated test)

Relative efficiency = 16/8

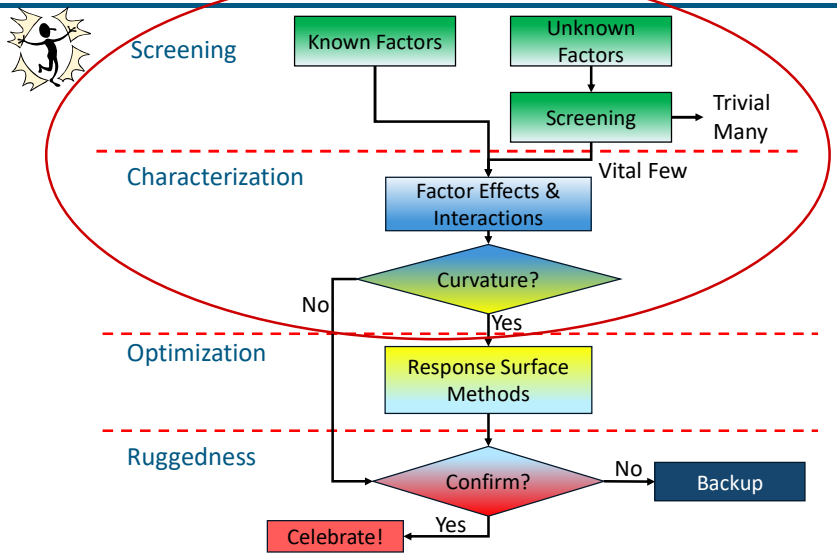
2 to 1!

"DOE led to about 40% experimental time saving."
- "Development cycle time reduction using design of experiments", *Fuel*, 9/15/22

"Design of Experiments Approach Halves Development Time."
-- *Chemical Processing*, 8/3/18

"Industry benchmarks DOE accompanied by 50-70% savings in time and cost."
- *AIChE SmartBrief*, 4/16/24

Strategy of Experimentation



Screening/Characterization

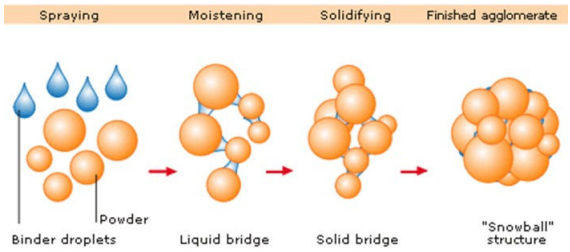
Purpose: Quickly sift through a large number of potential factors to discard the trivial many. Then follow-up with an experiment that focuses on the vital few.

Tool: Two-level factorial designs:

1. Fractional for resolving main effects in minimal runs.
2. Full (or less fractional) to resolve two-factor interactions.

Characterization Case Study
Wet Granulation

Wet granulation uses a liquid binder to lightly agglomerate the powder mixture. The amount of liquid and processing conditions must be carefully controlled to prevent the granules from becoming too hard or too soft (friable).



Wet Granulation Characterization
Factors and Levels

Factors: 7 (6 to 50) ◉ Horizontal ○ Vertical

	Name	Units	Type	Low	High
A [Numeric]	Binder solution	litre	Numeric	2.75	3.25
B [Numeric]	Granulation time	min	Numeric	3	6
C [Numeric]	Residual humidity	%	Numeric	1	3
D [Numeric]	Sieve calibre	mm	Numeric	1	1.2
E [Numeric]	Lubrification time	min	Numeric	2	5
F [Numeric]	Compression	kN	Numeric	7	10
G [Numeric]	Press speed	RPM	Numeric	30	50

Standard Two-Level Design Builder
Choices for 7-Factor Characterization

Even with half fraction, 64 runs required: Too many!

Factors

Runs

Runs \ Factors	2	3	4	5	6	7	8	9
4	2^{2}	2^{3-1}_{III}						
8		2^{3}	2^{4-1}_{IV}	2^{5-2}_{III}	2^{6-3}_{III}	2^{7-4}_{III}		
16			2^{4}	2^{5-1}_{V}	2^{6-2}_{IV}	2^{7-3}_{IV}	2^{8-4}_{IV}	2^{9-5}_{III}
32				2^{5}	2^{6-1}_{VI}	2^{7-2}_{IV}	2^{8-3}_{IV}	2^{9-4}_{IV}
64					2^{6}	2^{7-1}_{VII}	2^{8-2}_{V}	2^{9-3}_{IV}
128						2^{7}	2^{8-1}_{VIII}	2^{9-2}_{VI}
256							2^{8}	2^{9-1}_{IX}
512								2^{9}

No worries—Stat-Ease software offers a modern alternative needing only 30 runs.

Minimum-Run Designs (up to 50 factors)
Considerable Savings Over Standard Fractions

Characterization		
Factors	Std Res V	MR5*
6	32	22
7	64	30
8	64	38
9	128	46
10	128	56
11	128	68
12	256	80
13	256	92
14	256	106

Screening		
Factors	Std Res IV	MR4**
9	32	18
10	32	20
11	32	22
12	32	24
13	32	26
14	32	28
15	32	24
16	32	26
17	64	28

* Oehlert & Whitcomb, "Small, Efficient, Equireplicated Resolution V Fractions of 2^k designs …", Fall Technical Conference, 2002: www.statease.com/pubs/small5.pdf

** Anderson & Whitcomb, "Screening Process Factors In the Presence of Interactions," Annual Quality Congress, American Society of Quality, Toronto, 2004: www.statease.com/pubs/aqc2004.pdf

Demonstration
Process Characterization

Stat-Ease software makes it easy it to set up this experiment design, model the results, analyze them statistically and find the most desirable settings to maximize hardness and minimize friability.

Wet granulation
max hardness, min friability

Stat-Ease Screening/Characterization Success Story for API Process Development

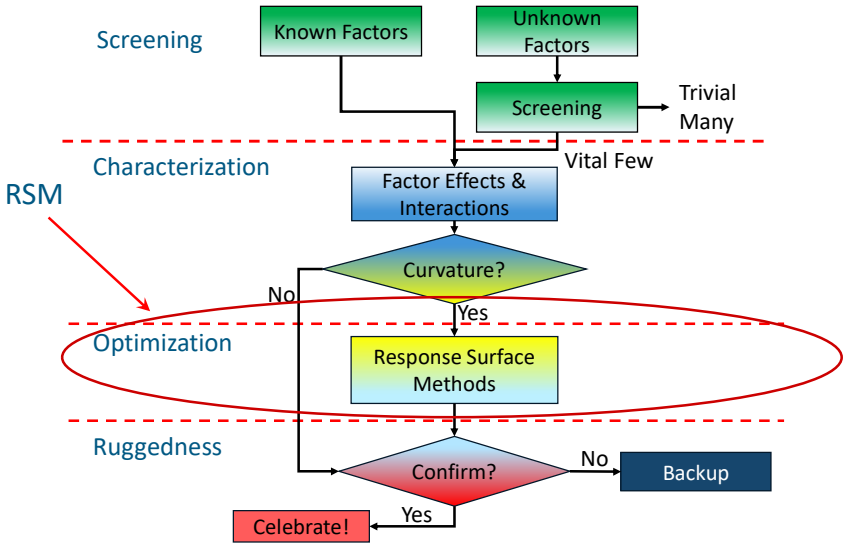
- "The Role of Fractional Factorial and D-Optimal Designs in the Development of QbD Pharmaceutical Production Processes"* presented by Dr. Daniel Tray, API Chemistry, GlaxoSmithKline, at the 7th Euro DOE Conference, Paris, 2018, features a case study applying a resolution IV, two-level fractional factorial design, 5 factors in 20 runs, 2 blocks, with 2 center points per block.

"We use DoE in early phase development to rapidly screen reagents and solvents in a structured manner."

Build this res IV GSK design

*Posted at www.statease.com/events/doe-user-meetings/7th-european-doe-user-meeting/

Strategy of Experimentation



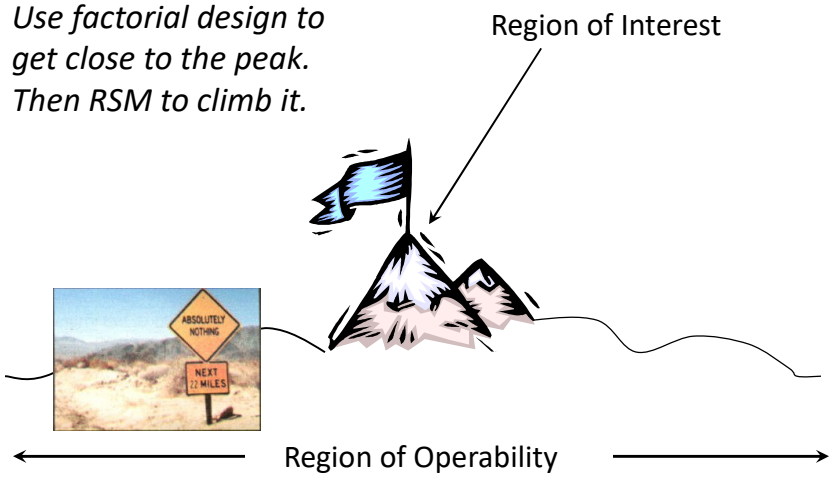
Response Surface Methods (RSM)
When to Apply It (Strategy of Experimentation)

1. Fractional factorials for screening such as MR4
2. High-resolution fractional, such as MR5, or full factorial for characterization of interactions *(add center points at this stage to test for curvature)*
3. Response surface methods (RSM) for optimization

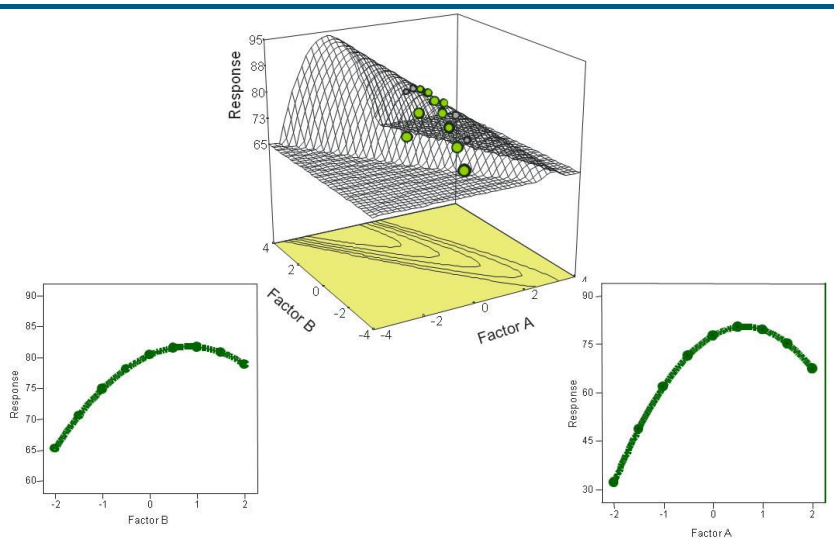
Contour maps (2D) and 3D surfaces guide you to the peak.

RSM: When to Apply It

Use factorial design to get close to the peak. Then RSM to climb it.



RSM vs OFAT



RSM: Process Flowchart

Subject Matter Knowledge
(Plus, Factorial Screening)

↓

Vital Few Factors (x's)

↓

Process → Measured Response(s) (y(s))

↓

Fitting*

↓

Polynomial Model

↓

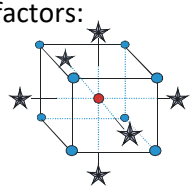
Response Surface

"All models are wrong, but some are useful." - George Box

RSM Case Study *(1/3)*
Fermentation Optimization

A bioengineer ran a central composite design (CCD)—a tried-and-true RSM—to maximize output of an antibiotic from fermentation of *Streptomyces coelicolor* by systematically varying two factors:

A. Perfluorodecalin (PFC) – an oxygen carrier
B. Glucose (Glc)



The responses were:

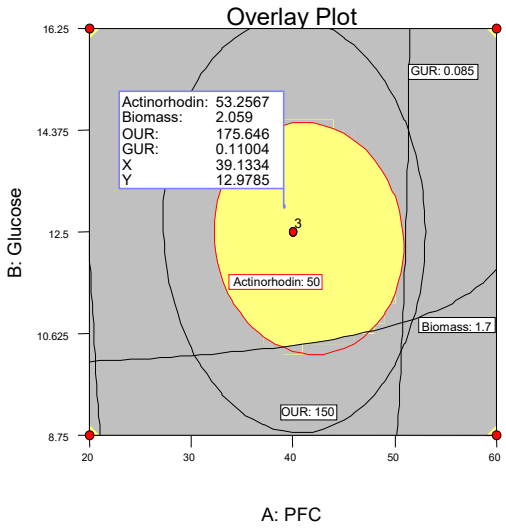
1. Actinorhodin (ACT) – indicator of antibiotic
2. Biomass (Bio)
3. Oxygen uptake rate (OUR)
4. Glucose uptake rate (GUR)

*("Response surface methodological approach for inclusion of perfluorocarbon in actinorhodin fermentation medium," *Process Biochemistry* 38 (2002) 667-673.)

RSM Case Study *(2/3)*
CCD Template and Fermentation Results

Std	Type	A: PFC %, v/v	B: Glc g/l	ACT mg/l	Bio g/l	OUR mgO_2/l h	GUR g/l h
1	Factorial	20.00	8.75	18	1.346	86	0.082
2	Factorial	60.00	8.75	30	1.450	84	0.031
3	Factorial	20.00	16.25	19	2.900	96	0.085
4	Factorial	60.00	16.25	24	1.780	82	0.032
5	Axial	11.72	12.50	19	2.308	43	0.048
6	Axial	68.28	12.50	22	1.600	59	0.012
7	Axial	40.00	7.20	32	1.100	125	0.110
8	Axial	40.00	17.80	32	2.300	128	0.120
9	Center	40.00	12.50	54	1.985	176	0.108
10	Center	40.00	12.50	52	1.889	168	0.109
11	Center	40.00	12.50	55	2.100	184	0.110

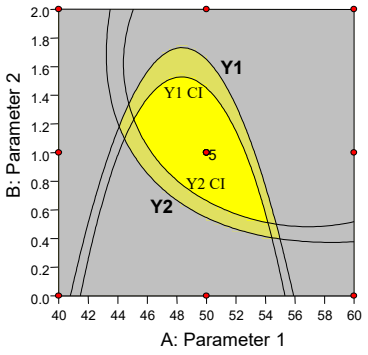
RSM Case Study *(3/3)*
The Sweet Spot! (Add CI for safer QbD)



Antibiotic RSM
Rebuild, re-open & analyze
Optimize and overlay
Add CI & set flag

RSM Experiment to Establish
Quality by Design (QbD)

- Graphical optimization allows users to show a conservative operating window framed within confidence, prediction or tolerance intervals. For example, this overlay plot pushes in from the boundaries with the confidence interval ("CI"), which is appropriate for functional process development aimed at improving the average performance.



RSM QbD (do not demo—time too short)
(an FCD for k=2, thus equivalent to full three level)

Mixture Design*

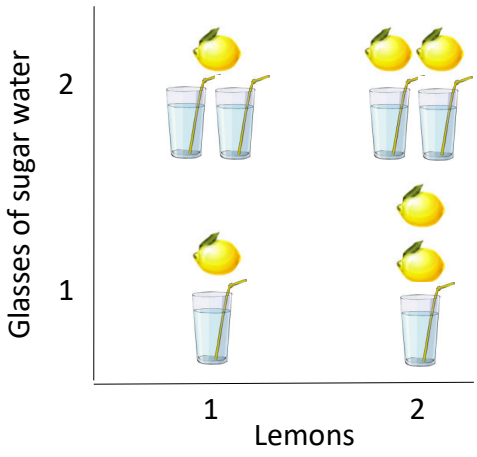
Considerations:

- Factors are ingredients of a mixture.
- The response is a function of proportions, not amounts.
- Given these two conditions, fixing the total (an equality constraint) facilitates mixture modeling as a function of component proportions.

Let's try forcing a factorial design onto a mixture.

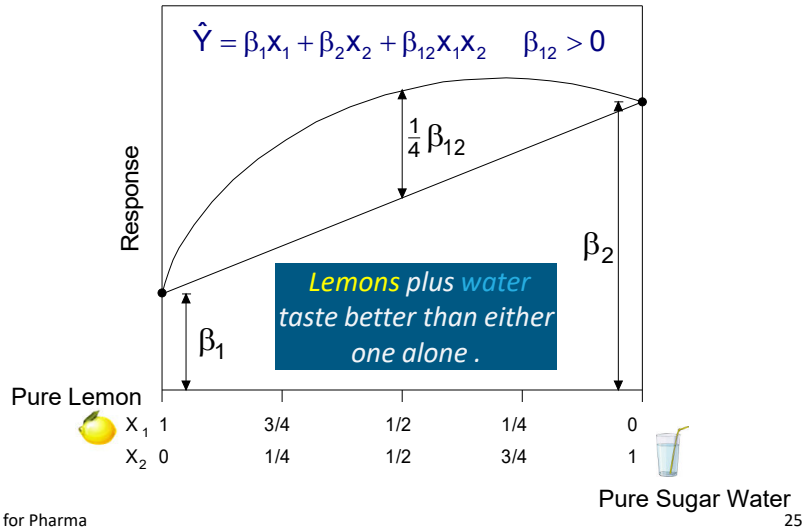
*(Pioneered by Henry Scheffé, U Cal., 1957)

Forcing (squeezing?) factorial design on a mixture: Lemonade

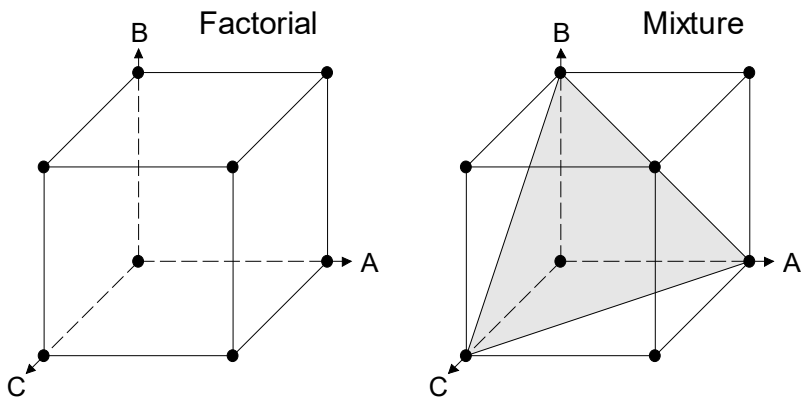


Mixture Design and Modeling (sweet!)

Two components: Quadratic (synergistic)

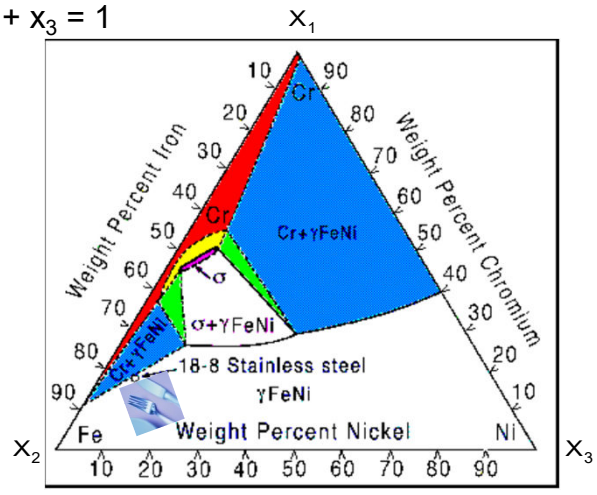


Three-Component Mixture

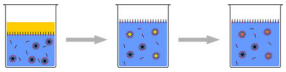


Ternary Diagram for Mixture Composition
(for example, stainless steel flatware)

$x_1 + x_2 + x_3 = 1$



Mixture Case Study



For a pharma prep, formulators* varied three surfactants in an aqueous dispersion of polymeric nanospheres:

A. P188 (Poloxamer 188 NF)
B. PE40MS (Polyoxyethylene 40 monostearate NF)
C. PSFAE (Polyoxyethylene sorbitan fatty acid ester NF)

They measured the film-forming properties:

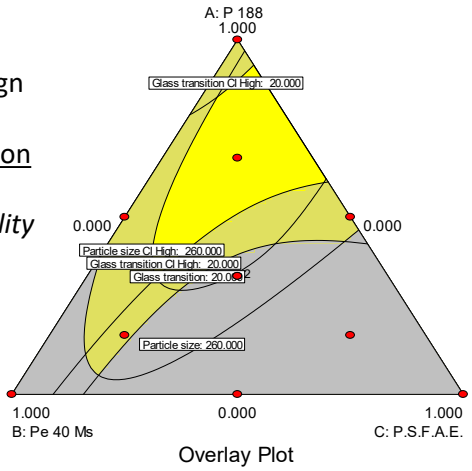
1. Particle size, nm *(< 250 nm desired)*
2. Glass transition, deg C *(< 17.5°)*

Pharma prep
Rebuild, analyze, optimize
& show sweet spot with CI's

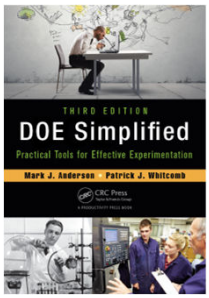
*(Frisbee, S.E., McGinity, J.W., "Influence of Nonionic Surfactants on the Physical and Chemical Properties of a Biodegradable Pseudolatex," *European Journal of Pharmaceutics and Biopharmaceutics*, V 40, No. 6 (Dec 1994).)

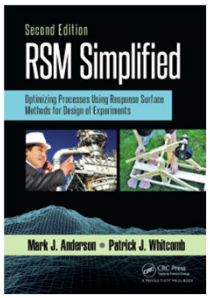
Framing the Sweet Spot for QbD

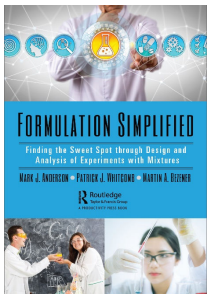
- Graphical optimization now frames the functional "design space" where all modeled responses for a unit operation fall within confidence intervals: *Ideal tool for quality by design (QbD).*



References
*DOE/RSM/Formulation Simplified Series**







**Anderson, et al, Taylor & Francis, Productivity Press, New York, NY.*

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Do you agree?

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by Deploying DOE for Pharma.

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Stay on for some chat if you like.