Putting DOE to Good Use for Developing Active Pharmaceutical Ingredients (APIs)

There are many attendees today! *To avoid disrupting the Voice over Internet Protocol (VoIP) system, I will mute all. Please use the Questions feature on GotoWebinar. Feel free to email questions to stathelp@statease.com, which we will answer off-line.*
-- Martin

*Presentation is posted at www.statease.com/webinar.html

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Stat-Ease, Inc.

- Provider of DOE software, training & consulting
- Founded in 1982
- Employs over a dozen professionals plus a worldwide network of resellers
- Mission is "Statistics Made Easy"
- Honored multiple times by American Society of Quality (ASQ) Chemical and Process Industries Division with Shewell Award recognizing excellence in presentation, scientific quality and applicability
- Develop and publish the Design-Expert® software. **Recently released Design-Expert version 11.**

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Today's Webinar

The purpose of today's webinar is:

- to provide a broad overview of the **major types** of DOE.
- show relevant DOE pharma examples (mostly API).
- demonstrate **useful** functionality of **Design-Expert** software.
- provide resources for those interested in learning more.

Webinar Outline

- The Basics
- Factorial Designs
- Response Surface Designs
- Mixture Designs
- Other Designs, Practical Tips & Tricks, and Conclusions
- Resources and More Information

Webinar Outline

- **The Basics**
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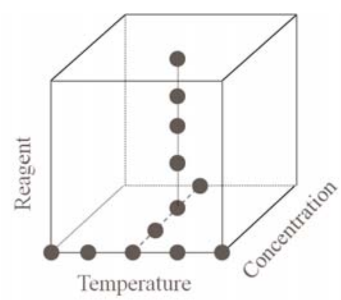
The Basics

- One Factor at a Time (OFAT) experimentation, trying to maximize yield varying three factors:

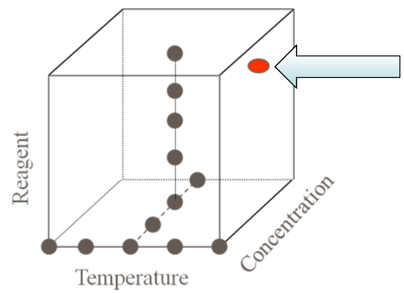


12 runs

(Graphics courtesy of the Innovatives Medicine Initiative.)

The Basics

- OFAT experimentation, trying to maximize yield varying three factors.



If the maximum yield actually occurs here, we will <u>completely</u> MISS IT!

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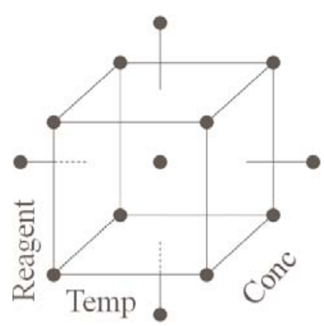
The Basics

- Design of Experiments, trying to maximize yield varying three factors:



15 runs

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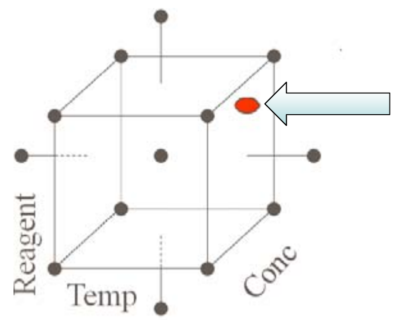
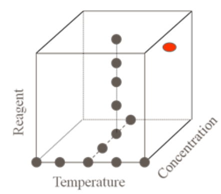
The Basics

- Design of Experiments, trying to maximize yield varying three factors.

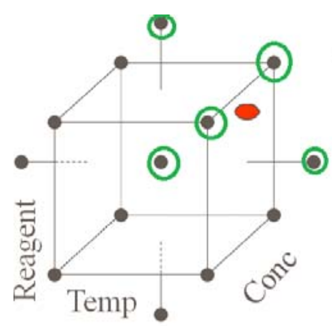


If the maximum yield actually occurs here, can we detect it?



The Basics

- Design of Experiments, trying to maximize yield varying three factors:



We can build a statistical model that uses the green points to **interpolate** the yield at points we didn't run.

If the data we collect is good, we should be able to get pretty close to the maximum yield when we do numerical optimization.

Summary

- Benefits of a proper DOE include:
  - Thorough coverage of the DOE space
  - Ability to detect factor **interactions** and non-linear behavior
  - Better understanding of the relationship between the factors and the responses
  - More **accurate** (and better) optimization results
  - **More** information with **fewer** runs
- DOE may seem intimidating and complicated, but software (such as Design-Expert software) can make it **easy!**

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Factorial Designs

- Very simple design
  - **k** factors are varied
  - Each factor can take either a low (-) or high (+) value
- **Goal of Factorial DOE**: statistically determine which of the factors impact the response in a non-trivial way.
- Factors can be varied simultaneously (vs OFAT).

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Factorial DOE Example

- Researchers were trying to determine which factors affected the yield of a chemical reaction. The varied the following factors:

Factor	Units	Low Level (−)	High Level (+)
rxn time	minutes	80	100
Temperature	deg C	140	150
addition rate	ml/min	4	6

- Yield was measured in grams. Ideally, they would like to increase yield by 3 grams.
- A 2^3 full factorial design was used.

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Factorial DOE Example

- The unrandomized design w/responses looks like:

	Factor A	Factor B	Factor C	Response
Std order	rxn time min	temperature deg C	addition rate ml/min	yield grams
1	80	140	4	76.3
2	100	140	4	81.6
3	80	150	4	86.3
4	100	150	4	75.6
5	80	140	6	79.4
6	100	140	6	81.8
7	80	150	6	89.1
8	100	150	6	79.3

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Factorial DOE Example

- Results

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	135.56	3	45.19	11.59	0.0192	significant
A-rxn time	20.48	1	20.48	5.25	0.0836	
B-temperature	15.68	1	15.68	4.02	0.1154	
AB	99.40	1	99.40	25.50	0.0072	
Residual	15.59	4	3.90			
Cor Total	151.15	7				

- Reaction time and temperature on their own don't impact the yield, but they strongly **interact** with one another.
- Addition rate does not appear to meaningfully impact the yield.

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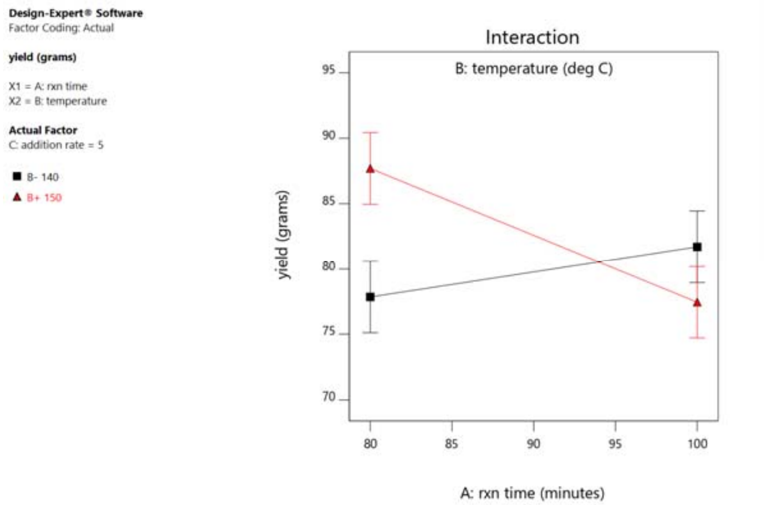
Factorial DOE Example



Factorial Design Tips & Tricks

- Choose the low and high level of each factor to target a change you are interested in detecting. A range that is too narrow or too wide likely result in disappointment.
- Can add **center points** to detect curvature in the center of the design space.
- Choose fractions of full factorials designs to reduce the number of runs. In particular, check out Minimum Run Screening (MR4) and Minimum Run Characterization (MR5) designs in the Design-Expert software.
- If you have too many factors of interest, you can run a **screening experiment** first, and then run a small follow up experiment later with the (hopefully) small number of factors that survived screening.

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Response Surface Designs (RSM)

- More involved than factorial designs
  - **k** factors are varied
  - Each factor has a low (-1) and high (+1) of interest, but can take values between (or even slightly outside) the low and high.
- **Goal of RSM DOE**: build a statistical model that approximates the relationship between the factors and response(s). Use this model to optimize the process.

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RSM Example

Murat Elibol reports on the use of RSM to <u>**maximize**</u> antibiotic production by *Streptomyces coelicolor*. He performed a central composite design on two factors:

A. Perfluorodecalin (PFC) (20 - 60% v/v)
B. Glucose (8.75 – 16.25 g/l)

The **four** responses were:

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

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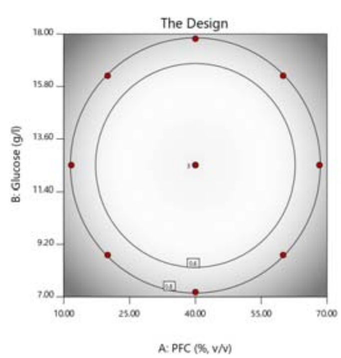
RSM Example

The central composite design looks like:

Run	Factor 1 A:PFC %, v/v	Factor 2 B:Glucose g/l	Response 1 Actinorhodin mg/l	Response 2 Biomass g/l	Response 3 OUR mgO2/l h	Response 4 GUR g/l h
1	20.00	8.75	18	1.3	86	0.08
2	60.00	8.75	30	1.4	84	0.03
3	20.00	16.25	19	2.9	96	0.09
4	60.00	16.25	24	1.8	82	0.03
5	11.72	12.50	19	2.3	43	0.05
6	68.28	12.50	22	1.6	59	0.01
7	40.00	7.20	32	1.1	125	0.11
8	40.00	17.80	32	2.3	128	0.12
9	40.00	12.50	54	2.0	176	0.11
10	40.00	12.50	52	1.9	168	0.11
11	40.00	12.50	55	2.1	184	0.11



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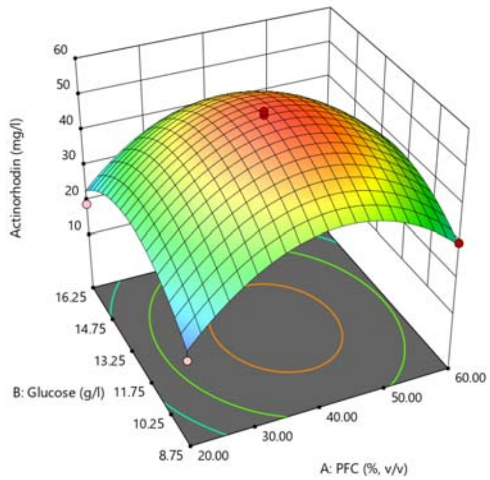
RSM Example

Where can we maximize antibiotic production?



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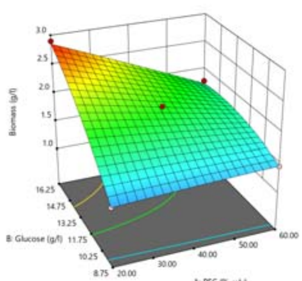
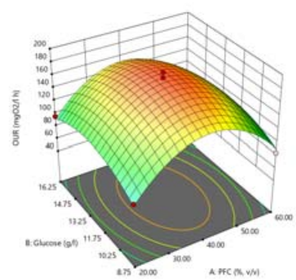
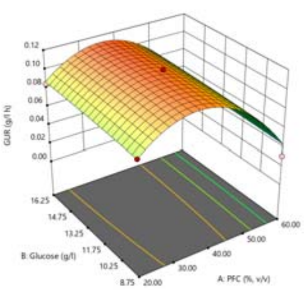
RSM Example







No other information was provided about the other three responses.

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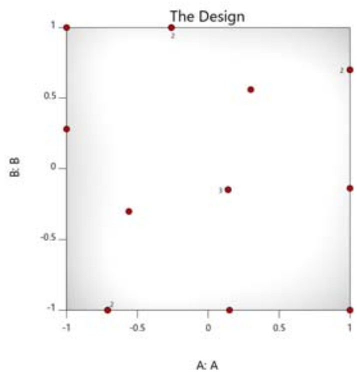
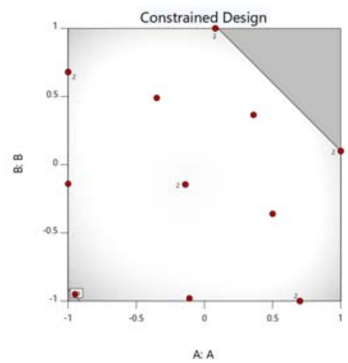
RSM Design Tips & Tricks

- Accurately defining the DOE space is critical. Avoid performing runs in regions where you know ahead of time “there will be no reaction”, “the response will be zero”, “the reactor will blow up”, etc.





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RSM Design Tips & Tricks

- Add replicates to enable pure error estimates and lack of fit testing.
- Familiarize yourself with Design-Expert’s Optimal RSM Design builder for non-standard problems.
- Consider **split-plot designs** if one of your factors is very difficult to change.
- Consider using **discrete factors** if your factor is numeric, but can only take a fixed amount of values (e.g. # of passes).

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Mixture Designs

- Designs focused on formulation
  - **k** components are varied
  - Each component has a lower or upper bound. All component levels will be at or between these bounds
  - Components **must sum** to a fixed number (e.g. 100 volume %)
- **Goal of Mixture DOE:** build a statistical model that approximates the relationship between the mixture components and response(s). Use this model to optimize the process.

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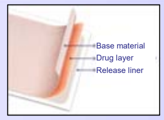
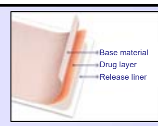
Mixture Example
Transdermal Drug Delivery



A transdermal patch is a medicated adhesive patch that is placed on the skin to **deliver** a specific dose of medication through the skin and into the bloodstream.

One of the main types of transdermal patch is the “single-layer drug-in-adhesive”. **The adhesive layer of this system also contains the drug**. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Mixture Example



Here are the four components (and constraints) for our TDD patch:

50% ≤ High MW PIB* ≤ 70%

10% ≤ Low MW PIB* ≤ 20%

4% ≤ crosslinking **Monomer** ≤ **7%**

1% ≤ permeation **Enhancer** ≤ **2%**

20% API

Total = 100 wt %

API is held constant

** PIB: polyisobutylene*

Mixture Example

Responses:

- t(50%) – the time measured in hours for 50% API release.
- shape – a factor describing the release profile:
  shape = $(t_{75\%} - t_{25\%})/t_{50\%}$
  shape = 1.0 *zero order; constant release*
  shape = 1.5 *first order; proportional release*
- Crystal – Stability assessment, low crystal growth (measure in %) demonstrates stability.
- Tack – the target for tack is 0.43 N/mm^2.

Mixture Example

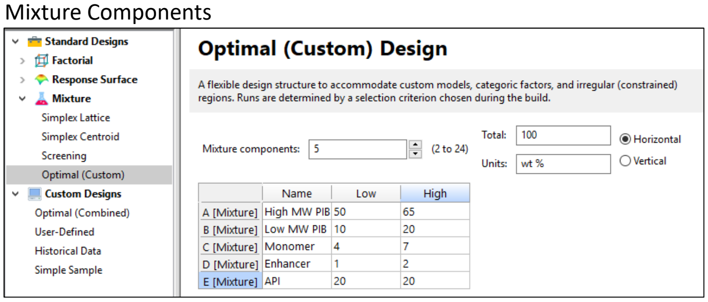
Optimization Goals:

Response	Goal		LL	UL
t(50%)	target →	8	6	10
shape	minimize		1	1.5
Crystal growth	minimize		0	10
Tack	target →	0.45	0.35	0.55

Mixture Example

Stat-Ease statistics made easy

Mixture Components



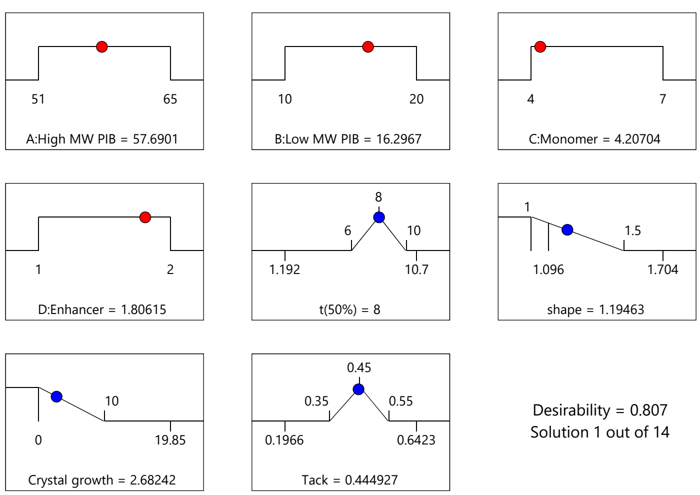
Design Specification

Responses

Name	Units
t(50%)	h
shape	factor
Crystal growth	%
Tack	N/mm^2

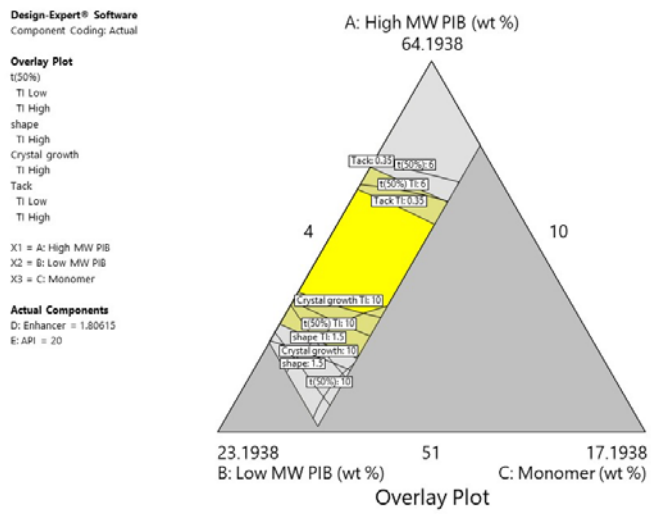
Mixture Example

Stat-Ease statistics made easy



Desirability = 0.807
Solution 1 out of 14

Mixture Example



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Mixture Design Tips & Tricks

- **Don't** try to re-work a mixture design into a factorial or RSM design. In most cases, the resulting experimental design and subsequent analysis will be inferior to that of a mixture design.
- Most mixture designs will need to be built as computer-generated optimal designs – canned, off-the-shelf designs are very limited.
- Mixture designs generally have better properties if the component ranges (high – low) are *roughly* the same size.
- Include some replicated blends if possible. These will enable estimating the pure error and give a lack of fit test.
- Free Stat-Ease webinar on Mixture DOE: https://www.youtube.com/watch?v=MP3k0VBcK7I

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Other Designs

- Combined mixture-process designs
  - **Example:** coating formulation + amount of coating applied to a tablet. Goal is to achieve a target dissolution profile.
- Split-plot designs
  - Designs for hard-to-change factors
- Space-filling design
  - Spread runs out as far as possible from one another to avoid any large gaps in the DOE space. Useful for exploratory studies.
- And many, many more!

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Practical Tips & Tricks

- **Plan**, plan, and plan some more
  - What factors/mixture components to vary?
  - What are the low and highs? These define the DOE space.
- **Evaluate** a design before performing the experiment
  - **Factorial** designs: check power
  - **RSM/Mixture** design: check fraction of design space (FDS)
  - Mentally scan the runs (high time + high temp + high pressure = … ?)
- **Randomize** as much as is feasible
- Ensure responses can be **accurately measured**
- **Be very careful** when extrapolating beyond the DOE space
- Consult with a DOE professional if needed. It is **much** cheaper to fix problems **before** the experiment is run.

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Bonus Practical Tips & Tricks

- **Block** the experiment on known sources of variability
  - **Examples:** operators, batches of raw materials
- Don't choose your problem to fit a particular design, choose your design to fit the problem (computer-generated optimal designs come in handy here)
- If you optimize your response, do a few confirmation runs to validate your experimental results. Make sure you can reproduce the results!
- Free webinar "Practical DOE – Tricks of the Trade" (advanced) https://www.youtube.com/watch?v=J725EHSe7Yw

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Design of Experiments for Pharma (DEPH)

- If you found this webinar useful, consider taking our two-day, computer-intensive workshop **Design of Experiments for Pharma**.
- Topics Covered:
  - Factorial, Response Surface, and Mixture Designs
  - Computer-generated optimal designs
  - Optimization and Quality by Design (QbD)
- Example Case Studies:
  - Tableting
  - Extended release coating
  - API development
  - Quality by Design

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How to Get Help

- Search publications posted at www.statease.com.
- In Stat-Ease software press for Screen Tips, view reports in annotated mode, look for context-sensitive Help (right-click) or search the main Help system.
- Explore the Stat-Ease Experiment Design Forum http://forum.statease.com (read only).
- E-mail stathelp@statease.com for answers from Stat-Ease's staff of statistical consultants.
- Search for the Stat-Ease YouTube Channel.

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Support for DOE

- The triannual *Stat-Teaser* newsletter (if you don't opt out)
- Bi-Monthly *DOE FAQ Alert* e-mail (if you don't opt out)
  - Subscribe at: www.statease.com/doealertreg.html.
- StatsMadeEasy blog at www.statsmadeeasy.net.

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Thank you for joining us today!

Best of luck in your future DOE work!

-Your Friends at Stat-Ease, Inc.

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