iFormulate

Introduces…

Design of Experiments for Formulators

iFormulate Webinar

12th July 2018

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This webinar is being recorded and will be made available

The audience is muted and you may ask questions using the question function in GoToWebinar

This webinar will last around 45 minutes

PROGRAMME

- Introductions
- Design of Experiments for Formulation
- Benefits of using DoE
- Case study supporting QbD
  - Blending for formulation
- Training Course in Design of Experiments
- Q&A

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INTRODUCTIONS

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Your Speakers

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A Little About iFormulate

- A company founded in 2012 by two experienced industry professionals…
- Combining diverse experiences, knowledge and wide range of contacts:
- …polymers, materials science, chemistry, imaging, dyes, pigments, emulsion polymerisation, biocides, anti-counterfeiting, environmental, formulation, consultancy, marketing, business development, strategy, regulatory, training, events, R&D, innovation
- Complementary network of Associates

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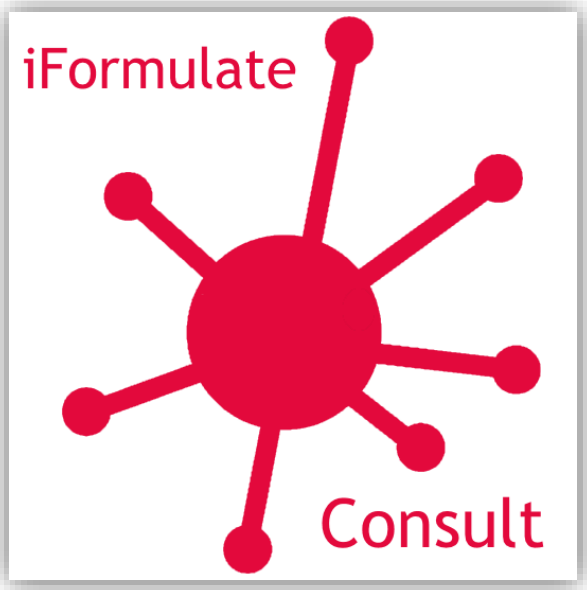
Our Services



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Design of Experiments for Formulation Chemists

Dr Paul Murray

Design of Experiments for Formulators

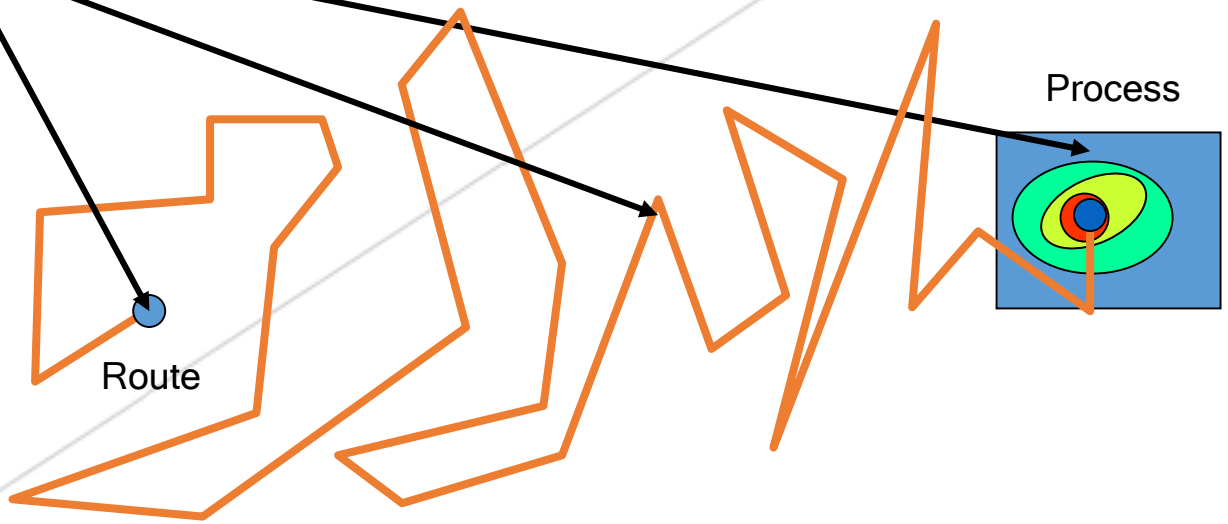
Webinar, July 2018

Introduction

- Design of Experiments for formulation
- Benefits of using DoE
- Case study supporting QbD
  - Blending for formulation

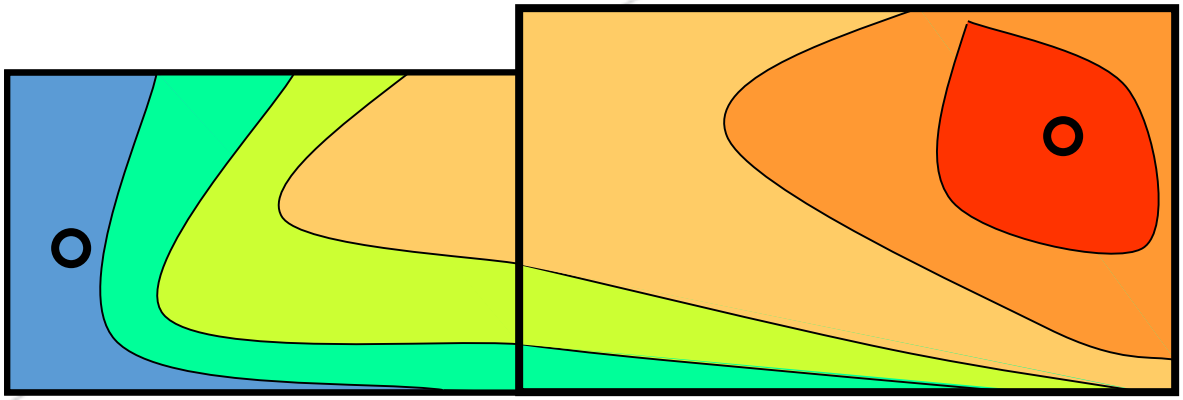
Traditional Approach

- Starts from a route
- Finds a process
- Perhaps struggles to understand it



DoE for Process Understanding

- Starts from a Route
- Understands the factors that affect the chemistry
- Designs a process on the basis of knowledge



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Design of Experiments (DoE)

- DoE, Statistical Experimental Design or FED (Factorial)
- DoE is an efficient, structured way to investigate potentially significant factors and their cause-and-effect relationships on an experimental outcome
- Careful factor selection increases the chances of extracting useful information
  - which factors to change
  - the range of the variation
- DoE provides information about the way the total system works
- Utilises statistical methods to extract and interpret the relationships between the factors

So… development of a formulation

- Formulation
  - Tablet, capsule, liquid, ……
- Bulking agent
- Caking agent
- Slipping agent

- For tableting
  - Speed, pressure ……

- For liquids
  - Solvents, additives ……

So… Formulation processes

Factors

Active ingredient
Binder
Slip agent
Bulking agent
Disintegrant
Surfactant
Formulation equipment
Formulation type

Discrete

Formulant Ratios
Particle size
Active concentration
Compression force
Temperature
Spray pattern/rate
Mixing

Continuous

Responses

Dissolution time
Dissolution profile
Tablet strength
Humidity stability
Active Ingredient Stability

Formulation processes

- Options for dosage forms: tablets, ointments, capsules, suspensions, gels…
  - Generally a separate design required for each type
- Granulation
  - Particle size, amount of binder, mixing, drying…
- Tableting
  - Compression force, tableting speed, tablet size…
- Tablet coating

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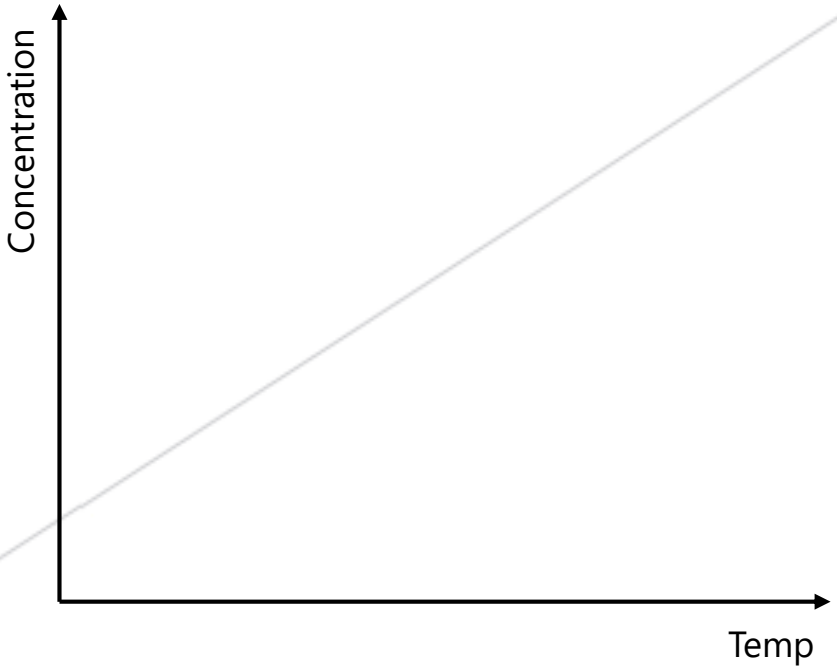
OVAT

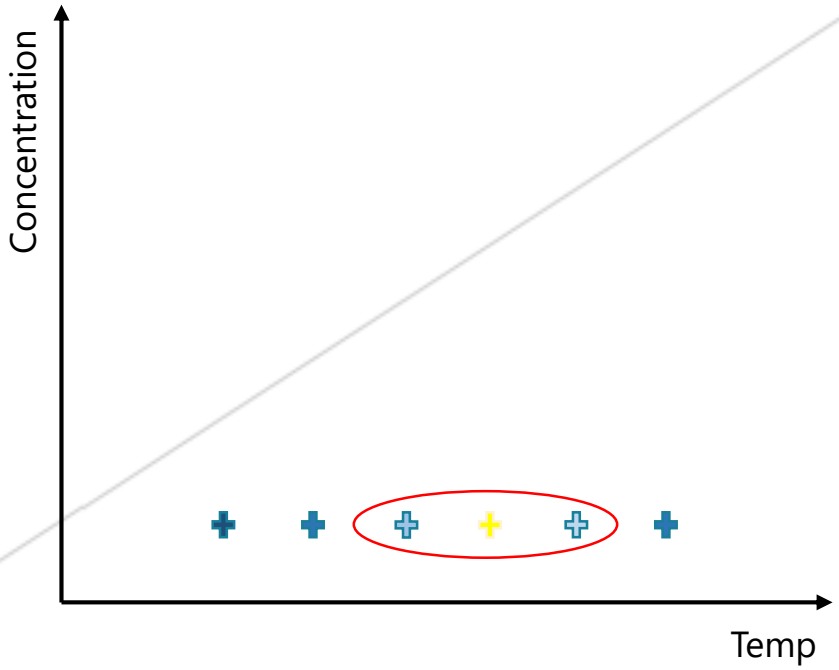
One Variable at a Time

One Variable at a Time (OVAT)



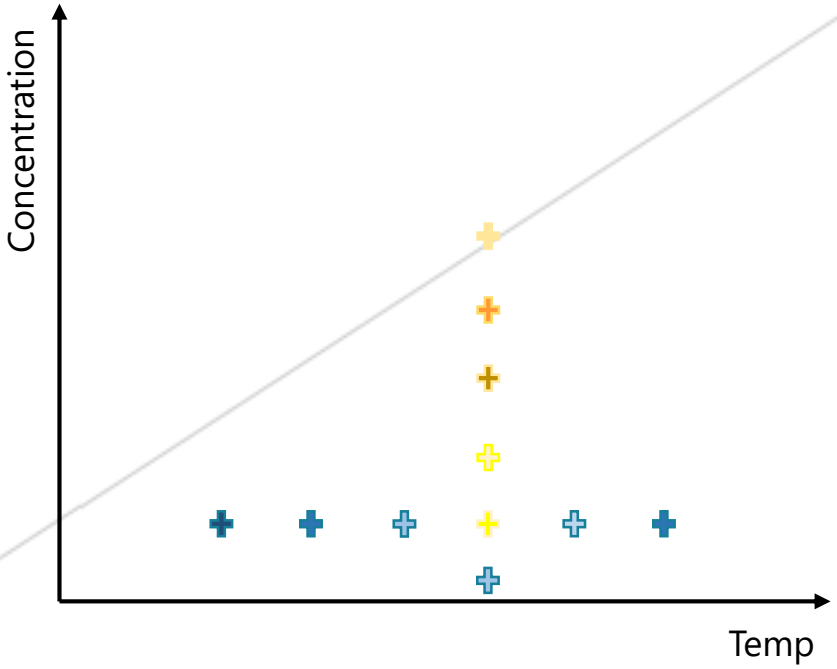
- Consider the performance of a reaction in relation to two factors - concentration and temp

One Variable at a Time (OVAT)

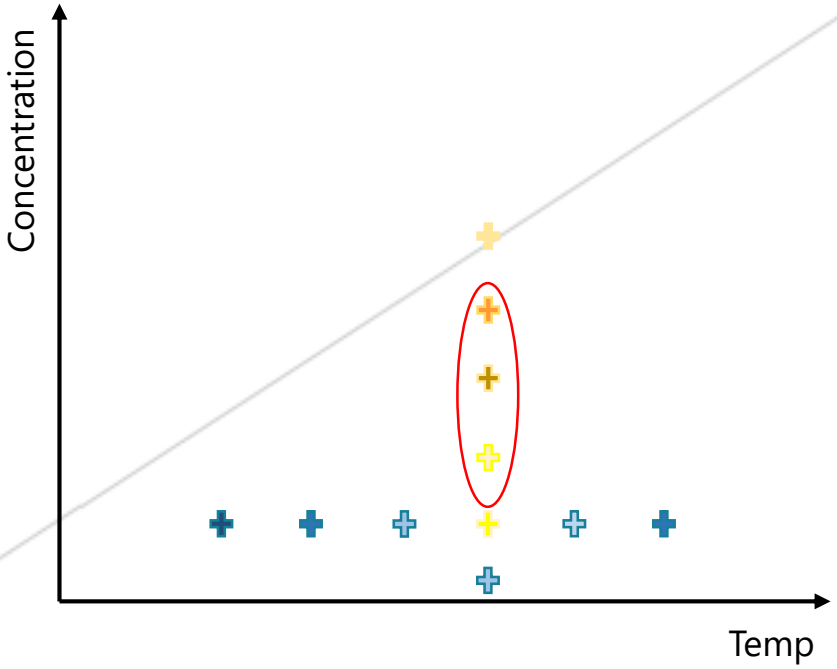


- From an arbitrary chosen starting point one factor is varied

One Variable at a Time (OVAT)

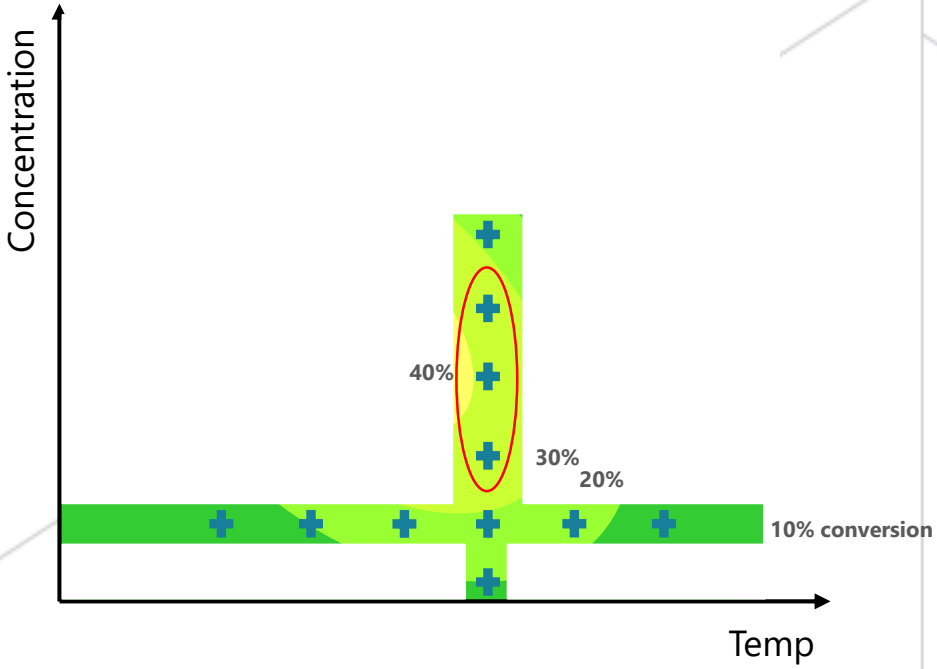


One Variable at a Time (OVAT)



- An artificial ‘local’ optimum is identified

One Variable at a Time (OVAT)



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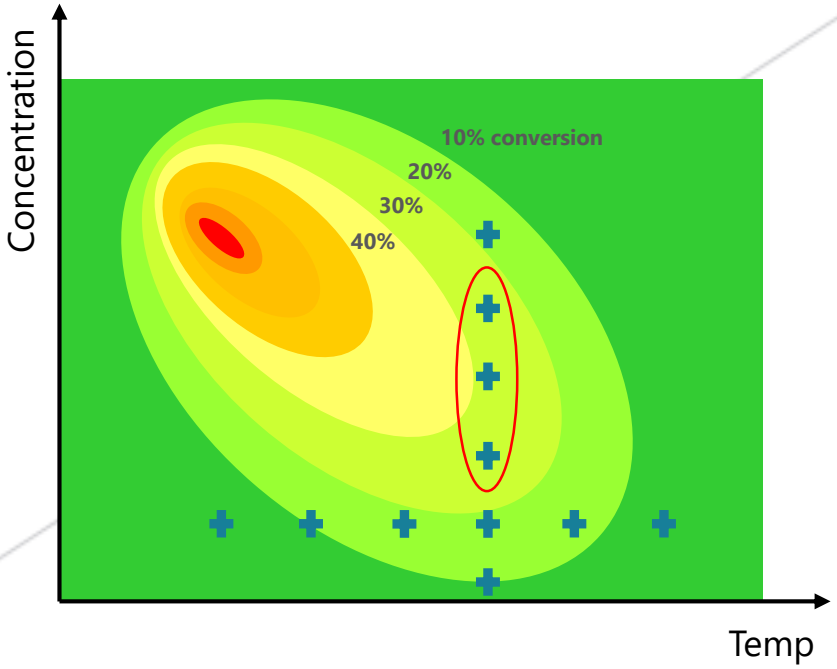
One Variable at a Time (OVAT)

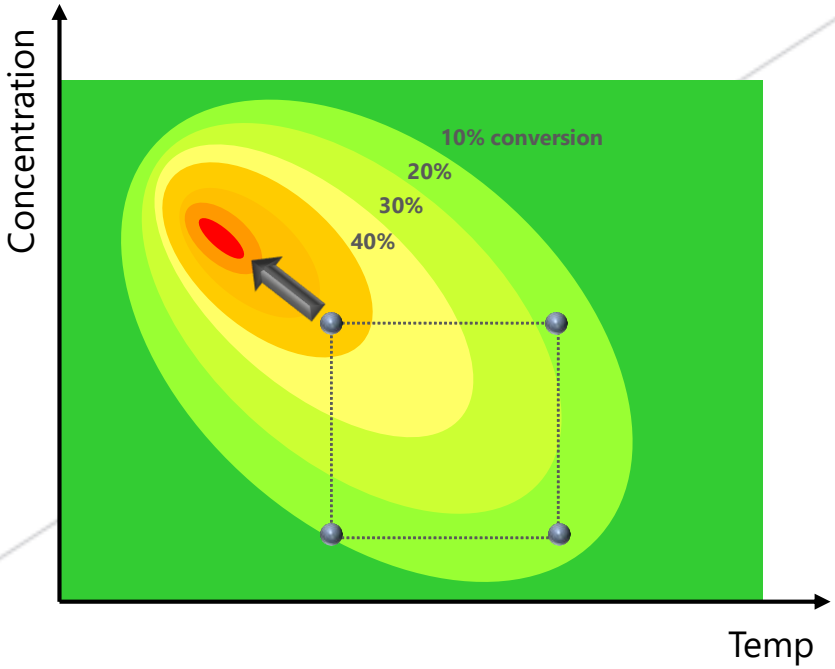


- An artificial ‘local’ optimum is identified

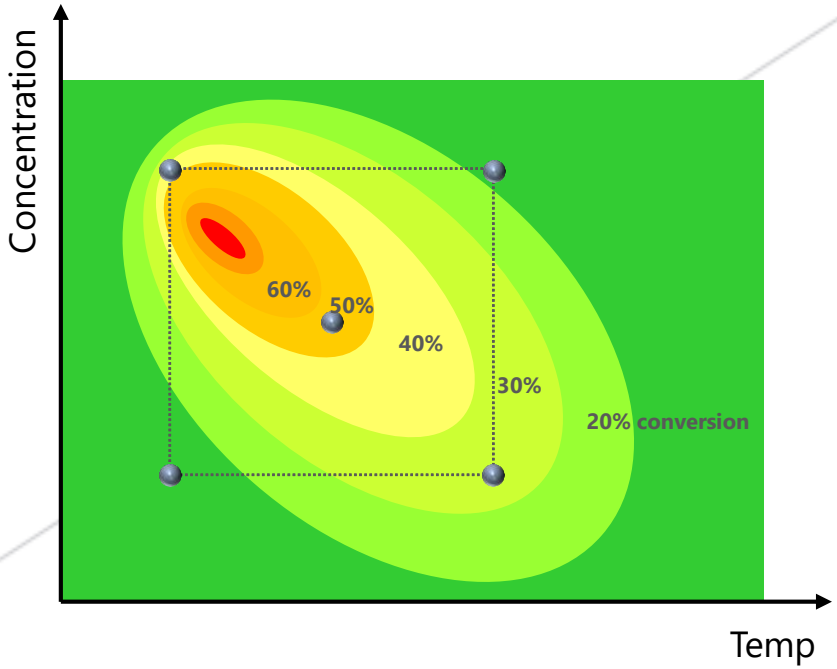
One Variable at a Time (OVAT)

- The genuine optimum may be missed
  - the experimental approach may make it impossible to find!
- Inefficient use of resources
  - better conditions are available
  - 11 experiments carried out
- Limited coverage of chemical space (design space)
- No information of dependency of one parameter on another
  - interactions
- No measure of inherent variability
  - experimental error

DoE: Screening Design



DoE: Optimisation



What will DoE do for you?

- A well-performed experiment will provide answers to questions such as:
  - What are the key variables/factors in a process?
  - At what settings would the process deliver acceptable performance?
  - What are the key main and interaction effects in the process?
  - What settings would bring about less variation in the output?
  - Does the supplier or quality of a material effect the process?

What will DoE do for you?

- A good experimental design will:
  - Avoid systematic error
  - Be precise
  - Allow estimation of error
    - To provide confidence interval and significance of the results
  - Have broad validity

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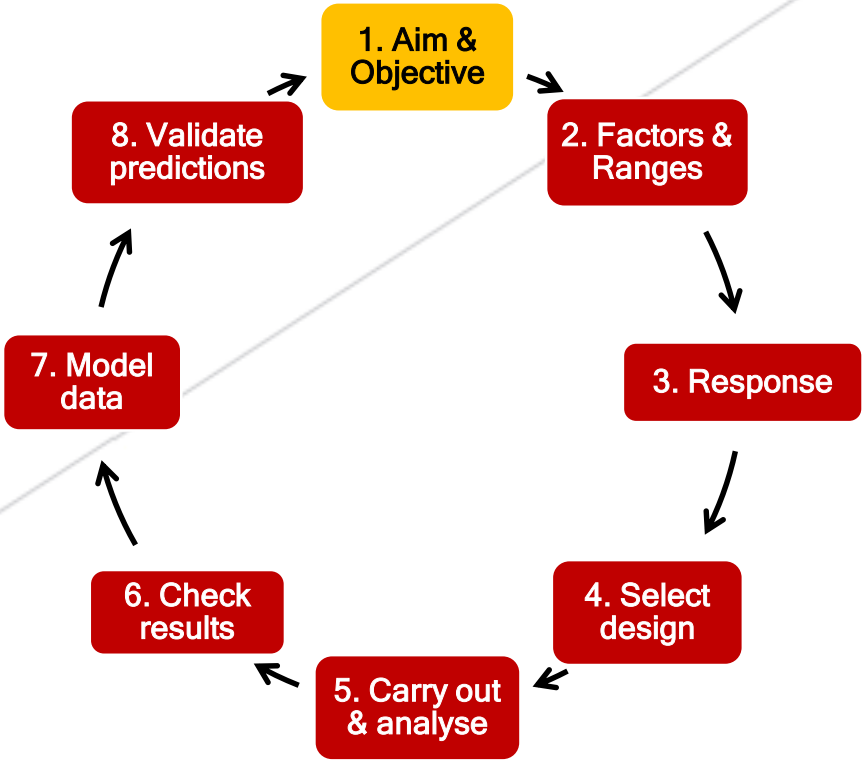
DoE

Designing Experiments – Improving Answers

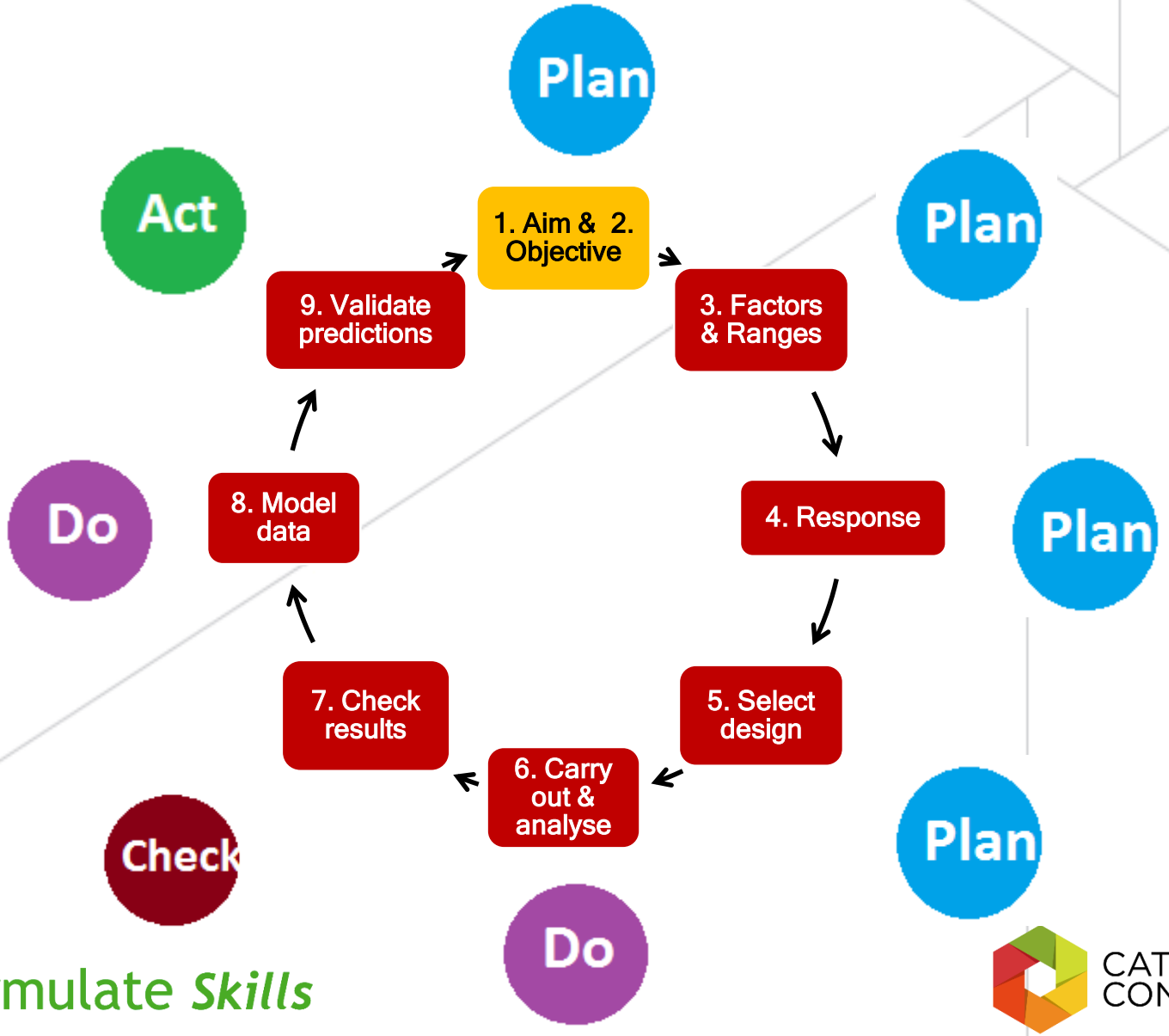
The Experimental Design Process

- The validity of an experiment is directly affected by its construction and execution
- Attention to the design of the experimental is extremely important

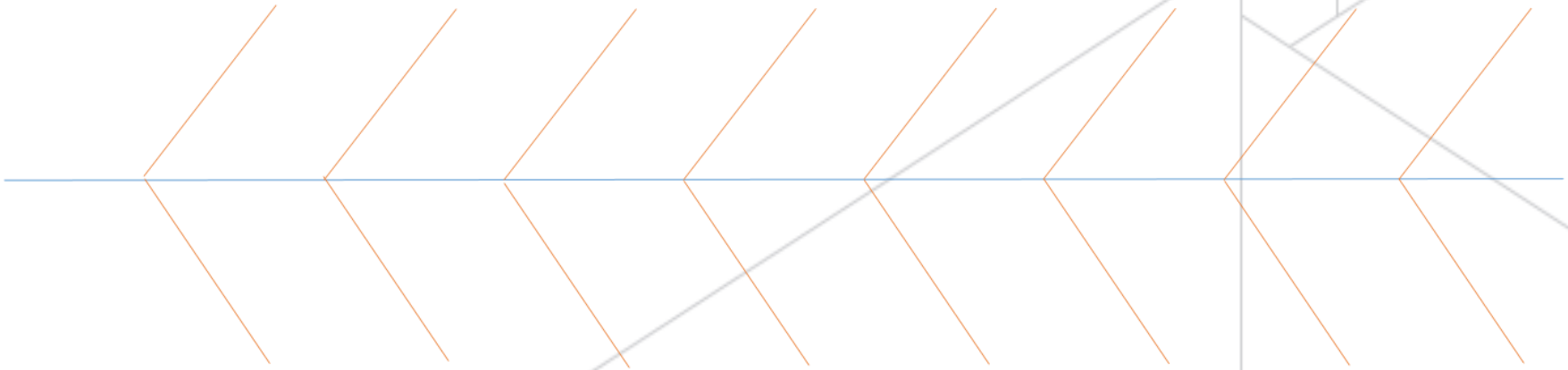
The DoE Process



The DoE Process



Identify Factors

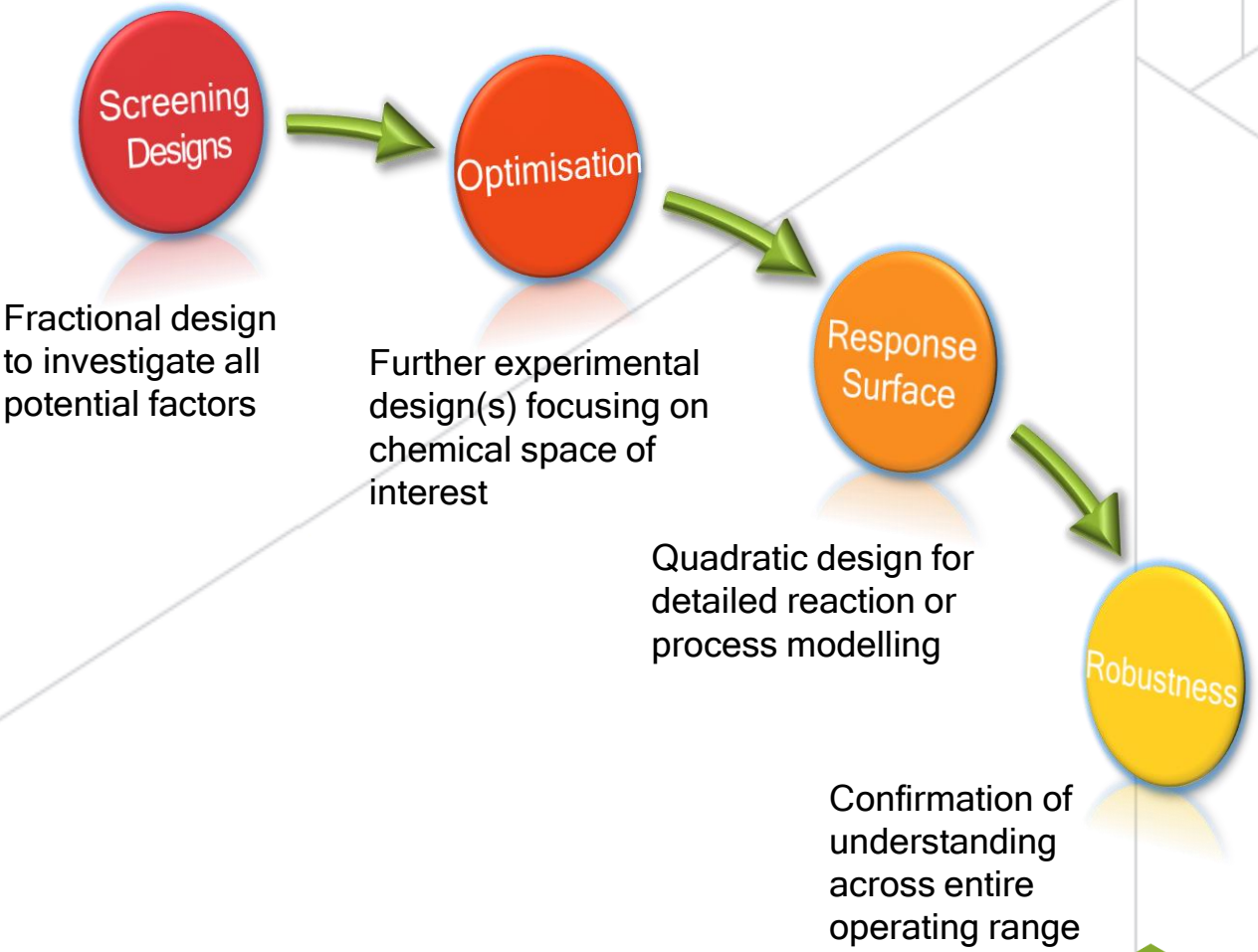


- Consider all steps in the process
  - Order of addition
  - Equipment
  - Reagents, additives
  - Rates of heating, cooling, mixing .....
  - Grades of material

Selecting Responses

- Maximise information from experimental data
  - enough of the right type of data is available
- Responses should
  - give accurate and consistent results
  - closely replicate actual experimental outcome
  - minimise variability between repeats
  - measure change as close to the event as possible
    - even minimal work-up as can lead to additional error
  - vary more than the ‘noise’ of the measurement area as a result of the changes

Design Selection



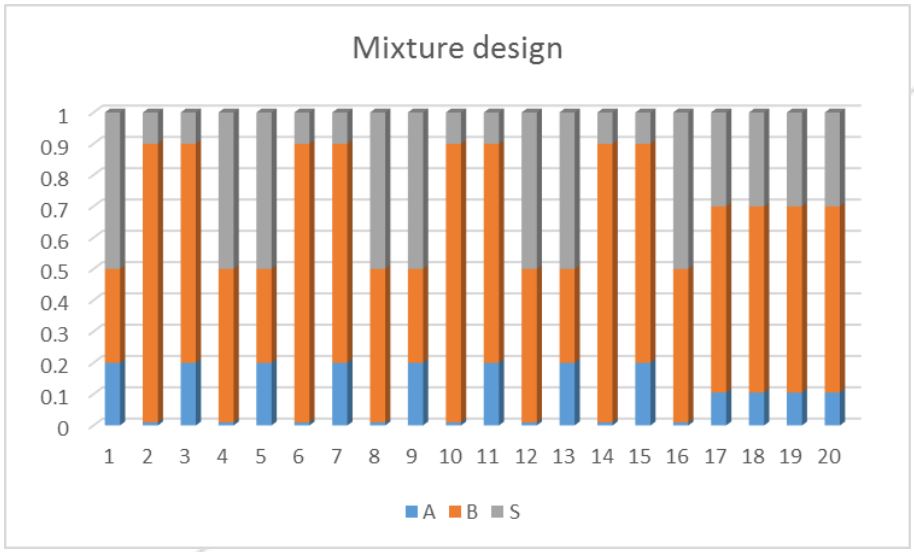
Mixture Designs

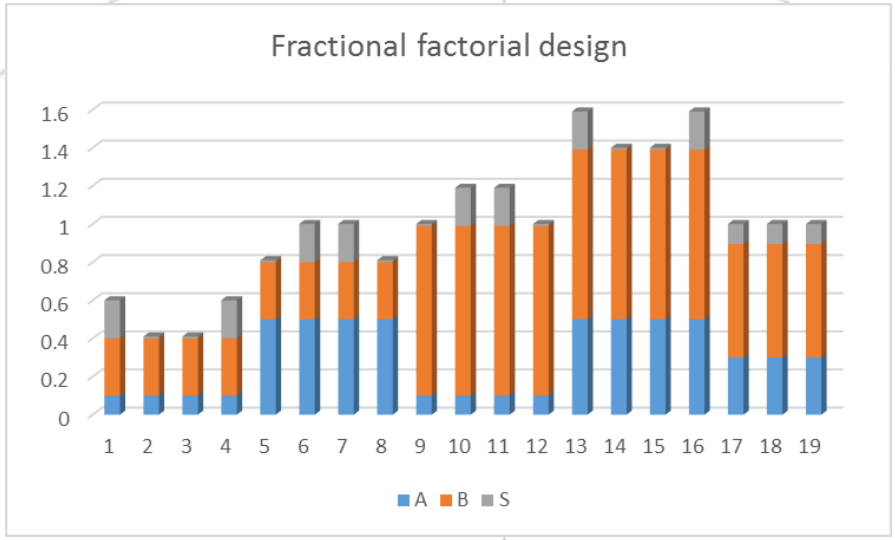
- Ideal for formulation
- Look at factors as a fraction of whole
- Analyse response against both mixture and process factors simultaneously
- Uses D-optimal design

Benefits of mixture design

- A key deliverable is amount of active in a fixed weight/volume
- Mixture design allows everything to be varied while fixing the final weight/volume
- This would be very hard to achieve with all other design types as factors are completely separate from each other and therefore dose weight/volume would vary considerably
  - All at low would give very low weight/volume and vice versa

Mixture vs Factorial designs





Case Study: blending parameters

- Quality Risk Assessment (QRA) on a tableting process shows Active Pharmaceutical Ingredient (API) particle size, moisture control, blending and lubrication steps have the potential to affect the assay and content uniformity critical quality attributes (CQAs)
- A study of the parameters likely to affect blending was conducted to develop a design space

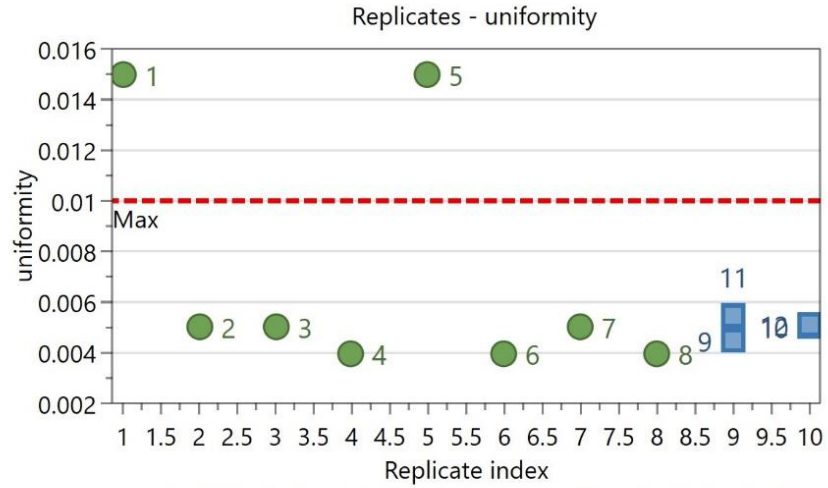
DoE for blending: factors & ranges

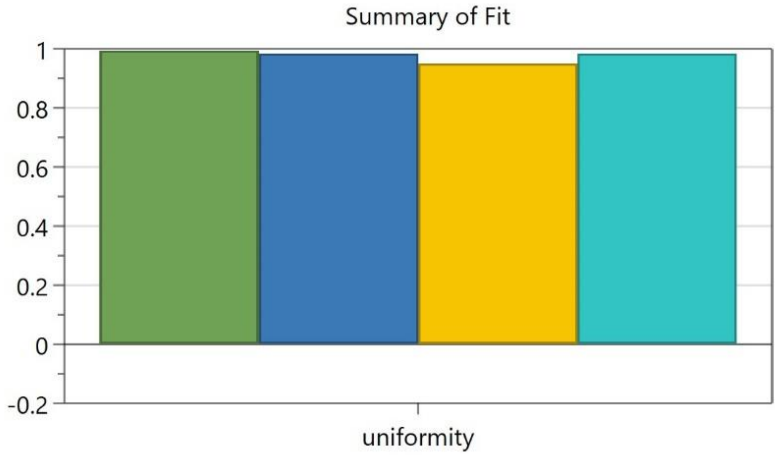
- Factors investigated
  - Blender type
  - Rotation speed
  - Blending time
  - API particle size
- Purpose: to assure that the blend is uniform
  - Analysed by NIR, target uniformity of <0.01
- Perform DoE to develop the design space

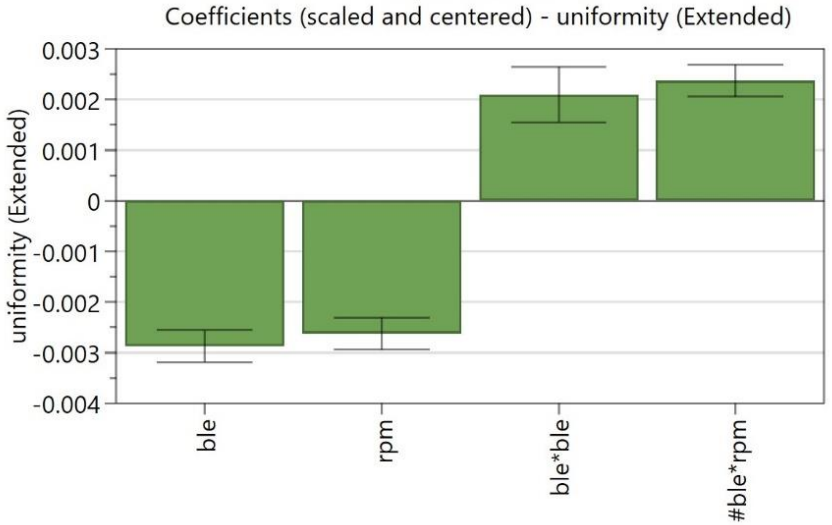
DoE: Select and perform design

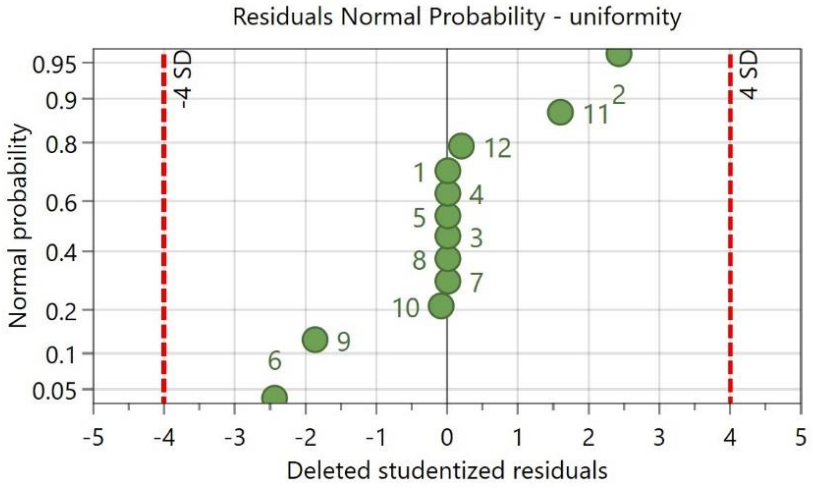
Exp no	Run	blending time	rpm	blender type	particle size	uniformity
1	2	2	10	v type	5	0.015
2	7	16	10	v type	40	0.005
3	10	2	30	v type	40	0.005
4	5	16	30	v type	5	0.004
5	6	2	10	drum	40	0.015
6	1	16	10	drum	5	0.004
7	8	2	30	drum	5	0.005
8	11	16	30	drum	40	0.004
9	3	9	20	v type	20	0.0045
10	12	9	20	drum	20	0.005
11	9	9	20	v type	20	0.0055
12	4	9	20	drum	20	0.0051

Overview plot

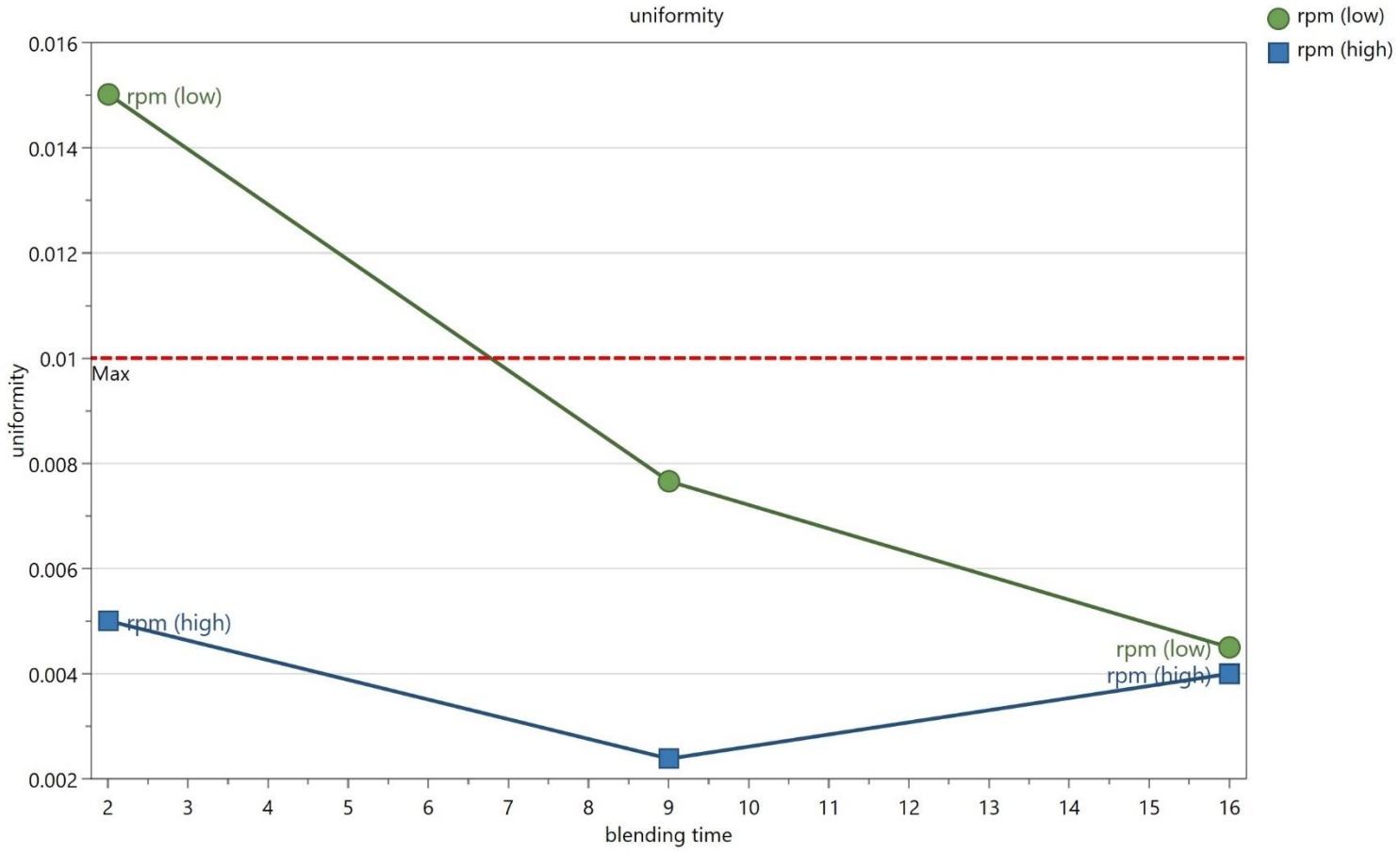




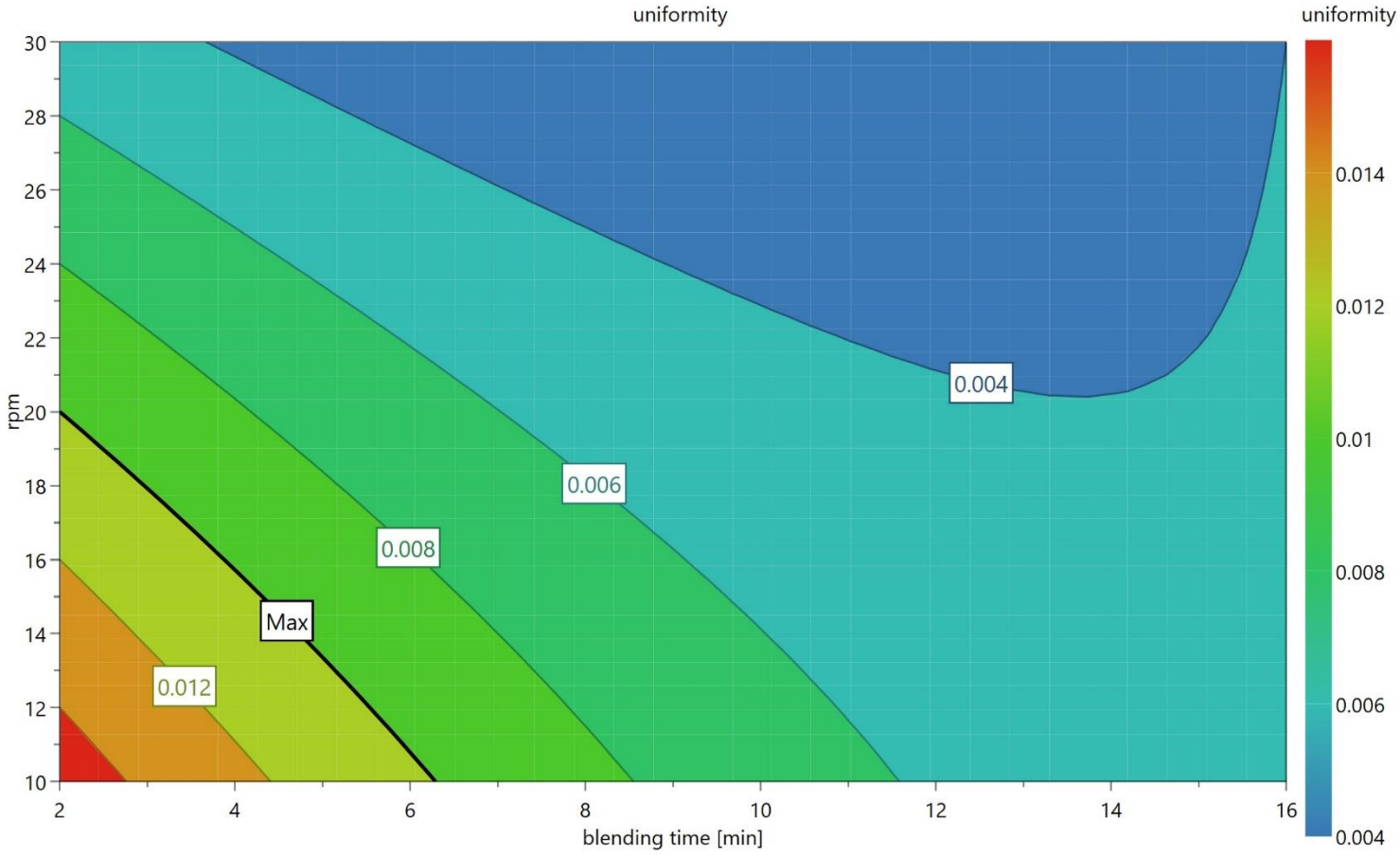




Interaction, Ble*rpm



Contour plot



Optimum conditions: 30 rpm, 11 min blending time for uniformity of 0.0025

DoE Summary

- Particle size and blender type are insignificant
- Model explains 99% and predicts 98% of the data
  - Squared term required, additional experiments recommended to define squared term
- Uniformity of <0.01 required
  - levels as low as 0.0025 are predicted to be possible
- If you wanted to achieve 0.0025 uniformity, another experiment can be carried out to confirm the conditions

DoE Summary

- Model identifies the important factors
- Model identifies setting for important factors
- Model requires quadratic and interaction terms
- DoE does this efficiently (12 experiments, additional experiments required to validate model)

Summary

- DoE is a powerful tool
- You need to avoid the pitfalls
  - Incorrect factor selection
  - Investigation of appropriate ranges
  - Inappropriate or inaccurate responses
  - Validate the model by carrying out the prediction
- A good DoE will give you much more information for a fraction of the work

Design of Experiments for Formulators

- New two day training course
- December 4th and 5th 2018
- East Midlands UK
- Early Bird £995 plus VAT before 1st October
- £1149 plus VAT after
- More details and registration
  - https://iformulate.biz/design-of-experiments-for-formulators/

Thanks for listening

- Any questions
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