iFormulate Introduces...

Design of Experiments for Formulators

iFormulate Webinar
12th July 2018
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
INTRODUCTIONS
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
Our Services

iFormulate Consult

iFormulate Strategic

iFormulate Skills

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

**Responses**

- Dissolution time
- Dissolution profile
- Tablet strength
- Humidity stability
- Active Ingredient Stability

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iFormulate Skills

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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
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

[Diagram showing Concentration vs Temp with data points]
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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- 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
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

1. Aim & Objective
2. Factors & Ranges
3. Response
4. Select design
5. Carry out & analyse
6. Check results
7. Model data
8. Validate predictions
The DoE Process

1. Aim & 2. Objective
2. Factors & Ranges
3. Response
4. Select design
5. Carry out & analyse
6. Check results
7. Model data
8. Validate predictions
9. Predictions

Do
Act
Plan
Check
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
Fractional design to investigate all potential factors

Further experimental design(s) focusing on chemical space of interest

Quadratic design for detailed reaction or process modelling

Confirmation of understanding across entire operating range
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

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Overview plot

Replicates - uniformity

Summary of Fit

Coefficients (scaled and centered) - uniformity (Extended)

Residuals Normal Probability - uniformity
Interaction, Ble*rpm
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 4\textsuperscript{th} and 5\textsuperscript{th} 2018
- East Midlands UK
- Early Bird £995 plus VAT before 1\textsuperscript{st} October
- £1149 plus VAT after
- More details and registration
  - \url{https://iformulate.biz/design-of-experiments-for-formulators/}

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Thanks for listening

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