Establishing Design Space for Lyophilized Drug Products

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Overview

- Introduction
  - Design Space
  - Lyophilization
- Scientific Basis for Process Design
  - Process Development
- Defining Design Space
- Conclusion

Quality by Design

- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8 R2)
Design Space

- The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- Working within the design space is not considered as a change.
- (ICH Q8 R2)

Proven Acceptable Range (PAR)

- A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.
- A combination of PARs developed from univariate experimentation does not constitute design space... may lack an understanding of interactions between the process parameters and/or material attributes.
- (ICH Q8 R2)

Lyophilized Drug Products

- Solid dosage forms
- Aseptically produced
- Unit operations for processing are frequently the same as those used for sterile liquids.
Unit Operation Design Space

- The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design that spans multiple operations. (ICH Q8 R2)

Lyophilization

Process of removing water from liquid formulations in order to increase stability of the dosage form.

1. Freezing
2. Primary Drying / Sublimation
3. Secondary Drying / Desorption
Critical Processing Parameters (CPPs)

- A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8 R2)
- Lyophilization has three CPPs:
  - Shelf (inlet) Temperature
  - Chamber Pressure
  - Time

Science of Process Design

- First Step: Fully Characterize the (bulk) material at low temperatures
- Second Step: Cycle Development Studies
- Third Step: Target and Boundary Studies
Low Temperature Characterization

- Low Temperature Characterization
  - Electrical Resistance (ER)
  - DSC / DTA
  - FDM
- Minimal quantity of bulk material required.
- Determines Solidification Temperature and Collapse/Melt temperature.

Phase Transition Determination

**ER**
Difference in electrical conductivity between fluid and solid material as a function of temperature.

**FDM**
Direct physical observation of product behavior while freezing and freeze drying at higher magnification, correlating observations with temperature.

**DSC / DTA**
Difference in heat input (removal) between sample and reference as temperature is changed linearly.

**Electrical Resistance**

![Graph showing Electrical Resistance over time and temperature for 7% w/v KCl Solution.](image_url)
**Phase Transition Determination**

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**Differential Scanning Calorimetry**

- **Endotherm**
  - Release of energy with material progressing to a lower energy state
  - Glass Transition = \( T_g \) or \( T'_g \)

- **Exotherm**
  - Energy consumed with material progressing to a higher energy state

- **Shift in heat capacity with transition from solid to liquid state**

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**Phase Transition Determination**

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Difference in heat input (removal) between sample and reference as temperature is changed linearly.
Solidification Temperature

- Temperature at which the entire formulation exhibits behavior of a solid.
- Variation in supercooling and nucleation
- Influenced by thermal history
- More accurate: Results upon warming
  - The temperature at which the product begins to exhibit the behavior of a liquid.

Threshold Temperature

- Temperature the product needs to remain below, while in the presence of ice, to maintain the original structure established during freezing.
- Influenced by thermal history
- Dependent on nature of solutes
  - Amorphous
  - Crystalline
Science of Process Design

- First Step: Fully Characterize the (bulk) material at low temperatures
- Second Step: Cycle Development Studies
- Third Step: Target and Boundary Studies

Cycle Development

- Product Temperature Profiling
  - Vary Shelf Temperature
  - Vary Chamber Pressure
  - Assess impact on resulting product (temperature) during primary drying
- Sequential Stoppering to determine appropriate amount of time in Secondary Drying
Target Cycle

- Each Product should have target critical process parameters which include the appropriate processing conditions of shelf temperature, chamber pressure, and time.
- When identifying target conditions the chosen process should be reproducible and produce consistent product having good batch uniformity.

Science of Process Design

- First Step: Fully Characterize the (bulk) material at low temperatures
- Second Step: Cycle Development Studies
- Third Step: Target and Boundary Studies

Defining Design Space

- Design Space - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- Material attributes defined in terms of
  - Product temperature required during processing
  - Morphology (amorphous or crystalline)
  - Resulting product characteristics
Defining Design Space

- Target and Boundary Studies
  - Three batches at Target conditions
    - Demonstrates process reproducibility
    - Confirms consistent product qualities
  - Four batches at Boundary conditions
    - Envelopes processing conditions
    - Establishes proven acceptable range

Boundary Studies

- Based on the target processing conditions there should be a upper and lower limit to the critical processing parameters of shelf temperature and chamber pressure.
- For example ± 5°C of the target shelf temperature and ± 20 microns of the target chamber pressure.
- This provides a range around the target processing conditions.
- A total of four studies to be performed based on a two factorial design of shelf temperature and chamber pressure: High/High, High/Low, Low/High, and Low/Low.

Acceptable Boundary Conditions

- Graph showing temperature and chamber pressure ranges with critical points indicating acceptable boundary conditions.
Boundary Studies

- Parameters to Vary
  - Shelf inlet temperature
  - Chamber pressure
- Parameters Not Varied
  - Time
  - Condenser Temperature
  - Ramp Rates

Time

- Timing mechanism is essentially a timer (for automated operations).
- Likelihood of lot-to-lot variation is low (i.e., reproducibility batch-to-batch should be high).
- No need to vary or establish range.

Condenser Temperature

- Process requirements include need for a surface to condense water vapor.
- Surface must be cold enough at the specified pressure (vacuum) setting.
- For process to be effective, condenser must not exceed a certain temperature.
- No need to establish a range, as this is essentially a pass/fail criteria (maximum allowable temperature).
Ramp Rate
- Change in target setpoint after a specified time.
- Rate of freezing can impact cake structure and solid matrix for certain products.
- Need to have consistent batch-to-batch thermal profile to minimize lot-to-lot variability.

Boundary Parameters
- Define acceptable critical process parameter range
- Verify with product analysis and stability

New Frontiers
- Use of heat and mass transfer theory to define design space and predict level of process variance.
- Develop an approach to measuring variability within a batch based on predictive model.
- Currently working on measuring variance to predict collapse in model product types.
Conclusions

- Critical processing parameters for lyophilization can be determined experimentally and are based on science.

- The science applied in process design for new products can be applied to older, established products.

Conclusions

- The current accepted approach of using Target and Boundary conditions meets the requirements for Design Space when combined with other relevant development data.

- The resulting data package provides a better understanding of the manufacturing process.

Questions?

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