Application of the QbD (Quality by Design) Approach for Coating Drug Eluting Stents (DES)

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Outline

• Primer on DES
• The QbD approach
• Experimental methodology
• Results
• Conclusion
Drug Eluting Stents

- Implanted for treatment of atherosclerosis
- Drug coated to prevent restenosis
- Drugs spray coated onto bare metal stents
- DES stays permanently in a patient’s artery
  - Low tolerance for failure
- Manufactured in small batch sizes
  - Extensive end product testing is not feasible
Common quality issues: high variability in total drug content and rate of drug elution
Attributed to variation in the coating process
Why QbD?

• QbD advocates use of a science and risk based approach to enhance product and process understanding
• Facilitates consistent manufacture of desired quality products
• Adopted QbD paradigm to understand the ultrasonic spray coating process for DES
  – A step by step approach was followed
Step by Step QbD Approach

- **Product profile**
  - QTPP (Quality Target Product Profile) and CQA were determined for the DES

- **CQAs**

- **Risk assessment**
  - Ishikawa approach to understand factors affecting drug elution

- **Design space**
  - Established for ultrasonic coating process via statistically based multiple DOE (Design of Experiment)

- **Control strategy**

- **Continual Improvement**
QTPP & CQA

**QTPP for a DES**
- Potency and strength
- Bioavailability/local activity/bio-performance
- Adequate insertion
- Purity and integrity
- Stability
- Identity

**CQA for a DES**
- Amount of drug in the coated stent i.e. assay
- Content uniformity of coated stent
- Coating uniformity of an individual stent
- Biocompatibility (e.g. degradation of polymer, in-vivo polymer absorption)
- Drug elution rate
- Stent mechanical properties (includes stiffness and compliance, depends on intended duration inside the body)
- Particulates/extraneous matter
- Degradants/related substances
- Endotoxins
- Residual solvents
- Sterility
- Polymer shelf life
- Device shelf life
- Identity
Materials

PLGA poly(lactic-co-glycolic acid)

Acetone

Tetrahydrofuran (THF)

Everolimus (Drug)
Experimental Setup

Coating Procedure:
1. Coating solution flows to nozzle
2. Ultrasonic atomizes the spray
3. N2 focuses the solution
4. Motor rotates and moves the stent while the solution is sprayed
5. Stent is taken to vacuum oven to dry
6. Weigh stent
Some Common Coating Defects

FIBERS

EXCESS COATING AT THE STENT ENDS

LARGE PARTICLE DEFECT ON THE STENT

WEBBING

LIQUID DROP ON THE NOZZLE

500μm

2mm
## Impact of Parameters on Spray Type

Coating parameters resulting in the formation of a drop on the nozzle or fibers have opposing effects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drop on nozzle avoided by:</th>
<th>Fibers avoided by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>Shroud gas pressure</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>Ultrasonic power</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>% THF</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>Temperature</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>Distance</td>
<td>no effect</td>
<td>higher</td>
</tr>
</tbody>
</table>
DOE Approach

**SCREENING DOE**
Fractional factorial DOE

*Six factors:*
1. % Tetrahydrofuran (THF)
2. Solution flow (µl/min)
3. Nozzle to stent distance (mm)
4. Temperature (°C)
5. Rotation (rpm)
6. Shroud gas pressure (psi)

*Responses:*
- Coating roughness measured using SEM
- Amount of drug elution at 30 min and 48 hours

**OPTIMIZATION DOE**
Full factorial DOE

*Four factors:*
1. % THF
2. Solution flow (µl/min)
3. Nozzle to stent distance (mm)
4. Temperature (°C)

Rotation speed and Shroud gas pressure fixed

Same responses measured as screening DOE
Optimization DOE: Experimental Conditions

Percent THF in Solution

40% THF

70%THF

100% THF

Solution Flow Rate (μl/min)

Distance from stent to the nozzle (mm)

7.5 17.5 12.5 7.5 17.5

19 °C 19 °C 19 °C 19 °C 19 °C

29 °C 29 °C 29 °C 29 °C 29 °C

19 °C 19 °C 19 °C

29 °C 29 °C 29 °C

70% THF

100% THF
Measure of Coating Roughness

Scale 1 to 4, 1: Smooth; 4: Rough
Coatings sprayed at the greatest nozzle-stent distance (17.5 mm) tended to be rougher.
Drug Elution

- Dissolution apparatus simulates drug release from coated stent
- Samples of elution media are removed at specified time points for HPLC analysis
- After 48 hours of elution, stent is dried and weighed,
- Surface texture and defects are studied by AFM and SEM
Sample Elution Profiles

SCREENING DOE

OPTIMIZATION DOE
Dissolution Model

\[
\% \text{ Accumulated drug elution } (t) = A1 \times (1 - e^{-A2\times t}) + A3\sqrt{t}
\]

### Elution Mathematical Model

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Definition</th>
<th>Max Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Early drug release</td>
<td>1.32</td>
</tr>
<tr>
<td>A2</td>
<td>Sustained drug release</td>
<td>1.11</td>
</tr>
<tr>
<td>A3</td>
<td>Late drug release</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Analysis of Optimization DOE data

DOE data analyzed using Minitab.
Responses considered include: coating mass, mass ratio (coating mass/ drug-polymer solution sprayed), coating roughness, A1, A2, A3
Results from Optimization DOE

Contour plots from optimization DOE

Design space is the rectangle that indicates the region of the nozzle-stent distance versus temperature that will minimize roughness, minimize burst release and maximize long term release of drug.
Conclusion

• Application of the QbD methodology enhanced our understanding of the stent coating process
• Nozzle to stent distance and temperature were identified to be critical parameters affecting the coating roughness and drug elution kinetics
• Explore opportunities to apply similar methodology to other drug-device combinations
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