Development of Dropwise Additive Manufacturing of Pharmaceutical Products

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Motivation

• Industry has limitations in advancing manufacturing technology
  ▪ FDA regulations
  ▪ Solids processing
  ▪ Biochemical effects

• Processes are often
  ▪ Large-scale
  ▪ Batch

• Use of large-scale batch processing leads to:
  ▪ Many rejected batches
  ▪ Long production time
  ▪ Low automation/control
Dropwise Additive Manufacturing of Pharmaceutical Products (DAMPP)

- Mini-manufacturing
- Drop-on-demand (DoD) inkjet printing technology
- Deposition of API onto an edible substrate to create individual dosage forms

Liquid Dispensing Technology (LDT) at GlaxoSmithKline is used to deposit solvent-based formulations on inert tablets.
Advantages of Drop-on-Demand Technology

• Ease of fluids processing as opposed to solids
• Potential of creating uniform drops in a wide range of sizes
• Precise and low-waste
• Flexibility in use
  ▪ Drop size
  ▪ Drop material: solvent, solvent-polymer or melt-based system
  ▪ Substrate: film, tablet, capsule
  ▪ Drop deposition pattern
• Quick changeover between different products and dosage levels
• “Combination drugs” by layering multiple APIs
• “Individualized medicine” to tailor dosage to patient based on their specific therapeutic response
Process
DAMPP Manufacturing Process

- Pump Controllers
- Temperature Controllers
- CPU
- Staging Controller
- Drop Deposition Process
DAMPP Manufacturing Process

- Reservoir
- Pump
- Nozzle
- Camera
- Substrate Heater + Fans
- xy Staging
Take into account scientific, engineering and technical considerations

1. Preparation of formulation to be printed

1. Selection of proper system depends on API and desired dosage form
   - Solvent- or melt-based
   - Crystalline or amorphous form

2. Printable fluid
   - Dissolved particles
   - Liquefied
   - Suitable material properties
2. Selection of substrate material

- Films (porous or non-porous)
- Inert tablets
- Capsule filling
- Wells or molds
4. Drop generation

- Formation of satellite drops
- Behavior dependent on material properties
- Prediction of behavior
- Extensive on-line monitoring

5. Drop deposition

- Drop velocity
- Nozzle height
- Drop size
- Interaction with substrate

6. Creation of drop pattern

• Efficient use of substrate
• Avoid coalescing drops
  ▪ Drug morphology
  ▪ Solvent evaporation or polymer solidification time
• Consider multi-layered dosage forms
3. Control of printing material

- Maintain content uniformity and API morphology
- Stabilize material properties
- Liquefy melt-based formulations

7. Control of substrate conditions

- Increase rate of solvent evaporation or melt solidification
- Control dosage form morphology

8. Confirmation of dosage quality

- Verify presence of drug and that drug is completely in desired form
Real Time Process Management

- Automatic execution
- Precise control of dosage amount
- On-line monitoring and sensing
- Optimal process variables

DAMPP SYSTEM

Exceptional Events Management
Detect, diagnose, mitigate abnormal events

Regulatory Control
Regulate important variables

Monitor Product Quality
Meet specifications

Automation
Synchronous operation of all unit operations
Automation: Inputs

- Inputs
  - Drop deposition settings
  - Temperature settings
    - Off for solvent-based formulations
    - On for melt-based formulations
    - Substrate heating or cooling
Automation: Outputs

- **Outputs**
  - Time stamp
  - Location
  - Temperature
  - Center of drop within image
  - Drop image
  - Drop number
  - Image number
Automation: Outputs

- Outputs
  - Time stamp
  - Location
  - Temperature
  - Drop image
  - Drop number
  - Image number
Automation
Automation
Exceptional Events Management

Compare drop number and image number

- Identify mismatch between number of triggered drops and number of drop images acquired
- Detect faults that occur due to:
  - Drop falling without being triggered
  - Drop not falling when triggered
  - Image not acquired of triggered drop
Exceptional Events Management

**Drop > Image**
- Image not acquired of triggered drop

**Drop < Image**
- Drop falling without being triggered

- Camera system failure
- Drop is not ejecting from nozzle
Products
Solvent-Based Dosage Forms

- Solvent + Polymer + API
- Amorphous
  - 30:70 Naproxen:PVP
- Semi-crystalline
  - 70:30 Naproxen:PVP
- Deposited on HPMC films
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drop Size</th>
<th>Intended Dosage (mg)</th>
<th>Average Dosage Amount (mg)</th>
<th>Standard Deviation (mg)</th>
<th>RSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amorphous</td>
<td>S</td>
<td>10</td>
<td>10.295</td>
<td>0.226</td>
<td>2.19%</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>10</td>
<td>10.190</td>
<td>0.128</td>
<td>1.25%</td>
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<tr>
<td></td>
<td>S</td>
<td>25</td>
<td>24.585</td>
<td>0.0001</td>
<td>0.44%</td>
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<tr>
<td></td>
<td>L</td>
<td>25</td>
<td>26.895</td>
<td>0.0003</td>
<td>1.17%</td>
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<tr>
<td>Semi-crystalline</td>
<td>S</td>
<td>10</td>
<td>10.978</td>
<td>0.0001</td>
<td>1.33%</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>10</td>
<td>11.200</td>
<td>0.0005</td>
<td>4.09%</td>
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<tr>
<td></td>
<td>S</td>
<td>45</td>
<td>42.910</td>
<td>0.002</td>
<td>5.72%</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>45</td>
<td>44.135</td>
<td>0.001</td>
<td>3.17%</td>
</tr>
</tbody>
</table>

- Sample size of 6-8 dosage forms
- RSD generally < ~4%
Morphology Analysis using X-Ray Diffraction

Apparent Crystallinity

Drop Size (1=Smallest, 5=Largest)

- Amorphous
- Semi-crystalline with PVP
Dissolution Analysis

- Amorphous, D2
- Amorphous, D3
- Semi-crystalline with PVP, D2
- Semi-crystalline with PVP, D3

Time (min)

Percent Dissolution (%)

- Amorphous, S
- Amorphous, L
- Semi-crystalline with PVP, S
- Semi-crystalline with PVP, L
### Proportion of crystal edges on surface

<table>
<thead>
<tr>
<th>Drop Size</th>
<th>Edge of Drop</th>
<th>Center of Drop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Average</td>
</tr>
<tr>
<td>S</td>
<td>35.93%</td>
<td>58.81%</td>
</tr>
<tr>
<td>RSD</td>
<td>25.50%</td>
<td>61.97%</td>
</tr>
</tbody>
</table>

The images show the distribution of crystal edges at different locations on the surface. The table above presents the average proportion of crystal edges at the edge and center of the drop, along with the relative standard deviation (RSD) for each location.
Conclusion

Dropwise Additive Manufacturing of Pharmaceutical Products is an innovative, viable mini-manufacturing method

- **Process**
  - Automation strategy in place to ensure proper material deposition
  - Control strategy in development to provide regulatory control and detect and mitigate faults

- **Products**
  - Created with either solvent-based formulations or polymer-melt-based formulations
  - Reproducible dosage forms with varied morphology and adequate dissolution behavior
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Questions?