Process Drift in the Manufacturing of Transdermal Drug Products

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Benefits of Transdermal Delivery

- Delivers API directly into the systemic circulation avoiding hepatic first-pass effect
- Typically reduces certain types of reported adverse events
- Maintains the desired drug concentration with less variability
- Daily or weekly dose intervals provide better compliance of recommended dosing intervals
- Patch formulation convenient for patients who have difficulty swallowing oral drugs
Examples of transdermal drugs in development or marketed

**Depression**
- Buspirone
- Bupropion

**Parkinson's**
- *Ropinirole*
- Pergolide
- *Pramipexole*
- *Rotigotine*

**Anxiety**
- Alprazolam

**Alzheimer's**
- Tacrine
- Memantine
- Rivastigmine

**ADHD**
- Methylphenidate
- Amphetamine

**Birth Control**
- Estrogen/Progestin Combinations (various)

**Motion Sickness**
- Scopolamine

**Epilepsy**
- Clonazepam

**Pain**
- Buprenorphine (Chronic)
- Fentanyl (Chronic)
- Sufentanyl (Chronic)
- Levorphanol (chronic)
- Various NSAIDs (Arthritic)
- *Triptans (Migraine)*
- Lidocaine

**Urinary Incontinence**
- *Tolterodine*
- Oxybutynin

**Allergies**
- Azelastine

**Obesity**
- Phentermine
- Methamphetamine

**Hypertension**
- Enalapril
- Clonidine
- *Ramipril*
- Timolol

**Nausea**
- *Granisetron*

**Male Hypogonadism/ Female Sexual Dysfunction**
- Testosterone

* Under patent protection by originator
## Properties of Commercialized Transdermal Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight</th>
<th>Daily Dose</th>
<th>Smallest Patch Size (cm²)</th>
<th>In-Vivo Permeation Rate (μg/cm²/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>303.35</td>
<td>0.33 mg/day</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>227.09</td>
<td>1.6 mg/16 hrs.</td>
<td>5.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Clonidine</td>
<td>230.1</td>
<td>0.1 mg/day</td>
<td>3.5</td>
<td>1.19</td>
</tr>
<tr>
<td>Estradiol</td>
<td>272.38</td>
<td>0.1 mg/day</td>
<td>10.0</td>
<td>0.42</td>
</tr>
<tr>
<td>Norethindrone Acetate</td>
<td>340.45</td>
<td>0.14 mg/day</td>
<td>9.0</td>
<td>0.65</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>296.40</td>
<td>0.02 mg/day</td>
<td>20.0</td>
<td>0.042</td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>327.47</td>
<td>0.15 mg/day</td>
<td>20.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Nicotine</td>
<td>162.23</td>
<td>7.0 mg/day</td>
<td>7.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Testosterone</td>
<td>288.42</td>
<td>2.5 mg/day</td>
<td>7.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>336.5</td>
<td>0.6 mg/day</td>
<td>10.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>234.34</td>
<td>21.33 mg/12 hrs.</td>
<td>140.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>357.49</td>
<td>3.9 mg/day</td>
<td>39.0</td>
<td>4.16</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>233.31</td>
<td>12.0 mg/12 hrs.</td>
<td>12.5</td>
<td>80.0</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>467.6</td>
<td>0.75-3 mg/7 days</td>
<td>25.0</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Types of Transdermal Systems

• Some of the first marketed transdermal patches contained a drug *reservoir* and a control release membrane

• Most of the recently approved patches are of the *matrix* type where the drug is formulated into the adhesive and allows the skin to regulate the permeation
Types of Transdermal Systems

Figure 1
Reservoir Transdermal Patch Construction
- Backing Layer
- Drug
- Membrane
- Adhesive
- Liner

Figure 2
Drug-in-Adhesive Matrix Patch Construction
- Backing Layer
- Drug/Adhesive Matrix
- Adhesive Layer
- Liner
Process Drift

- Once a transdermal product is developed, approved and marketed special care is required to maintain its performing quality attributes
- Various factors can cause Process Drift during manufacture of raw materials and the drug product
- Extensive expertise can be required to address these types of problems
Lessons Learned

• One of the first US marketed transdermal products was Transderm Scōp® for the treatment of motion sickness

• Commercial availability of Transderm Scōp was negatively impacted by inappropriate process drift as follows:
  – Product changed from one of the innovator’s division to another
  – Sourcing of API was changed to a less costly supplier
  – Physicochemical characterization was not performed but the new API met all the approved specifications
  – After the product was on the market for a short while crystals began appearing on the drug product
  – The division selling the product did not understand the event nor did the new API supplier
  – Product was not available for commercial distribution for more than two years
Lessons Learned

• A reservoir type estrogen/progestin combination product ran into supply chain shortages in Europe
• Commercial availability was negatively impacted by inappropriate process drift as follows:
  – This patch contained a control release membrane manufactured by a melt extrusion process
  – After producing the membrane for several years some extruder parts suffered excessive wear but this was considered normal
  – The membrane’s permeation characteristics were altered causing the routine dissolution test to fail specifications
  – A comprehensive design of experiments was required to identify the root cause and correct the problem
Lessons Learned

• A recall of leaky reservoir type fentanyl patches was recently reported
• Safety concerns of a CII opioid overdose was cause for immediate action
• The most likely causes for this product defect were process drift or operator error
Lesson Learned

• Neupro (Rotigotine Transdermal System) withdrawn from US market due to crystallization observed on the surface of the patch
• FDA requested reformulation of the drug product
• Process drift or overlooked material incompatibility the likely cause
Processing Parameters and Raw Materials Variation

• Processing parameters are established and validated prior to FDA approval and product launch

• Adherence to validated parameters is crucial to ensure product performance and regulatory compliance

• Sourcing of API and other excipients from alternate vendors need to be fully characterized before they are used in commercial batches
Transdermal Manufacturing Steps

• Most recently developed transdermal products are classified as matrix patches
• The manufacturing steps to make such a patch typically consist of the following:
  – Dissolution of API and all excipients into a homogeneous solution
  – Coating of the mixture, removal of solvents, monomers and polymerization of matrix layer
  – Slitting of the matrix layer into smaller rolls
  – Patch fabrication, pouching and secondary packaging
Critical Processing Parameters

• **Solutions**
  - Order of addition, mixing speeds, times and conditions (jacketed/open/closed vessel)

• **Coating/Drying**
  - Machine speed, temperature and air flow rate

• **Slitting**
  - Machine speed, roll width and tension

• **Fabrication/Pouching**
  - Machine speed, temperature, sealing pressure and appropriate function of all detection devices

• **Secondary Packaging**
  - Similar to oral dosage forms
Quality by Design

• Better understanding of the formulation (i.e. functionality of excipients and stability of the formulation)
• Better understanding of the manufacturing process
• Better control of the critical quality attributes
• Better plan to deal with process drift
Quality by Design Considerations

• What is known
• What is not yet known
• Formulation design space development
• Process design space development
• Control strategy development
Formulation Variables

**INPUT**

1. Adhesive composition
2. API% in matrix (drug load)
3. Excipients % in matrix
4. Drug solubility in matrix
5. Coat weight (drug load)
6. Drug matrix size (drug load)
7. Adhesiveness provided by matrix

**UNCONTROLLED INPUT**

1. Human cadaver skin variation
2. Franz cell set up variation
3. Analytical errors
4. Operator/equipment for mixing and coating

**CONTINUOUS FACTORS**

1. Temperature
2. Humidity

**OUTPUT**

1. Toxicological profile
2. Preclinical skin irritation profile
3. Cadaver skin flux rate
4. In vitro dissolution stability
5. Adhesive strength stability
6. Release strength stability

Transdermal Formulation Development
Process Variables

**INPUT**

Discrete factors:
1. Operator/machine
2. Analytical errors
3. Air quality

Continuous factors:
1. Humidity
2. Sedimentation rate of the slurry
3. Air flow rate drift

**OUTPUT**

1. Coat weight uniformity
2. API content uniformity
3. Residual solvent content
4. Degradation product
5. Dissolution rate profile
6. Appearance

UNCONTROLLED FACTORS
coating process
Develop Risk Management Strategy

• Follow the priority list to tackle each risk
• Develop risk management strategy accordingly
Outcome

• The critical attributes are identified.
• The potential risks in the formulation and in the manufacturing process are identified.
• The control strategies will be developed
• Less surprise in process drift and better handling of its occurrence
Process Analytical Technologies

• Roles in dealing with process drift
  – Real time detection
  – Real time action

• Available technologies: Infrared, Near-Infrared, Raman Spectroscopy, UV-VIS Spectroscopy
Conclusions

• Trivial process changes can become big problems in the drug product production
• Experience and knowledge are essential to solve process drift issues
• Quality by Design and Process Analytical Technology can help to better understand materials compatibility and control the process drift
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