Characterization and Control of Reactive Components in Film Coatings

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Presentation Outline

- Prior work on reactive impurities in coating formulations
- Colorcon work on reactive impurities
- Conclusions: Impurity control strategies
Potentially Reactive Excipients & Excipient Impurities

- Aldehydes
  - formaldehyde
- Hydroperoxides
- Organic acids
  - citric acid
  - formic acid
- Reducing sugars
  - dextrose/glucose
  - lactose
- Metals
- Solvents
- Water

Proposed Mechanism for Oxidative Degradation of Polyethylene Glycol to Form Formaldehyde and Formic Acid

Two degradants formed (20% of API degraded after 6 weeks at 40°C/75% relative humidity).

- NFV from reaction with formic acid
- NMV from sequential reaction with formaldehyde and then formic acid
- Both formaldehyde and formic acid originated from PEG 3350 in the coating (also comprising cellulose acetate).

Degradants were controlled by lowering the PEG concentration in the coating so that the PEG remained compatible with cellulose acetate – i.e. not free to migrate into the core.

A degradant (reaction product of formaldehyde with irbesartan) was characterized in tablets coated with Opadry II white comprising PEG.

The degradant was initially detected after long-term stability storage of the coated tablets at 50°C for 9 weeks.

Degradant formation was confirmed by evaluating a binary blend of the coating with irbesartan after 8 days at 65°C.

Degradant formation was ultimately controlled by removing PEG from the coating.

Formic acid and formaldehyde are present in a variety of excipients.


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Amgen Derivitization Technique (60°C)

Derivitization carried out in a GC headspace vial.
# Formic Acid and Formaldehyde Detection in Film Coating Components (Colorcon, 2008)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Number of Lots</th>
<th>Formic acid (ppm)</th>
<th>Formaldehyde (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl alcohol</td>
<td>12</td>
<td>34.2 ± 6.0</td>
<td>5.6 ± 2.6</td>
</tr>
<tr>
<td>HPMC 2910 (3 cP)</td>
<td>6</td>
<td>57.7 ± 10.7</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>HPMC 2910 (6 cP)</td>
<td>6</td>
<td>97.5 ± 27.5</td>
<td>14.7 ± 3.3</td>
</tr>
<tr>
<td>HPMC 2910 (15 cP)</td>
<td>6</td>
<td>67.7 ± 25.9</td>
<td>12.8 ± 5.7</td>
</tr>
<tr>
<td>PEG 400 (no BHT)</td>
<td>3</td>
<td>14.7 ± 7.6</td>
<td>7.7 ± 2.3</td>
</tr>
<tr>
<td>PEG 3350 (no BHT)</td>
<td>3</td>
<td>10.3 ± 2.1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PEG 3350 (w/ BHT)</td>
<td>3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Triacetin</td>
<td>3</td>
<td>16.3 ± 5.5</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not detected (no evidence of any peaks).

Farrell TP, Ferrizzi DF. Determination of Trace Formic Acid and Formaldehyde in Film Coatings Comprising Polyvinyl Alcohol (PVA). *2008 AAPS Annual Meeting (Atlanta, GA), Poster W4262.*
Formic Acid & Formaldehyde Levels in PVA-based Opadry® II White Formulations Comprising PEG with or without BHT

Retrospective stability investigation – all retains were stored in sealed containers at temperatures < 30°C.

Farrell TP, Ferrizzi DF. Determination of Trace Formic Acid and Formaldehyde in Film Coatings Comprising Polyvinyl Alcohol (PVA). 2008 AAPS Annual Meeting (Atlanta, GA), Poster W4262.
Formic Acid & Formaldehyde Levels in a PVA-Based Opadry II Formulation (w/ TiO₂; BHT-free PEG)

Formic Acid Level (ppm) vs. Storage Condition

Formaldehyde Level (ppm) vs. Storage Condition

Study Design

- **Product:** PVA-based Opadry II white dry powder (BHT-free PEG)
- **Packaging:** standard commercial containers (polyethylene bag within a cardboard box)
- **Storage conditions:** 25°C/60%RH, 30°C/65%RH, 40°C/75%RH
- **Pulls:** 3, 6, 12, 24 & 36 months (40/75 through 6 months only)
- **Analytical methods:** standard methods previously described

Formic acid and formaldehyde levels modestly increase and then plateau.
Formic Acid & Formaldehyde Levels in a PVA-Based Opadry II Formulation (w/TiO$_2$, Red 30 and Red 40 lakes; BHT-free PEG)

Study Design
- **Product:** PVA-based Opadry II red aluminum lake colorants (BHT-free PEG)
- **Packaging:** standard commercial containers (polyethylene bag within a cardboard box)
- **Storage conditions:** 25°C/60%RH, 30°C/65%RH, 40°C/75%RH (25°C back up only)
- **Pulls:** 3, 6, 12, 24 & 36 months (40/75 through 6 months only)

Formic acid and formaldehyde levels were significantly lower when lakes were used.
## Forced Degradation of Excipients at 60°C in Sealed Ampoules

**Formic acid concentration in ppm**

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Time Zero</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>T8/T0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA</td>
<td>41</td>
<td>42</td>
<td>45</td>
<td>1.01</td>
</tr>
<tr>
<td>HPMC 6 cP</td>
<td>59</td>
<td>72</td>
<td>83</td>
<td>1.41</td>
</tr>
<tr>
<td>PEG 3350 (no BHT)</td>
<td>5</td>
<td>802</td>
<td>782</td>
<td>156.40</td>
</tr>
<tr>
<td>PEG 3350 (with BHT)</td>
<td>&lt; 5</td>
<td>25</td>
<td>52</td>
<td>~10.00</td>
</tr>
</tbody>
</table>

Formic acid levels increase at the fastest rates for pure PEG.
**Forced Degradation of Excipients at 60°C in Sealed Ampoules**

Formaldehyde concentration in ppm

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Time Zero</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>T8/T0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0.83</td>
</tr>
<tr>
<td>HPMC 6 cP</td>
<td>11</td>
<td>16</td>
<td>18</td>
<td>1.64</td>
</tr>
<tr>
<td>PEG 3350 (no BHT)</td>
<td>5</td>
<td>20</td>
<td>28</td>
<td>5.60</td>
</tr>
<tr>
<td>PEG 3350 (with BHT)</td>
<td>&lt;5</td>
<td>6</td>
<td>9</td>
<td>~2.00</td>
</tr>
</tbody>
</table>

Formaldehyde levels also increase at the fastest rates for PEG.
Iron and other residual transition metals promote PEG degradation. Aluminum lakes appear to inhibit formic acid formation or complex it once formed.
Formic Acid Levels in PVA-based Opadry II Formulae in Sealed Ampoules at 40 & 60°C (PEG with or without BHT)

BHT significantly inhibits formic acid formation at both 40 and 60°C.
Conclusions: Formaldehyde and Formic Acid Control Strategies

- Controlling impurities may not necessarily mean eliminating excipients
  - Use antioxidants with PEG-containing excipients.
  - Fully assess the impact of using excipients/colorants comprising redox active metals when PEG-containing excipients are used:
    - evaluate film coatings with aluminum lake pigments
  - Examine temperature dependence of degradant formation and consider processing and storage temperature limitations.
  - Reduce the level of PEG-containing excipients.
  - Explore substitution of PEG-containing excipients when other control strategies are unsuccessful.
Acknowledgements

- Mr. David Ferrizzi – Sr. Manager - Analytical Services (Colorcon)
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