Understanding and mitigating the consequences of undesired crystallisation taking place during washing of active pharmaceuticals

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Introduction

Important to maintain physico-chemical crystal properties throughout isolation

- Crystallisation
- Filtration
- Washing
- Drying
- Secondary processing

Washing plays a key role in isolation:
- To remove unwanted crystallisation solvent & impurities
- Crystallisation continues whenever there is super-saturation and particles

Project Aim & Objective

A wash solvent guide is designed to look at various important factors while selecting a wash solvent:

- Efficient removal of mother liquor and prevent cake desaturation
- Assist during drying
- Requirements for good wash solvent
- Remove impurities without dissolving API
- Wash solvent viscosity-density
- API recovery (washing yield)
- No crystal morphology change
- No anti-solvent effect - Avoid API specific impurities nucleating during washing

This project looks at developing a screening methodology to quantitatively analyse the propensity for precipitation of API and its impurities during the washing process.

Materials & Method

- This analysis is conducted on paracetamol crystallised from three different crystallisation solvents; ethanol, isopropanol and isooamyl alcohol
- Three wash solvents are evaluated; heptane, acetanilide and isopropyl acetate
- Saturated solution is prepared using paracetamol and two related impurities (at 2mol%: metacetamol & acetalitriol
- For wash solution, different ratios of crystallisation and wash solvents are used: 90-10, 75-25, 50-50, 40-60, 30-70, 20-80, 10-90, 100% wash solvent (% by volumes)

Anti-solvent screening procedure:

1. Centrifuge tube & filter weighing
2. Addition of saturated crystallisation solution in centrifuge filter
3. Addition of wash solution in centrifuge filter
4. Mixing of solution present in the filter using a vortex shaker for 1 minute
5. Centrifugation for separation of solid and liquid phase
6. Weighing of centrifuge filter and tube at the end. Collection of liquid phase in glass vial 2
7. HPLC analysis performed on both the solid precipitate and final liquid filtrate
8. Solubility of paracetamol was also measured in binary solvent mixtures of crystallisation and wash solvent at 22°C using gravimetric analysis

Results

- Anti-solvent effect observed from previous 1ml glass vial procedure (where 300µL of saturated solution and 700 µL of wash solution is used):

<table>
<thead>
<tr>
<th>Wash Solvents</th>
<th>Heptane</th>
<th>Acetanilide</th>
<th>Isopropyl acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>40-60%</td>
<td>No nucleation</td>
<td>10-90% (w/w)</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>40-60%</td>
<td>No nucleation</td>
<td>0-100% (w/w)</td>
</tr>
<tr>
<td>Isooamyl alcohol</td>
<td>20-80%</td>
<td>No nucleation</td>
<td>No nucleation</td>
</tr>
</tbody>
</table>

- Anti-solvent effect observed from centrifuge filter vial method (where 120 µL of saturated solution and 280 µL of wash solution is used):

<table>
<thead>
<tr>
<th>Wash Solvents</th>
<th>Heptane</th>
<th>Acetanilide</th>
<th>Isopropyl acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>30-70%</td>
<td>No nucleation</td>
<td>No nucleation</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>30-70%</td>
<td>No nucleation</td>
<td>No nucleation</td>
</tr>
<tr>
<td>Isooamyl alcohol</td>
<td>10-90%</td>
<td>No nucleation</td>
<td>No nucleation</td>
</tr>
</tbody>
</table>

Delayed precipitation of solutes observed using the centrifuge vial method is due to the kinetics of nucleation (mixing and scale of the experiment?).

- Two distinct examples:

  - **Ethanol – Acetanilide**: no anti-solvent effect was observed

  - **Ethanol – Heptane**: anti-solvent effect was observed

Conclusion & Future Work

- Poorly designed washing process can result in uncontrolled crystallisation of both API and impurities, affecting final product quality
- Binary solvent mixture's solubility data (crystallisation & wash solvent) assist in developing washing strategy that prevents product dissolution & agglomeration
- Ethanol – Heptane system, washing should be carried out in steps (first wash: 40:60 ratio (cryst : wash solvent) of wash solution; final wash: pure heptane)
- In future, this work on mapped wash solvent composition boundaries will be used to explore the role of uncontrolled washing on product purity and agglomeration

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