Formulation for Stability: Moving Beyond Excipient Compatibility

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Reactive Excipients

• Some degradation due to direct excipient-drug reaction
• Example: Maillard reaction between secondary amines (amino acids) and reducing carbohydrates (e.g., lactose)—leads to brown colors + multiple products
• Relatively uncommon (other than this reaction)
Reaction with Excipient Impurities/Degradants

• Peroxides
• Formaldehyde (and other aldehydes)
• Acids
  • Formic acid
  • Acetic acid
Non-reactive Excipient Impact

- Effects proportional to interfacial contact
- Specific degradation will show different effects
- Some degradation mechanisms will be more sensitive than others to excipients
Drug Concentration Impact in Solid Formulations

• Impact of concentration (approximation):

\[ \log k = \alpha \log \frac{100\%}{%\text{active}} + \log k_0 \]

• \( \alpha \) may be independent of temperature/RH
• \( \alpha \) may depend on T/RH (catalysis)
Example

*CP-481715 tablets*

Example

G. Scrivens; 2017 Presentation from Science of Stability Conference

Mixed with MCC
Example

A. Dill; 2015 Presentation from Science of Stability Conference

Prasugrel Pediatric

Log k vs. log(100%/%API) at different temperatures:
- 25°C: 0.2% Drug Load
- 30°C: 0.6% Drug Load
- 40°C: 0.2% Drug Load

Temperature points:
- 25°C (0.2% Drug Load)
- 30°C (0.6% Drug Load)
- 40°C (0.2% Drug Load)
Excipient Compatibility

• Binary blend stability (often rank order)
  • 1:1 API:Excipient
  • Representative API level:Excipient level
Problems with Binary Excipient Compatibility

- For low level excipient, greatly exaggerates issues
  - Often leads to excluding magnesium stearate
- Since true interaction is base on log-log scaling, formulation stability is not a weighted average of the binary stabilities
- Rank order not appropriate
  - Excludes good enough excipients
- Stability studies can be slow delaying product development
Screening Stability (Rank Order)

Two formulations screened 2 weeks, 70°C/75%RH

<table>
<thead>
<tr>
<th>Formulation</th>
<th>70°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.18</td>
</tr>
<tr>
<td>B</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Which formulation should you proceed with for ambient (25°C/60%RH) storage?
Longer shelf-life

The graph shows the relationship between the natural logarithm of the rate constant ($\ln k$) and the reciprocal of the temperature ($1/T$). The points A and B represent different temperatures:

- **70°C**
- **60°C**
- **50°C**
- **25°C**

The graph indicates that as the temperature decreases, the rate constant $k$ increases, leading to a longer shelf-life.
Screening Stability (Rank Order)

- Rank order from high temperature often opposite to room temperature
- Rank order does not distinguish formulations that are all good or all bad
Excipient Compatibility Formulation Development
(Real Time Stability)

**Long development time for stable formulations**

Traditional Formulation Development: 6-12 mos.

1. API-excipient binary blends → 3-6 mo
2. Use data to design formulations → 3-6 mo
3. Develop final formulation

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Rapid Formulation Development: ASAPprime® Tiered Approach

- Full formulations prepared (e.g., tablets, capsules)
  - 3-4 Tier 1 full formulations
  - Low API concentration (worst case)
- ASAP studies conducted
- Tier 1 formulations work for most APIs and enable fast development
- If Tier 1 fails, Tier 2 formulations used
- Rare that we need to go past this
- Must justify formulation used: do not need excipient compatibility for regulatory submissions.
Rapid Formulation Development

ASAP-Based Formulation Development using Tiers: 1-4 mos.

- 2-3 1st tier formulations
  - 3 wk
  - Develop final formulation

- 2-3 2nd tier formulations
  - 3 wk
  - Develop final formulation

- 2-3 3rd tier formulations
  - 3 wk
  - Develop final formulation

Develop final formulation

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# Example Tier 1 Tablet Formulations

<table>
<thead>
<tr>
<th>Function</th>
<th>Ingredient</th>
<th>Formulation 1 wt%</th>
<th>Formulation 2 wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>API</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Diluent (ductile)</td>
<td>MCC</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Diluent (brittle)</td>
<td>Lactose</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Diluent (brittle)</td>
<td>Mannitol</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Croscarmellose sodium</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Crospovidone</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Binder</td>
<td>HPC</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Binder</td>
<td>Povidone</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td>Magnesium stearate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td>Stearic acid</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Tiered Approach to Formulation Development

Advantages to ASAP Approach

• Fewer resources, much shorter time-line
• Most cases can go straight to experienced (manufacturable) formulation (and processing) space
• Does not rule out effective excipients based on rank-order or exaggerated binary results