Proteins at Interfaces: Formulation Approaches
Minimizing Device Interface Incompatibilities

Mariana N. Dimitrova, Principal Scientist, Ph. D.
Formulation Sciences Department, MedImmune

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Outline

1. Combination products for protein therapeutics
2. Challenges with interfacial incompatibilities
3. Case study: formulation approaches minimizing interface incompatibilities
4. Formulation solutions and approaches
Combination Products Offer Valuable Advantages

◆ Improved compliance
  – Minimizing dosage errors
  – Improved patient safety
    • Prevent undesirable needle-sticks

◆ Product differentiation
  – User convenience
  – Competitive product profile

◆ Device specific advantages
  – Improved cost of goods due to minimal overfill (PFS)
Device Related Challenges Developing Robust Combination Products

**Physical/chemical instabilities caused by leachables**
- Tungsten, Fe-ions from needle, stopper leachables
- Heterogenous particles, chemical modifications, particles, soluble aggregates, unfolded protein

**Interface incompatibilities:**
- Air bubble, polymers, silicone oil, stopper
- Soluble aggregates, particles, adsorption losses, unfolded protein

**Device specific:**
- Oxygen permeability, glass delamination, needle clogging, light exposure
Common Materials in Devices in Direct Contact with the Protein Therapeutics

- Glass
  - Long term storage experience
  - Glass breakage
  - Glass delamination
  - Adsorption to the solid surfaces
  - pH shift
  - High degree of thermal expansion
  - Prone to UV degradation
  - Flammable

- Cyclic polyolefin
  - Enable novel primary container dimensions, i.e. reservoirs
  - Oxygen permeability
  - Adsorption to solid interfaces
  - Interfacial incompatibilities

- Polyethylene
  - Potential for stress cracking (HDPE)
  - Prone to UV degradation
  - Oxidation prone

- Polypropylene
  - High degree of thermal expansion
  - Oxidation prone
  - Flammable

- Polyester
  - Thermoplastic elastomer
  - Interfacial incompatibilities
  - Adsorption to solid interfaces

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Formulation and User Requirements
Related Challenges

◆ Formulation development
  – High concentration liquid formulations
    – Viscosity, tonicity, osmolality, etc.
  – Materials of construction compatibility
  – Acceptable levels of leachables (silicone oil, tungsten, etc.)
  – Formulation optimization for the specific device
    • Surfactant optimization

◆ User requirements
  – Accurate, painless, convenient, fast… administration
    • Small fill volume
    • < 10s injections
    • <27G needles
Formulation, Device and User Requirements

Drug Product Stability (Formulation requirements)

Device Requirements

User Requirements

Tug of War
Particle Formation is Most Common Challenge in Incompatible Devices

- Examples of syringes incompatible with a monoclonal antibody
  - A: incompatible material of the syringe barrel
  - B: exceeding the defined tolerable levels of silicone oil and tungsten

![Visible particles after 9 months at 2-8°C](image)

**A**

**B**
Case Study: Formulation Approaches Minimizing Interface Incompatibilities

- Interfacial incompatibility leading to conformational changes at the interfaces
- Impacting product CQAs: visible particle formation, subvisible particles (SVP), protein concentration loss
- Formulation approaches resolving interface incompatibilities
# Interface Incompatibilities

<table>
<thead>
<tr>
<th>Product Attributes</th>
<th>Glass</th>
<th>Polyester*</th>
<th>Polyethylene**</th>
<th>Polypropylene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein concentration loss</td>
<td>No</td>
<td>No</td>
<td>Yes (25%)</td>
<td>Yes (5-10%)</td>
</tr>
<tr>
<td>Visible particles</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SVP</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Example SVP images by MFI</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Structural changes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Interfacial compatibility</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Incompatible</td>
<td>Incompatible</td>
</tr>
</tbody>
</table>

* Polyethylene Terephthalate Glycol (PETG)
** High Density Polyethylene (HDPE)
Trace Elements Analysis by ICP-MS

- No significant difference was seen in the trace elemental profile
- Calcium was found to be high in compatible and incompatible containers

<table>
<thead>
<tr>
<th>Trace Elements</th>
<th>PETG (ppb)</th>
<th>HDPE (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>13.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Copper</td>
<td>2.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Iron</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Calcium</td>
<td>1103.0</td>
<td>1096.0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>21.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Aluminium</td>
<td>4.1</td>
<td>&lt; LOQ</td>
</tr>
</tbody>
</table>
Particle Composition Analysis by SEM-EDX and FTIR

- Majority of particle contained only protein (denatured)
- Isolated particles contained leachables
  - Polyethylene containers: Ti and Si
  - Polypropylene containers: Carboxymethyl cellulose
Interface Incompatibilities Caused Structural Changes (DSC)

- Protein structural perturbations/unfolding appear to be the main root cause for the observed interface incompatibilities
Formulation Approaches Resolving Interface Incompatibilities

- Formulation development preserving protein structure at the interfaces
- Two formulations were developed resolving the interfacial incompatibilities
Formulation Excipients Imparted Colloidal Stabilization

High-throughput Dynamic Light Scattering

- Self-association as a function of the protein concentration was not observed in the formulations preventing interfacial incompatibilities (Formulations B and C).
Interaction parameter (kD) is obtained from plot of diffusion coefficient vs. concentration. Positive kD indicates repulsive interactions whereas negative values suggest attractive interactions.

Lower negative kD value are indicative of minimized protein-protein attractive interactions in the stabilizing formulations B and C.
## Formulation Approaches Resolving Interface Incompatibilities

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Compatible Interfaces</th>
<th></th>
<th>Incompatible Interfaces</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-10µm</td>
<td>≥ 10µm</td>
<td>≥ 25µm</td>
<td>2-10µm</td>
</tr>
<tr>
<td>Formulation A</td>
<td>897</td>
<td>2</td>
<td>0</td>
<td>29387</td>
</tr>
<tr>
<td>Formulation B</td>
<td>689</td>
<td>53</td>
<td>17</td>
<td>1162</td>
</tr>
<tr>
<td>Resolving incompatibilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation C</td>
<td>819</td>
<td>130</td>
<td>46</td>
<td>795</td>
</tr>
<tr>
<td>Resolving incompatibilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- The two formulations preventing protein perturbation/structural changes at the interfaces minimized SVP and visible particles formation (SVP analysis by MFI)
Case Study Summary and Control Strategy

- Structural perturbations, significant protein concentration loss and particle formation (visible and SVP) were detected at multiple incompatible interfaces for a protein therapeutic.

- Control and mitigation strategy:
  - Developed two formulations preventing interface structural perturbations, particle formation and protein concentration loss
  - Evaluated compatible materials of construction
Formulation Approaches Improving Interface/Device Compatibility

- Extensive evaluation of compatible materials of construction of the device
  - Syringe, cartridge, stopper, etc.

- Formulation optimization/robustness evaluation with the specific device:
  - Real size/surface area (surfactant optimization)
  - Real life stresses during transportation, clinical administration, etc.

- Acceptable levels of lubrication (silicone oil) in the device

- Decoupled evaluation studies to define the acceptable levels of extractables and leachables
  - Primary container or device components in direct contact with the product

- In partnership with the device engineers evaluate device and patient/user requirements and the potential impact on the formulation.
  - E.g. solution viscosity and needle gauge selection

- Early compatibility risk assessment input into the design of the device
Summary

- Integrating protein therapeutics with devices it is important to consider:
  - Product requirements and characteristics
  - Device performance and requirements
  - Patient/user interface

- We’ve seen, through a case study, the impact of interfacial incompatibilities on Drug Product CQAs and how to resolve them utilizing formulation approaches

- Combination product risk assessment
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