Improving Suspendibility of a Water-Insoluble Active in a Reconstitutable Powder for Oral Suspension

Jeff Williamson, Dr. Brad Gold, Allen Lawson, Keith Moore

OBJECTIVE
To improve the suspendibility of a water-insoluble active pharmaceutical ingredient (API) in a sorbitol-based reconstitutable powder for oral suspension formulation using two novel excipients Sentry™Polyox™WSR N80, NF (polyethylene oxide) and Avicel CL-611® NF (microcrystalline cellulose/carboxymethylcellulose sodium).

BACKGROUND
Reconstitutable powders for oral suspension are a widely accepted dosage form in the industry, especially with actives that may have stability issues when dispersed in an aqueous vehicle. Powders for oral suspension can be formulated with, but not limited to, various functional excipients such as suspending agents, binders, antimicrobial excipients, glidants, buffers, flavors, and sweeteners processed in a granulation and/or dry blend process.

In this case study, API (X) is a highly insoluble compound with a particle size of approximately 14 microns and targeted as a powder for oral suspension dosage form. Sentry™Polyox™WSR N80, NF (polyethylene oxide) and Avicel CL-611® NF (microcrystalline cellulose/carboxymethylcellulose sodium) were added in the proposed formulation in order to explore their nominal concentrations to improve suspendibility of the active, feasibility of processing, and impact on physical (i.e. sedimentation rate, viscosity) and chemical analyses (API assay).

Once the final formulation was selected, the POS formulation was processed using conventional pharmaceutical processing equipment and formulation techniques in both small scale and large scale quantities.

METHODOLOGY
Materials
- Sentry™Polyox™WSR N80, NF (polyethylene oxide), supplied by Dow Chemical, Inc.
- Avicel CL-611® NF (microcrystalline cellulose/carboxymethylcellulose sodium), supplied by FMC, Inc.
- Various formulation excipients supplied by ISP, Western Flavors Inc., Cabot, and SPI Polyols Inc.
- Various analytical reagents required for assay analysis
Manufacturing Equipment
Small Scale
• Key KG-5 High Shear Granulator
• Overhead mixer equipped with standard impeller blade
• Masterflex peristaltic pump equipped with size No. 14 platinum-cured silicone tubing
• Glatt GPCG-1 Fluid Bed Dryer
• Quadro Comil
• Keith V-shell Blender

Large Scale
• Fielder PMA-100 High Shear Granulator
• Pressurized spray vessel and transfer lines
• O’Hara Fluid Bed Dryer with 100L bowl attachment
• Fitzmill Model M
• Gemco 3 Cubic Foot Slant Cone Blender

Analytical Equipment
• Jasco 1500 Series HPLC System with a Phenomenex Luna Phenyl-Hexyl Column, 3-micron, 100 X 4.6 mm
• Brookfield DV-III+ Rheometer with Small Sample Adapter Set

Formulation Rationale
An API (X), with limited aqueous solubility and distinct color, was formulated in a sorbitol-based reconstitutable powder for oral suspension. The initial formulation was reasonably unsuccessful in maintaining a suitable suspendibility of the active. Sentry™Polyox™WSR N80, NF and Avicel CL-611® NF were added to the formulation in an attempt to physically increase the suspendibility of the active when compared to control.

The first formulation was evaluated using Sentry™Polyox™WSR N80, NF at concentrations of 1-2% w/v of reconstituted product. In a separate formulation, Avicel CL-611® NF was added in concentrations of 1-2% w/v of reconstituted product.

Polyethylene Oxide, NF
(Sentry™ Polyox™ WSR N80 NF, Dow Chemical)
Function: Mucoadhesive, tablet binder, thickening agent

Microcrystalline Cellulose and Caboxymethylcellulose Sodium, NF
(Avicel CL-611®, FMC Biopolymer)
Function: Coating agent, tablet and capsule disintegrant, tablet binder, stabilizing agent, suspending agent, viscosity increasing agent
## RESULTS

### Sedimentation Evaluation

**Table 1: Sedimentation Evaluation with Sentry™Polyox™WSR N80, NF**

<table>
<thead>
<tr>
<th>Elapsed Time</th>
<th>Control</th>
<th>0.5% w/v PEO</th>
<th>1.0% w/v PEO</th>
<th>1.5% w/v PEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>45mL liquid, 10mL foam</td>
<td>46mL liquid, 15mL foam</td>
<td>46mL liquid, 55mL foam</td>
<td>45mL liquid, 25mL foam</td>
</tr>
<tr>
<td>10 minutes</td>
<td>16mL void volume</td>
<td>5mL void volume</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>20 minutes</td>
<td>30mL void volume</td>
<td>5mL void volume</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

**Table 2: Sedimentation Evaluation with Avicel CL-611 ® NF**

<table>
<thead>
<tr>
<th>Elapsed Time</th>
<th>Control</th>
<th>2% w/v Avicel CL-611 ®</th>
<th>1% w/v Avicel CL-611 ®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>45mL volume with foam layer</td>
<td>55mL volume with foam layer, viscosity change (thicker than control)</td>
<td>55mL volume with foam layer, slight viscosity change (slightly thicker than control)</td>
</tr>
<tr>
<td>10 minutes</td>
<td>10-15mL void volume</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>20 minutes</td>
<td>30mL void volume, 5mL of foam</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>30 minutes</td>
<td>30mL void volume, 5mL of foam</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>18 hours</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>
**FIGURE 1** – Sedimentation Evaluation with Sentry™Polyox™WSR N80, NF

Left to Right – Control, 0.5% w/v PEO, 1.0% w/v PEO, and 1.5% w/v PEO after 20 minutes

**FIGURE 2** – Sedimentation Evaluation with Avicel CL-611®, NF

Left to Right – Control, 2.0% w/v Avicel CL-611, and 1.0% w/v Avicel CL-611 after 20 minutes
FIGURE 3 – Viscosity Profile of API (X) Formulations

Table 3 – Assay Data of API (X) Formulations

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>% API (X) Label Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>97.8</td>
</tr>
<tr>
<td>Formulation with 1.5% w/v Avicel CL-611® NF</td>
<td>99.6</td>
</tr>
<tr>
<td>Formulation with 1.5% w/v Sentry™Polyox™WSR N80, NF</td>
<td>102.8</td>
</tr>
</tbody>
</table>
DISSCUSSION AND CONCLUSIONS
Sentry™Polyox™WSR N80, NF and Avicel CL-611® NF were selected in this case study due to their rapid rate of hydration and functional classification. As we have seen, Tables 1 and 2 (along with Figures 1 and 2) show the increased suspendibility of API (X) over time when Sentry™Polyox™WSR N80, NF and Avicel CL-611® NF were added to the formulation. Figure 3 shows the viscosity profile as a result of adding the two excipients, which increases with their increasing concentrations. Table 4 and Figure 5 show that the addition of these excipients did not interfere with the assay or dissolution profile.

In conclusion, Sentry™Polyox™WSR N80, NF and Avicel CL-611® NF increased the suspendibility of a water-insoluble API (X) in a reconstitutable powder for oral suspension.