**Effect of residual solvents on the surface characteristics of lyophilized product**

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**OBJECTIVES**

The objectives of this study were (i) to study the effect of different residual/organic solvents (isopropyl alcohol, acetone, Toluene) on the surface characteristics of lyophilized product (ii) to confirm the root cause of cake puffing and pitting during lyophilization while using two different sources of API.

**BACKGROUND**

Freeze-drying process consists of three major steps: (i) freezing (ii) primary drying, & (iii) secondary drying. Freezing is the first step of the lyophilization process and has profound effect on product quality and process as it affects the cake appearance, integrity, reconstitution time, finished product (assay & impurities) and stability of the product.

API (active pharmaceutical ingredient) from two different sources (S1 and S2) were used to develop a lyophilization cycle with same formulation and process parameters (freezing rate of 0.25 °C/min to -40°C) including primary and secondary drying. Lyophilized cake with S1 was smooth but cake puffing and cake pitting were observed for S2. To overcome this issue, effect of freezing rates on the product characteristics were studied.

The cake puffing and puffing could be due to solvents present in the API. Hence, residual/organic solvents (isopropyl alcohol, Acetone, and Toluene with freezing points of -89.5°C, -94.3°C and -96.0°C respectively) present in the API were studied.

**METHODS**

A) Freeze-drying of residual organic solvents: Placebo (mannitol and sodium acetate in water for injection) was prepared in bulk. The solution was divided into four sublots and was spiked with Isopropyl alcohol, Acetone, Toluene and an equal mixture of these solvents. The final volume of 5 mL of placebo solution in a 10 mL vial with 0.1 mL and 0.3 mL of organic solvent per vial. The vias were placed in lab lyohilizer and freezing was performed at -52°C followed by primary (0.6°C/min) and secondary drying (23°C).

B) Freeze-drying cycle: The freeze-drying cycles at the R&D scale was developed using Virto 25 XL lab lyophlizer

(i) Single step freezing: Freezing rates of 0.16°C/min and 0.34°C/min were used to freeze the product to -40°C.

(ii) Two step freezing: Two step freezing at rates of 0.21 °C/min and 0.34°C/min followed by 0.11 °C/min freezing to -40°C followed by 0.11 °C/min to -40°C were studied.

C) Fill volume: Fill volume level of 5 mL in 10 mL vial was studied for both S1 and S2 at lab and pilot scale.

D) Scale-up of freeze-drying process: The optimized freeze-drying cycle was scaled up using 500 mL lyophlizer (Millipore).

**RESULTS**

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Testing</th>
<th>Lab Scale</th>
<th>Pilot Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cake Appearance</td>
<td>Smooth surface</td>
<td>Smooth surface</td>
<td>Smooth surface with no puffing and pitting</td>
</tr>
<tr>
<td>Cake Integrity</td>
<td>Conforms</td>
<td>Conforms</td>
<td>Conforms</td>
</tr>
<tr>
<td>Reconstitution time</td>
<td>&lt; 1 minute</td>
<td>&lt; 1 minute</td>
<td>&lt; 1 minute</td>
</tr>
<tr>
<td>Moisture Content</td>
<td>0.51%*</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>pH of the reconstituted solution</td>
<td>(i) 7.91</td>
<td>2.9*</td>
<td>3.0</td>
</tr>
<tr>
<td>Physical Product</td>
<td>106.9%*</td>
<td>106.4%*</td>
<td>99.5%*</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>0.15%*</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Freezing Rates (°C/min)</td>
<td>(i) 0.16°C/min</td>
<td>(ii) 0.34°C/min</td>
<td>(i) 0.16°C/min</td>
</tr>
</tbody>
</table>

* Data for batch with freezing rate of 0.34 °C/min

**CONCLUSIONS**

- The surface morphology of the lyophilized product may be affected by the residual solvent present in the product and surface characteristics will vary based on the type of residual solvent.
- The modification of the freezing step in the lyophilization cycle can result in acceptable morphology of the lyophilized cake when solvent levels in the API is changed.

**REFERENCES**


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