Freeze drying (lyophilisation) is a stabilisation method that is widely used in the pharmaceutical industry for drugs, vaccines, antibodies and other biological material. Freeze drying can be a complex process to handle effectively but despite improvements in analytical and process science a number of misconceptions persist. Below we look at a selection of those we encounter most often.

1. **Colder condenser temperatures mean faster freeze drying**

   It is often thought that a colder condenser will improve freeze drying and “suck the water out faster”. However it is if difference in vapour pressure between product and condenser that drives the process, not the condenser temperature alone.

   Increasing the pressure differential between product and condenser will speed up the process. However lowering the temperature of the condenser is less efficient than raising the temperature of the product. If we consider table 1 below we can see that the pressure differential decreases as temperature drops; for example the pressure difference between 70°C and 80°C is just 0.0021mbar, whereas the difference between 0°C and 10°C is 3.505mbar.

<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>mbar</th>
<th>Microns</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.1048</td>
<td>4579</td>
</tr>
<tr>
<td>-4</td>
<td>4.3730</td>
<td>3280</td>
</tr>
<tr>
<td>-8</td>
<td>3.1011</td>
<td>2326</td>
</tr>
<tr>
<td>-10</td>
<td>2.5998</td>
<td>1950</td>
</tr>
<tr>
<td>-12</td>
<td>2.1758</td>
<td>1632</td>
</tr>
<tr>
<td>-16</td>
<td>1.5092</td>
<td>1132</td>
</tr>
<tr>
<td>-20</td>
<td>1.0346</td>
<td>776</td>
</tr>
<tr>
<td>-40</td>
<td>0.1288</td>
<td>96.6</td>
</tr>
<tr>
<td>-80</td>
<td>0.0005</td>
<td>0.4</td>
</tr>
</tbody>
</table>

   *Table 1 Vapour pressure of ice*

   Of course, the product temperature cannot be forced above its collapse point during primary drying. However a more favourable thermal profile might be generated via reformulation, which would then allow the freeze drying process to be driven more quickly.

   Colder condensers are designed to process non-aqueous solvents which have a low freezing point. Unnecessarily cold condensers will increase the cost and complexity of the equipment and also increase running costs.

2. **“One size fits all” cycle development**

   In both manufacturing and development it’s not uncommon to find one cycle borrowed for other applications. We have seen one instance where one cycle was used for over 200 different products! The reality is, a freeze drying cycle needs to be optimized for a specific product, batch parameters and freeze dryer. An unsuitable cycle will be inefficient at best and can even risk process failure.

   Even seemingly small changes can have significant effects. For example, if the container size is changed the product may dry more quickly (requiring additional thermal energy from the shelf to counteract sublimation cooling) or more slowly (requiring less heat energy and extended primary drying). Formulation changes including the type or amount of active ingredient will affect the thermal characteristics of the product overall. A small change in fill volume could increase the overall vapour load of the batch, decreasing the drying rate or even overloading the condenser.
Scaling up from development to production is particularly important as production equipment tends to have different process capabilities. For example, laboratory freeze dryers often feature lower condenser temperatures than those in production systems. When changing equipment proper consideration should be given to the implications and testing carried out.

3. **Vials can be filled to any depth**

Product freeze-dries from the top (surface) down and as it does, a layer of dried product gradually builds up on top of the remaining frozen product. This dried layer creates an increasing impedance to the sublimated water vapour trying to escape from below. The thicker the layer of dried product, the more difficult it is for the vapour to escape. Drying will slow, the effect of sublimation cooling will decrease, and product temperature will rise. In some cases this may risk collapse, but even in less serious instances the rate of drying will continue to slow and the process will be increasingly inefficient.

Where conditions allow, maximum product depth should be in the region of 12-15mm. This is relevant both for product in vials and bulk product.

4. **It doesn’t matter how a product is frozen—it’s the drying that’s important**

The purpose of freeze drying is to create a dry product, so often the focus is on the drying stages.

Fundamentally it is important to ensure that the product is thoroughly frozen before the drying stage starts as the vacuum applied in primary drying will cause any unfrozen product to “boil”. To ensure the product is thoroughly frozen it is vital to know its freeze / melt temperature, which may be significantly lower than the point at which it appears solid.

The manner in which freezing is undertaken will also affect how drying progresses. Large ice crystals create an open
structure with large paths through which vapour can escape, facilitating easier drying. Small, less contiguous crystals imply narrower vapour paths with consequent impedance to vapour flow and potentially longer drying times. As a rule, fast freezing (such as dipping in LN2) creates small crystals while slow freezing (overnight in a -20°C freezer) creates large crystals. Annealing is often used to encourage a favourable ice crystal structure.

However large ice crystals can be damaging to biological products. Cells can be damaged by the growth of crystals, while solute concentration and surface induced denaturation can also damage proteins. Therefore cooling rates and ideal crystal matrix structure will vary from product to product.

5. Drier (lower final moisture content) is always better

Freeze drying aims to increase the stability of a product by reducing the moisture levels, so it is easy to assume that the drier the product, the better.

However many products can be damaged by overdrying. Biological products such as cells, proteins and vaccines will typically require higher moisture content than simple chemicals, but the target final moisture content will depend on the specifics of each product and formulation. Stability studies should be carried out to ascertain what the ideal moisture content.

Overall moisture content is an important metric, but in practice water may be present in a variety of “forms” – free, adsorbed, chemically bound, hydration shells (e.g. of proteins), water of crystallisation, not all of which may be directly linked to the activity or stability of the product in question.

Different types of measurement method measure the water differently. It is advisable to use several measurement techniques in combination, especially during development and trials.

It’s also important to note that secondary drying is an increasingly slow process and that obtaining an extra 1 or 2% reduction in moisture content may add many hours to process time. A product with 0% moisture will never be achieved, and a balance must be struck between product stability and practicality.

Want to know more?

A free introductory guide to freeze drying is available on request—visit www.biopharma.co.uk/introduction-to-freeze-drying. Alternatively contact us to arrange a chat with one of our scientists.