Typical questions asked during presentations:

Fundamentals of Freeze Drying – 5 Science Modules

Q: How can sterile filtration impact solute crystallisation?

A: Sterile filtration is designed to remove particles larger than 0.22um; this typically means ice nucleation is delayed and the formulation spends more time in the liquid state below 0°C, a phenomenon known as supercooling. This can affect solute crystallisation in different ways, sometimes encouraging solute crystals to form in the absence of ice, and sometimes delaying solute crystallisation further, depending on the type and concentration of the solutes in question.

Q: If annealing can be used to change the ice crystal structure, then can it be used to reduce total lyophilisation time?

A: Yes – in fact, it is often used to reduce total cycle time. For this to be achieved, the additional time spent performing the annealing step will need to be more than offset by the reduction in primary drying time, so it may not reduce the cycle time for products that already dry quite rapidly (e.g. high collapse temperature/low volume) but it can be very effective in many cases. Annealing can also promote solute crystallisation and lead to better batch uniformity.

Q: Is collapse temperature independent of drying pressure?

A: Yes, the collapse temperature is intrinsic to the formulation, although it can be influenced by cooling rate and annealing. Pressure will not affect the collapse temperature, although it should be remembered that pressure does have an effect on heat transfer during primary drying, and therefore, it is still an important consideration when developing the lyo cycle.

Q: Are temperature probes commonly used during manufacturing of clinical samples or commercial products?

A: Nowadays, it is less common to use temperature probes (particularly wired probes) in clinical or commercial lyophilisation cycles than, say, 25 years ago. This is primarily because they require manual intervention to place them into the product containers, which many argue can compromise the sterility of the filling and loading process. It is now much more typical to use probes in technical/engineering/validation runs and then to run the 'validated process' after that.

Q: Have you always found Pirani gauge readings merge with Capacitance Manometer readings at the end of primary drying?

A: They do not always merge as such – this is due to a number of factors: firstly, it depends on what the two gauges read in a dry empty chamber at the pressure in question; secondly, while a CM gauge will typically have <1% tolerance, a Pirani or Thermocouple gauge will often have 10-15% tolerance, although they can be adjusted to give them better accuracy at the pressure levels that are used most frequently (at the expense of accuracy in different regions of their operational range); thirdly, they may be in quite different locations on the product chamber, and therefore, this can lead to slight differences in the readings during primary drying even if both gauges match in a dry chamber.

Freeze Drying Systems – 4 Engineering Modules

Q: Why does shelf fluid level alter during cycles

A: Fluid in system contracts and expands due to temperature changes so it is normal to see level dropping during freezing phase and rising during drying. Monitor level of thermal fluid when machine is shut down and at ambient conditions.

Q: How do you remove air from the thermal fluid system

A: Generally, it is good practise to vacuum dehydrate the system and then fill from the lowest point whilst still under vacuum.

Q: Will shelf mapping indicate air in the system

A: Pockets of air tend to remain in the shelf, so temperature mapping will highlight areas where flow is not good across the shelf or shelves. Pockets of air within the shelf will show up as temperature deviations against other probe readings.

Q: How often should vacuum pump oil be changed

A: This depends on individual cycles and how aggressive the cycle reacts to the pump oil. It is good practise to change oil on a regular basis following machine usage but it is much easier and cost effective to change vacuum pump oil rather than the pump itself. It is not uncommon for some end users to change vacuum pump oil between batch runs if they have an aggressive cycle.

Q: Despite fitting an oil mist eliminator there appears to be oil around the exhaust.

A: Oil eliminators usually have a cartridge insert installed which over time will become saturated and will lead to oil being carried out through the exhaust. It is usual for these cartridges to be replaced before they become ineffective.

Q: If the machine is not used on regular basis what routines can be carried out to check operation before batch cycles.

A: Most manufacturers have a dedicated functional or performance test that can be used to periodically check the operation and integrity of the machine. If a set cycle is not available it is relatively simple to set up a recipe profile to prove systems are operating correctly. Like most mechanical systems they seem to be less problematic when running on a regular basis rather than being used infrequently.

Q. Is there a simple test to check the trapping capacity of the process condenser.

A. Carry out an “ice slab” test to load the condenser. Fill trays of water onto the shelves and run a freeze-drying cycle to sublimate the water vapour onto the condenser. The ice build-up using this method eliminates the dry layer and vapour resistance when using product.

Q: Can you tell the difference during pressure rise testing between a leak and moisture contamination.

A: A leak within the freeze drier will have a linear rise from the set point over a given time. Moisture will give an uneven rise in pressure and it is not uncommon to see the pressure spike up at irregular intervals.

Q: Is there anything we need to do to prepare a machine for leak testing

A: The machine should be in a dry and clean condition prior to the test. If possible, use the same parameters each time so that you build up some information for historical trends.

Q. Sometimes ice/frost build up can be seen on the drain line during evacuation of the machine.

A. This is generally associated with moisture retention in the drain line following de-icing or sterilisation. It can be an indication that the drying time is not sufficient or possibly that the drain valve is not sealing correctly. This may also lead to longer evacuation times to reach the transition point to start primary drying.

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