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TECH BRIEF: CONSIDERATIONS WHEN SPECIFYING ULTIMATE FREEZE DRYING VACUUM

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One of the conditions inherent to the freeze drying process is that of a proper vacuum. An evacuated chamber is essential to the vapor-pressure relationship necessary for the sublimation of ice directly into vapor. For sublimation to occur, the vacuum level must be at least below the triple point of water which is well documented to be 0°C (273.16°K) and 4.58 Torr (4,580 milliTorr or 0.00603 atm). Once below this point is it possible to change the state from ice directly from vapor without passing through a liquid phase.

Surveys of Hull customer requirements indicate that most freeze drying cycles have been developed with primary drying pressure control maintained in the 100 to 400 milliTorr range. As far as can be ascertained, there is no evidence of freeze drying in a production cycle with primary vacuum control below 75 milliTorr.

There are scientific and practical reasons for the above. First is a consideration of the vapor leaving the vials and making its way to the condenser. Basic physics tells us that $P_1V_1 = P_2V_2$ (Boyle's Law), thus the lower the pressure, the larger the volume of the same mass of gas. In freeze drying this expansion is quite large. When drying at 100 milliTorr, the expansion factor of water vapor leaving the vials is 7,600 times the volume that the vapor would otherwise occupy at one standard atmosphere. At 50 milliTorr this expansion doubles to a factor of 15,200 and at 5 milliTorr it will have increased twenty-fold over the expansion at 100 milliTorr.

The next consideration is that even in an internal condenser system, there is a finite area through which the vapor can flow from the vials to the condensing plates. Often the most constricted section of this flow path is the area between the top of the vials and the bottom of the shelf above the vials. Now since the maximum speed of the vapor is limited by the speed of sound in the vapor (approximately 1250 ft/sec at -20°F), there is a maximum mass of vapor, which can be transported from the vials to the condenser per unit time.

The above means that at 50 milliTorr, one can only transport one half the vapor mass from the vials to the condenser as one can at 100 milliTorr. Still using 100 milliTorr as our basis, it also follows that at 5 milliTorr, one can only transport 1/20th of the mass while at 200 milliTorr, one can transport twice the mass. Hull Company is aware of customers who in the past experienced uneven drying caused in part by too low a vacuum. The impeded flow of vapor from vials located toward the center of the product drying shelves prevent the product in this area from drying as quickly as product located towards the perimeter of the shelves.

Vacuum level in the chamber also has an effect on the transfer rate of heat from the shelves to the product. As Steven Nail has shown[1], conduction by the gas present in the chamber plays a major part in the overall heat transfer, which occurs during primary drying. Nail found that increasing the chamber pressure from 0.04 mm to 1.3 Hg (40 to 1300 milliTorr) resulted in a 160% increase in primary drying rate. Of course, the optimum drying pressure for each product must be determined experimentally. Increasing pressure too much can result in "melt back," that is in the product temperature rising above the phase transition temperature which results in the collapse of the frozen structure and a failure of the freeze drying process.

Finally there is the consideration of the vapor pressure of ice and condensing temperatures. To optimally utilize the condenser refrigeration system, common practice is to maintain a condenser or ice surface temperature of about -50°C. As can be seen in the following table, the vapor

[1] Steven L. Nail, "The Effect of Chamber Pressure on Heat Transfer in the Freeze Drying of Parenteral Solutions" Journal of the Parenteral Drug Association (Sept./ Oct. 1980) p. 400 - 410.

pressure of ice at -50°C can be interpolated to be approximately 30 milliTorr. This means that if the chamber were at 5 milliTorr, ice would de-sublime off the plates. The resulting vapor would be pulled into the vacuum pumps and contaminate the oil in the pumps.

Vapor Pressure of Ice	
T (Deg. C)	P (MilliTorr)
-72	1.43
-68	2.61
-64	4.64
-60	8.08
-56	13.8
-52	23
-48	37.8
-44	60.9
-40	96.6
-36	150.7

Table 1: The Vapor Pressure of Ice at Various Temperatures

The problem is similar during secondary drying. During secondary drying there is very little de-sublimation occurring at the condenser. The decreased load heat causes the condensing plates to become colder, decreasing in temperature to approximately -70°C depending on conditions.

But even though the plates are at -70°C (with a corresponding vapor pressure of 2 milliTorr), the ice that has accumulated on the plates during primary drying has an insulating effect. The difference in temperature between the condenser surface and the outer ice surface varies depending upon the condensing rate and the ice thickness. Beisswenger has shown that this insulating effect can result in ice surface temperatures on the order of 20°C warmer than the condensing plate temperature. Thus, even during secondary drying, the condenser "surface" temperature often remains at -50°C, which still does not permit chamber pressures below 30 milliTorr. [2]

Conclusion

To summarize, when developing freeze dryer specifications and subsequent product freeze drying cycles, one should keep in mind that there are practical limits to ultimate system vacuum requirements. Surveys indicate that most cycles are not dried at pressures below 100 milliTorr. The lower the chamber pressure the greater the chance of choking of flow from the product vial to the condenser. Too low a pressure in the area of the condensing plates can also result in ice de-subliming off the plates and into the vacuum pumps, contaminating the oil.

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[2] Harry L. Beisswenger, "Product Improvement Through Advanced Freeze Drying Techniques" Bulletin of the Parenteral Drug Association Vol. 23, No. 2 (Mar./Apr. 1969), p.90 - 100.