RESIDUAL GAS ANALYSIS

Monitoring Decomposition of Thermally Sensitive Materials During Pharmaceutical Freeze-Drying

Freeze-drying is a technique commonly used in the pharmaceutical industry to stabilize sensitive drug and biological products prior to long-term storage. In a typical cycle, the product is first dispensed into vials and loaded into the freeze-dryer. The material is then frozen on cooled shelves to separate the solvent from the solute. Once solidified, a vacuum system lowers the ambient pressure surrounding the product to induce sublimation. These conditions are held until all frozen solvent is removed. The product is then sealed in vacuum before the system returns to atmospheric pressure. The shelf life of freeze-dried products ranges from months to years, depending on storage conditions and material properties. Ongoing innovation in the pharmaceutical sector has led to the introduction of highly complex systems, many of which exhibit high thermal sensitivity. In some cases, freeze-drying these materials too aggressively can lead to decomposition of the active pharmaceutical ingredient or other critical components in the formulation. Residual Gas Analysis (RGA) is an effective process analytical technology that can mitigate this behavior while simultaneously providing a means to optimize the freeze-drying process.

Experimental

The Transpector® CPM 3 compact process monitor is a quadrupole RGA integrated with a research and development freeze-dryer (REVO® by Millrock Technologies Inc.) to monitor the gas composition inside of the process chamber during the freeze-drying process. Transpector CPM 3 contains a series of dosing orifices to permit sampling of high-pressure gases up to 1 Torr. An image of the setup is shown in Figure 1. The tested formulations consisted of sucrose and ammonium bicarbonate of varying concentration dispensed into 20R type I glass tubing vials. The RGA monitored gas composition in the freeze-dryer from 0.5-200 amu with a resolution of 0.1 amu. Mass spectra for compounds typically found in freeze-drying are shown in Table 1.

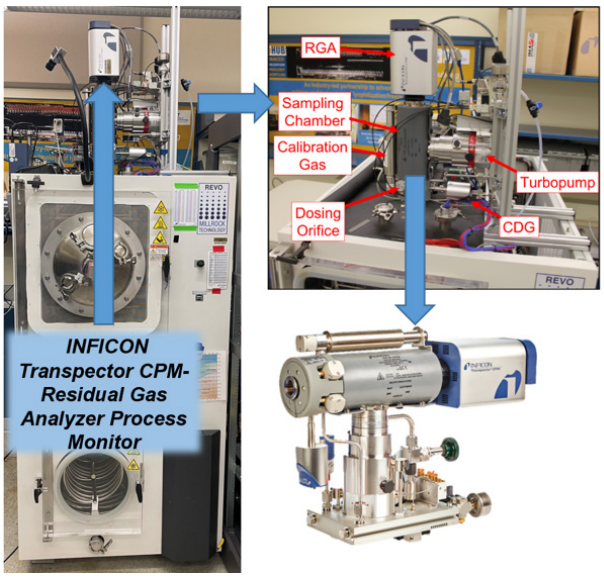

Figure 1: INFICON Transpector CPM 3 installed on Millrock REVO lyophilizer in the LyoHub Demonstration Facility at Purdue University.

Mass Spectra of Species Commonly Found in Freeze-Drying

Compound	Mass	Relative Abundance
N_2	28	1
	14	0.138
H_2O	18	1
	17	0.212
	16	0.009
	19	0.005
	20	0.003
CO_2	44	1
	28	0.098
	16	0.096
	12	0.087
	45	0.012
NH_3	17	1
	16	0.801
	15	0.075
	14	0.022
	18	0.004
O_2	32	1
	16	0.218
Ar	40	1
	20	0.146

Table 1: Mass Spectra of Species Commonly Found in Freeze-Drying

Results: Model API Documentation with Bulking Agent

An aqueous formulation of ammonium bicarbonate (0.5% w/v) and sucrose (5% w/v) was freeze-dried to simulate decomposition of a thermally sensitive active pharmaceutical ingredient (API).

The process data from the freeze-dryer and corresponding signals from the RGA are shown in Figures 2a and 2b, respectively. The formulation was initially frozen to -40°C near atmospheric pressure. Once solidified, the pressure was reduced to 70 mTorr and the shelf temperature was raised to -20°C. This sequence of steps induces sublimation of the water ice and marks the beginning of the primary drying phase. According to Figure 2b, the primary constituent in the process gas during this period is water vapor (m/z=18). Trace nitrogen (m/z=28) was also present. Nitrogen ballast gas is introduced by freeze-drying systems to maintain a constant pressure as the sublimation rate varies throughout the cycle. After an elapsed time of around 18 hours, the water vapor signal began to decrease as the water ice was fully consumed.

It should be noted that indications of this endpoint are also provided by the Pirani vacuum gauge in Figure 2a. The Pirani gauge is a gas-dependent pressure sensor that is typically calibrated in nitrogen. Referencing this device to the absolute pressure (provided by a capacitance manometer) provides an indication of water vapor composition. However, although the Pirani method is a useful, low cost, and straightforward technique, it is unable to distinguish between different gases in non-binary systems. The nitrogen signal in Figure 2b increased sharply at the end of the primary drying as the machine introduced additional ballast gas to maintain pressure. The argon principal peak (m/z=40) increased proportionally during this event. The nitrogen gas is boiled off from a liquid source and is known to contain condensed argon. This observation was therefore reasonable and expected. The increasing product temperature after 18 hours was also met with a proportional increase in m/z=15.

This is believed to be a fragment of ammonia vapor and indicates mild decomposition of the dried solid. Note that ammonia has a principal peak at m/z=17. This is also an isotope of water vapor, so the ammonia contribution is likely obscured by its strong signal. Any remaining water bound to the dry solid at the end of primary drying is removed by increasing the shelf temperature in a process known as secondary drying. Typical temperature for this process range between room temperature and 40°C. Secondary drying occurred at an elapsed time of 33 hours and let to a simultaneous increase in water vapor and decrease in nitrogen as the system attempted to maintain a constant pressure. Following the peak, water and ammonia traces then decayed towards the baseline. Close examination of the water vapor (m/z=188 and m/z=17), carbon dioxide (m/z=44), and ammonia (m/z=15) traces indicate subtle differences in desorption rates. The consequences of this behavior were not investigated but could provide useful data to formulation development and process optimization.

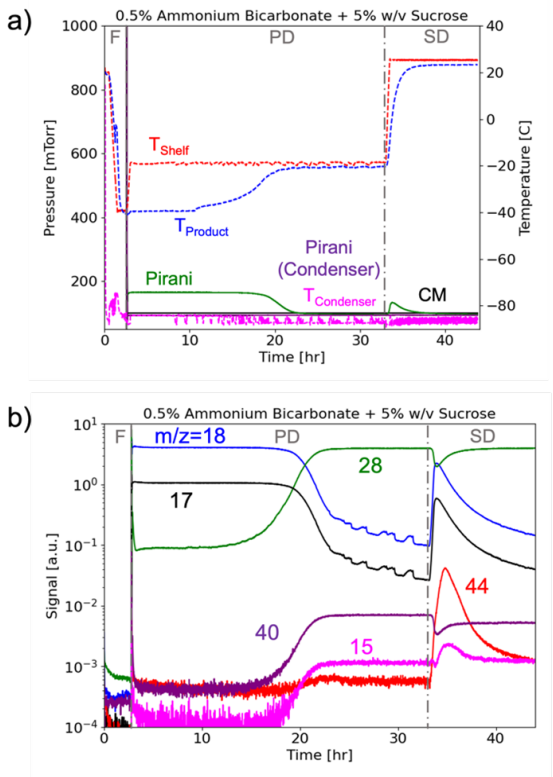

Figure 2: Freeze drying process (a) and RGA (b) data for a model pharmaceutical system containing thermally sensitive active pharmaceutical ingredient and bulking agent[1].

aial47a1

Model API Decomposition

An identical experiment was conducted using pure aqueous ammonium bicarbonate to investigate the decomposition process in more detail. These results are summarized in Figure 3. Similar to the previous formulation, the majority of the vapor composition throughout primary drying is water vapor. However, near the end of this phase, the increase in product temperature led to a sharp increase in m/z=44 and m/z=15. The response from these masses confirms that thermal decomposition of the ammonia salt is occurring in vacuum. It also highlights the utility of monitoring off-principal peaks when investigating compounds that have strongly overlapping spectra. A second sharp response was also seen during secondary drying followed by a decay to a constant value. In this case, all ammonium bicarbonate had sublimed, and product vials were empty at the conclusion of the cycle.

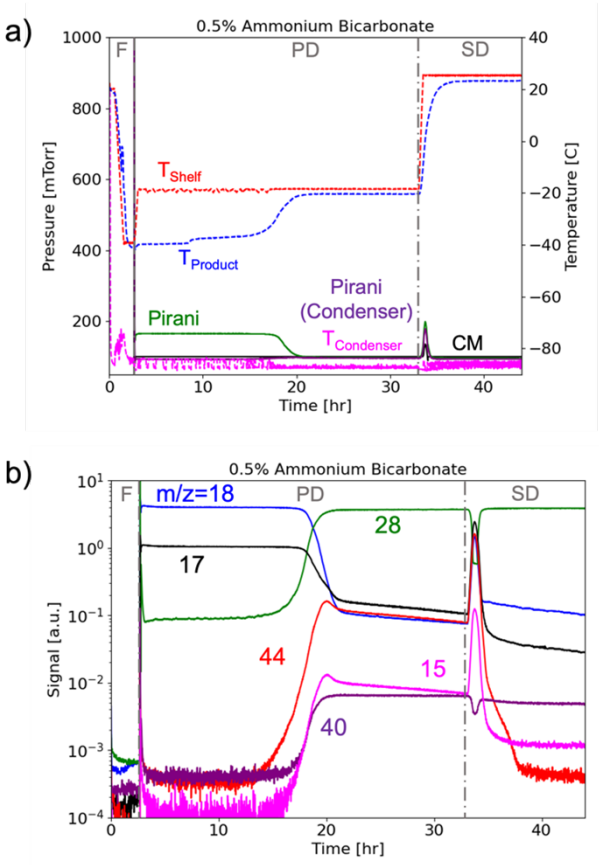

Figure 3: Freeze drying process (a) and RGA (b) data for a model thermally sensitive active pharmaceutical ingredient[1].

Conclusion

Historically, quadrupole mass spectrometry has been used in the pharmaceutical freeze-drying industry for detecting leaks and evaluating cycle endpoint. Recently, this technique has provided a useful tool for cycle development and optimization of sensitive formulations. This note applied the INFICON Transpector CPM 3 to investigate the decomposition of ammonia salts during the freeze-drying process. Ammonia and water vapor have tightly overlapped spectra, especially near the principal peak region. This characteristic makes identification of the individual species difficult. The high sensitivity and performance of the INFICON Transpector RGA allows off-principal and unique m/z traces to be monitored with high precision. This capability provides significant value to formulation development scientists looking to dry life-saving drugs and biologics with the highest speed possible, while also preserving stability and efficacy.

For more information → inficon.com

[1] Strongrich, A. D., Tobyn, M., Iyer, L. K., Park, Y., Hong, J., & Alexeenko, A. A. (2023). In-Process Vapor Composition Monitoring in Application to Lyophilization of Ammonium Salt Formulations. Journal of Pharmaceutical Sciences, 112(1), 264-271.

[2] Liechty, E.T., Strongrich, A.D., Moussa, E.M. et al. In-Situ Molecular Vapor Composition Measurements During Lyophilization. Pharm Res 35, 115 (2018). https://doi.org/10.1007/s11095-018-2395-4.

[3] Ganguly, A., Stewart, J., Rhoden, A., Volny, M., & Saad, N. (2018). Mass spectrometry in freeze-drying: Motivations for using a bespoke PAT for laboratory and production environment. European Journal of Pharmaceutics and Biopharmaceutics, 127, 298-308.

aial47a1