

Monitoring pharmaceutical solvent drying processes using the Thermo Scientific Prima PRO Process Mass Spectrometer

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Keywords

- Federal Drug Administration
- Process Analytical Technology
- Active Pharmaceutical Ingredient
- Loss on drying
- CFR 21 Part 11
- Continuous process analysis
- Improving process understanding
- Variable pressure inlet

Introduction

A key stage in many pharmaceutical processes is the complete or partial removal of a solvent, or solvents, from a product or intermediate. The drying process required can occur in a variety of process vessels, including vacuum dryers, tray dryers and rotary dryers.

In the past, the success of the drying process was measured upon conclusion by simply taking a sample for laboratory analysis. Organic solvent concentrations in the active pharmaceutical ingredient (API), or intermediate, were measured by gas chromatography; residual water levels were typically checked by performing a Karl Fischer titration. The amount



of residual solvent was defined by the loss on drying (LOD). If the sample failed the LOD test for one or more of the solvents, the drying process had to be restarted. If the drying took place under a vacuum, additional complications in terms of both sampling the API and re-starting the dryer were likely to occur.

This possibility led to a tendency to increase drying times to avoid a failed LOD test. However, additional process problems were created. Because the drying stage is often a rate-limiting step during manufacturing, an increased drying time had an adverse effect on production lead times. In many cases, the only way to circumvent this bottleneck was to increase drying capacity at great expense.

There were also too many cases when the product was over dried. The results were production problems downstream and an increased possibility for damaging effects on the polymorphic form of the final product.

The PAT initiative

In 2004, the Federal Drug Administration's Process Analytical Technology (PAT) initiative focused attention on the implementation of process analytical techniques to improve process understanding in the pharmaceutical industry. The drying process was an obvious candidate for investigation and PAT teams began the search for suitable techniques for continuous process analysis.

Disadvantages of spectroscopic techniques

Initially, many PAT teams considered spectroscopic techniques such as near infra-red (NIR) technology for product drying. Superficially, these techniques were attractive as they sampled directly in the bulk API. However, there are several drawbacks to this approach, including:

- The sampling probes become coated by the API.
- In the case of paddle dryers, retractable probes are needed to avoid probe damage by the rotating paddles.
- The probe only provides a 'spot' sample and is not representative of the total residual solvent in the product.
- Many API drying processes involve the removal of two or more solvents from a potential list of over 30 compounds, requiring complex chemometric modeling to turn the spectroscopic data into process-friendly concentration data.

Advantages of mass spectrometry techniques

In contrast, gas analysis using process mass spectrometry offers advantages of simplicity in both sampling and data manipulation, including:

- Taking samples from the headspace above the product to ensure effective measurement of the bulk product in the dryer and to help avoid problems caused by a lack of homogeneity in the product.
- Collecting samples at the dryer outlet, either in the vacuum suction line or the outlet air line, is a simple and straightforward procedure that only requires a Swagelok™—type connection, a heated sample line, and a basic particulate filter with a disposable element.

- Operating at high vacuum, typically 10⁻⁵ to 10⁻⁶ mbar, to make sampling from vacuum drying processes quite practical.
- Confirming vacuum integrity, either by looking for air leaks or by helium leak checking.
- Using the fragmentation patterns of the molecules in the mass spectrometer's ion source which are effectively 'fingerprints' to simplify the analysis of even complex mixtures; for example, figure 1 shows the fragmentation pattern for n-propanol while figure 2 shows that of iso-propanol.

While much useful data and understanding was gained by implementing gas analysis mass spectrometers on drying processes, many users experienced problems over time. These problems fell into three main categories:

- Contamination of the mass spectrometry analyzer
- Problems of sampling over wide pressure ranges
- Converting mass spectrometry data into concentration data.

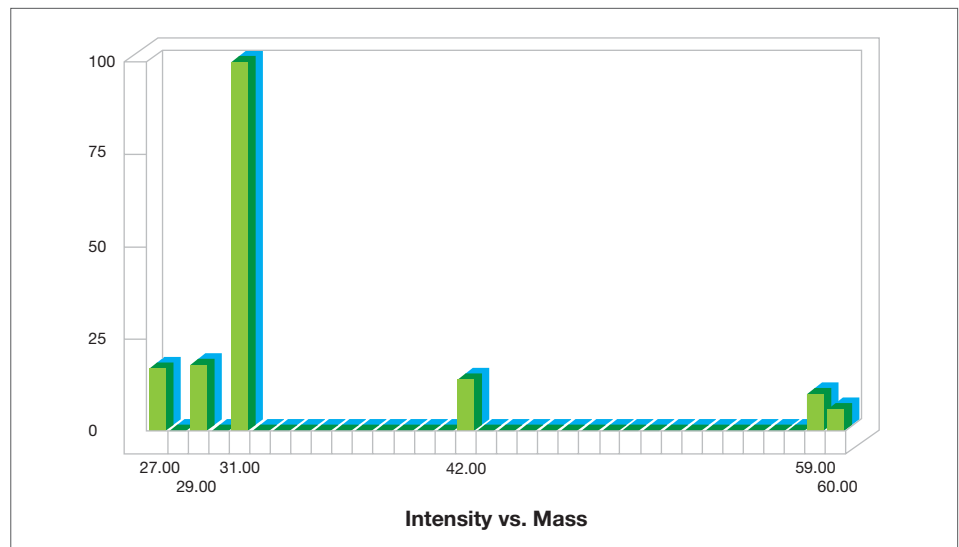


Figure 1. Fragmentation pattern for n-propanol as generated by the Thermo Scientific™ GasWorks Software.

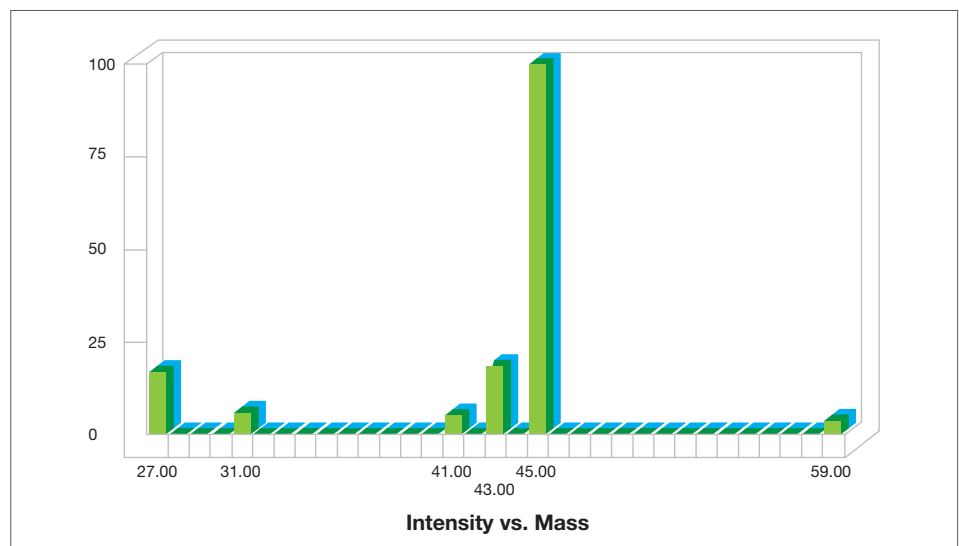


Figure 2. Fragmentation pattern for iso-propanol as generated by the Thermo Scientific™ GasWork Software.

Analyzer contamination

Early on, the mass spectrometers used during solvent drying were invariably based on quadrupole analyzers. This type of analyzer is notoriously prone to contamination by hydrocarbons that cause analyzer drift and require the mass spectrometer to be taken offline for cleaning.

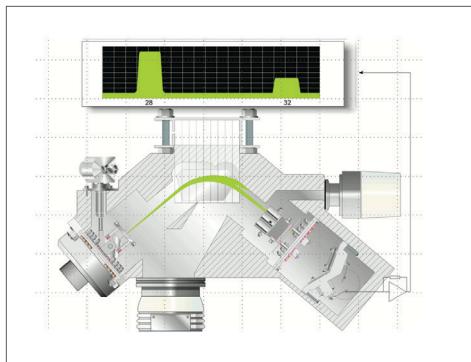


Figure 3. The magnetic sector analyzer within the Prima PRO Process Mass Spectrometer.

A highly reliable and precise alternative is the Thermo Scientific™ Prima™ PRO Process Mass Spectrometer that features a magnetic sector analyzer (figure 3). Based on thirty years of industrial mass spectrometry experience, the magnetic sector analyzer has proven to offer unrivaled performance for industrial online gas analysis. Key advantages of the magnetic sector Analyzer include improved precision, accuracy, long intervals between calibrations, and resistance to contamination. Typically, analytical precision is between 2 and 10 times better than a quadrupole analyzer, depending on the gases analyzed and the complexity of the mixture.

A unique feature of the analyzer's magnet is that it is laminated and its scanning speed is equivalent to that of quadrupole analyzers, offering the unique combination of rapid analysis and high stability.

This combination allows for rapid, extremely stable analysis of an unlimited number of user-defined gases. The scanning magnetic sector is controlled with 24-bit precision using a magnetic flux measuring device for extremely stable mass alignment.

Furthermore, the enclosed ion source within the analyzer ensures high sensitivity, minimum background interference and maximum contamination resistance. This high-energy (1000 eV) analyzer offers extremely rugged performance in the presence of gases and vapors that have the potential for contaminating the internal vacuum components and has a proven track record of monitoring high percent level concentrations of organic compounds without experiencing drift or contamination.

Sampling from vacuum drying processes

In principle, the mass spectrometer is ideal for monitoring vacuum processes as the analyzer itself is operating at high vacuum. However, it is vitally important that the pressure in the mass spectrometer remains constant as the process pressure changes from atmospheric down to the vacuum levels required to dry the product. If the pressure within the mass spectrometer is not controlled, the signals will rise and fall in line with the sample pressure, rendering the output data useless.

Early mass spectrometry vacuum drying systems used a single control valve, typically a voltage sensitive orifice (VSO) valve, that was linked to a gauge monitoring the sample pressure. As the sample pressure changed, the VSO valve opened and closed to maintain a constant pressure in the mass spectrometer. While it worked quite

well for simple vacuum processes, it suffered from a number of serious limitations, including:

- At low pressures, typically less than 10 mbar, the valve was almost completely open which limited the amount of control available; at around 5 mbar, the valve was 100% open, meaning there was absolutely no control of the mass spectrometer pressure below this point.
- For customers needing to monitor multiple dryers, the mass spectrometer was required to switch between a dryer at high pressure at the start of the drying cycle and a dryer at low pressure at the end of its cycle; the control valve had to adjust to these pressure swings as quickly as possible but the response characteristics of a single valve are unfortunately inadequate for this type of duty; long delays have to be built in to the stream switching times, particularly as the solvents are at opposite extremes of the concentration range.



**Thermo Scientific
Prima PRO Process Mass
Spectrometer**

Variable pressure inlet

The variable pressure inlet within the Prima PRO mass spectrometer contains not one but two control valves working in opposition – as one valve opens the other closes. This combination ensures a wide dynamic range and fast, precise control. In fact, the inlet controls the analyzer pressure at just 0.1 mbar, enabling it to handle sample pressures down to 0.3 mbar.

The variable pressure inlet is shown in schematic form in figure 4. Figure 5 shows the Prima PRO mass spectrometer fitted with the multipoint inlet that is capable of sampling from up to 10 dryers. A single point inlet is also available for R&D and pilot plant users.



Figure 5. The Prima PRO Process Mass Spectrometer with the multipoint variable pressure inlet attached.

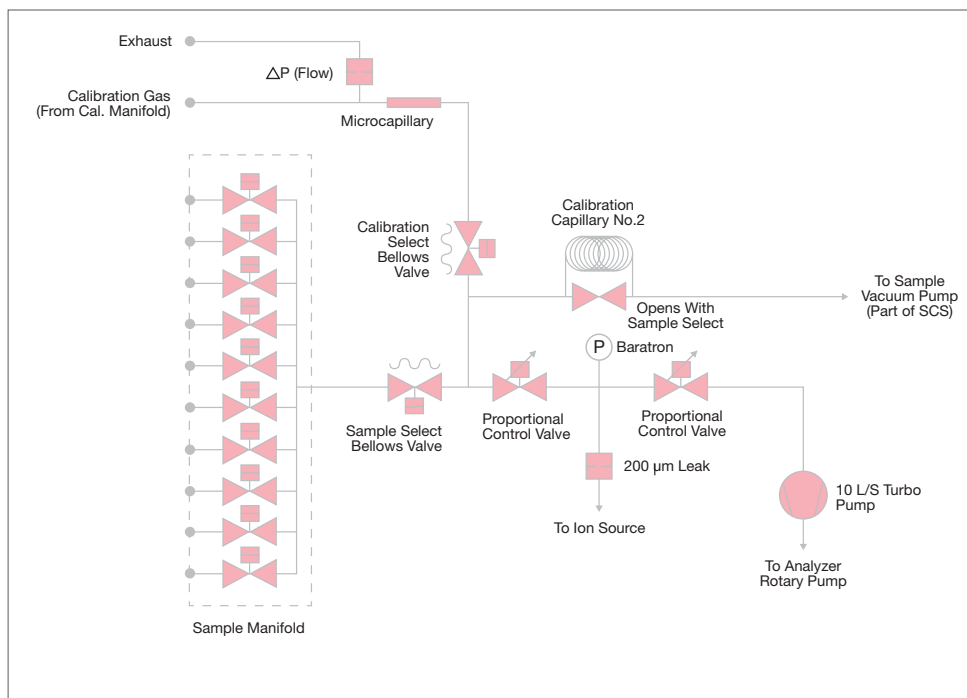


Figure 4. A schematic diagram of the variable pressure inlet within the Prima PRO Process Mass Spectrometer.

Using mass spectrometry data to control the drying process

Early mass spectrometers used for solvent drying only supplied qualitative information by monitoring ion currents from the principal peaks of the solvents of interest. While this information helped users begin to understand the dynamics of the drying process, the analyzer drift and consequent lack of repeatability between drying runs limited the technique's suitability for process control. In some cases, the nitrogen signal at mass 28 was used as an internal standard to produce a 'relative response' but this data was only available in certain cases. In addition, it did not help in cases where there was significant overlap between the solvent fingerprints and where one peak could not be uniquely assigned to one solvent.

When using the Prima PRO mass spectrometer, the variable pressure inlet allows the introduction of calibration gases under software control, enabling the Thermo Scientific GasWorks software to provide solvent concentrations rather than solvent ion currents. The unique combination of magnetic sector stability, precise inlet pressure control, and GasWorks quantitative software ensures the process data produced by the Prima PRO mass spectrometer is accurate and reliable. A range of industry standard communication protocols enables the transfer of this data to process control systems to optimize drying processes. GasWorks software is fully CFR 21 Part11 compliant.

An example of a typical two-solvent drying curve is shown in figure 6. It depicts the removal of water and iso-propanol as the pressure drops from atmospheric to 2 mbar. The inlet pressure remains constant at 0.1 mbar throughout the process.

Summary

The Prima PRO process mass spectrometer offers the best available online measurement precision and stability for dryer process monitoring and control. Its fault-tolerant design combined with extended intervals between maintenance as well as simplified maintenance procedures ensure maximum availability of the analyzer. The plug-n-play standard service kit that is shipped with each unit is shown in figure 7. The reliability of the Prima PRO mass spectrometer is reflected in its industry-best three year parts and labor warranty.



Figure 7. Prima PRO Process Mass Spectrometer service kit.

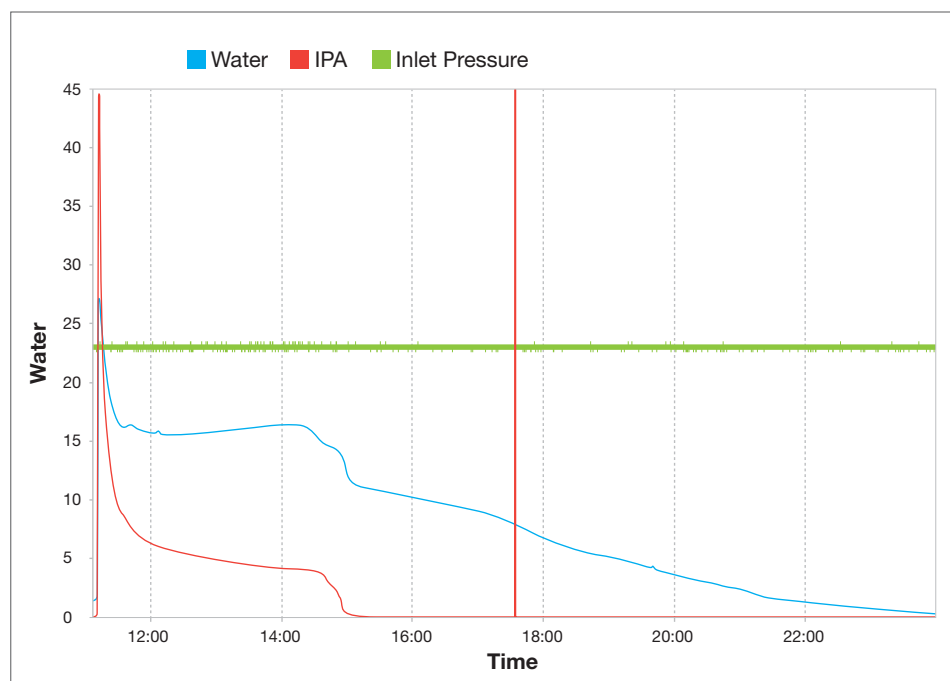


Figure 6. Two-solvent vacuum drying curve indicating the removal of water (blue line) and iso-propanol (red line) as the pressure drops from atmospheric to 2 mbar while the inlet pressure (green line) remains constant at 0.1 mbar.

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