

Advances in Process Mass Spectrometry for product drying in the pharmaceutical industry - learning lessons and applying QbD concepts to instrument design

Graham Lewis, Thermo Fisher Scientific, Winsford, Cheshire, United Kingdom

Key Words

- Federal Drug Administration (FDA)
- Process Analytical Technology (PAT)
- Active Pharmaceutical Ingredient (API)
- Loss on Drying (LOD)
- Quality by Design (QbD)



Introduction

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

In the past, the success of the solvent drying process was simply measured at the end by taking a sample for laboratory analysis and the amount of residual solvent was defined by the Loss on Drying or LOD. If the sample failed the LOD test for one or more of the solvents then the drying process had to be restarted. If the drying took place under vacuum this provided additional complications in terms of both sampling the active pharmaceutical ingredient (API) and re-starting the dryer.

This process results in a tendency to increase drying times to avoid a failed LOD test. However, it created additional process problems. The drying stage is often a rate-limiting step in the manufacturing process so the increase of drying times has an adverse effect on production lead times. In many cases the only way around this bottleneck is to increase drying capacity, at great expense.

There are also too many cases when the product was over dried. This often caused production problems downstream and could also have damaging effects on the polymorphic form of the final product.

The PAT Initiative

In 2004 the Federal Drug Administration's (FDA) Process Analytical Technology (PAT) initiative focused attention on the benefits of implementing process analytical techniques to improve process understanding in the pharmaceutical industries¹. The solvent drying process was an obvious candidate for investigation and PAT teams began the search for suitable techniques for continuous process analysis².

Initially many PAT teams considered spectroscopic techniques such as Near Infra-Red (NIR) for product drying. This option was considered because the technique samples directly in the bulk API; however there are several drawbacks to this approach.

- Sampling probes can become coated by the API.
- In the case of paddle driers, retractable probes are needed to avoid damage by the rotating paddles.
- The probe only provided 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 thirty compounds. This required complex chemometric modelling to turn the spectroscopic data into process-friendly concentration data.

In contrast to spectroscopic techniques, gas analysis mass spectrometry (MS) offers significant advantages of simplicity in both sampling and data manipulation for the solvent drying application.

- The MS samples from the headspace above the product, effectively measuring the bulk product in the dryer and avoiding problems caused by a lack of homogeneity in the product.
- The MS samples at the dryer outlet, either in the vacuum suction line or the outlet air line. This is uncomplicated and straight-forward, requiring just a simple gas-tight connection, heated sample line, and basic particulate filter with disposable element.
- The MS operates at high vacuum, typically 10^{-5} to 10^{-6} mbar; sampling from vacuum drying processes and is therefore quite practical.
- The MS can be used to check for vacuum integrity either by looking for air leaks or by helium leak checking.
- The fragmentation patterns of the molecules in the MS ion source are effectively ‘fingerprints’, simplifying the analysis of even complex mixtures. As an example, figure 1 shows the fragmentation pattern for n-propanol; figure 2 shows that of iso-propanol. Both figures are from the Thermo Scientific Gas-Works process MS software package.

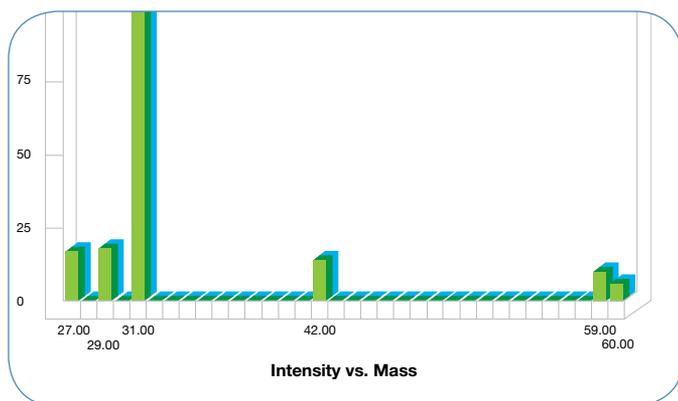


Figure 1.
Fragmentation pattern for n-propanol as generated by the Thermo Scientific GasWorks Software.

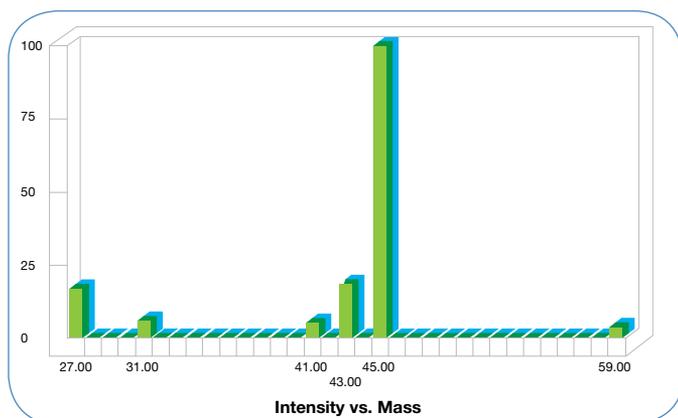


Figure 2.
Fragmentation pattern for iso-propanol as generated by the Thermo Scientific GasWorks Software.

While much useful data and understanding were 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 MS analyzer
- Problems of sampling over wide pressure ranges
- Converting raw MS data into concentration data

The early MS systems used for solvent drying were invariably based on quadrupole analyzers. These analyzers are notoriously prone to contamination by hydrocarbons, causing analyzer drift and finally requiring the MS to be taken off-line for cleaning.

Using magnetic sector technology

With thirty-years of experience in the industrial process environment, we have designed and manufactured both quadrupole and magnetic sector mass spectrometers. We have seen the most optimal performance derive from the use of a magnetic sector based analyzer in online process gas analysis applications.

The development of the Thermo Scientific™ Prima™ PRO Process Mass Spectrometer is the result of our cumulative experience and was designed as a rugged, reliable process analyzer based on fault tolerant design concepts with simplicity and ease of use at its heart.

Key advantages of magnetic sector analyzers 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 complexity of the mixture.



Thermo Scientific™ Prima™ PRO process mass spectrometer with multipoint inlet

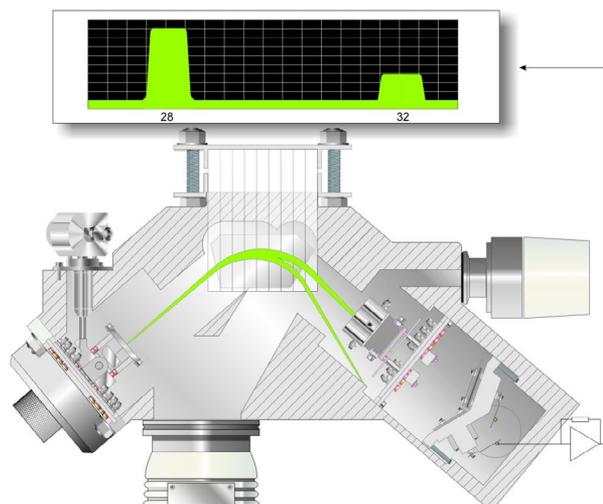


Figure 3. Magnetic sector of the Prima PRO process mass spectrometer

A unique feature of the Prima PRO process mass spectrometer magnet is that it is laminated. The analyzer scans at speeds equivalent to that of quadrupole analyzers, offering the unique combination of rapid analysis and high stability. This allows the rapid and 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.

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

Figure 3 shows a schematic of the magnetic sector contained within the Prima PRO process mass spectrometer analyzer. The broad flat-topped peaks that characterize this technique are optimized for long-term stability. Magnetic sector mass spectrometers have 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 MS analyzer itself is operating at high vacuum. However it is vitally important that the pressure in the MS remains constant as the process pressure changes from atmospheric down to the vacuum levels required to dry the product. If the MS pressure is not controlled, the MS signals will rise and fall in line with the sample pressure, rendering the output data useless.

The early MS vacuum drying systems used a single control valve, typically a Voltage Sensitive Orifice (VSO) valve 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 MS. This worked quite well for simple vacuum processes but suffered from a number of serious limitations:

- At low pressures, typically less than 10 mbar, the valve was almost completely open, limiting the amount of control available. At around 5 mbar the valve was 100% open, meaning there was absolutely no control of the MS pressure below this point.
- Many customers need to monitor multiple dryers; the MS therefore had 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; unfortunately the response characteristics of a single valve are inadequate for this duty. Long delays had to be built in to the stream switching times, particularly if the solvents were at opposite extremes of the concentration range.

Variable Pressure Inlet

To meet these application demands the variable pressure inlet needs to contain not one but two control valves working in opposition – as one control valve is opening, the other is closing. This ensures a wide dynamic range and fast, precise control. The Prima PRO process mass spectrometer employs a Variable Pressure (VP) inlet is shown in schematic form in figure 4. It can control the MS analyzer pressure at just 0.1 mbar and handle sample pressures down to 0.3 mbar.

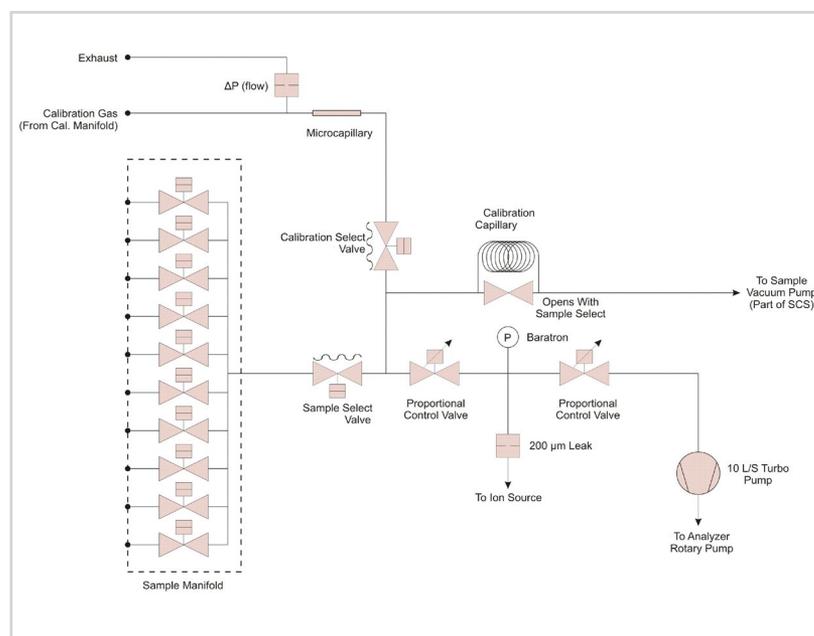


Figure 4. Schematic of the variable pressure inlet.

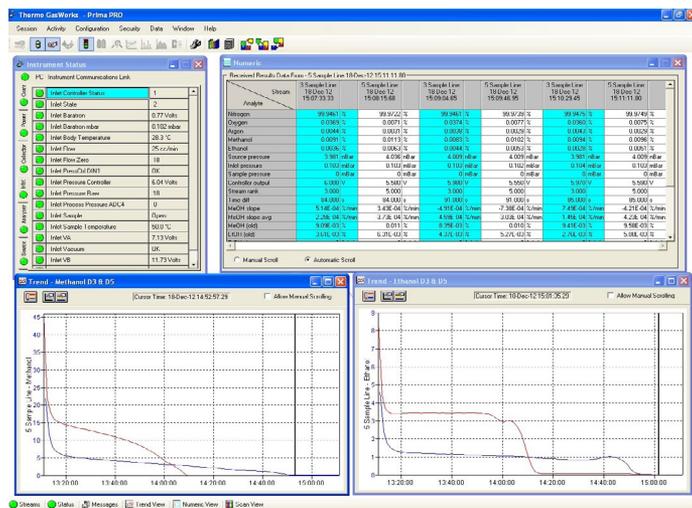


Figure 5. Results as reported with Thermo Scientific GasWorks software.

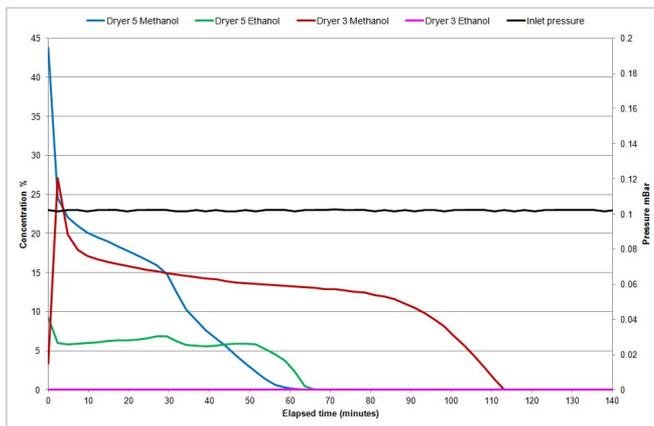


Figure 6. Example of MS solvent drying data – two solvents (methanol and ethanol) monitored in two dryers

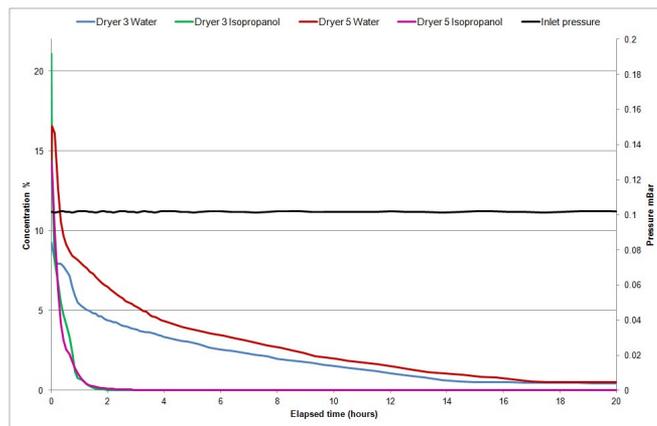


Figure 7. Example of MS solvent drying data – two solvents (water and iso-propanol) monitored in two dryers

Using MS data to control the drying process

The early mass spectrometers used to monitor solvent drying processes were small quadrupole analyzers and only supplied qualitative information. They monitored ion currents from the principal mass spectral peak for each solvent of interest. While this 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 nitrogen could be used as an internal standard to produce a 'relative response', but this was not always available. And it does not help in cases where there is significant overlap between the solvent fingerprints, and one mass spectral peak cannot be uniquely assigned to one solvent.

The variable pressure inlet of the Prima PRO process mass spectrometer can introduce calibration gases under software control and GasWorks software provides solvent concentrations rather than solvent ion currents. It is of course fully CFR 21 Part 11 compliant. Figure 5 shows a typical results screen from Thermo Scientific GasWorks software, showing both numeric and trend displays of solvent concentrations, system parameters and derived values.

Applying QbD concepts to instrument design

The process mass spectrometer and its variable pressure inlet need to be tested rigorously to the demanding standards of the pharmaceutical industry. Historically this testing was carried out at the customer site, by connecting the MS to the customer's vacuum dryers and monitoring drying processes. However as these dryers operated in a production environment there was difficulty to test the analyzer against the widest range of process challenges without impacting throughput. Too often this led to inadequate testing and problems arising after systems had been permanently installed. Pharmaceutical companies then tended to lose confidence in the MS, retaining the laboratory LOD test to call the API product dry.

Quality by Design (QbD) is a well understood process in the pharmaceutical industry. It is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and Quality Risk Management. It can be defined as follows:

- Define target product quality
- Design product and manufacturing processes
- Identify critical quality attributes, process parameters, and sources of variability
- Control manufacturing processes to produce consistent quality over time

Our engineers utilized a similar approach to the concepts of QbD, referred to as practical process improvement. A program developed by Ed Zunich to improve customer allegiance by improving the entire experience for the customer and shares many concepts with QbD:

- Apply logical simplicity
 - Utilize practical methods and tools
 - Involve everyone
 - Identify problem, analyze data, find solution, test
 - Standardize on new process

The decision to develop a process mass spectrometer suitable for the solvent drying application, prompted the creation of a multi-discipline PPI project team to better understand customer requirements, review customer experiences, analyze customer problems, and produce an effective solution. It quickly became apparent that if a QbD/PPI approach to the design of our solvent drying MS was to succeed, we needed to test designs in-house, challenging the designs over a wide range of sample pressures, solvent combinations, and solvent concentration ranges.

We needed to be able to connect the MS to multiple dryers to prove it can accommodate situations when one dryer is at the start of the drying run, at high pressure and high solvent concentrations, and the next dryer in the sequence is at the end of the drying run, at low pressure and low solvent concentrations.

We therefore built a solvent drying test unit in our factory located in Winsford, Cheshire, UK. Figures 6 and 7 (page 4) show examples of solvent drying data from a Prima PRO mass spectrometer connected to the test unit. In Figure 6 the MS switches between two dryers that are pumped down from atmospheric pressure to 1 mbar over the drying run. There is methanol and ethanol in one dryer but only methanol in the other dryer. Note that there is no cross-talk between the two dryers throughout the run and the inlet pressure stays constant at 0.1 mbar as the sample pressure drops and the MS switches between the two vacuum dryers.

Figure 7 shows the same two dryers, this time containing water and iso-propanol. Again there is no cross-talk on either solvent between the two dryers and the inlet pressure stays constant at 0.1 mbar as the MS switches between the two vacuum dryers.

Summary

The use of QbD concepts as part of a Practical Process Improvement project has led to the development of a solvent drying test unit that allows us to replicate the API drying process in our factory, ensuring hardware and software of the Prima PRO process mass spectrometer meet the demands of our customers.

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 and simplified maintenance procedures ensures maximum availability. The standard service kit shipped with every Prima PRO process mass spectrometer is shown in Figure 8; our confidence in the reliability and performance of the Prima PRO process mass spectrometer is reflected in the industry-best 3 year parts and labor warranty.



Figure 8. Prima PRO process mass spectrometer service kit.

References:

1. Guidance for Industry: Food & Drug Administration, “PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance”, September 2004 (www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf)
2. Mario Hellings, Tom Van den Kerkhof, Koen De Smet, Johnson and Johnson, “Applying PAT in Chemical Process Development”, European Pharmaceutical Review Issue 3 2009

thermoscientific.com

© 2014 Thermo Fisher Scientific Inc. All rights reserved. All trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries. Specifications, terms and pricing are subject to change. Not all products are available in all countries. Please consult your local sales representative for details.

United Kingdom
Ion Path, Road Three
Winsford, Cheshire CW73GA UK
Ph: +44 (0) 1606 548 741
Fax: +44 (0) 1606 548 711

United States
1410 Gillingham Lane
Sugar Land, TX 77478
Ph: (800) 437-7979
Fax: (713) 727-0404

China
Unit 702-715, 7/F Tower West
Yonghe Plaza No. 28
Beijing 100007 CHINA
Ph: +86 (10) 8419-3588

India
A-101, ICC Trade Tower
Senapati Bapat Road
Pune 411016 Maharashtra INDIA
Ph: +91 (20) 6626-7000

Thermo
SCIENTIFIC

Part of Thermo Fisher Scientific