Application Note

Monitoring Solvent Drying Processes in the Pharmaceutical Industry with the Prima PRO Process Mass Spectrometer

Key Words

- 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. 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 drying process was simply measured at the end by taking a sample for laboratory analysis. Organic solvent concentrations in the Active Pharmaceutical Ingredient (API) or intermediate were measured by GC; residual water levels were typically checked by carrying out a Karl Fischer titration. 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 API and re-starting the dryer.

This led to a tendency to increase drying times to avoid a failed LOD test. However this created additional process problems. The drying stage is often a rate-limiting step in the manufacturing process so increasing drying times had an adverse effect on production lead times. In many cases the only way around this bottleneck was to increase drying capacity, at great expense. There were 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 Process Analytical Technology (PAT) initiative focussed attention on the benefits of implementing process analytical techniques to improve process understanding in the pharmaceutical industries. The drying process was an obvious candidate for investigation and PAT teams began the search for suitable techniques for continuous process analysis.

Initially many PAT teams considered spectroscopic techniques such as Near Infra-Red (NIR) for product drying. Superficially they were attractive as they sampled directly in the bulk API; however there were several drawbacks to this approach.

Disadvantages of spectroscopic techniques

- Sampling probes became coated by the API.
- In the case of paddle driers, retractable probes were needed to avoid probes being damaged by the rotating paddles.
- 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 thirty compounds. This requires complex chemometric modelling to turn the spectroscopic data into process-friendly concentration data.

Thermo Scientific Prima PRO with variable pressure inlet

Advantages of mass spectrometry technique

In contrast, gas analysis mass spectrometry offers advantages of simplicity in both sampling and data manipulation.

- 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 simple and straight-forward, requiring just a Swagelok™-type 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 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 Thermo Scientific's GasWorks process MS software package.

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 MS analyzer
- Problems of sampling over wide pressure ranges
- Converting MS data into concentration data

Analyzer contamination

Early MS systems used for solvent drying were invariably based on quadrupole analyzers.

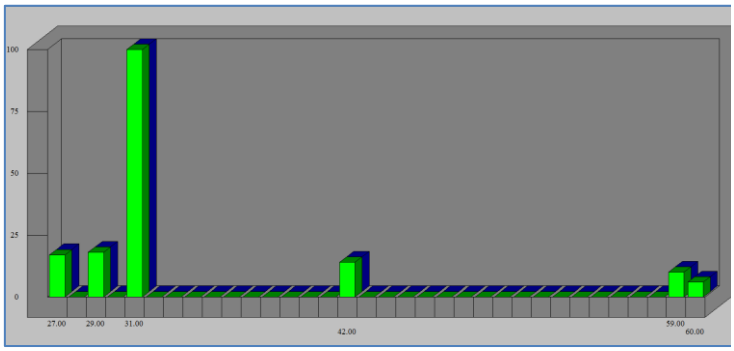


Figure 1: Fragmentation pattern for n-propanol

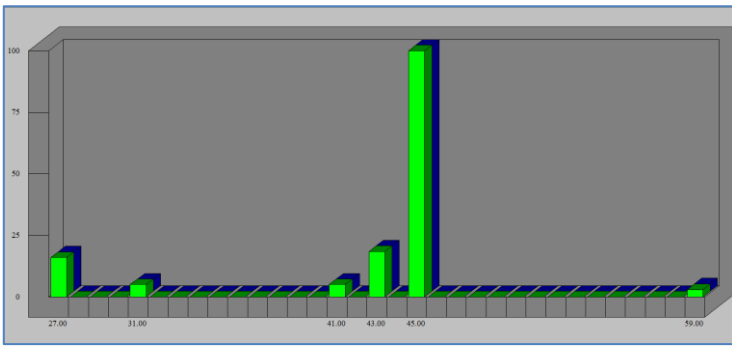


Figure 2: Fragmentation pattern for iso-propanol

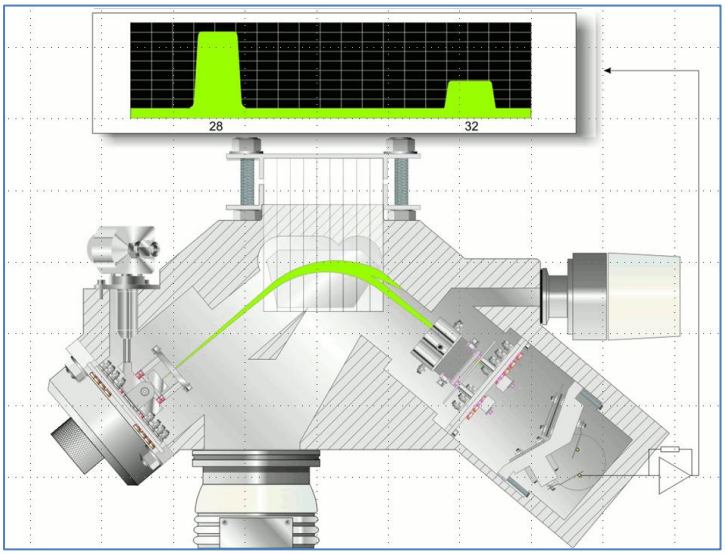


Figure 3: Prima PRO's magnetic sector analyzer

These analyzers are notoriously prone to contamination by hydrocarbons, causing analyzer drift and finally requiring the MS to be taken off-line for cleaning.

At the heart of the Prima PRO is a magnetic sector analyzer which offers unrivalled precision and accuracy.

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.

A unique feature of the Prima PRO magnet is that it is laminated. Our 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. Prima PRO has a proven track record of monitoring high percent level concentrations of organic compounds without experiencing drift or contamination.

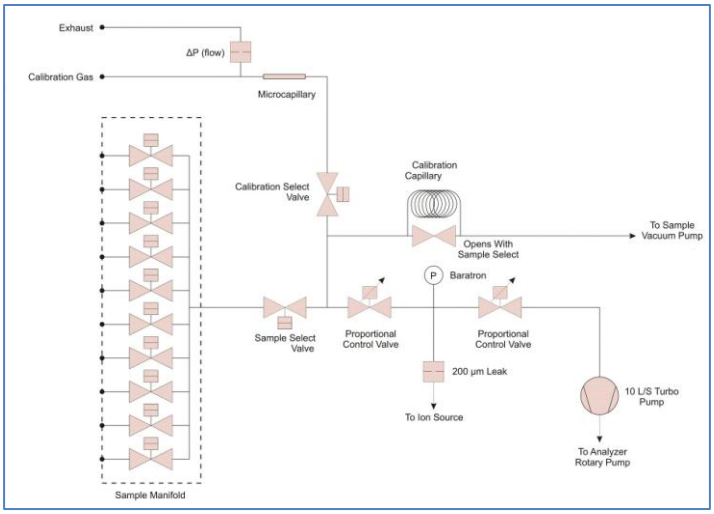


Figure 4: Prima PRO 's variable pressure inlet

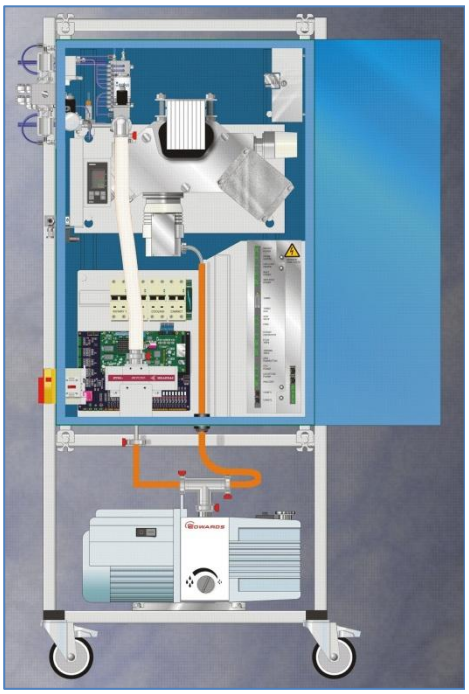


Figure 5: Prima PRO with multi-point variable pressure inlet

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 VSO (Voltage Sensitive Orifice) valve linked to a gauge monitoring the sample pressure. As the sample pressure changes the VSO valve opens and closes 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 is almost completely open, limiting the amount of control available. At around 5 mbar the valve is 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 has 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 has 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 have to be built in to the stream switching times, particularly as the solvents are at opposite extremes of the concentration range.

Prima PRO Variable Pressure Inlet

Our VP inlet contains not one but two control valves working in opposition – as one valve opens the other closes. This ensures a wide dynamic range and fast, precise control. The inlet controls the analyzer pressure at just 0.1 mbar and can therefore handle sample pressures down to 0.3 mbar.

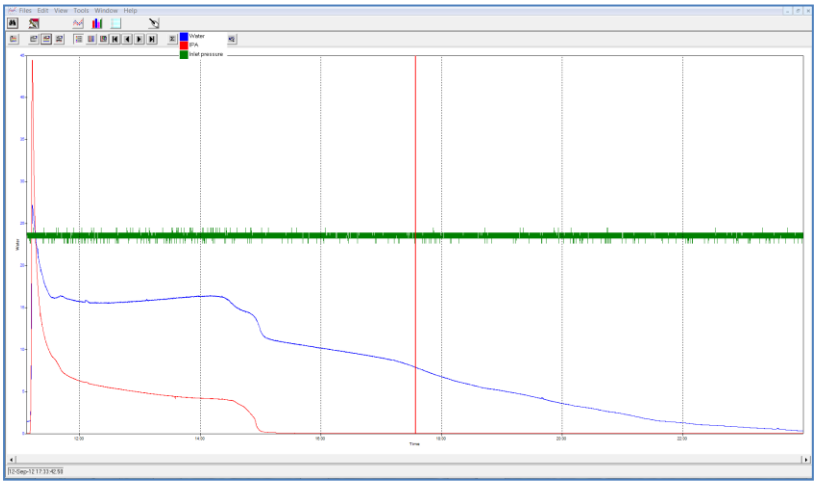
The VP inlet is shown in schematic form in figure 4. Figure 5 shows the Prima PRO fitted with the multipoint inlet version, capable of sampling from up to 10 dryers. A single point inlet is also available for R&D and pilot plant users.

Using MS data to control the drying process

The early mass spectrometers used on solvent drying only supplied qualitative information; they monitored ion currents from the principal peaks of the solvents 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 the nitrogen signal at mass 28 is used as an internal standard to produce a 'relative response', but this was only available in certain cases. And it does not help in cases where there is significant overlap between the solvent fingerprints and one peak cannot be uniquely assigned to one solvent.

The Prima PRO's VP inlet allows the introduction of calibration gases under software control, so our GasWorks MS software gives solvent concentrations rather than solvent ion currents.

Figure 6: Example of 2-solvent vacuum drying data



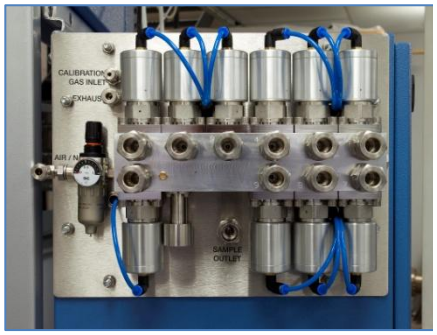
The unique combination of magnetic sector stability, precise inlet pressure control and GasWorks quantitative software ensures the process data produced by the Prima PRO is accurate and reliable. A range of industry standard communication protocols can transfer this data to process control systems to optimize drying processes. GasWorks is fully CFR 21 Part11 compliant.

An example of a typical two solvent drying curve is shown in Figure 6. This shows the removal of water (blue) and iso-propanol (red) as the pressure drops from atmospheric to 2 mbar. The inlet pressure is shown in green – note it stays constant at 0.1 mbar throughout.

Summary

Prima PRO 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 is shown in figure 7; our confidence in the Prima PRO's reliability is reflected in the industry-best 3 year parts and labor warranty.

Figure 7: Prima PRO standard service kit



Prima PRO multipoint VP inlet

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