APPLICATION NOTE

Prima PRO Process Mass Spectrometer

Generating reliable quantitative solvent drying process data in the pharmaceutical industry

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Key Words

- Federal Drug Administration
- Process Analytical Technology (PAT)
- Active Pharmaceutical Ingredient (API)
- CFR 21 Part 11
- Variable pressure inlet
- Fragmentation patterns
- Quantitative analysis
- Calibration

Introduction

The Federal Drug Administration's Process Analytical Technology (PAT) initiative has led to a wide variety of process analytical techniques being applied to various stages of pharmaceutical manufacturing processes. A key production stage that has received a great deal of attention is the drying process, the complete or partial removal of a solvent or solvents from an Active Pharmaceutical Ingredient (API) or intermediate. Gas analysis mass spectrometry has been used extensively on a wide range of dryers, including filter dryers, vacuum dryers, tray dryers, rotary dryers and spray dryers. This application note describes how a novel liquid calibration inlet can be used with the Thermo Scientific™ Prima PRO™ process mass spectrometer to produce reliable quantitative solvent drying data to optimize the drying process.

Background

Before PAT the success of the drying process was measured by taking a sample for laboratory analysis, and the amount of residual solvent defined by Loss On Drying (LOD). If the sample failed the test, the drying process was restarted. If drying took place under vacuum, additional complications sampling the API and re-starting the dryer were likely. This led to increased drying times and the risk of over-drying the API.

Since PAT, gas analysis mass spectrometers have been used for a number of years, to monitor solvent levels in the headspace above the API during drying processes. They have provided valuable insights and helped improve many drying processes:

- Monitor and improve drying stages
- Improve product quality
- Reduce drying times
- Increase consistency between batches
- Reduce over drying

However, the early systems were only able to provide qualitative or semi-quantitative data. They monitored a single ion in the mass spectrum for each solvent and assumed that peak was uniquely representative of that specific solvent. This may be a reasonable assumption in a single-solvent system, but it is almost certainly subject to significant errors in a two- or three-solvent system because of interference caused by fragmentation of the solvent molecules in the MS ion source. For example, Figure 1 shows the fragmentation patterns for ethyl acetate and isopropanol.
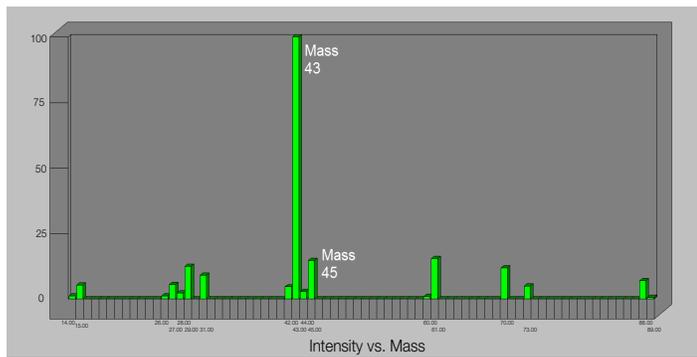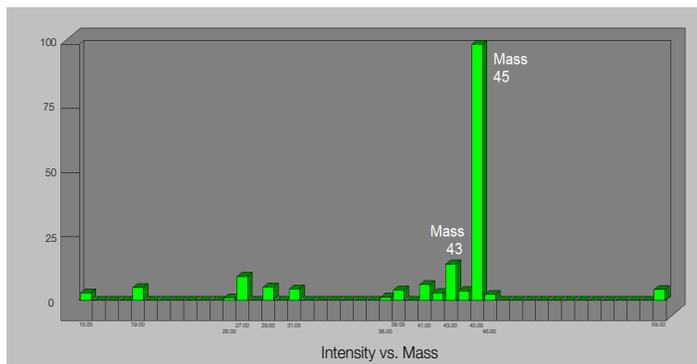
Figure 1 Fragmentation patterns for ethyl acetate and isopropanol

The two molecules have different principal peaks, mass 43 for ethyl acetate and mass 45 for isopropanol, however there is significant interference between the two spectra. Ethyl acetate produces a fragment peak at 45, similarly isopropanol produces a fragment peak at 43. This interference is made worse by the fact that the two solvents exhibit different levels of sensitivity in the MS ion source. Isopropanol's sensitivity relative to nitrogen is 1.27, whereas ethyl acetate is more sensitive, with a relative sensitivity of 1.62. So isopropanol's interference on ethyl acetate is effectively increased by almost 30%.

Another significant disadvantage of these early systems was that their results were simply expressed in units of ion current. These signals were extremely susceptible to drift, making it difficult to correlate data from different drying batches. In some cases the nitrogen ion current could be used as an internal standard, giving results in the form of a 'solvent ratio'. However this could only be used if there was a stable nitrogen purge through the dryer.

Advantages of quantitative analysis

Gas analysis mass spectrometers have overcome these limitations in many different applications by using gas calibration cylinders to measure the relative sensitivities and fragmentation patterns of the species of interest. The mass spectrometer then generates results in units of concentration, usually expressed in mole % or mole ppm, using matrix inversion software to correct for mass spectral overlaps in the

sample. The next stage in the solvent drying application was therefore to apply these more sophisticated mass spectrometers to provide quantitative multi-component solvent data. This offered the additional benefit that system performance could be validated against a certified blend cylinder, to prove the MS was measuring the solvents of interest accurately.

However the use of calibration cylinders for the solvent drying application presents additional challenges to the user. Firstly, although the MS will need to measure very high solvent concentrations at the start of the drying run, it is not possible to obtain cylinders with high concentrations of organic solvents, and even the cylinders that are available with low solvent concentrations tend to be quite expensive with a limited shelf life.

Secondly, to measure each solvent's fragmentation pattern, we need to ensure there is no other interfering compound in the cylinder. So, from the example above, we could not have a calibration cylinder containing ethyl acetate and isopropanol because we need to measure the ratio of mass 43 to mass 45 for each solvent in isolation. As organic solvents tend to produce many fragment peaks, in practice this means that each solvent requires its own calibration cylinder. This may be feasible in a production environment with a limited range of solvents requiring analysis, but in R & D environments where many different solvents may be of interest, the use of multiple cylinders with limited shelf lives adds significant costs and complexities to the adoption of MS.

Thirdly, water is a frequently used solvent and it is impossible to obtain a calibration cylinder containing a known concentration of water.

We at Thermo Fisher Scientific felt the best way to assist the implementation of MS in the solvent drying application would be to provide a means of calibrating the MS with pure liquids. We have therefore adapted our proven Variable Pressure (VP) Inlet to accommodate a liquid calibration inlet.

Prima PRO Variable Pressure inlet with liquid calibration

The inlet is shown in Figure 2. The inlet can sample from up to 10 dryers and can accommodate sample pressures ranging from atmospheric down to 0.3 mbar. The early solvent drying MS inlets just used a single control valve to attempt to maintain a constant pressure in the MS inlet, closing at high sample pressures and opening as pressure drops. This approach suffered from two key 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.

- In a multi-dryer installation the MS will have to switch between a dryer at high pressure at the start of a drying cycle and a dryer at low pressure at the end of a cycle. A single control valve has to adjust to these pressure swings as quickly as possible, but its response characteristics are inadequate for this duty. Long delays have to be built in to stream switching times, particularly as the solvents are at opposite ends of the concentration range.

Calibration gas inlet from calibration manifold (up to 24 calibration gases)

Manual valve

Liquid sample vial

Figure 2 Prima PRO Variable Pressure inlet with liquid calibration inlet.

Prima PRO's VP inlet uses two control valves working in opposition – as one valve opens the other closes, ensuring a wide dynamic range and fast, precise pressure control. This means Prima PRO can switch between dryers at widely differing pressures and still provide reliable, stable solvent concentration data.

The liquid calibration comprises a manual on/off valve and a glass sample vial into which around 2 ml of solvent is placed. When the manual valve is opened, the sample vacuum pump boils off the solvent giving a stream of pure vapor. The inlet system introduces the vapor into the ion source at the same fixed pressure as a process sample or gas calibration sample. The solvent concentration will be at 100 mole %, and it doesn't matter that different solvents have different vapor pressure, the inlet pressure controller will maintain the same fixed inlet pressure. The sample vial does not need to be heated to vaporize the solvent.
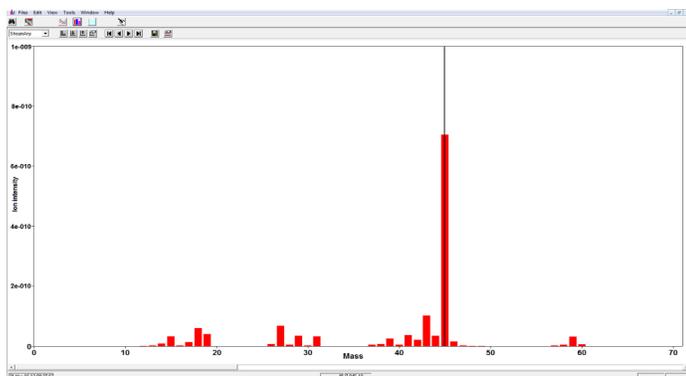
Figure 3 GasWorks calibration fingerprint scan for isopropanol

As with gas calibration, a fingerprint scan can be generated for the liquid calibration, to verify that the correct pure solvent has been used. Figure 3 shows the Thermo Scientific™ GasWorks™ calibration fingerprint scan for isopropanol.

A detailed calibration report is generated for every calibration; this is part of the functionality available within GasWorks to enable conformance with the requirements of the FDA's Guidance for Industry 21 CFR Part 11.

Application Development

We use a solvent drying test rig to simulate customer drying applications and demonstrate Prima PRO's selectivity and flexibility. The unit has two vacuum dryers connected to the Prima PRO by heated sample lines. The dryers can be heated, purged with nitrogen, and pumped down to 2 mbar. We use microcrystalline cellulose, a common excipient, to represent the API in the dryer.

To demonstrate the Prima PRO's selectivity, the system was challenged with a combination of five solvents: methanol, ethanol, tetrahydofuran, cyclohexane and ethyl acetate. Figure 4 shows the GasWorks analysis method set up to monitor these five solvents, together with nitrogen and oxygen. The solvents exhibit a significant degree of spectral overlap; four of the five solvents contribute to the signals at mass 31 and mass 43, and three solvents contribute at mass 45.


Figure 4 GasWorks Analysis Method for nitrogen, oxygen, methanol, ethanol, tetrahydofuran, cyclohexane & ethyl acetate

The inlet pressure was set to control at 78 µbar and the liquid calibration inlet was used to calibrate the five solvents. Nitrogen and oxygen were calibrated using a single cylinder through the gas calibration inlet.

One of the dryers was loaded with all five solvents, the other was loaded with just one solvent, ethanol. GasWorks was set to monitor all five solvents in both dryers. Oxygen was also monitored, to verify there were no leaks in the dryers or sample lines. The drying run was started and the vessels pumped down from atmospheric pressure to 2 mbar. The drying data are displayed in Figures 5 and 6. As well as the concentrations of the five solvents and oxygen, the readings for inlet pressure are also displayed.

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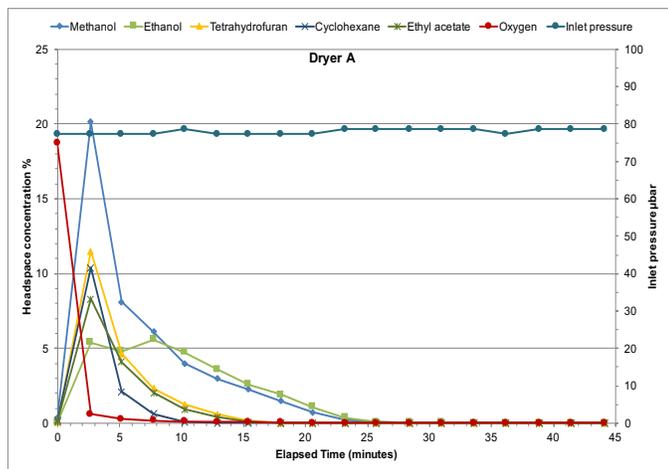
Figure 5 Solvent drying run for dryer containing methanol, ethanol, tetrahydofuran, cyclohexane and ethyl acetate
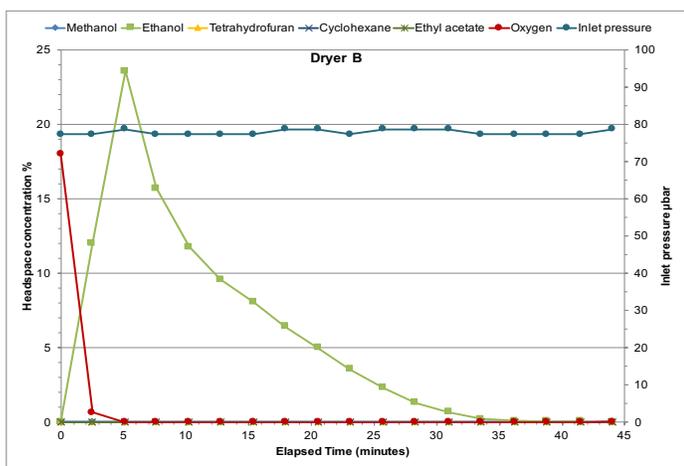
Figure 6 Solvent drying run for dryer containing ethanol only

Despite the high degree of spectral overlap exhibited by the five solvents, the only solvent that is recorded in the second dryer is ethanol, there is no interference from the other four solvents. The combination of liquid calibration, GasWorks software and Prima PRO's magnetic sector analyzer ensures a high degree of selectivity even when

monitoring a complex combination of solvents such as this. Throughout the drying run the inlet pressure remains stable at the set point of 78 µbar, despite the pressure in the dryers dropping from atmospheric to 2 mbar.

Summary

Gas analysis MS offers many advantages for monitoring API solvent drying processes:

- MS samples the headspace above the product, measuring the bulk API in the dryer and avoiding problems with grab samples for spectroscopy techniques caused by lack of homogeneity.

- MS sampling is simple and straight-forward, just requiring a compression type connection to the dryer outlet, heated sample line and basic particulate filter with disposable element.

- MS operates at high vacuum, typically 10^{-5} to 10^{-6} mbar; sampling from vacuum drying processes is therefore quite practical.

- MS can check for vacuum integrity either by looking for air leaks or by helium leak checking.

- MS fragmentation patterns are effectively 'fingerprints', simplifying the analysis of even complex mixtures.

However, if the MS can only generate qualitative or semi-quantitative data, its results will be subject to inaccuracies, particularly for multi-solvent systems, and drift. If the MS is to be used as part of a PAT solvent drying process control project, it must produce accurate, reliable quantitative data, even for multi-dryer, multi-solvent systems. Prima PRO offers three significant advantages to help achieve this aim:

- Magnetic sector MS provides stable fragmentation patterns and resistance to contamination

- Variable pressure inlet with two control valves ensures MS inlet pressure remains stable even when switching from high to low pressure sample points

- Easy, simple calibration with either gases or liquids ensures accurate quantitative data

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