

On-Line Monitoring of Vacuum Dryers Using Mass Spectrometry

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Abstract:

Mass spectrometry was used to monitor vacuum-drying endpoints in the laboratory and pilot plant to demonstrate feasibility of its application. The technique is relatively simple to interface to existing equipment at minimal cost, requires no direct sample contact, and is generally applicable to multiple dryer configurations. Results of the feasibility study showing the monitoring of multiple solvents, along with correlation of the mass spectrometric technique to conventional percent loss on drying (LOD) measurements, are discussed.

Introduction

Vacuum drying is routinely used in Pfizer's pilot and manufacturing plants for drying of pharmaceutical intermediates and drug substances. Currently the drying endpoint is determined, in part, by guessing when to remove a sample and then analyzing it for dryness.³ This operation involves lowering the dryer temperature, breaking vacuum, removing a representative sample, and performing an analysis in the laboratory to test for dryness. All of these activities are time intensive. These operations also pose the potential for worker exposure. Furthermore, drying operations are often rate-limiting in the production environment, and thus there is significant potential cost savings in minimizing the time that material remains in the dryer.

Background

There are only a few papers in the literature on the general topic of on-line monitoring of vacuum dryers. In one paper, near-IR (NIR) spectroscopy was demonstrated in a pilot plant rotary dryer installation using a gas cell.⁴ A NIR probe in direct contact with the wet product was also successfully demonstrated within Pfizer using an agitated comber dryer.⁵ Mass spectrometry was chosen in the present work because of its high sensitivity, specificity to multiple solvents, and the ease and non-invasiveness in which it can be interfaced to a vacuum system.⁶ Another significant advantage with

mass spectrometry is that essentially little or no method development is required for this application other than to select the ions of interest.⁷ An excellent paper by Walsh and LaPack compares process MS against other on-line methods and provides a guide for deciding on a preferred analytical technique.⁸ Competitive advantages of process MS mentioned in their paper were its speed, sensitivity, and reliability.

One drying paper that utilized mass spectrometry presented preliminary data obtained from a Guedu pilot-scale vacuum dryer.⁹ The authors demonstrate that a correlation between the MS response and percentage of volatiles is possible, but they do not attempt to distinguish which drying regimes should be correlated. The present work demonstrates for the first time the use of mass spectrometry to monitor vacuum tray-dryer effluent in a pharmaceutical pilot plant and its response to different drying regimes.

Experimental Section

The instrument used in this work was a Ametek/Dycor Quadrupole Gas Analyzer, model M100DEF,¹⁰ upgraded to have a mass range of 1–200 Da. The Dycor System 2000 software was used to control and collect mass spectra. The capillary was a 10 m silica column 0.05 mm in diameter.¹¹ For the laboratory studies, the capillary was fed through a syringe needle pierced into the rubber vacuum hose leading from the dryer effluent. The needle was then withdrawn back up the column while keeping the capillary inside the hose, thus forming a vacuum-tight seal.

For the pilot plant feasibility studies, the capillary was interfaced with the pilot plant vacuum system using a standard gas chromatography septum inserted inside a $\frac{9}{16}$ in. Swagelok nut used to maintain a vacuum seal. The mass spectrometer was positioned in a general purpose electrical classification area while the capillary was fed through a small conduit to reach the vacuum system in the adjacent room. A diagram of the spectrometer interface to the vacuum system is shown in Figure 1.

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(3) In some cases internal drying temperatures can provide clues that drying has completed. However, it is likely to be highly dependent on the accuracy and location of thermocouples, etc.

(4) Coffey, C.; Predoehl, A.; Walker, D. Dryer Effluent Monitoring in a Chemical Pilot Plant via Fiber-Optic Near-Infrared Spectroscopy. *Appl. Spectrosc.* **1998**, *52* (5), 717–724.

(5) Hammond, S. Internal communication, Pfizer Global Manufacturing, Sandwich, UK.

(6) The mass spectrometry approach is a non-contact method. Techniques that require the sensor be in contact with the wet cake can lead to problems of obtaining representative samples and have other issues such as cleaning etc.

(7) The masses of interest can be determined from a simple scan of the solvent(s) to determine the mass fragment patterns or simply referring to a mass spectral library available on many MS software bundles.

(8) Walsh, M.R.; LaPack, M. A. On-Line Measurements using Mass Spectrometry. *ISA Trans.* **1995**, *34*, 67–85.

(9) Colin, T. Vacuum Dryer Endpoint Prediction Using Process Mass Spectrometry. *At-Process* **1997**, *3* (1,2), 63–70.

(10) Ametek Process Instruments, 150 Freeport Road, Pittsburgh, PA 15238.

(11) ChromTech, Inc., Apple Valley, MN.

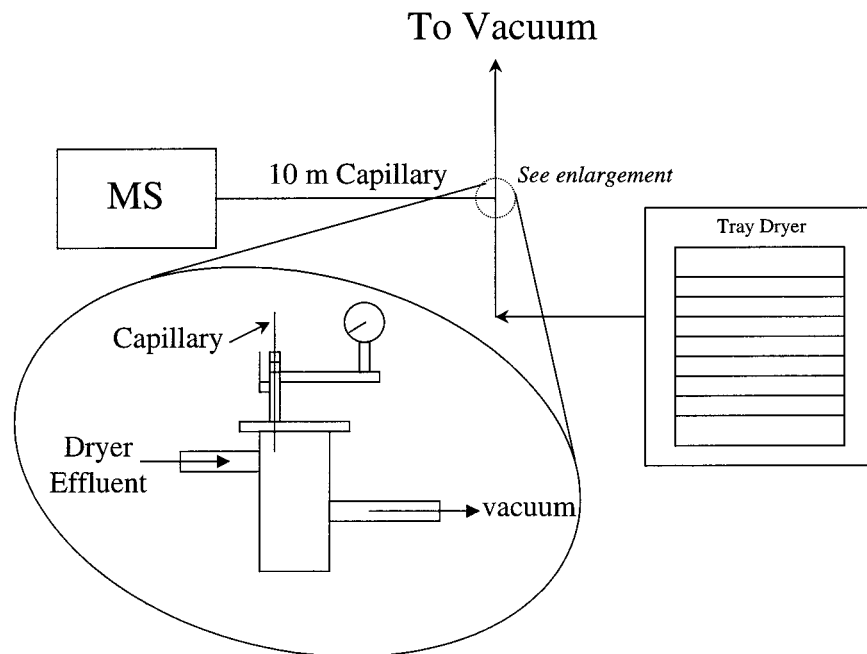


Figure 1. Configuration of mass spectrometer interfaced to the pilot plant vacuum system. The inlet to the spectrometer was a 10 m glass capillary column. The driving force for the sample to enter the spectrometer is simply the pressure difference between the high vacuum in the spectrometer (10^{-5} Torr) compared to the lower vacuum level in the dryer system which is approximately 29 in. of Hg or 23 Torr (absolute).

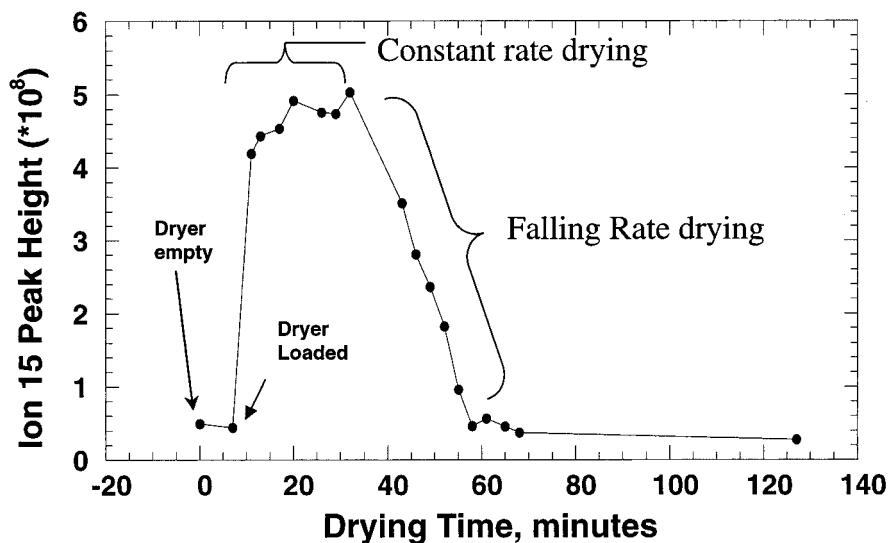


Figure 2. Drying profile of a 5 g sample of filter-aid wet with methanol and placed in a laboratory vacuum oven held at 50 °C and 15 in. of Hg vacuum. The mass spectrometer was initiated to get a base line for about 7 min at which point the sample was then placed in the oven and the vacuum applied. The methanol vapor concentration, as measured by the abundance of $m/z = 15$, was monitored as a function of time. Ion 15 is attributed to the CH_3^+ ion formed from ionization of the parent methanol molecule in the mass spectrometer.

Results

Feasibility studies were performed in the laboratory using the Ametek/Dycor system, initially for several simple cases, to gain an understanding on the responsiveness of the spectrometer under different conditions. In one case, a few grams of filter-aid were wetted with methanol, and the vapor phase was monitored via the vacuum dryer effluent. An ion specific to methanol, $m/z = 15$, was monitored during this experiment and is profiled in Figure 2. The data show a sharp rise in methanol concentration, where it remains, at an almost steady concentration, for about 30 min. This is followed by

gradual decline in methanol concentration as the material eventually goes to dryness over the next 40 min. The drying of porous solids typically exhibits a constant-rate period where the moisture movement within the solid is rapid enough to maintain saturated conditions at the surface.¹² In this scenario, the rate is controlled by the rate of evaporation which depends on the rate of heat transfer to the evaporating surface. This situation is analogous to moisture evaporating from a body of liquid and is essentially independent of the

(12) *Perry's Chemical Engineers Handbook*, 7th ed.; Perry, R. H., Green, D. W., Eds.; McGraw-Hill: New York, 1997.

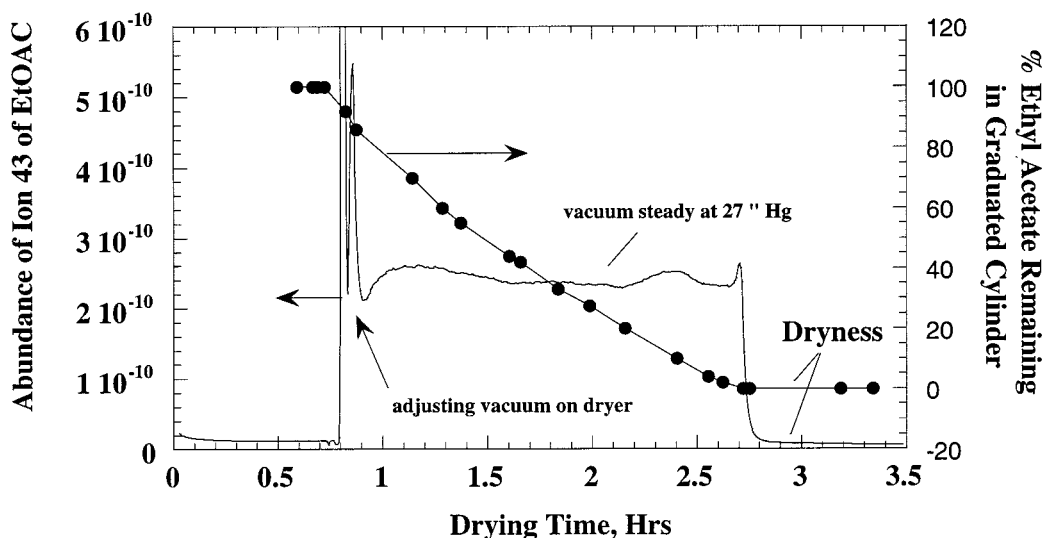


Figure 3. Mass spectrometer monitoring during the evaporation of 10 ml of ethyl acetate in a 10 ml graduated cylinder placed inside a vacuum oven which shows how the vapor phase concentration changes with time. The left ordinate refers to the ion $m/z = 43$ abundance of ethyl acetate. The right ordinate refers to the % volume of ethyl acetate remaining in a graduated cylinder. The ion abundance during the evaporation remains essentially constant. These data simulate the constant-rate drying regime in solids during which the solid surface remains saturated with solvent.

nature of the solids (Perry's). Following the constant-rate period, a critical point is reached where the surface no longer remains saturated with liquid. At this point the drying enters into the falling-rate regime where the drying depends largely on the structural properties of the solid, on the heat transfer, and on the diffusional mass transfer of the liquid through the solids.¹³

To better understand the constant-rate drying regime, an experiment was performed using 10 mL of pure ethyl acetate in a 10 mL graduated cylinder placed inside the vacuum oven and monitored as it evaporated to dryness. The volume of solvent remaining in the graduated cylinder was recorded visually through the glass door while ion $m/z = 43$ was monitored from the dryer effluent via the mass spectrometer. These data are shown in Figure 3 at a drying temperature of 40 °C and 27 in. of Hg of vacuum. Once the sample was loaded and the vacuum level applied, there was an immediate response of the MS as seen in the sharp rise in Figure 3 at 0.8 h (which is when the experiment began). Also note that the vapor phase solvent concentration remains virtually constant (i.e., constant-rate drying) until all of the liquid has evaporated away to dryness even though the volume steadily decreases. The sharp spikes observed in Figure 3 at the beginning of the drying occurred while the vacuum level was being adjusted to 29 in. of Hg causing the liquid to bump. At this point the vacuum was reduced and maintained at 27 in. of Hg until the end of the experiment. This particular experiment (Figure 3) simulates the constant-rate drying regime exhibited in porous solids. Furthermore, it confirms that the vapor phase remains saturated and of constant concentration until the sample either reaches dryness as in the pure liquid case or reaches the critical moisture content.¹⁴

The importance of this relatively simple experiment is that loss on drying data (LOD) will not correlate with vapor phase concentration (i.e., MS response) during the constant-rate drying regime because by definition the vapor phase concentration remains steady while the material is drying. However, after the critical moisture content is reached the rate of vapor leaving the solid tapers off and drying enters the falling rate regime. In the falling rate regime, it appears that mass spectrometric response correlates well with LOD as is demonstrated in the next experiment.

A sample, wet with both hexane (65 vol %) and ethyl acetate (35 vol %), from a pilot plant batch was dried in a laboratory vacuum oven. One objective was to learn whether ion abundance would correlate to LOD in the falling-rate period for drying. A 25 g sample wet with hexane and ethyl acetate was placed in the oven and equilibrated at 35 °C and monitored by MS. Samples were removed from the vacuum oven every 15 min for LOD determination. The LOD and MS profiles are shown in Figure 4. When the vacuum is broken, air displaces the solvent vapors, which explains the sharp drops in solvent concentration in the MS profile between the samples. A correlation was tested by taking the LOD data and spectrometer responses measured in Figure 4 and plotting them in Figure 5. Specifically, in Figure 5 are the data points representing the % LOD versus the hexane ion, $m/z = 57$, measured immediately before the sample was removed from the dryer. The initial LOD was obtained prior to loading into the vacuum oven, and the MS response indicates a relatively constant vapor phase concentration extrapolated back to the critical moisture content depicted in Figure 5. For all subsequent samples it appeared that the drying rate was in the falling-rate regime and closely correlated with MS response. This was in contrast to the constant-rate drying regime exemplified in Figure 3 where no correlation was found. The sample used in the experiment,

(13) Foust, A. S.; Wenzel, L. A.; Clump, C. W.; Maus, L.; Anderson, L. B. *Principles of Unit Operations*, 2nd ed.; Wiley & Sons: New York, 1980.
 (14) *Critical moisture content* occurs at the end of the constant-rate period. It is not a unique property of the solid but rather depends on the pore structure of the solid, sample thickness, and overall drying rate (Foust et. al., 1980).

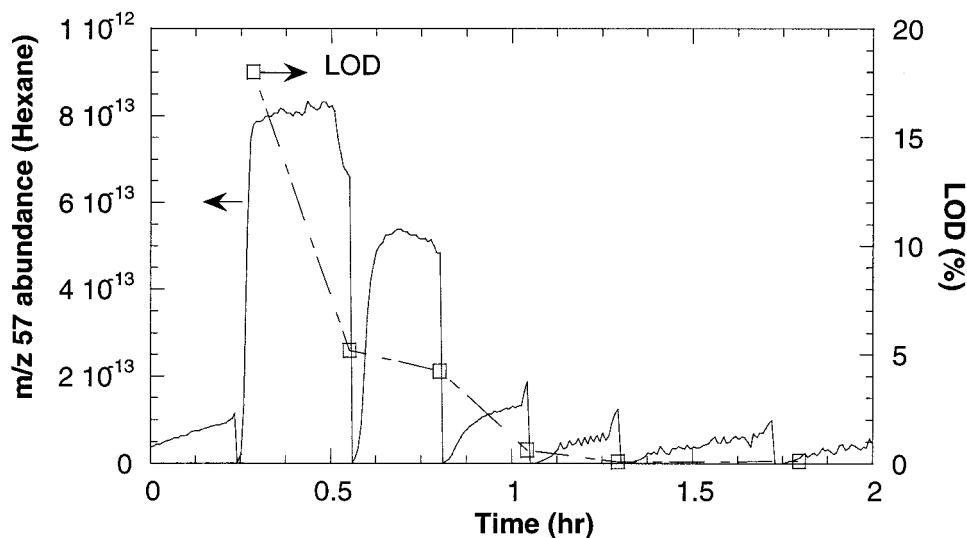


Figure 4. Laboratory data for a 25 g sample of pharmaceutical intermediate wetted with a 65:35 volume ratio of hexane:ethyl acetate held at 35 °C and 28 in. of Hg vacuum. The left ordinate shows the ion $m/z = 57$ abundance, unique to hexane, overlaid with % LOD data (right ordinate) obtained by manually removing samples from the dryer. The opening of the dryer to obtain the LOD samples caused the perturbations seen in the spectrometer response.

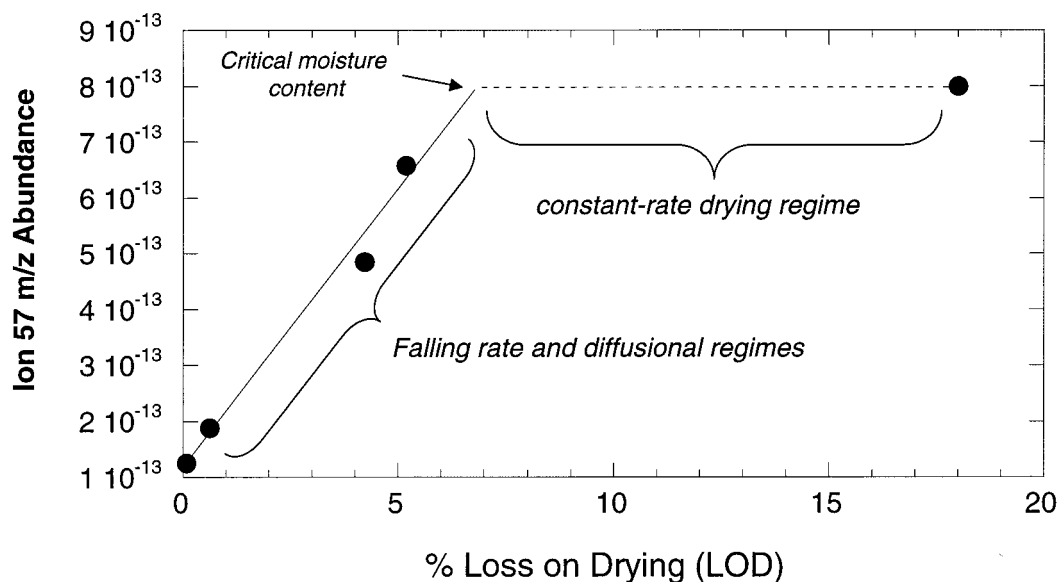


Figure 5. Correlation of spectrometer response with extent of dryness of the sample or LOD using the data from Figure 4. The left axis is the ion abundance values plotted for hexane, $m/z = 57$, obtained immediately prior to a sample being taken for LOD. The purpose of this plot is to illustrate the correlation of vapor phase concentration with MS data during the falling-rate period of drying in contrast to the constant-rate period.

shown in Figure 5, actually also contained a small amount of ethyl acetate that contributed to the LOD; however, it is present in much lower levels than hexane. More recently we have employed battery-powered balances within the vacuum oven to obtain virtual % LOD without having to break vacuum. Figure 6, for example, illustrates the simultaneous collection of the mass of solids and ion abundance as a function of time while maintaining vacuum for a water wet pharmaceutical intermediate.

Pilot Plant Scale

A 40 kg batch of a pharmaceutical intermediate wet with hexane (65 vol %) and ethyl acetate (35 vol %) was charged to a 2.72 m³ pilot plant tray dryer. Vacuum was applied (29

in. of Hg), and the temperature was raised to 42 °C. A 10 m capillary was interfaced to the vacuum system using a Swagelok fitting and a septum where the capillary inlet was placed in the dryer's vapor effluent stream. No provisions were made to prevent condensation within the capillary, and no problems were experienced in this regard.

The profile obtained from the mass spectrometer during the pilot plant drying is shown in Figure 7 (bottom). The internal dryer temperature profile is shown in Figure 7 (top). The MS data show a sharp response to both hexane and ethyl acetate ions. Ion $m/z = 43$ is common to both hexane and ethyl acetate but is weighted more toward ethyl acetate as it is the dominant ion of the parent ethyl acetate molecule and is a only minor ion of hexane. Thus, the $m/z = 43$ profile

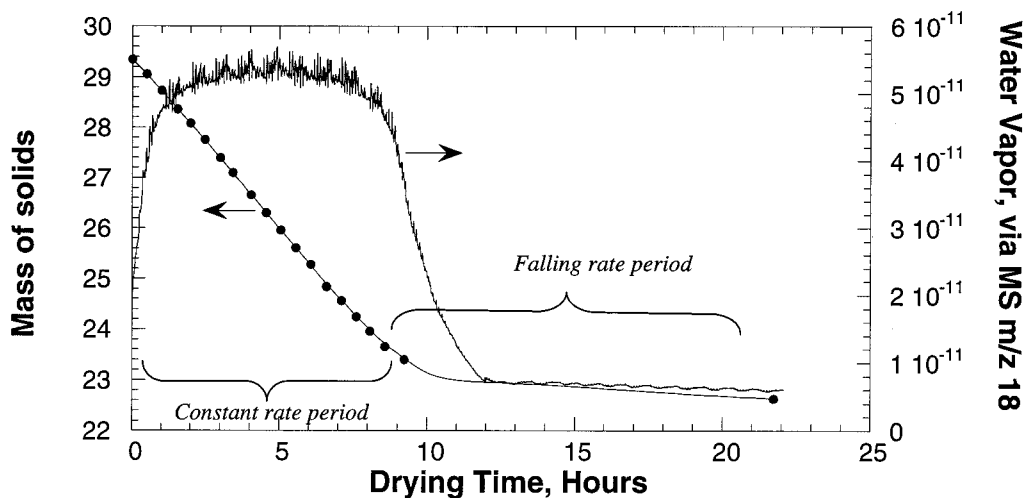


Figure 6. Drying of a water wet pharmaceutical intermediate at 10 in. of Hg vacuum and 30 °C with a nitrogen sweep flowing at 1 SLM (standard liter per minute). The left axis is the mass of wet cake as monitored by a battery-powered balance with readings taken through the glass door. The right axis is the abundance of water $m/z = 18$ as measured by mass spectrometry. Humidity level within the dryer follows a similar profile to the MS reading as expected.

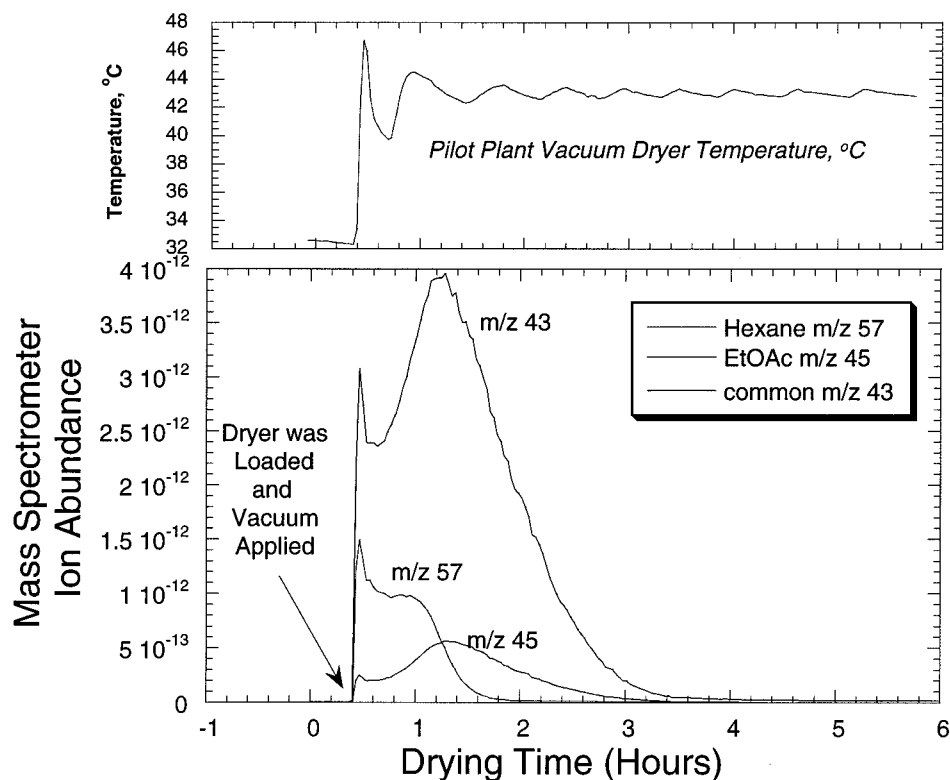


Figure 7. Drying profiles obtained from a 40 kg pilot plant batch of pharmaceutical intermediate wet with hexane and ethyl acetate in a ratio of (65:35). The initial % LOD for the wet cake was 18%. The material was placed in a vacuum tray dryer at which point vacuum was applied and the temperature raised to a set point of 43 °C and 28 in. Hg of vacuum. These data show that hexane, $m/z = 57$, present in larger concentration dries faster than the ethyl acetate, appearing to be largely removed in less than 2 h. The ethyl acetate, $m/z = 45$, is slower, appearing to be removed in about 4 h. Also monitored was $m/z = 43$ which is an ion common to both hexane and ethyl acetate and thus appears to be a weighted average of the two curves going through a maximum at 1.5 h. The weighting factor is a function of the percent vapor concentration and the extent to which that particular ion makes up the parent molecule.

depends on the relative concentrations of each solvent present, the fragmentation percentage of $m/z = 43$ to the respective parent ions, and the temperature of the dryer as it influences the vapor pressure of each solvent. This helps explain why the MS profile for the common ion $m/z 43$ exhibited the sharp peak initially (due to the overshoot of

temperature in the dryer), and that the maximum tended to correspond to the maximum in the ethyl acetate $m/z 45$ profile. The pilot plant MS profiles are confounded by the changing temperature inside the dryer, but it appears that the falling-off period occurs after 1 h for hexane and at about 1.4 h for ethyl acetate as seen in Figure 7.

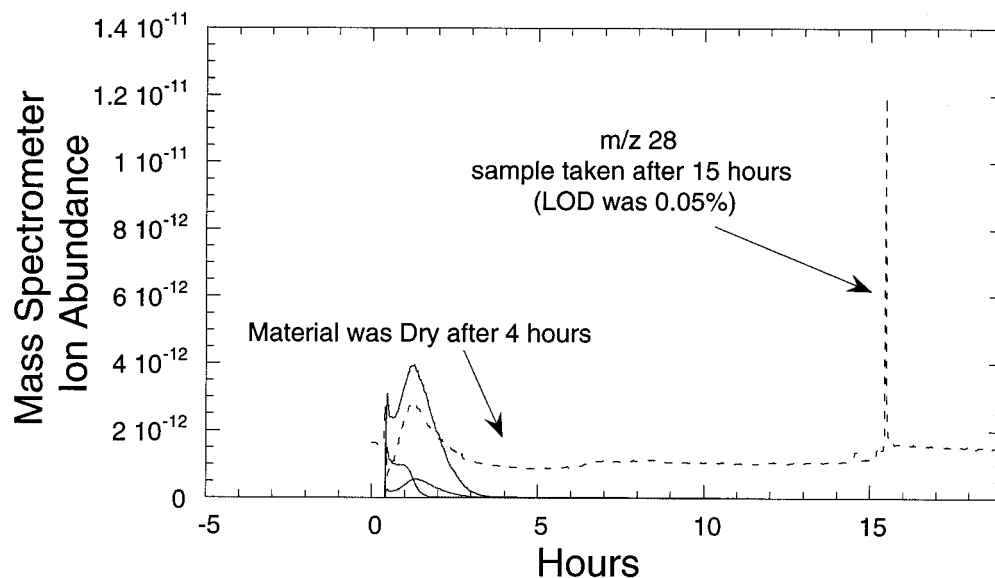


Figure 8. Pilot plant drying profile shown in Figure 4 extended to 20 h. Ion 28 was monitored to indicate changes in nitrogen concentration from breaking vacuum. This indicated that a manual sample was pulled from the dryer at approximately 15 h. The mass spectrometer data suggests that steady state was achieved after 4–5 h, and thus approximately 10 h could have likely been saved from the drying operation.

Another important observation from Figure 7 is the selectivity that the spectrometer provided for each solvent. The method indicated that hexane, which was present in the larger ratio¹⁵ due to process conditions, and possessing a lower boiling point (69 °C) is removed much more rapidly than the ethyl acetate (bp 77 °C). The magnitude of the relative ion abundances of $m/z = 57$ (hexane) and $m/z = 45$ (ethyl acetate) cannot necessarily be used to correlate relative concentrations to each other because each ion does not represent the same percentage of the parent molecule being ionized, as mentioned above. To quantify these profiles into vapor phase concentrations would require calibrations against known standards under precise operating conditions. The main benefit of the data afforded from Figure 7 is that it indicates that steady state is reached after approximately 4–5 h and that the material should then be sampled for dryness. Achieving steady state will not necessarily guarantee the material to be dry to the desired specification, but this tool should provide important guidance as to when samples should be taken, and thus could likely save weeks of drying time per year by eliminating unnecessary drying time. Thus, this technology should provide a valuable process control tool for multibatch campaigns, once the endpoint can be recognized with certainty after the first few batches. Ultimately, one could conceive of a validated process where the spectrometer would be used exclusively to identify endpoints for particular products, eliminating the need for LOD testing prior to dryer discharge.

In the case of the pilot plant experiment, the 40 kg batch was not actually sampled until after 15 h, which is revealed in Figure 8. Pilot plant operators were not using the MS as guidance at this point. Note that during the MS monitoring it is usually a good idea to save ion m/z 28 which provides

a measure of nitrogen concentration (but may have common ions from the solvents, too). By monitoring ion m/z 28 it is obvious when vacuum was broken and the sample pulled, in this case, after 15 h. The data suggest this material would have been dry perhaps as early as 4 or 5 h, potentially saving 10 h of drying time. Experience will have to be gained for a particular product or campaign with this technology to determine how long steady state should be held to ensure the dryness specification is reached. This is envisioned to take no more than 2 or 3 batches to develop a process control strategy using the mass spectrometer as a monitoring device. In this case after 15 h the LOD was 0.05% which was within the specification of 1% LOD.

Conclusions

From a practical point of view, mass spectrometry for the monitoring of dryer effluent to indicate steady state and endpoint is relatively easy and offers numerous advantages over other techniques. The work described here confirmed how the mass spectrometer responds to different drying regimes. Namely, during the constant-rate drying regime, the sample is drying but the vapor phase concentration remains steady. It is not until the drying enters the falling-rate regime that the spectrometer response begins to reflect and correlate with the extent of dryness. We intend to use this technology primarily to indicate that steady state has been reached during the drying of pharmaceutical intermediates/products to minimize potential worker exposure and to avoid unnecessary hold times. It is likely that once experience is gained from using the data for this purpose, especially in a multicampaign production environment, significant time- and cost savings will be realized. A permanent process MS is being considered for at least one of Pfizer's pilot plants in 2000.

(15) The wet cake contained hexane and ethyl acetate in a ratio of 65:35 by volume.

Acknowledgment

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