Microwave Assisted Vacuum Drying and End Point Determination Using Mass Spectrometry, Part I

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Abstract:

On-line mass spectrometry (MS) was investigated as a tool to monitor microwave vacuum drying operations on laboratory scale. Using several different solvents and calcium carbonate solids, MS was used to monitor the drying end point of single and multiple solvent wet cakes. The microwave drying rates for polar solvents were shown to have a linear correlation with solvent heat of vaporization. Mass spectrometry profiles were also shown to correlate with other drying end point parameters, including rate of recovered solvent, product temperature, and microwave reflected power.

1. Introduction

The pharmaceutical industry is one in which the final product quality must meet rigid specifications. Product deterioration (e.g., by thermal decomposition, oxidation, or unremoved organic solvent) must be avoided. To prevent thermal decomposition, vacuum drying is employed to facilitate solvent evaporation at reduced temperatures (typical temperature range: 30−50 °C). However, conventional vacuum drying can sometimes result in long and highly energy-intensive drying processes, sometimes resulting in processing bottlenecks.[1] Most conventional vacuum ovens (i.e., tray dryers) rely on conduction heat transfer from hot plates, which is slow, is difficult to control, and requires a large surface area.[2] Microwave drying offers a much more rapid method of moisture removal due to its volumetric (internal) heating mechanism. Microwave vacuum drying combines the advantages of high-speed solvent removal at reduced temperatures.

One of the most critical parameters in the drying of pharmaceuticals is the determination of the desired endpoint, usually at a specified moisture content. In the absence of on-line process analytical technology (PAT) like MS, the drying endpoint is usually determined by a trial and error approach, whereby a sample is removed and analyzed for dryness. This operation involves lowering the dryer temperature, breaking vacuum, removing a representative sample,

and performing an analysis in the laboratory to test for dryness. These operations are time intensive and also pose the potential for worker and product exposure.

Application of PAT tools such as MS to determine endpoint during microwave drying operations will protect against potential thermal decomposition due to potential overheating from extensive drying times and significantly reduce drying cycle times and energy requirements. Since microwave vacuum drying rates are considerably faster than conventional vacuum dryers, it is crucial to utilize a drying endpoint tool to (1) identify a time-point to test for dryness, and thus limit the number of samples and overall drying time and (2) ensure the product is not "over-dried", which can lead to decomposition if the product temperature gets too high.

The on-line MS technique is relatively simple to interface to existing equipment at minimal cost, requires no direct sample contact, is applicable to multiple dryer configurations, and may be used to indicate when the batch should be sampled for dryness. Because dryer operations are often rate-limiting in the production environment, utilizing on-line MS to monitor the microwave dryer endpoint provides a significant potential cost savings in minimizing the time that material remains in the dryer.

The following drying endpoint indicators were also monitored and correlated with MS response for the present work:

(1) Recovery rate of liquid - as drying endpoint is approached, rate of liquid recovery will decrease;

(2) Reflected power - will generally increase when solvent has evaporated (if product does not absorb microwaves);

(3) Product temperature - will increase after drying endpoint is reached.

The main objectives of this research were as follows:

(1) Further develop correlation between MS signal and drying endpoint for single and multiple solvent wet cakes.

(2) Determine microwave vacuum drying rates of various solvents, commonly used in the pharmaceutical industry, and relationship with associated physical properties (i.e., boiling point, heat of vaporization).

To date there are no references available in the literature specific to the topic of microwave drying endpoint monitoring using on-line mass spectrometry. There are 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

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(1) Mujumdar, A. S. *Handbook of Industrial Drying*; Marcel Dekker: New York, 1995; pp 743−773.
(2) Metaxas, A. C.; Meredith, R. J. *Industrial Microwave Heating*; Peter Peregrinus LTD: London, United Kingdom, 1983; pp 70−102.
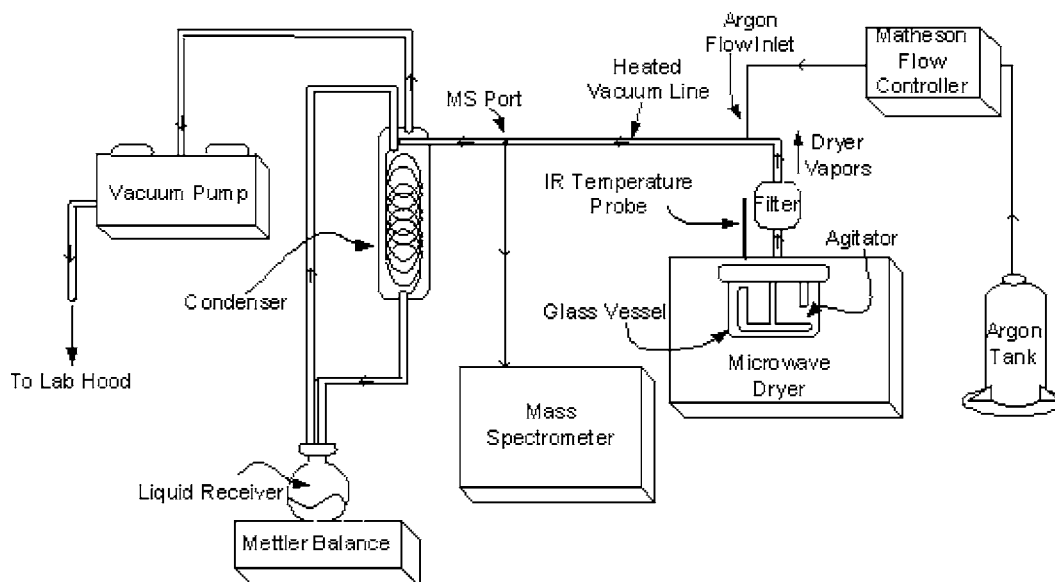
Figure 1. Pro-C-ept microwave dryer setup showing MS sample point, argon flow inlet, and condenser/liquid recovery system.

using a gas cell.[3] The disadvantages of the NIR technique are that it requires method development prior to drying new products and is less selective for monitoring multiple solvents. Conversely, mass spectrometry is a noninvasive method, since the MS port is interfaced with the vacuum line, and requires little method development other than to select the ions of interest. Previously we have demonstrated the use of mass spectrometry to monitor vacuum tray-dryer effluent in a pharmaceutical pilot plant and its response to different drying regimes (i.e., constant rate drying, falling rate drying).[4] A paper by Walsh and LaPack compare process MS against other on-line methods and provide a guide for selecting a preferred analytical technique.[5] Competitive advantages of process MS mentioned were its speed, sensitivity, and reliability.

The present work demonstrates for the first time the use of MS to monitor the microwave vacuum drying endpoint. The results of this research offer significant benefits for drying operations in the pharmaceutical industry.

2. Experimental Section

2.1. Microwave Dryer - Laboratory Scale. The Pro-C-epT[6] Mini-Turbo Wave (MTW) microwave dryer, with the Mi-Mi-Pro microwave mixer/granulator, was used to conduct laboratory studies. The MTW is designed for small quantity powder and liquid processing, with a capacity of batches up to 500 g (range 80−500 g) of dry product. The unit is equipped with a glass process vessel and a plastic-compound (PEEK)/Hastelloy central agitator blade. The system is a complete microwave vacuum processor with computer control and data acquisition. The microwave frequency is set at 2450 MHz, with a power input range of 50−300 W. The vacuum range suitable for microwave drying is 400 mbar

down to 30 mbar. Additional on-line parameters include product temperature (measured by an IR probe), agitator torque and rpm, microwave reflected power, and oven air temperature. Figure 1 shows the microwave dryer setup.

The mass spectrometer is interfaced with the vacuum line of the microwave dryer system to monitor the dryer end point. Argon ($m/z = 40$) is introduced at a constant flow of 10 standard cubic centimeters per minute (sccm), upstream of the MS interface, and is used as a reference gas to obtain a relative response (solvent mass peak/reference mass peak) of the vapors in the dryer headspace. The argon flow is regulated using a Matheson flow controller. The MS relative response represents a relative concentration of the dryer effluent. The mass spectrometer is used to indicate dryness of the material when the MS relative response reaches a baseline value (i.e., relative vapor concentration approaches zero). Ions with specific masses are chosen depending on the solvent(s) being dried. 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. For example, during the drying of a methanol ($m/z = 31$) wet cake with argon ($m/z = 40$) as the reference gas, the MS relative response value is determined from the MS responses of the following ratio: 31/40. The advantage of using mass spectrometry for dryer monitoring is that the effluent stream usually consists of only one solvent and the reference gas, with no overlapping peaks. For the case of multiple solvent wet cakes, each component mass spectra must be reviewed to determine if overlapping peaks exist.

The dryer vacuum line is heated to 120−140 °C via heating tape to avoid condensing of vapors in the vacuum line. The MS line is also heated to 120 °C to avoid condensation of solvents with a boiling point greater than 65 °C. The dryer vapors are condensed, using ethylene glycol as a chiller medium, and collected in a receiver. The condenser temperature is set at −5 °C. The amount of condensate is measured using a Mettler-Toledo balance,

(3) Coffey, C.; Predoehl, A.; Walker, D. *Appl. Spectrosc.* **1998**, *52* (5), 717−724.
(4) am Ende, D.; Preigh, M.; Hettenbach, K.; Ahlijanian, P.; Ward, W., II. *Org. Process Res. Dev.* **2000**, *4* (6), 587−593.
(5) Walsh, M. R.; LaPack, M. A. *ISA Trans.* **1995**, *34*, 67−85.
(6) Pro-C-epT n.v., Industriepark Rosteyne 4, B-9060 Zelzate, Belgium.
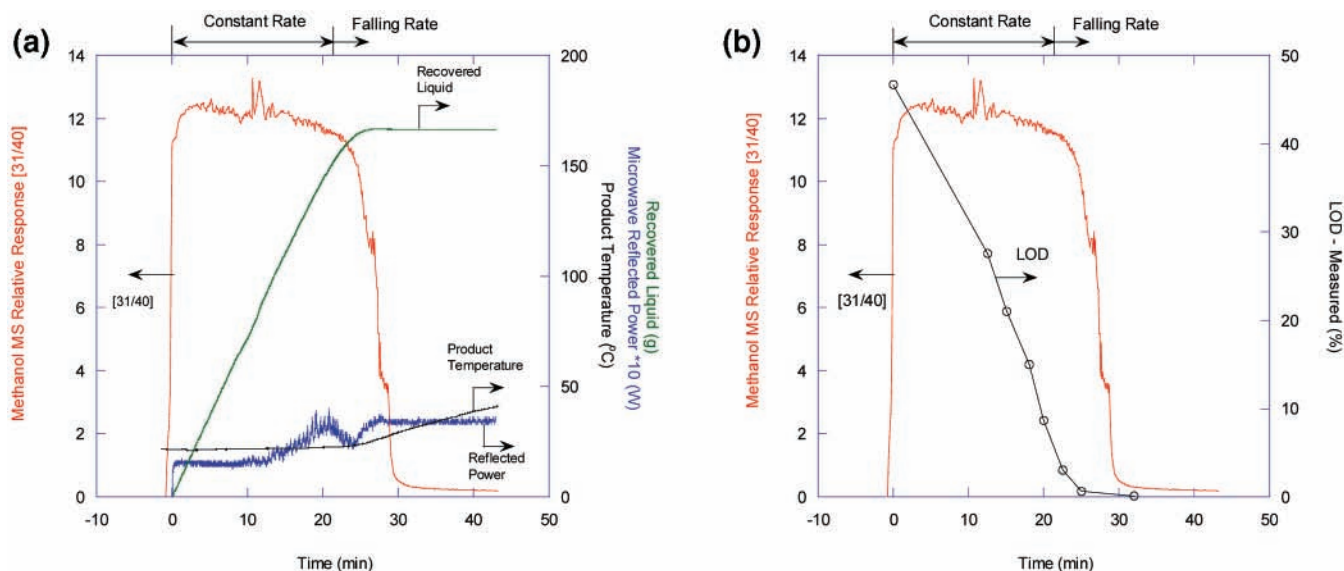
Figure 2. (a) Microwave drying profile of methanol (175 g) in calcium carbonate (200 g), showing methanol MS relative response on the left axis and liquid recovered, reflected power, and product temperature on the right axis. The microwave input power was 150 W, vacuum level = 100 mbar, air temperature = 35 °C, and argon input was 10 sccm (reference gas). (b) Methanol MS relative response is shown on the left axis, and loss-on-drying (LOD%), on the right axis. The LOD at $t = 25$ min was 0.64% and decreased to 0.085% at $t = 32$ min. The MS steady-state response is shown to correlate with product dryness.

recorded by the microwave dryer software. Once on-line mass spectrometry indicates steady state has been reached, the product is then tested for dryness via an off-line laboratory loss-on-drying (LOD) measurement. The specification for dryness for pharmaceutical intermediates and products is typically an LOD value of less than 1%. The loss-on-drying (LOD) values are based on "wet" moisture content, as defined in eq 1. The LOD instrumentation utilized is the Computrac (model MAX-2000) by Arizona Instruments.[7]

$$LOD(\%) = \frac{Liquid(g)}{Liquid(g) + Solid(g)} \times 100\% \qquad (1)$$

The experimental parameters for the microwave vacuum drying of calcium carbonate solids with various solvents include the following: 200 g of solids, 175 g of solvent, microwave power of 150 W, vacuum level of 100 mbar, and oven air temperature of 35 °C. The wet cake is prepared by adding the solvent to solids and then initially mixing in the microwave vessel before the microwave power is applied. Vacuum is initially applied to the wet cake approximately 30 s before the microwave power and hot air are initiated. The microwave vacuum dryings of various solvents were tested in duplicate to verify the average drying rate estimates.

2.2. Mass Spectrometry Equipment. (A) Low Boiling Point Solvents. The instrument used for low boiling point solvents (BP < 65 °C) for laboratory microwave drying analysis was an Ametek[8]/Dycor X-proof, multiport quadrupole mass spectrometer (model: Dycor ProMaxion) with a mass range of 1−300 daltons. The Dycor ProMaxion utilizes the Faraday cup for ion detection. The Dycor System 2000 software was used in tandem with the ProMaxion software

to collect mass spectra. The inlet capillary lines were polyetheretherketone (PEEK) tubing 0.030 in. in diameter and 5 ft in length. The capillary was maintained at ambient temperature, since condensing of low BP solvents was not a concern, and was interfaced to the vacuum line via Swagelok fittings. The vacuum pressure inside the MS was 5×10^{-6} Torr. The pressure difference between the vent line and the MS created the driving force for the introduction of gas sample through the capillary.

(B) High Boiling Point Solvents. The instrument used for high boiling point solvents (bp > 65 °C) for laboratory microwave drying analysis was the Pfeiffer Vacuum[9]/ OmniStar quadrupole mass spectrometer (model: GSD 300) with a mass range of 1−100 daltons. The Omnistar MS utilizes the Faraday cup for ion detection. The Quadstar 422 software was used to collect mass spectra. The inlet capillary lines were stainless steel tubing 0.005 in. in diameter (i.d.) and 5 ft in length. The capillary was maintained at 120 °C to avoid condensation of high bp solvents and was interfaced to the vacuum line via Swagelok fittings. The vacuum pressure inside the MS was 5×10^{-6} Torr.

3. Results and Discussion

3.1. Correlation Between MS Signal and Drying Endpoint. The effect of microwave vacuum drying rates of calcium carbonate wetted with various solvents was investigated. The results for the microwave vacuum drying run of methanol in calcium carbonate are shown in Figure 2a and b. The methanol vapor profile (ion 31/ion 40) is shown to correlate with dryness, whereby the relative response remains constant (at ion 31/ion 40) until $t \approx 22$ min and then sharply decreases to baseline. The methanol relative response profile correlates well with recovered liquid, product

(7) Arizona Instruments, 4114 E. Wood Street, Phoenix, AZ 85040.
(8) Ametek, 150 Freeport Road, Pittsburgh, PA 15238.

(9) Pfeiffer Vacuum, 24 Trafalgar Square, Nashua, NH 03063.
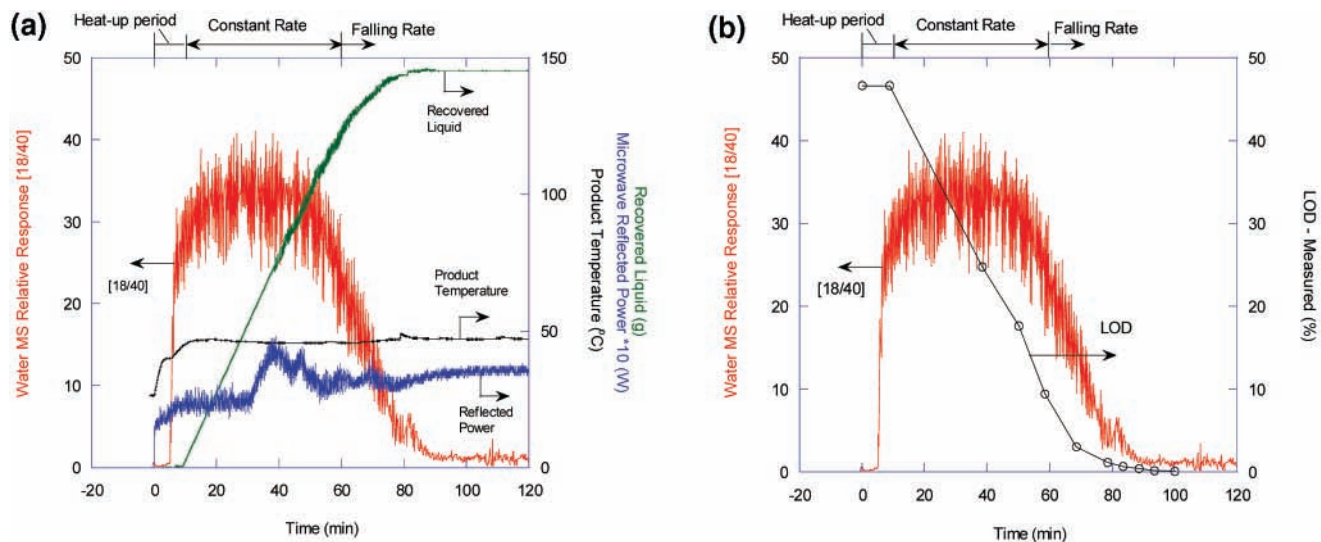
Figure 3. (a) Microwave drying profile of water (175 g) in calcium carbonate (200 g), showing water MS relative response on the left axis and showing liquid recovered, reflected power, and product temperature on the right axis. The microwave input power was 150 W, with a vacuum level of 100 mbar, an air temperature setting of 35 °C, and an argon input of 10 sccm (reference gas). (b) Water MS relative response is shown on the left axis, and loss-on-drying (LOD%), on the right axis. The LOD at $t = 85$ min was 0.68%. The MS steady-state response is shown to correlate with product dryness.

temperature, and reflected power endpoint parameters (Figure 2a). The recovered liquid profile is shown to increase linearly during the constant drying period and then displays a decreasing slope with time (falling rate period) until dryness is reached (at $t \approx 25$ min). The initial evaporation of methanol is shown immediately after the start of the microwave power input, since the initial product temperature is above the methanol boiling point (bp) at 100 mbar (bp = 15.9 °C).

The microwave reflected power is a relative measure of the microwave absorbance by the wet cake; i.e. the lower the reflected power, the higher the amount of microwave power absorbed. Microwave absorbance of methanol (polar solvent) is approximately 2 orders of magnitude higher than that of calcium carbonate solids.[10] The microwave reflected power is shown to initially rise to a low level (at $t = 0$, due to the high methanol content); increase as the surface moisture is evaporated [towards the end of the constant rate period, as shown by the "bump" in the profile]; then decrease slightly as the remainder of methanol is driven from the pores (falling rate period); and then increase to a maximum and remain constant after dryness is reached. The constant reflected power indicates that the methanol has been removed, and the higher reflected power is due to the lower microwave absorbance by the calcium carbonate solids. Product temperature is constant during methanol removal (slightly above the boiling point temperature of methanol at 100 mbar (16 °C)) and then increases gradually after dryness. The product temperature increase indicates that the calcium carbonate solids are heated, via microwave energy, as the moisture content approaches zero.

Figure 2b shows the methanol MS response correlation with the measured LOD profile. The LOD profile was developed from seven separate experiments, by pulling individual samples and measuring moisture content at

individual time points. The initial LOD ($t = 0$) was calculated based on the amount of methanol added to calcium carbonate. Note: the sample was too wet to measure LOD for $t < 12.5$ min. The initial LOD was 46.7%, and the LOD at $t = 25$ min was 0.64%. The average drying rate for methanol was 7.0 g/min. On-line process MS may be used to determine when to test for dryness, depending on the LOD specification (i.e., for an LOD requirement of <1%, a sample may be taken at approximately $t = 25$ min).

The results for the microwave vacuum drying run of water-wet calcium carbonate are shown in Figure 3a and b. The water profile (ion 18/ion 40) is shown to correlate with dryness, whereby the response is delayed initially during the heat-up period, remains constant (at ion 31/ion 40 = 40) until $t \approx 60$ min, then decreases to baseline at $t \approx 90$ min. The recovered liquid profile shows an initial delay until $t \approx 8$ min as the temperature rose until the boiling point for water was reached, increases linearly during the constant drying period, and then displays a decreasing slope with time (falling rate period) until dryness is reached (at $t \approx 85$ min, LOD < 1%). In comparison, the methanol in calcium carbonate wet cake does not show a delay in MS response or recovered liquid, since the wet cake reaches its boiling point at the start of the microwave power input (as the vacuum level of 100 mbar is approached). The product temperature profile for water shows an initial heat-up period from 25 °C ($t = 0$) to the boiling point of water at 100 mbar (46 °C, $t \approx 8$ min), then remains steady during the constant rate period, and increases slightly as product dryness is reached (80−85 min). Reflected power is shown to follow a similar profile as compared to methanol, resulting in a constant value after dryness is reached.

Figure 3b shows the water MS response correlation with the LOD profile. The LOD was determined from nine separate experiments between $t = 40−100$ min, by pulling individual samples and measuring moisture content. The

(10) Cliff, M. J. *I. Chem. E. NW Branch Papers* **1986**, *3*, 4.1−4.12.

Table 1. Solvent properties and microwave drying results with CaCO$_3$

	solvent[a]				drying time[d] (min)	average drying rate[e] (g/min)
	boiling point[b] (°C)		heat of vaporization[b] (kJ/ml)	loss factor[c]		
name	100 mbar	1013 mbar				
acetone	1.2	56.2	0.422	1.3	20	8.8
tetrahydrofuran	8.7	66.0	0.394	N/A	21	8.3
2-propanol	33.6	82.4	0.594	2.9	22	8.0
ethanol	29.1	78.5	0.726	8.6	24	7.3
methanol	15.9	65.0	0.925	13.6	25	7.0
water	45.9	100.0	2.443	6.1	85	2.1
hexane	9.8	68.8	0.242	0	35	5.0
heptane	35.4	98.5	0.250	0	55	3.2

[a] Solvent input = 175 g, calcium carbonate = 200 g. [b] CRC Handbook of Chemistry and Physics, 75th edition, heat of vaporization based on 25 °C. [c] Cliff, M. J., *Institute of Chemical Engineers*, 1986, no. 3, 4.1−4.12. [d] This work: microwave input = 150 W, vacuum = 100 mbar, oven air temperature = 35 °C, drying time estimated as duration from initiation of MW power to leveling of recovered liquid profiles. [e] Average drying rate = solvent input/drying time.
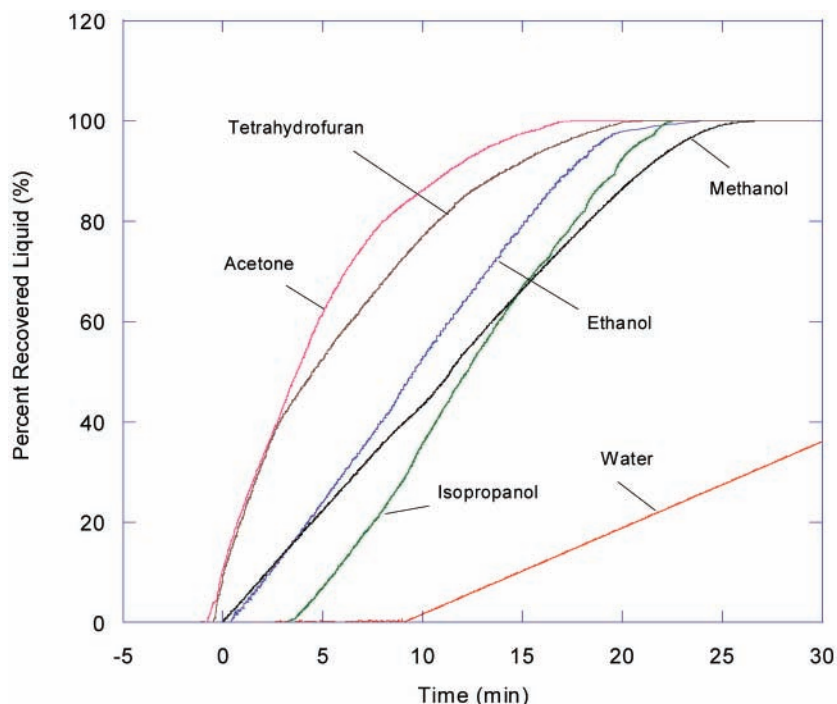

Figure 4. Microwave vacuum drying recovered liquid profiles for various polar solvents in calcium carbonate. The microwave power input (@ $t = 0$) was 150 W, with an oven air temperature of 35 °C and a vacuum level of 100 mbar.

initial LOD ($t = 0$) was calculated based on the amount of water added to calcium carbonate. Note: the sample was too wet to measure LOD for $t < 40$ min. The initial LOD was 46.7%, and the LOD at $t = 85$ min was 0.68%. The average drying rate for water is 2.1 g/min. Note that the falling rate drying period is relatively short as compared to the constant rate drying period, which indicates that the majority of the heating is surface drying and calcium carbonate is a nonhygroscopic solid.

3.2. Microwave Vacuum Drying Rates of Various Solvents. The microwave drying of additional solvents with calcium carbonate resulted in similar profiles. The solvents analyzed, solvent properties, and corresponding drying times/rates are shown in Table 1. The relative drying rates for various solvents can be observed by the difference in slope of the percent recovered liquid line, during the constant rate drying period (Figure 4). The recovered liquid profiles

were converted to a percent basis in order to compare relative recovered liquid rates, since the condenser trapping efficiency differs for each solvent. Methanol, acetone, and tetrahydrofuran showed no delay in initial recovered liquid profiles, since their respective boiling points at 100 mbar are below the starting product temperature (∼25 °C). Ethanol and 2-propanol showed short delays, since their respective boiling points were above the starting product temperature, and water displayed a significant delay.

The average drying rate for alcohols resulted in a range of approximately 7−9 g/min, whereas the average drying rate for water was approximately 4 times lower (2.1 g/min). The microwave drying rates for polar solvents have a linear correlation with the solvent heat of vaporization and, to a lesser degree, with the solvent boiling point (Figure 5). Polar solvent drying rates also have a linear correlation with the
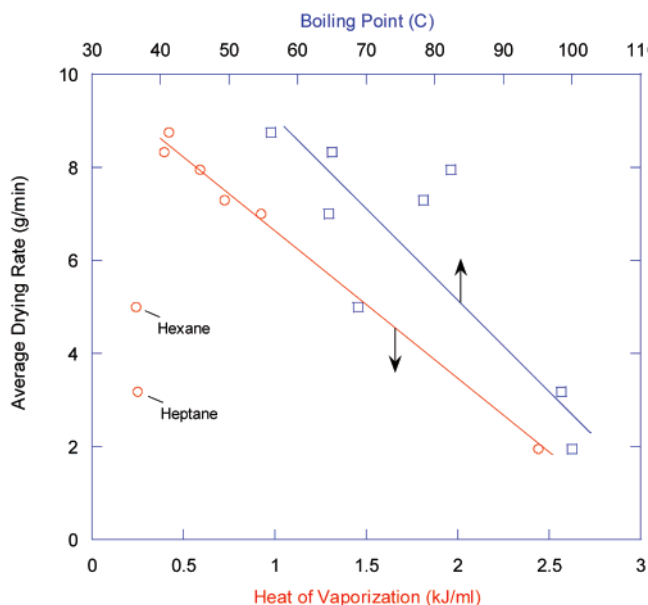
Figure 5. Drying rate versus heat of vaporization (lower *X*-axis) and boiling point (upper *X*-axis) profile for various solvents. The drying rate has a good linear correlation with the heat of vaporization for polar solvents ($R^2 = 0.996$) and, to a lesser degree, with boiling point ($R^2 = 0.835$).

solubility parameter (Hildebrands), which is proportional to the molar energy of vaporization.[11]

The relative drying rates for the solvents were shown to be only partially dependent on the loss factor (Table 1), since the loss factors for acetone and 2-propanol are less than one-half that of water and their respective drying rates are more than 4 times faster than water. The loss factor is a relative measure of the amount of energy a dielectric material can dissipate in the form of heat and is the product of the relative dielectric constant (polarizibility) of the material and the loss tangent ("viscosity" of the material).[12] Note that the loss factor for nonpolar solvents (i.e., hexane, heptane) is zero and microwaves are not absorbed. The loss factors for polar solvents are approximately 2 orders of magnitude higher than those for common solids (i.e., calcium carbonate) (Cliff, 1986). The following sources are cited for further detail regarding microwave drying mechanisms.[2,13]

The microwave drying rates for nonpolar solvents do not follow a linear correlation with heat of vaporization, as shown by the outlier points in Figure 5. Hexane has the lowest heat of vaporization but resulted in a significantly lower drying rate compared to other solvents with low heat of vaporization values (i.e., acetone, 2-propanol). Heptane, although having a similar heat of vaporization value as hexane, resulted in the second lowest drying rate due to its high boiling point. The microwave reflected power profiles for hexane and heptane in calcium carbonate were constant for the entire run, based on the microwave absorbance of calcium carbon-

ate solids only, which is not surprising since nonpolar solvents are transparent to microwaves. The heat required for evaporation is generated by the microwave adsorption of calcium carbonate solids, in addition to the hot air supplied (35 °C). Nonpolar solvents tend to have very low latent heats of vaporization because, due to their nature, there is no hydrogen bonding or similar forces within the liquid.

3.3. MS Analysis for Multiple Solvent Wet Cakes/ Azeotropes. During API manufacturing, the situation often arises where the wet cake to be dried consists of multiple solvents. Figure 6 shows the MS monitoring results of a 50/ 50 wt % mixture of ethyl acetate/hexane in calcium carbonate. Despite the fact that it is relatively transparent to microwaves, hexane (bp = 68.7 °C, heat of vaporization = 0.242 kJ/mL) is shown to vaporize before ethyl acetate (bp = 77.1 °C, heat of vaporization = 0.364 kJ/mL) due its lower heat of vaporization and boiling point, as indicated by the initial rise in the hexane MS response (57/40) to a constant level. The hexane evaporation rate is enhanced due to the microwave adsorption of ethyl acetate and corresponding heat generation. The MS response for ethyl acetate (45/40) is delayed initially then increases to a constant level as the hexane response returns to baseline. After most of the hexane has evaporated from the wet cake, the ethyl acetate MS response remains at a constant level and then returns to baseline indicating product dryness.

The ethyl acetate profile correlates with additional drying end points (recovered liquid, product temperature, reflected power) for product dryness (at $t = 21$ min). By observing the recovered liquid profile, the recovery rate is shown to level off as the ethyl acetate MS profile returns to baseline. The product temperature is shown to steadily increase as the hexane is removed, due to the higher boiling point of ethyl acetate, and then increase again after the ethyl acetate is removed, indicating product dryness (and heating of calcium carbonate solids). The reflected power is shown to initially increase to a high level, since hexane is nonpolar and does not absorb microwaves; then decrease as hexane is removed and ethyl acetate (polar solvent) absorbs microwaves; and then steadily increase to a maximum and remain constant after dryness is reached.

Figure 7 shows the microwave vacuum drying results of a 2-propanol and water mixture in calcium carbonate solids. The mixture of 12% water/88% 2-propanol (by wt) corresponds to a low boiling azeotrope at a vacuum pressure of 100 mbar.[14] The MS profiles show that 2-propanol and water are removed from the wet cake at the same rate, as both include a constant rate period followed by a short falling rate period. Another indication of azeotrope drying is that the product temperature during the constant drying rate period (34 °C) is close to the azeotrope boiling point for this mixture at 100 mbar (32 °C). In addition, the recovered liquid profile is shown to be linear during a majority of the drying period, indicating that water and 2-propanol are evaporated at the same rate. The water vapor profile (18/40) is shown to be 5 times higher than that of 2-propanol (45/40), which indicates

(11) Rodriguez, F. *Principles of Polymer Systems*; Hemisphere Publishing Co.: New York, 1989; pp 1−25.

(12) Mujumdar, A. S. *Handbook of Industrial Drying*; Marcel Dekker: New York, 1995; pp 345−372.

(13) Strumillo, C.; Kudra, T. *Drying: Principles, Applications and Design*; Gordon and Breach Science Publishers: Montreux, Switzerland, 1986; pp 369−405.

(14) Lide, D. R. *Handbook of Chemistry and Physics*; CRC Press: New York, 1994.
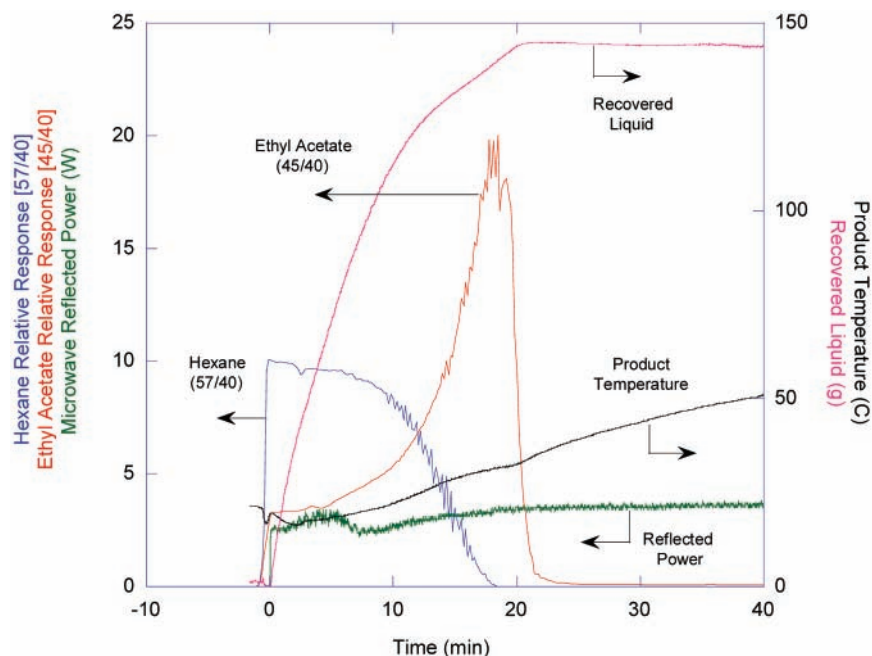
Figure 6. Microwave drying profile of ethyl acetate (80 g) and hexane (80 g) in calcium carbonate (200 g), showing hexane relative response (57/40), ethyl acetate relative response (43/40), and microwave reflected power on the left axis and showing recovered liquid and product temperature on the right axis. The microwave input power was 150 W, with a vacuum level of 100 mbar, an air temperature setting of 35 C, and an argon input of 10 sccm (reference gas). The product reached dryness at $t \approx 21$ min.
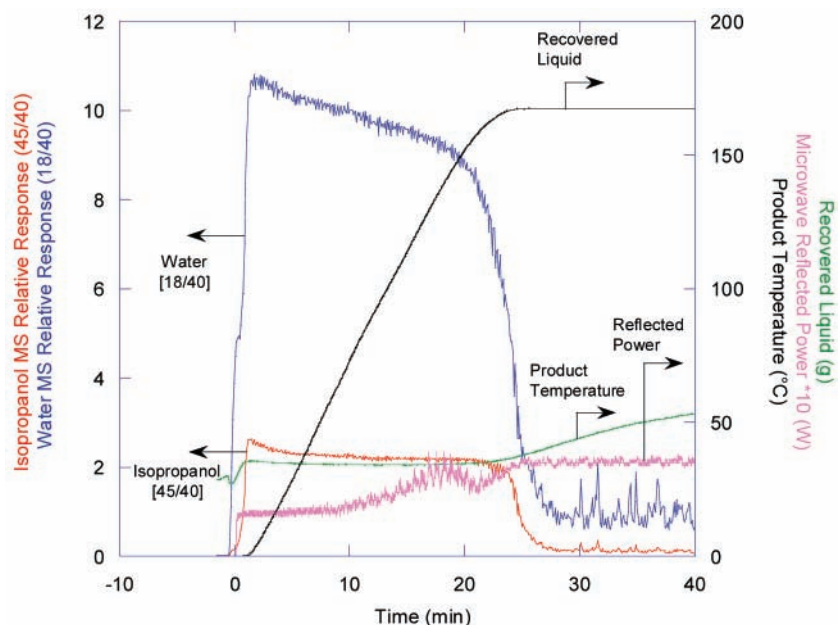
Figure 7. Microwave drying profile of 2-propanol (154 g) and water (21 g) in calcium carbonate (200 g), showing water MS relative response (18/40) and 2-propanol MS relative response (45/40) on the left axis and showing recovered liquid, product temperature, and reflected power on the right axis. The microwave input power was 150 W, with a vacuum level of 100 mbar, an air temperature setting of 35 °C, and an argon input of 10 sccm (reference gas). The product reached dryness at $t \approx 25$ min.

the MS ionization probability of water vapor is much higher than that of 2-propanol. The MS profiles for water and 2-propanol are shown to correlate with other drying endpoint parameters, including recovered liquid, product temperature, and microwave reflective power, whereby dryness is reached at approximately 25 min. The recovered liquid, reflected power, and product temperature profiles are analogous to the drying behavior of a single solvent. These results show the effectiveness of mass spectrometry for monitoring

multisolvent wet cakes and for the special case of monitoring azeotrope mixtures which could find further application as a PAT tool in distillation applications.

4. Conclusions

On-line mass spectrometry was shown to be a viable tool for identifying the drying endpoint during microwave assisted vacuum drying and complements other drying endpoint parameters including rate of recovered solvent, product

temperature, and microwave reflected power. The microwave vacuum drying rates of various polar solvents were shown to have a linear correlation with the solvent heat of vaporization and, to a lesser degree, with boiling point. A key benefit of using mass spectrometry as an on-line PAT tool for monitoring drying operations is that no upfront analytical method development is required, which is ideal for R&D manufacturing where only one batch of an intermediate or API may be run. The utilization of mass spectrometry during microwave vacuum drying of pharmaceutical products will further avoid unnecessary hold times and minimize potential worker and product exposure.