

USING MASS SPECTROMETRY TO MONITOR REACTOR SOLVENT COMPOSITION DURING SOLVENT SWAPS

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ABSTRACT

In the Pharmaceutical Industry it is a common practice to carry out reactions in various solvents that are chosen to aid in the reaction or separation process. There are many instances where solvents must be swapped between stages. In other instances water may be present from the reaction or from an extraction that has to be removed. These solvents are usually removed by one or more batch distillations. This paper will explain how mass spectroscopy of the vapor phase, during distillation, can be used to determine the desired endpoint.

INTRODUCTION

Batch manufacturing in the pharmaceutical industry is inherently difficult due to the stop, rebuild, and restart nature of the processes involved. Compounding this difficulty are the critical quality requirements for the end-product material, so it is easy to see why the pharmaceutical manufacturing space is burdened with time-consuming off-line quality assurance and control testing. Until recently, the use of on-line instrumentation for process monitoring and control was very limited, with unit operators relying on standard operating procedures and recipes to tell them how to control each step in the process. Further, because the quality assurance/control testing is conducted off-line, the results are typically not available until long after completion of the process.

The Food and Drug Administration's Process Analytical Technology (PAT) initiative is an enabling directive to move the manufacturing end of the pharmaceutical business into a more on-line analytics model, similar to those found in modern hydrocarbon processing and semiconductor manufacturing facilities. The availability of real-time measurements enables the manufacturer to streamline the process and correct processing errors as they occur. The logical result of the use of on-line analytics is to automate the process. By using collected data from multiple measurement sources to model a process, it becomes possible to predict and control the quality of the product being processed (1). Under the PAT philosophy, the quality control lab may be necessary to do spot checking from batch-to-batch; however, it will be the information coming from the on-line measurements that will trigger the release of the product, or initiate the next step in the process.

One technique that has been successfully applied for process monitoring applications in a variety of industries is on-line mass spectrometry (2-4). This technology is ideally suited to measure the composition of gas phase samples, so applying the technology for the monitoring a distillation process is a good fit. Other spectroscopic techniques can be applied to distillation monitoring (5), but mass spectrometry has many distinctive advantages. Among the advantages are the rapid response speed, superior selectivity and sensitivity, the ability to handle a wide range of sample pressures, the ability to simultaneously monitor a relatively large number of species, and the ability to detect and identify species in the sample that have not been accounted for in the instrument calibration. To the authors knowledge mass spectrometry has not been applied to monitoring distillations in the pharmaceutical production environment.

The purpose of the work outlined in this paper is to demonstrate that an on-line mass spectrometer can be used to quantitatively monitor the composition of the liquid-phase solvent in a vacuum distillation, by measuring the composition of the associated solvent vapor and through vapor-liquid equilibration curves. Specifically, the technology is demonstrated for the monitoring of a vacuum distillation, which accompanies a solvent swapping process. Solvent swapping is an important stage in a number of pharmaceutical operations (e.g., synthesis, product crystallization, etc.), so the ability to implement on-line monitoring and control can make a significant contribution to improving product quality and reducing production time.

EXPERIMENTAL

All of the work reported in this study was conducted at the GlaxoSmithKline Pilot Plant facility in Cork, Ireland. Two separate experiments were run to demonstrate the feasibility of using a quadrupole mass spectrometer for monitoring vacuum distillations. In the first demonstration the mass spectrometer was used to monitor a vacuum distillation employed to achieve a specific endpoint of solvent composition (i.e., in the liquid phase). The second demonstration was a solvent swap performed to remove water from the solvent matrix; in this case the objective was to monitor the composition of the liquid phase to determine that the water concentration was below a critical value. In both cases distillations were performed in a 700 gallon pilot vessel.

An AMETEK Promaxion process quadrupole mass spectrometer was used to collect all of the data reported in this study. The Process Mass Spectrometer was configured for a mass range of 1 - 200 AMU. Due to the hazardous area classification in the facility, an ATEX Zone 1 version of the spectrometer was used. A wide-pressure-range inlet system was used to couple the spectrometer to the process, so that the instrument could accept inlet sample pressures over the range of 1 Torr up to 20 psig. For the work reported here, the distillations were run at absolute pressures of 150 and 75 millibar.

A schematic view of the distillation setup is shown in Figure 1. The sampling point for mass spectrometer was located on the outlet line from the distillation vessel, just upstream of the condenser. A cutoff valve was used at the sample tap to allow the spectrometer to be connected/disconnected, without disturbing the distillation process.

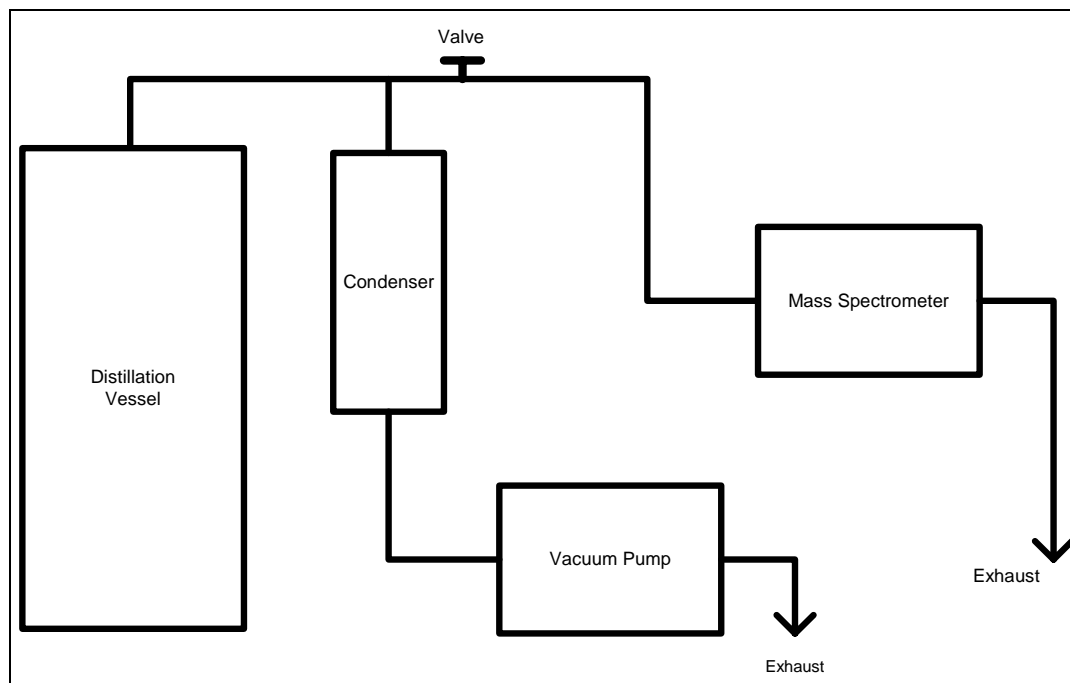


FIGURE 1. SCHEMATIC OVERVIEW OF THE DISTILLATION SETUP

Calculation of the vapor pressure curves for all solvents were performed with Aspen Tec software. With this software, the authors were able to model the relationships between the mole fraction of a component in the vapor phase, the temperature, and the corresponding mass fraction in the liquid phase.

RESULTS AND DISCUSSION

Prior to using the mass spectrometer to monitor any of the distillation processes, a test of the instruments linearity was performed. The instrument was coupled to the distillation vessel, which was flushed with ambient air. As the pressure in the vessel was reduced, the mass spectrometer was used to measure the partial pressures of both oxygen and nitrogen. The ratio between these two signals was then calculated. The ratio remains constant until the analyzer inlet pressure to the spectrometer was below 5 Torr. Below this pressure, the concentration ratio between the two components was observed to decrease. As such, the instrument was qualified for operation unless the analyzer inlet pressure dropped below the 5 Torr set point.

The next step was to set up a calibration method for each stage on the instrument. It was necessary to assign the set of peaks in the spectrum (i.e., mass-to-charge ratio) that would allow the instrument to measure the complete set of solvents used in each stage. The solvents in the first experiment were dichloromethane (DCM, mass 49) and isopropyl alcohol (IPA, mass 45). The second experiment had Water (mass 18), methyl cyclohexene (MCH, mass 83), methyl tertiary butyl ether (MTBE, mass 73) and acetonitrile (ACN, mass 40). Mass spectra for these solvents are shown in Figure 2.

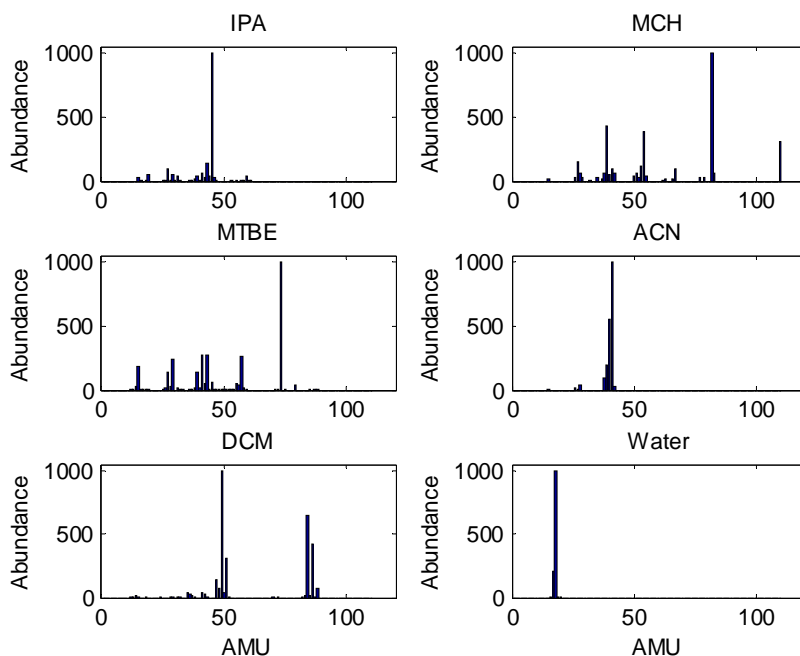


FIGURE 2. MASS SPECTRA FOR THE SET OF SOLVENT SPECIES USED IN THE VACUUM DISTILLATION

In the first set of experiments the use of the mass spectrometer for monitoring the distillation vapor of a solvent mixture, it was required to remove DCM to a controlled level of 5% in the liquid phase.

While the mass spectrometer response provides a direct and useful tool for monitoring the vapor phase composition and the relative rates of distillation for the various components of the solvent mixture qualitatively, the goal of this study was to demonstrate that mass spectrometry can quantitatively determine the composition of the liquid phase during distillation. The first step in establishing the quantitative correlations was to model the vapor-liquid relations for the solvents used in this matrix. Liquid-vapor equilibrium curves were calculated for the solvent matrix, under varying total pressures. From this family of curves, the weight fraction of DCM in the liquid phase was related to the vapor-phase concentration by the following equation:

$$X_{m,l} = \frac{1}{\left(-55.027 + 0.327174P + 56.21524X_v^{-1.605} - 0.33925PX_v^{-1.605} - 0.00077P^2 + 0.000811P^2X_v^{-1.605}\right)^{0.68119}} \quad (1)$$

Where $X_{m,l}$ is the weight fraction of DCM in the liquid phase, P is the absolute pressure in mbar, and X_v is the mole fraction of DCM in the vapor phase. With this approach, a series of vacuum distillation runs were performed.

The first of these experiments was run at an absolute pressure of 150 millibar and produced the results shown in Figure 3. It should be noted that each of the minor upsets observed in these data, are the result of disruption of the headspace pressure due to off-line sampling. Qualitatively, the correlation of the data recorded by the mass spectrometer and the results obtained by gas chromatographic analysis of grab samples was quite good. While the correlation was good, a correction factor of 1.8 was required for the DCM values to yield quantitative agreement. Specifically, the following relationship was used

$$X_{m,l}^* = \frac{fX_{m,l}}{\left(fX_{m,l} + X_{IPA,l}\right)} \quad (2)$$

Where f is the correction factor (i.e., 1.8), and $X_{IPA,l}$ is the weight fraction of IPA in the liquid phase.

Additional distillation runs were performed at an absolute pressure of 75 millibar. This sample pressure resulted in dropping the analyzer inlet pressure below the controlled 5 Torr, requiring a slightly different value of the correction factor; a value of 1.2 was determined for quantitative agreement with the reference method.

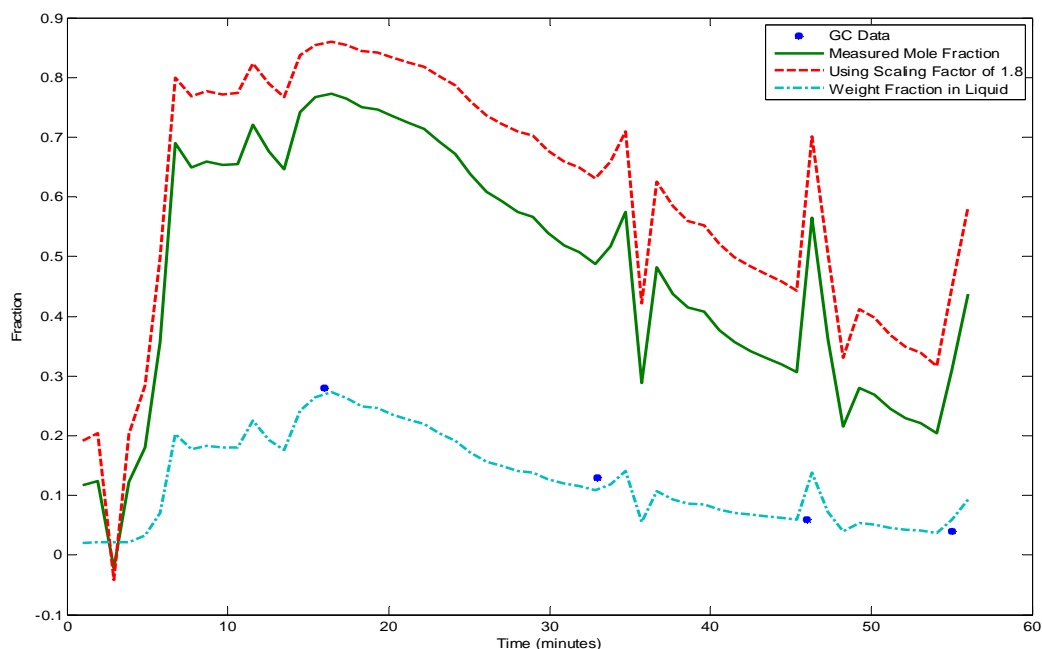


FIGURE 3. DATA RECORDED FOR 1ST DISTILLATION RUN AT A PRESSURE OF 150 MILLIBAR

Comparison data collected at the pilot plant for the corrected mass spectrometer readings and the gas chromatography results are presented in Table I. During the pilot plant run the analyzer inlet pressure remained above 5 Torr and a factor of 1.8 was used.

TABLE I. COMPARISON OF THE MEASUREMENTS OF DCM WEIGHT FRACTIONS IN THE LIQUID PHASE PRODUCED BY THE MASS SPECTROMETER WITH THOSE OBTAINED BY GAS CHROMATOGRAPHY

Measurements from GC	Measurements from Mass Spectrometer
7.8 %	6.9%
11.4%	11.2%
6.8%	6.5%
6.8%	7.1%

The last experiment demonstrated the capability of the mass spectrometer for monitoring a vacuum distillation process in which the objective was to remove components from the solvent matrix. Specifically, sequential batch distillation steps were used to remove water and MTBE from a solvent matrix that contained a mixture of water, MTBE, MCH, and ACN. To estimate the vapor fractions with the mass spectrometer it was first necessary to determine the relative response factors for each of the ion peaks used in the analysis (i.e., 18, 38, 73, and 83 AMU).

With these response factors, the mole fractions for the different components in the vapor were calculated with the following set of equations

$$X_{H_2O} = \frac{1.25I_{18AMU}}{Total} \quad (3)$$

$$X_{ACN} = \frac{5.0I_{38AMU}}{Total} \quad (4)$$

$$X_{MTBE} = \frac{0.5 * I_{73AMU}}{Total} \quad (5)$$

$$X_{MCH} = \frac{0.53I_{83}}{Total} \quad (6)$$

$$Total = 1.25I_{18AMU} + 5.0I_{38AMU} + 0.5I_{73AMU} + 0.53I_{83AMU} \quad (7)$$

Where X_i is the mole fraction of the i th component in the vapor phase and I_{iAMU} are the ion currents measured for the peak at the mass value specified.

Data recorded for this last distillation experiment are shown in Figure 4. At the beginning of the first distillation step, the vessel started at atmospheric pressure. As the pressure was reduced, the mole fraction of MCH in the vapor phase was observed to gradually increase as the mole fractions of the other three components were observed to decrease gradually, with the water vapor concentration leveling out after approximately 100 minutes. At approximately 150 minutes into the process, the vessel was returned to atmospheric pressure and charged with the next batch of solvent. On reducing the pressure the mass spectrometer followed the changing solvent composition in the vessel, until the mole fraction of water vapor decreased to near zero. The disturbance at the end of the plot was the result of breaking the vacuum in the system and returning the vessel to atmospheric pressure. From these data, it is clear that the mass spectrometer is able to provide the required trending indication for the water content in the solvent matrix. As such, this trend measurement can be used to measure the end point for each step in the solvent swap, so that only the minimum required processing time for each step is obtained. Because the duration of each stage in the solvent swap can be reduced, the overall throughput and profits for the manufacturer can be increased.

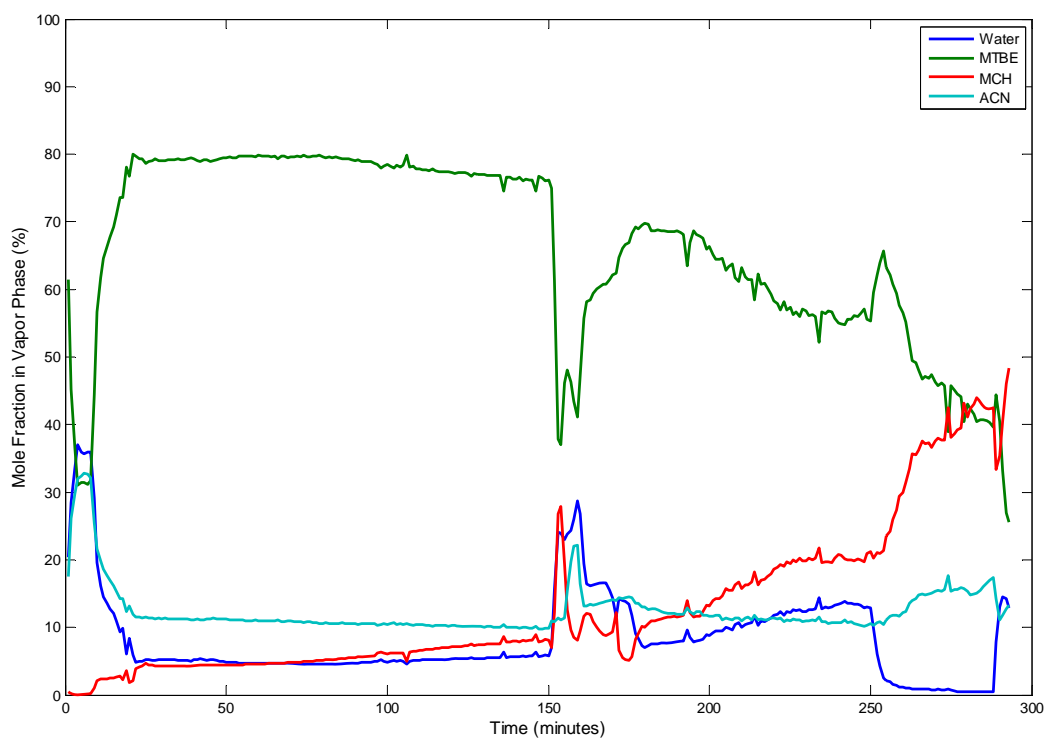


FIGURE 4. RESULTS FROM STAGE 4 DISTILLATION STEPS 1 AND 2.

CONCLUSIONS

The use of an on-line mass spectrometer was demonstrated for monitoring the vacuum distillation stage of a solvent swapping operation. This demonstration illustrated both the utility of the on-line measurement for monitoring the composition of the vapor phase in the distillation and the ability to correlate these vapor phase measurements to the liquid phase composition. Results produced by this technique were excellent qualitative agreement with off-line analysis conducted with gas chromatography; for quantitative agreement a correction factor was required. While this work was performed on a pilot plant scale, the authors propose that this technique could be implemented in a production environment to help reduce the overall cycle time of the solvent swapping process. Specifically, by monitoring the composition of the liquid solvent in real time, the process operators would be able to detect the endpoint of a given stage in the solvent swap, without needing to wait for the completion of a timed cycle or results from an offline analysis of grab samples.

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