

THE USE OF SELECTED ION FLOW TUBE MASS SPECTROMETRY (SIFT-MS) TO DETERMINE DRYING END POINTS FOR IN-LINE PROCESS MONITORING

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INTRODUCTION

Organic solvents are widely used in the manufacture of active pharmaceutical ingredients (API), however, their presence in the final product needs to be carefully controlled and as low as is reasonably possible. A number of processes are used to remove solvents, with drying usually being the last step used. Understanding and controlling the drying step is critical to the quality of the final product.

This Application Note describes the use of Selected Ion Flow Tube Mass Spectrometry (SIFT-MS) as a probe to measure the end point of a supercritical CO₂ extraction technique for drying paracetamol and demonstrates its suitability as an in-line monitor of continuous manufacturing processes.

Anatune would like to thank Georgia Sanxaridou at CMAC for the considerable amount of work detailed in this Application Note.

Selected Ion Flow Tube Mass Spectrometry (SIFT-MS) is a form of direct mass spectrometry that uses precisely controlled soft ionisation to enable real-time, quantitative analysis of volatile organic compounds (VOCs) in air, at detection limits as low as parts-per-trillion level (by volume; pptv). This eliminates the need for sample preparation, pre-concentration and chromatography. Figure 1 shows a schematic of the instrumentation.

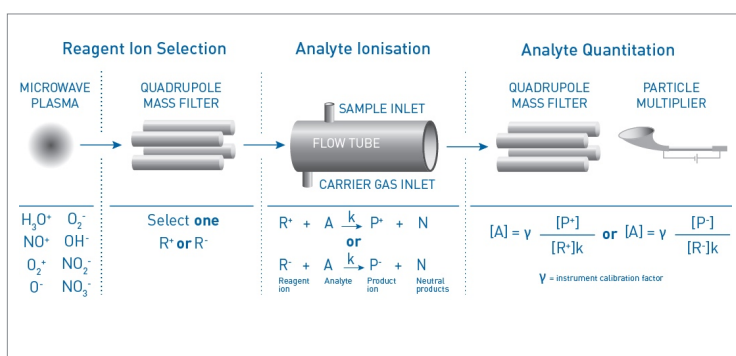


Figure 1: Schematic representation of the SIFT-MS technique

Reagent ion selection – A microwave discharge through moist air forms the standard SIFT-MS positive and negative ions; H₃O⁺, NO⁺, O₂⁺, OH⁻, O₂⁻, O⁻, NO₂⁻ and NO₃⁻ and these are then selected using a quadrupole mass filter.

Analyte ionization – The selected reagent ion is injected into the flow tube and excess energy is removed through collisions with the carrier gas (either nitrogen or helium). The sample is then introduced and an ion-molecule reaction takes place to form well-characterised product ions.

Analyte quantitation – Product ions and unreacted reagent ions pass into a second quadrupole mass analyser and the analyte concentration is calculated as a ratio of product ions to reagent ions multiplied by a rate constant, k, unique to that ion-molecule reaction.

The use of eight, selectable reagent ions, coupled with a library of known reaction products and reaction rates enables SIFT-MS to quantify multiple analytes, in real-time, without the need for prior chromatographic separation.

INTRUMENTATION

Syft Technologies' Voice 200ultra running LabSyft software (version 1.7.1). Helium carrier gas, HPI inlet.

Supercritical CO₂ extraction apparatus will be described later in this Note (figure 8).



Figure 2: Syft Technologies Voice 200ultra SIFT-MS

INITIAL INVESTIGATION

Prior to integration with the supercritical CO₂ extraction apparatus, samples of recrystallized paracetamol were analysed using a continuous purge of dry air over the sample held within a 20 mL headspace vial. The sample was held at 60°C and the flow of dry air was constant at 25 ml/min. The exhaust from the vial was passed into the SIFT-MS and the levels of degassed solvent was monitored. Figure 3 shows the results obtained for a 200 mg sample.

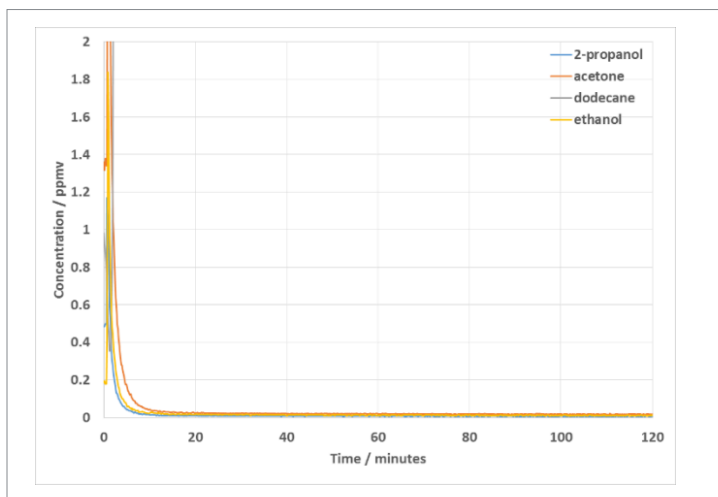


Figure 3: Initial analysis of paracetamol sample

To investigate the effect that temperature may have on the release of VOCs, samples were also analysed, as described above, at 40, 60 and 80°C. The results from these can be seen in figures 4 – 6.

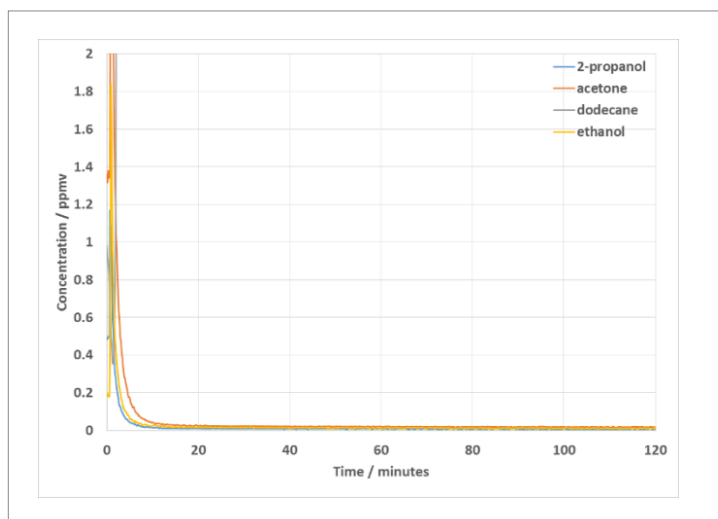


Figure 4: Solvent loss from sample heated to 40°C

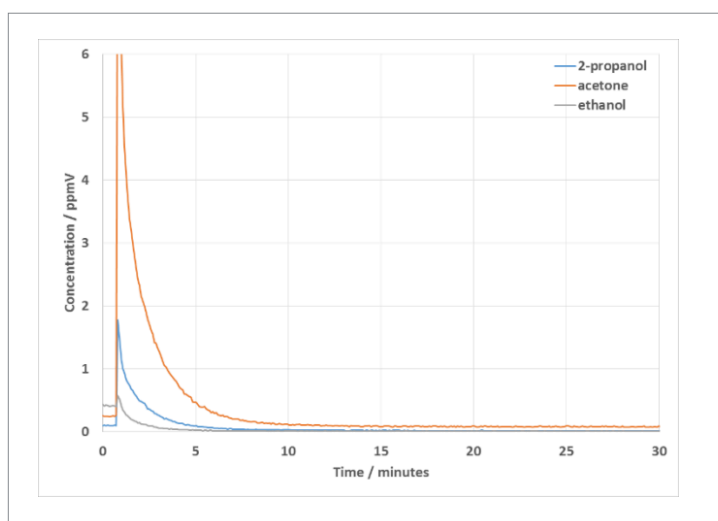


Figure 5: Solvent loss from sample heated to 60°C

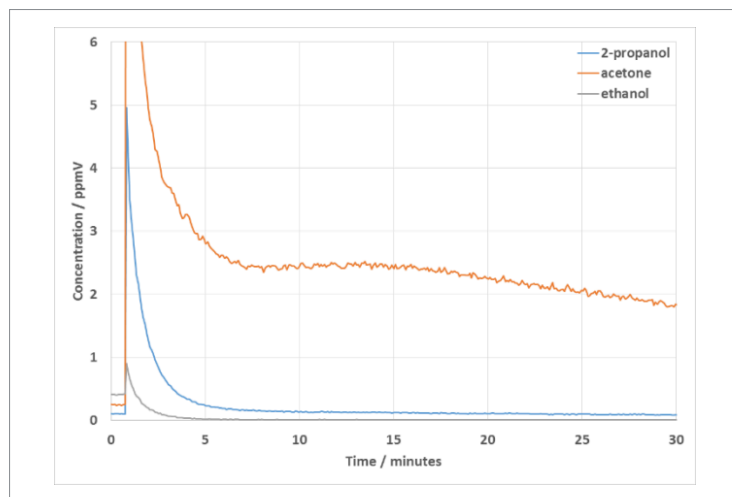


Figure 6: Solvent loss from sample heated to 80°C

It can be seen from the above results that acetone, ethanol and 2-propanol are all released from the samples and in most cases falling to background level concentrations as the air purge continues. A noticeable exception is acetone at elevated temperatures, particularly at 80°C where the concentration of acetone stays relatively constant at around 2 parts-per-million by volume (ppmV). The nature of this continuous degassing, without it falling to background levels, suggests the presence of an acetone solvate, only being released at suitably high temperatures.

For the supercritical CO₂ extraction study, paracetamol powder, wet with dodecane was used as the model solid-solvent system. For this reason, a final dry air purge experiment was performed on a wet paracetamol sample. Figure 7 shows the results and indicates that SIFTMS is able to detect dodecane in the concentration range required to monitor the drying end- point for the supercritical CO₂ extraction.

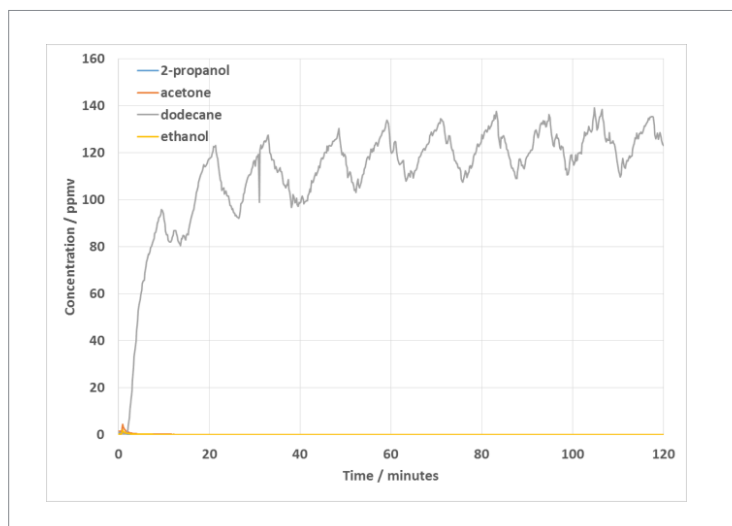


Figure 7: Dodecane loss from wet paracetamol sample

SUPERCritical CO₂ EXTRACTION

Figure 8 shows a schematic of the extraction apparatus used for the supercritical CO₂ drying of dodecane wetted paracetamol samples. The SIFT-MS was attached to the exhaust line of the apparatus and was used to directly measure the dodecane concentration, in real-time, of the CO₂ exhaust as an indication of sample dryness.

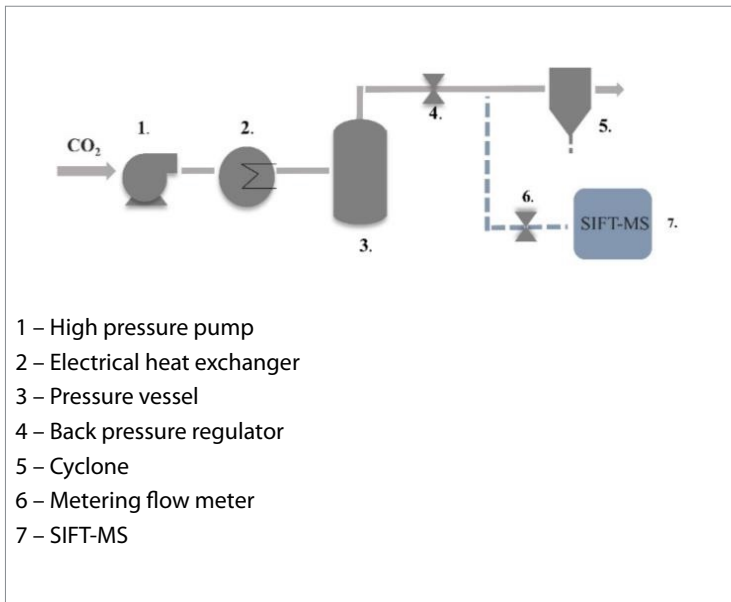


Figure 8: Schematic of supercritical CO₂ extraction apparatus

The conventional method of determining the end point of the extraction is to periodically measure the amount of solvent collected at the exit of the cyclone. As the end point is reached, the extraction becomes slow and the quantity of solvent precipitated in the vessel is too small for reliable measurements. At this point the SIFT-MS is used to measure solvent loss beyond the capabilities of the usual gravimetric methods. An additional reason for starting the SIFT-MS monitoring at this point is that prior to this, the solvent levels in the CO₂ exhaust are outside the range of the instrument.

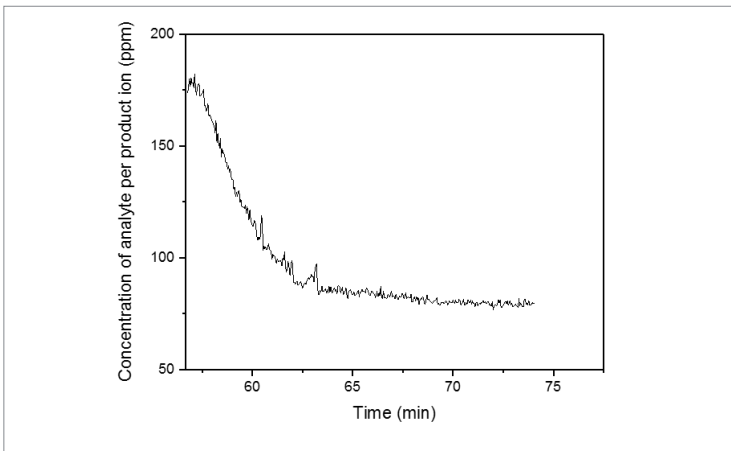


Figure 9: Loss of dodecane from sample

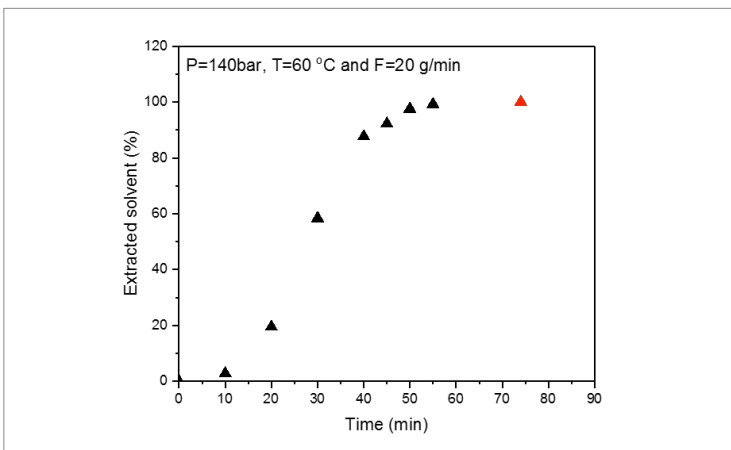


Figure 10: Example of solvent loss curve. Red point shows SIFT-MS derived end-point

It can be seen that by using SIFT-MS to monitor the final 20 minutes of drying, a more sensitive measurement can be made. This may be critical if regulatory limits for the solvent in the final product are particularly low.

Figure 11 shows the results for 4 samples subjected to differing preheating regimes prior to the supercritical CO₂ drying stage. As before, the early part of the curve is obtained gravimetrically, whilst the latter measurements are directly detected via SIFT-MS. As an additional confirmation of the level of dryness at the end point, the samples were also analysed by headspace SIFT-MS (as described in Application Note [AS191](#)). The results are detailed in Figure 12 and show good consistency at the end point.

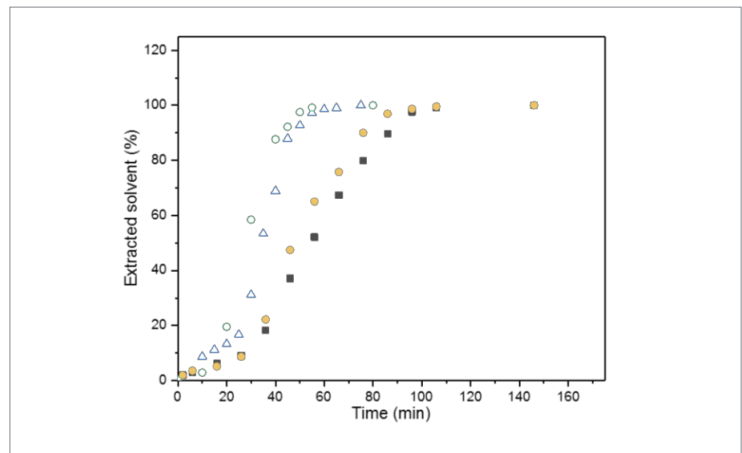


Figure 11: Four different extraction regimes

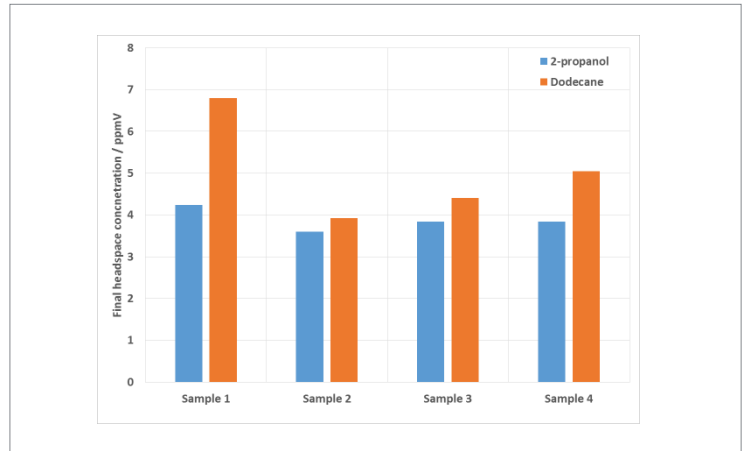


Figure 11: Headspace end-points for the different extraction regimes

DISCUSSION

This Application Note demonstrates the use of SIFT-MS to make direct in-line, real-time measurements of solvent drying processes. These processes are of particular interest to continuous pharmaceutical manufacturing. The data presented shows good sensitivity and allows drying end point measurements to be made that go beyond more traditional gravimetric approaches. The ability to generate data, in real-time offers significant benefits, allowing immediate feedback and control of these processes and potentially others used in continuous API manufacturing.