DRYING ENDPOINT MONITORING

USING SIFT-MS FOR ENHANCED MANUFACTURING OF ACTIVE PHARMACEUTICAL INGREDIENTS

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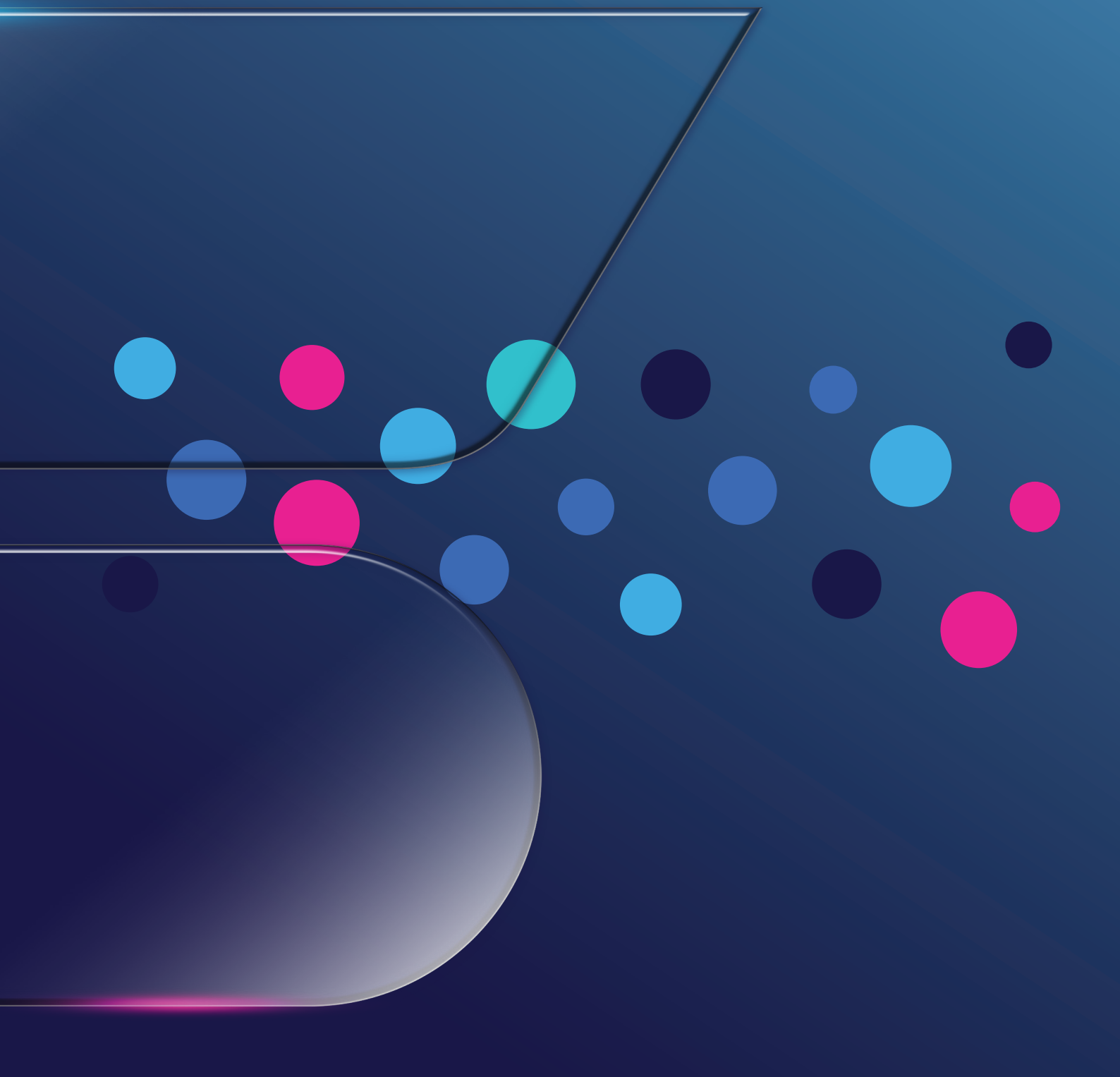


Abstract

Organic solvents are essential in the synthesis and purification of active pharmaceutical ingredients (APIs), but many exhibit some degree of toxicity and levels in formulated medicines are regulated. The presence of excess residual solvents in active pharmaceutical ingredients can lead to agglomeration during storage and hinder subsequent formulation steps. Replacement of conventional sampling and "weight loss on drying" determination of solvent content with online, real-time SIFT-MS measurement of trace solvent levels during drying provides a means by which the risk of offloading material, which would fail the residual solvent specification, is minimized and product quality can be improved. Moreover, online solvent analysis using SIFT-MS removes the guesswork from drying, saving energy and reducing total drying time compared to cautious drying protocols based on weight loss. SIFT-MS can be utilized both in conventional batch and continuous manufacturing.

INTRODUCTION

Organic solvents are widely used in primary pharmaceutical manufacturing of the APIs, both in synthesis and in isolation (crystallization, filtration, washing and drying) of the API to achieve the target crystal structure and purity. However, the presence of solvent residues in the final product can be hazardous to humans due to their inherent toxicity (United States Pharmacopeia, 2007). For this reason, all solvent residues from the up-stream processes should be removed at least to the extent that they meet the safety criteria defined by the International Council for Harmonisation of Technical Requirements for Human Use (ICH) guidelines (ICH Q3C R8 (2021)).

Solvent removal can, however, be challenging due to the need to maintain the integrity of the API and ensure that it maintains properties suited to downstream processing (e.g., by avoiding agglomeration). This study investigated supercritical CO_2 extraction technology for fast and effective removal of volatile solvents from an API at relatively low temperatures. The low viscosity and high diffusivity enable CO_2 molecules to pass through the pores of the solvent-wet cake, ensuring good contact with the API surface leading to successful extraction, minimizing the amount of organic solvent remaining in the product.

Conventional monitoring by gravimetric methods (e.g., periodic offline weighing) does not provide real-time information, and may not be sensitive enough to reliably determine solvent residues at the required levels and hence the true extraction/drying endpoint. Hence it can be both inefficient (drying for longer than required) and it requires lab confirmation of residual solvent content. For this reason, selected ion flow tube mass spectrometry (SIFT-MS) analysis was applied as an online process analytical technology to detect residual solvent past the weighing endpoint. This application note demonstrates the suitability of SIFT-MS both for online and offline applications in residual solvent analysis. Full details of the study can be found in the upcoming publication (Sanxaridou et al. (in preparation)).

METHOD

1. Materials

Paracetamol powder was chosen as a model API since it has low toxicity and very low solubility in non-polar compounds, including CO_2. n-Dodecane and propan-2-ol were used as wash and crystallization solvents, respectively. Paracetamol powder (approx. 100 µm particle size and 1.24 g cm-3 true density) was supplied by Mallinckrodt, propan-2-ol (≥ 99.5 % purity) by Sigma Aldrich, n-dodecane (≥ 99% purity) by Alfa Aesar and liquid CO_2 (> 99.8 % purity) by BOC. All the materials were used without further purification.

2. Experimental procedure

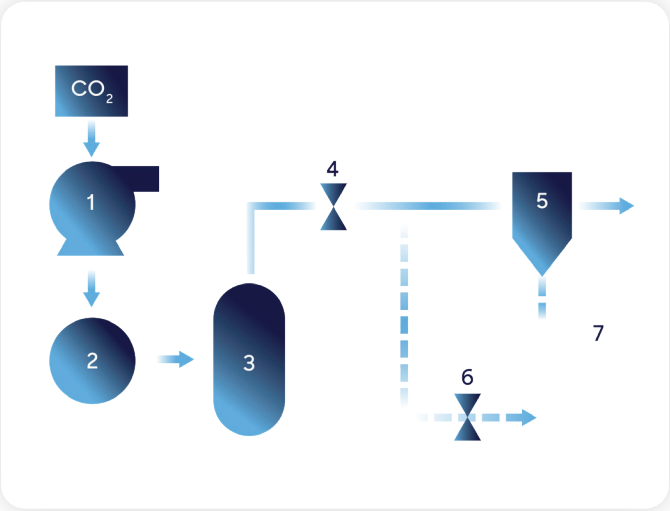
Briefly, the experimental procedure was as follows:

a. Preparation of the slurry. At the beginning of each experiment, a fresh slurry was prepared, with paracetamol powder suspended in a saturated paracetamol/propan-2-ol solution. Typically, the solid load constitutes 30 wt% of the slurry. After stirring the suspension for 5 min., it was discharged in a stainless-steel extraction basket custom-designed for drying using supercritical CO_2.

b. Filtration and washing. Filtration was conducted in a prototype set-up that enabled it to be performed under vacuum at ambient temperature.
n-Dodecane was used to wash the paracetamol cake. A quantity of approximately four times the wet cake's void fraction (ca. 0.42) was utilized, with the wash solvent split into two consecutive washing steps to maximize the efficiency of the displacement of the mother liquor.
At the end of washing, the filtration stops at the point where the meniscus of the liquid reaches the top surface of the cake, keeping it saturated in n-dodecane.

c. Supercritical CO_2 extraction/drying. The basket containing the wet n-dodecane cake was mounted in the supercritical CO_2 drying rig where the wash solvent was extracted. An overview of the extraction process coupled with SIFT-MS is shown in Figure 1. Liquefied carbon dioxide is pumped (1) at controlled flow rate through a heat exchanger (2) into the pressure vessel (3). There is a back-pressure regulator (4) that holds the pressure inside the vessel to the set point while CO_2 is continuously flowing through the cake at a constant rate. The CO_2-solvent mixture leaving the apparatus is throttled to 7-bar pressure into a cyclone to separate the two phases. As a result, the solvent precipitates in the cyclone and the gas goes to the exhaust. The exhaust is constantly sampled via a side stream to the SIFT-MS (7). A metering valve (6) is connected to the stream to reduce the pressure to 1 bar and control the flow rate to achieve a reliable SIFT-MS analysis.

Figure 1. Schematic diagram of the supercritical CO_2 extraction/drying process coupled with SIFT-MS; (1) high pressure pump, (2) electrical heat exchanger, (3) temperature-controlled pressure vessel, (4) back pressure regulator, (5) cyclone, (6) metering valve, (7) SIFT-MS instrument.



3. SIFT-MS analysis

This work utilized a Syft Technologies Voice200ultra SIFT-MS instrument operating on nitrogen carrier gas (online measurements) and helium carrier gas (headspace).

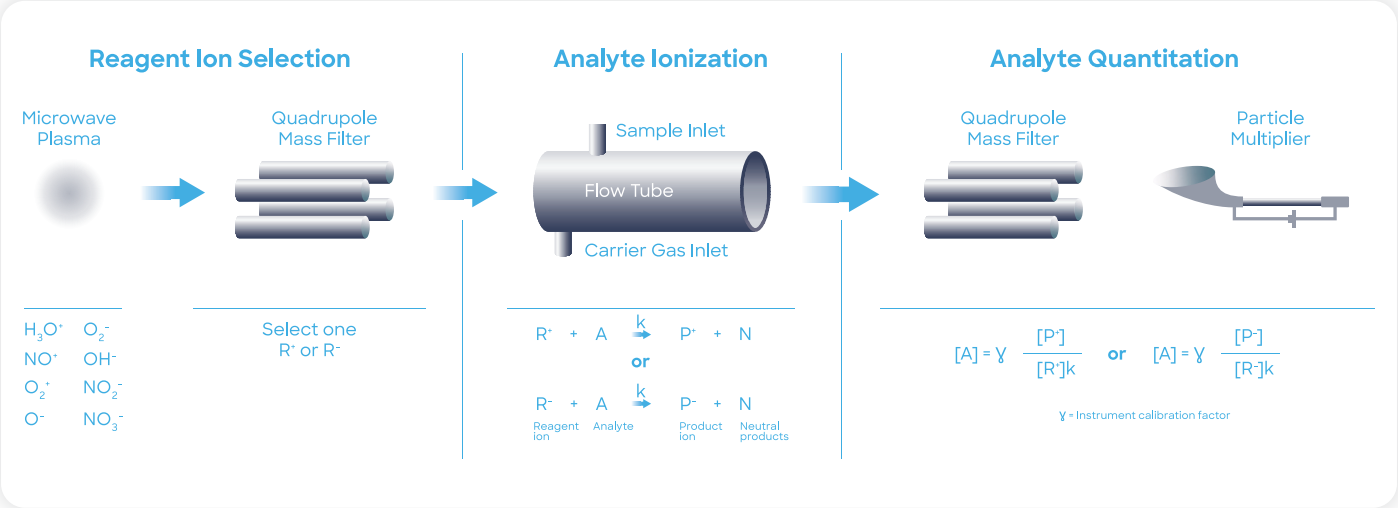
SIFT-MS (Figure 2) uses soft chemical ionization (CI) to generate mass-selected reagent ions (Smith et al. (2020)) that can rapidly react with and quantify VOCs down to part-per-trillion concentrations (by volume, pptV). Up to eight reagent ions (H_3O^+, NO^+, O_2^+, O^-, OH^-, O_2^-, NO_2^- and NO_3^-) obtained from a microwave discharge in air are now applied in commercial SIFT-MS instruments (Hera et al. (2017)). These reagent ions react with VOCs and other trace analytes in well-controlled ion-molecule reactions, but they do not react with the major components of air (N_2, O_2, and Ar). This enables direct, real-time analysis of air samples to be achieved at trace and ultra-trace levels without pre-concentration. Rapid switching between reagent ions provides high selectivity because the multiple reaction mechanisms give independent measurements of each analyte. The multiple reagent ions frequently remove uncertainty from isobaric overlaps in mixtures containing multiple analytes.

Analyses targeted the solvents of interest using selected ion mode (SIM). Analytical methods were created with the Method Editor module in the LabSyft software package (Syft Technologies).

Online measurements. A shut-off valve connected to the stream after the back-pressure regulator opens and continuous sampling takes place with the use of SIFT-MS online probe. Solvent concentration changes are tracked in real time in the gas phase and data points are recorded every 3 s.

Offline headspace analysis. After the extraction/drying, automated SIFT-MS headspace analysis (Robotic Pro MPS autosampler; GERSTEL, Mülheim, Germany) was used for rapid quantification of the actual solvent concentrations remaining in the cake. Approx. 200 mg of the processed material was transferred to a 20-mL headspace vial, which was sealed and then incubated at 80 °C for 20 min. Headspace was then sampled using a 2.5-mL headspace syringe (heated to 150 °C) and injected into the inlet at a flow rate of 3 mL min1 while the SIFT-MS instrument analyzed continuously for 90 s. For more information on headspace-SIFT-MS, refer to Perkins and Langford (2021a; 2021b).

Figure 2. Schematic diagram of SIFT-MS – a direct, chemical-ionization analytical technique.

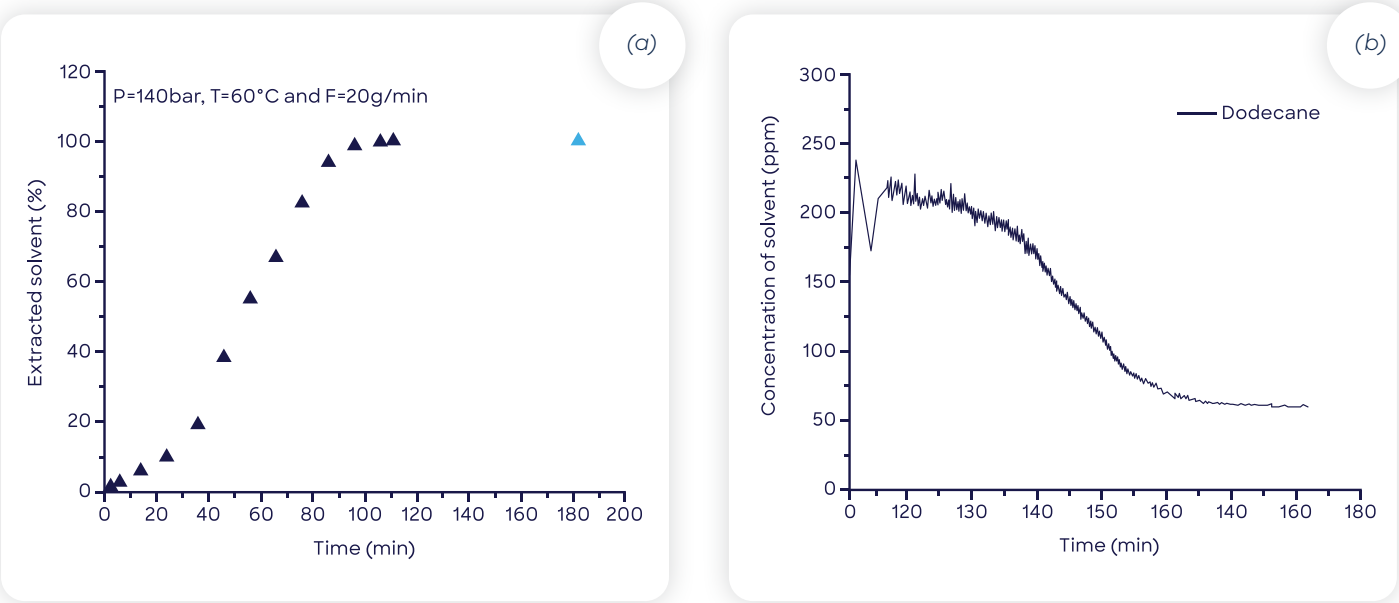


RESULTS AND DISCUSSION

Samples of 120g paracetamol powder wet in n-dodecane, were dried at a pressure of 140 bar, temperature of 60 °C, and CO2 flow rate of 20 g min1. The supercritical conditions were chosen with respect to the critical point of the binary CO2-dodecane system since negligible amounts of propan-2-ol were left in the cake after washing (full details are in Sanxaridou et al. (in preparation)). The drying endpoint by supercritical CO2 extraction was determined from extraction curves generated by measuring the amount of solvent collected at the exit of the cyclone at different time intervals (Figure 3(a)). When most of the solvent is removed from the cake, the extraction/drying rate is slow, and the quantity of solvent precipitated in the vessel is so small that is difficult to collect and measure with a balance. Figure 3(a) shows that a rough approximation of the extraction/drying endpoint is determined gravimetrically at approx. 110 min. This is the time at which online SIFT-MS analysis is initiated.
Figure 3(b) presents the n-dodecane concentrations in parts-per-million by volume (ppmV) obtained using SIFT-MS analysis as drying continues. The amount of n-dodecane in the CO2 phase decreases with time and after ca. 170 min. of extraction/drying the curve reaches a plateau, indicating that the end of the drying process has been reached. The extraction/drying stops at around 180 min. and the system is depressurized gradually, yielding at the end the solvent-free sample. The cake is weighed before and after extraction/drying allowing the total amount of the solvent removed from the sample to be estimated (shown as a blue triangle in Figure 3(a)). The full study is described in Sanxaridou et al. (in preparation) details operational and energy efficiencies obtained through use of supercritical CO2 drying coupled with online SIFT-MS analysis.

For the validation of the endpoint, the processed samples were analyzed using headspace-SIFT-MS analysis to determine the final solvent concentrations in the product. The propan-2-ol and n-dodecane solvent residues in the experiments described in Sanxaridou et al. (in preparation) were within the range 4-7 ppmV in the headspace. These measurements represent the relative solvent concentrations in the samples and in all cases, the solvents had been removed to a satisfactory level. Currently there is no permissible daily exposure (PDE) in the literature for allowable concentration limits of n-dodecane. For this purpose, an assumption was made considering the hazards and the properties of the solvent. According to the ICH guidelines (ICH Q2 R1 (1995)), solvents of similar chemical properties to n-dodecane, such as heptane, are classified as Class 3 solvents and the PDE is 5000 ppm. The values obtained verify that the product has been dried successfully dried and support adoption of SIFT-MS for online monitoring of the supercritical CO2 extraction/drying endpoint.

Figure 3. (a) Percentage of extracted dodecane versus time at P = 140 bar, T = 60 °C and F = 20 g min1 based on weighing. (b) Dodecane concentration changes over time obtained from the online SIFT-MS analysis.



CONCLUSIONS

· Process analysis using SIFT-MS enables the drying process to be monitored past the drying end-point measurable using conventional weighing methods. This delivers greater efficiencies for production, and lowers risk of thermally damaging sensitive APIs.

· Trace residual solvent measurements using SIFT-MS provide quantitative analysis of multiple residual solvents that can be correlated with PDEs, clearing the drug product for the next stage of formulation.

· The high sampling rate of SIFT-MS means that multiple drying stations can be monitored cyclically by one instrument when it is configured with a multiple-port inle.

· SIFT-MS instruments are easy to integrate with existing gas delivery systems, simple to operate, and require low user intervention.

· SIFT-MS can be utilized both in conventional batch and continuous manufacturing.

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