SIMPLE, RAPID ANALYSIS
OF FORMALDEHYDE IMPURITIES IN GELUCIRE EXCIPIENT USING SIFT-MS

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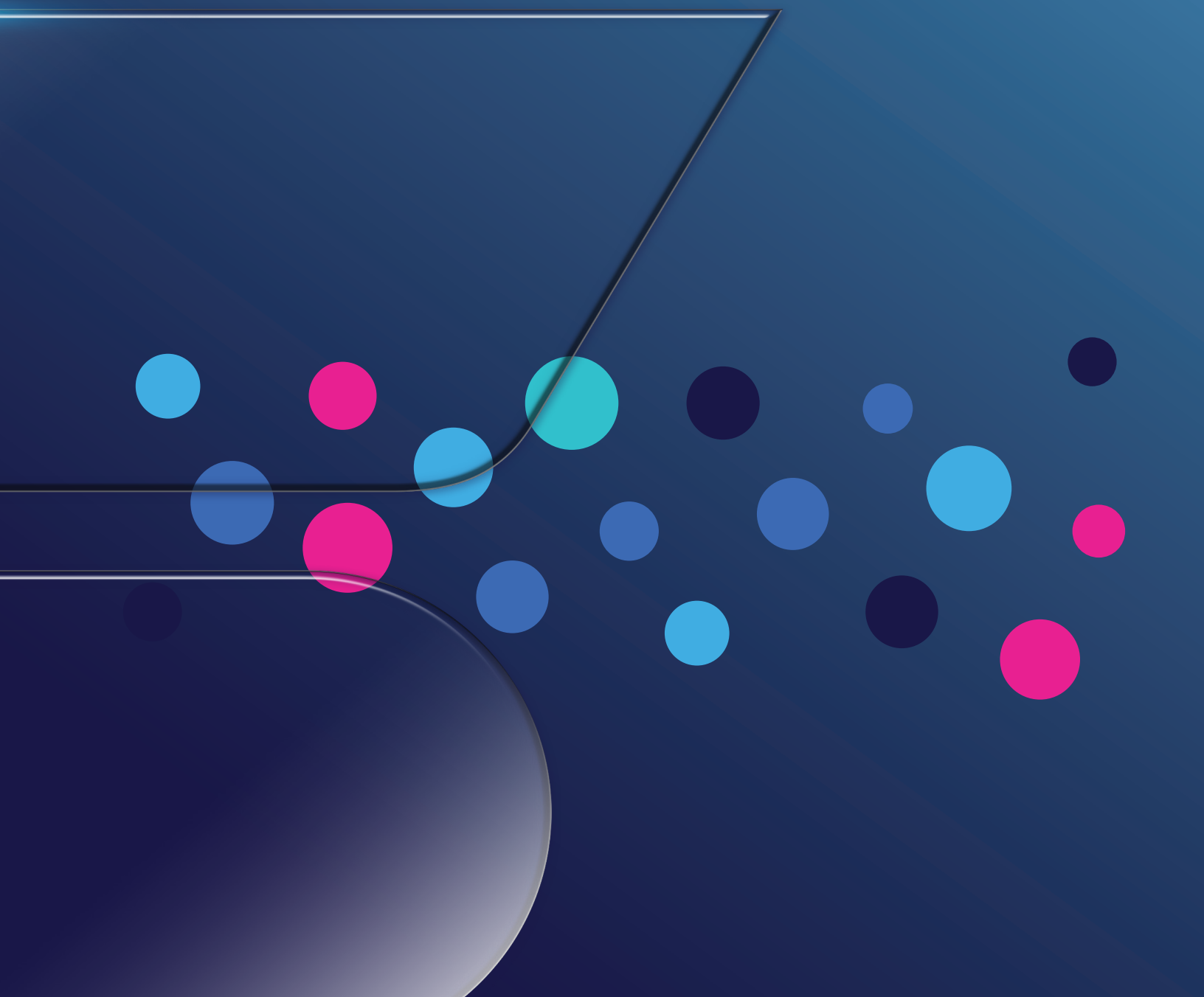


Abstract

Volatile compounds are common impurities in pharmaceutical products and are often of concern due to their toxicity. However, analysis using conventional chromatographic methods is slow, due to both sample preparation and chromatographic separation – especially for very polar compounds such as formaldehyde. In contrast, selected ion flow tube mass spectrometry (SIFT-MS) provides real-time, selective analysis of formaldehyde, by eliminating sample preparation and chromatographic separation through the application of ultra-soft chemical ionization directly to gas-phase samples. This means that formaldehyde analysis is both simple and very sensitive.

In this application note, formaldehyde is analyzed quantitatively in Gelucire excipient by using multiple headspace extraction (MHE) as a function of temperature. The results demonstrate that SIFT-MS can screen temperature-sensitive ingredients such as Gelucire to confirm that they are safe to use in formulations. Full MHE-SIFT-MS gives a daily throughput six-fold higher than the equivalent chromatographic methods, while throughput for static headspace analysis is ten-fold higher.

INTRODUCTION

Volatile compounds can be harmful to patient health if present in drug products or medical devices at levels that represent a toxicological risk. Formaldehyde is of particular concern, because it is a known human carcinogen (US NTP (2011), European Commission (2018)) and can arise from residual impurities in packaging materials (e.g., components made of polyoxymethylene, POM) or thermal degradation of certain ingredients (such as polyethylene glycol (PEG) ester surfactants used as excipients; see Panigrahi et al. (2018)).

Formaldehyde is, however, challenging to analyze using conventional chromatographic techniques due to its high polarity, high reactivity, and the need for sample preconcentration and derivatization. Alternatively, selected ion flow tube mass spectrometry (SIFT-MS) can analyze formaldehyde direct from air and headspace at toxicologically relevant concentrations. The direct-analysis approach utilized in SIFT-MS enhances risk-mitigation strategies for minimization of human exposure, potential product recalls and the resulting damage to brand, because routine testing can be conducted more rapidly and with increased frequency. Furthermore, both method development and validation are much faster.

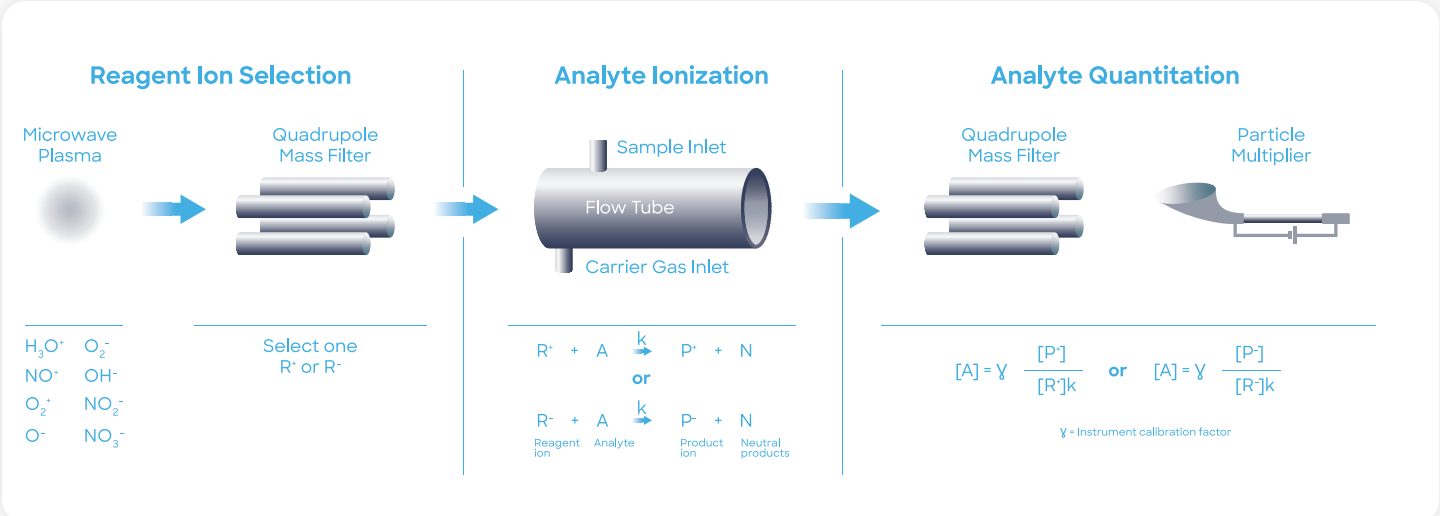
Validation of an analytical method for formaldehyde in the gas phase from a drug delivery device has been demonstrated previously (Wicks et al. (2022)). This application note describes simple analysis of formaldehyde in the headspace of Gelucire 44/14, a PEG ester, which is used as an excipient in drug products. By using the multiple-headspace extraction (MHE) technique, formaldehyde is easily quantified in Gelucire, with a throughput at least six-fold higher than chromatographic methods.

METHOD

1. The SIFT-MS technique

This work utilized a Syft Technologies Voice200*ultra* SIFT-MS instrument operating on helium carrier gas. SIFT-MS (Figure 1) 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-

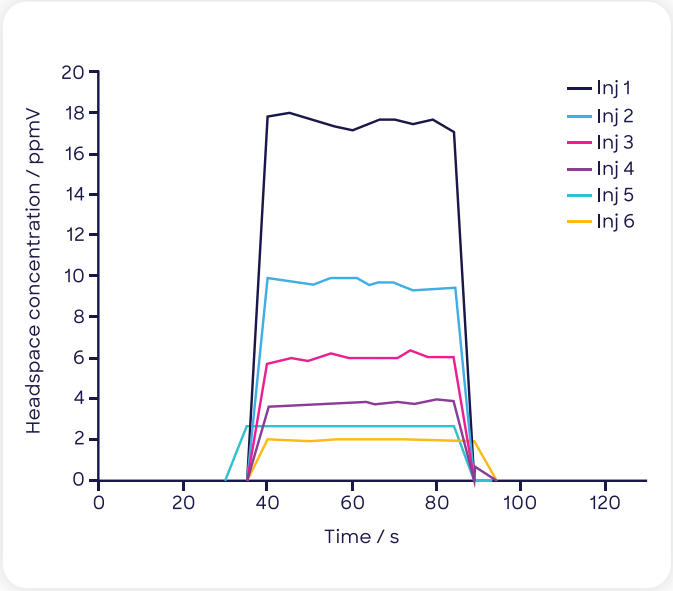
Figure 1. Schematic diagram of SIFT-MS – a direct, chemical-ionization analytical technique.



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.

Automated MHE analysis was carried out using a SIFT-MS instrument coupled with a multipurpose autosampler (MPS Robotic Pro, GERSTEL; Mülheim, Germany). The autosampler was controlled using GERSTEL's Maestro software. Here, each sample was incubated in a GERSTEL agitator throughout its six-cycle MHE sequence (see Perkins and Langford (2022a)). Headspace was sampled using a 2.5-mL headspace syringe (heated to 150 °C) and subsequently injected at a flow rate of 50 µL s^{-1} into the SIFT-MS instrument's autosampler inlet (heated to 150 °C) via a self-sealing GERSTEL septumless sampling head. Since the nominal sample flow into the SIFT-MS instrument is 420 µL s^{-1}, a make-up gas flow (ultra-high purity nitrogen) is also introduced through the sampling head. This dilution is accounted for in the final concentration calculations below. The analysis time for each sample was 120 s. Figure 2 shows the six injections for a sample incubated at 70 °C for 30 min. (Note that this incubation time optimizes the sequence, because it allows for multiple replicates to be interleaved.)

Figure 2. Real-time SIFT-MS analysis of formaldehyde: the headspace injections from six cycles of headspace generation in an MHE study of Gelucire 44/14 incubated at 70 °C.



2.SIFT-MS detection of formaldehyde

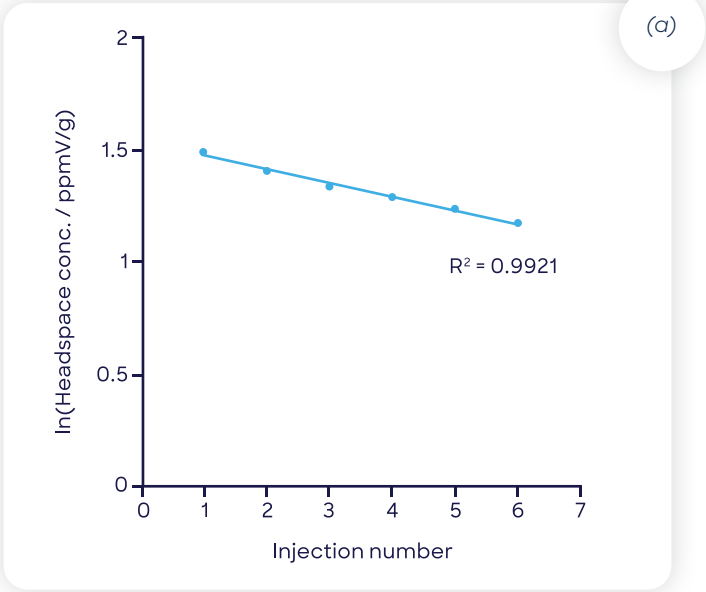
SIFT-MS selectively detects formaldehyde via the proton-transfer reaction shown in Eqn. 1 (Španěl and Smith (2008)).

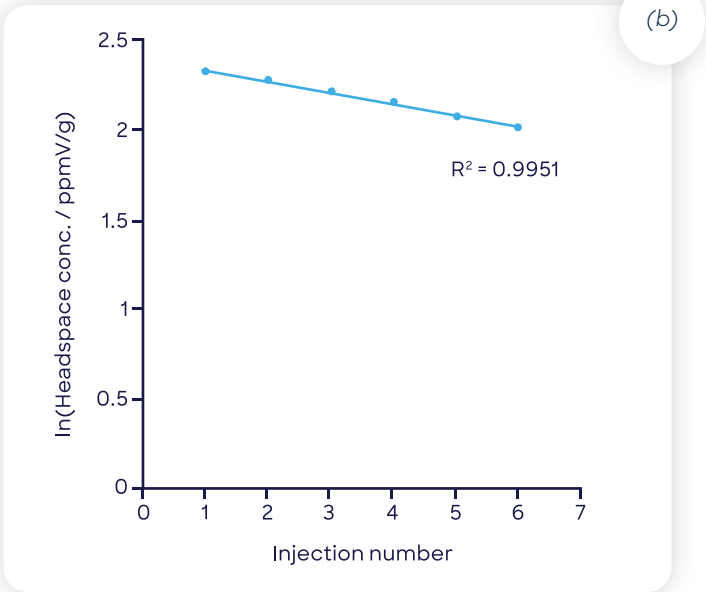
$$H_3O^+ + H_2CO \rightarrow H_3CO^+ + H_2O \quad (1)$$
$$k = 3\times10^{-9}\ cm^3\ s^{-1}$$

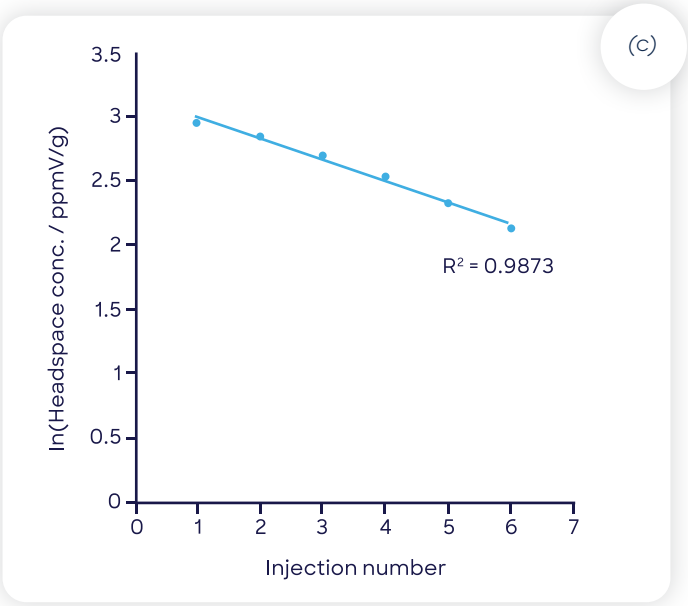
The H_3CO^+ product ion is detected at a mass-to-charge ratio (m/z) of 31. This product ion m/z is specific to detection of formaldehyde due to the soft ionization in SIFT-MS and its very infrequent occurrence for other volatiles. Formaldehyde quantitation was conducted using the literature reaction rate coefficient (k) above.

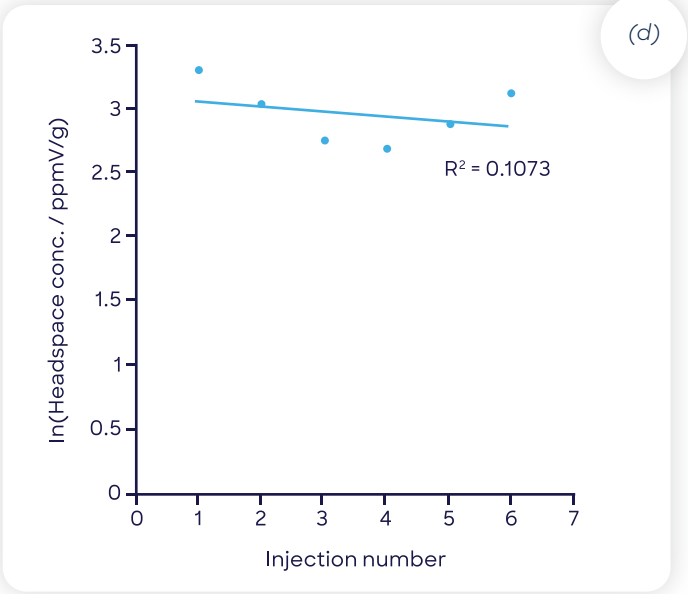
In this study, reported concentrations are the mean of the values obtained during injection; i.e., between about 40 and 80 s in Figure 2. Note that no internal standard was utilized. Typical analytical performance for formaldehyde is described in Wicks et al. (2022).

Figure 3. MHE-SIFT-MS data obtained for Gelucire 44/14 at four temperatures: (a) 40 °C, (b) 50 °C, (c) 60 °C, and (d) 70 °C. The first of the six replicates at a given temperature is shown; note the logarithmic concentration axis.









3.Samples

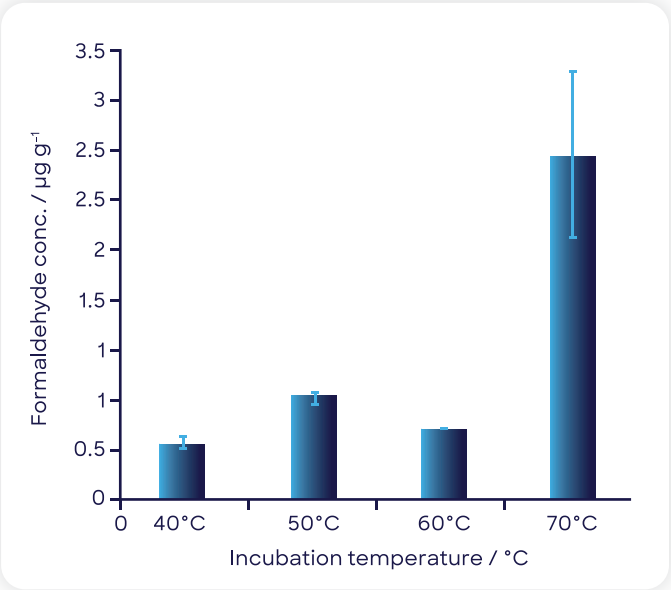
Commercially available Gelucire 44/14 excipient was supplied for analysis by a third-party. For SIFT-MS headspace analysis, 250 mg was placed in 20 mL headspace vials.

RESULTS AND DISCUSSION

Figure 3 shows typical results obtained using MHE-SIFT-MS for Gelucire 44/14 held at several incubation temperatures (40, 50, 60, and 70 °C). Linearity is good for 40 and 50 °C, while slight degradation is seen at 60 °C. At 70 °C the sample is actively degrading to form formaldehyde during injection 4 and the subsequent injections.

The concentration of formaldehyde in the Gelucire excipient is calculated from the first data point and slope (the area under the curve), as described in Perkins and Langford (2022b) (and references therein). The results (obtained from the mean of six replicates at each temperature) are shown in Figure 4. The results obtained at 40 and 50 °C represent the free formaldehyde concentration in the excipient at those temperatures. The dip from 50 to 60 °C is attributed to consistent low measurement of formaldehyde in the first injection at 60 °C with respect to the trend evident in later injections. This behavior likely indicates some degradation in the excipient at 60 °C, which becomes very evident at 70 °C. For 70 °C, the reported concentration is only indicative because there is continuous degradation of the excipient during incubation, producing formaldehyde additional to the product residue. (This observation is suggestive of the ease with which SIFT-MS might be applied to accelerated shelf-life testing.)

Figure 4. Concentrations of formaldehyde in Gelucire 44/14 at four temperatures: (a) 40 °C, (b) 50 °C, (c) 60 °C, and (d) 70 °C. These data are the mean of six replicates and error bars are one standard deviation.



These data demonstrate the ease with which an excipient can be analyzed quantitatively for formaldehyde emissions by using SIFT-MS. In contrast to conventional chromatographic methods, which require derivatization of formaldehyde between the headspace sampling and the chromatographic column, in SIFT-MS instruments the formaldehyde in the headspace is ionized and analyzed directly (Figure 2). Here, the gain in throughput is at least six-fold.

Further throughput gains can be made via correlation of the first injection with a full MHE run, as described in Perkins and Langford (2022b). This correlation can then be applied to static headspace analyses made on other samples in the batch. In the present study, this is possible in the temperature range where the MHE plot is repeatable and well-behaved (40 and 50 °C). For the method used here, 250+ samples from the same batch could be analyzed daily for formaldehyde content if just one MHE run was made to determine the correlation factor. A similar approach using GC would have 10-times lower throughput at approximately 25 to 30 samples per day, plus would require significant sample preparation time.

CONCLUSIONS

- SIFT-MS greatly simplifies formaldehyde detection and quantitation through direct, instantaneous, and sensitive (sub-ppbV) sample ionization, yielding sample throughputs of up to 250+ samples/day.
- Formaldehyde analysis using SIFT-MS is simple compared to chromatographic methods because sample derivatization is eliminated.
- Multiple headspace extraction enables formaldehyde concentrations to be obtained in the excipient itself, bypassing the challenges of creating standards in this challenging polymeric matrix.
- MHE-SIFT-MS throughput is significantly higher (at least six-fold, or 40+ samples per day) than MHE with conventional chromatographic techniques, because the rate-limiting chromatography step is removed, enabling multiple concurrent sample analyses to be undertaken.
- Under "well behaved" conditions, a single static headspace injection can be correlated with MHE. Depending on specific method requirements, 80 to 250 samples per day can be quantitatively analyzed using SIFT-MS.
- The SIFT-MS technique is applicable to both high-throughput analysis and real-time monitoring of formaldehyde impurities.

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