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Rapid, simultaneous determination of headspace oxygen and moisture in pharmaceutical packages using μGC

Hui Xu, Allen C. Templeton *, Marta Zwierzynski [1], Rajiv Mahajan, Robert A. Reed

Pharmaceutical Research and Development, Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486, USA

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Abstract

The rapid, accurate determination of headspace oxygen and moisture in various pharmaceutical packages is important for both product packaging development and the implementation of new packaging technologies. Current headspace oxygen measurement techniques suffer from serious drawbacks in terms of potential sampling contamination, lengthy analysis times, and large required analysis volumes. In addition, relatively few techniques currently exist for the convenient determination of headspace moisture in packaging systems. Efforts herein focused on the development and application of a new method for the rapid and simultaneous determination of headspace oxygen and moisture in pharmaceutical packages using micro-gas chromatography (μGC). Studies showed that both headspace oxygen and moisture could be simultaneously quantified in <90 s on sample volumes of 50–100 μL by employing μGC with dual chromatographic analysis modules. Sampling issues common to manual syringe-based injections were also alleviated in the current studies by use of the built-in diaphragm pump sampling interface of the portable μGC system. The performance of the analytical approach was evaluated and shown to exhibit excellent linearity, accuracy, and precision for both analytes. High sensitivity for headspace oxygen was demonstrated, allowing for levels of oxygen as low as 0.03% to be accurately quantified. The subject method was applied to measure the headspace oxygen and moisture in pharmaceutical blister packaging and glass vials.

Keywords: Headspace moisture; Headspace oxygen; Micro-gas chromatography; Pharmaceutical packaging; Blister packaging

1. Introduction

Recently we reported on a critical examination of five analytical approaches for the determination of headspace oxygen for pharmaceutical packaging applications [1]. As was discussed in this previous report, the development of modified atmosphere packaging is well established in the food and beverage industry and may have substantial utility for prolonging the shelf life of particularly oxygen sensitive oral pharmaceutical dosage forms. Fast, sensitive methods for monitoring headspace oxygen levels would greatly benefit the development and implementation of modified atmosphere packaging (MAP). Our previous research efforts explored the proper fit between headspace oxygen analysis technique and common packaging types employed for oral pharmaceuticals and pointed out that no single oxygen analysis technique is perfect for all packaging applications. For example, frequency modulation spectroscopy was found to be the technique of choice for examining headspace oxygen levels in optically transparent (at 762 nm) containers due to its non-destructive nature, accuracy, and analysis speed [1].

Several notable challenges were described in this previous research as in need of further investigation, including those associated with sampling and performing accurate oxygen measurements in pharmaceutical packaging of very small headspace volumes, such as blister packaging. One important advantage of gas chromatography relative to others techniques is small sample volume requirements, the chief difficulty lies in removing, transferring, and injecting

* Corresponding author.
E-mail address: allen_templeton@merck.com (A.C. Templeton).
[1] MRL Summer Intern from Delaware Valley College.

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a sample without contamination from oxygen found in atmospheric air. One approach to meet this challenge, gas-tight locking syringes, was implemented in previous work. Still, much care is required to circumvent contamination. Even when contamination from sample withdrawal, transfer, and injection steps is minimized, significant bias can still result from residual oxygen remaining in the syringe barrel. Previously, it was shown that this bias could be significantly reduced by utilizing syringe needles with low barrel volumes. Another disadvantage of conventional GC is the need for a relatively lengthy separation step to achieve oxygen separation from argon and nitrogen (∼8 min).

We turned our attention to μGC in the present study to take advantage of the extremely low sample volumes required for analysis, sampling advantages unique to μGC instrumentation, and the shortened analysis times that could be achieved with microscale instrumentation. In addition, the potential to perform a rapid, simultaneous analysis of both headspace oxygen and moisture seemed possible due to the dual module capability of μGC instrumentation. For many products, elevated headspace moisture levels can result in chemical (e.g., hydrolytic degradation) and physical changes. The latter have been associated with a slowing in drug dissolution during stressing studies. Thus, it is important to accurately measure and control headspace moisture for many products by use of desiccants or controlling environmental humidity to which the product is exposed. Another important consideration is the measurement of water activity and the important relationship this variable plays in microbial growth in solids.

This report focuses on the development and application of a new method for the rapid and simultaneous determination of headspace oxygen and moisture in pharmaceutical packages using micro-gas chromatography (μGC) [2–9]. Studies focused on the development and optimization of the analytical technique, investigation of key performance parameters, and application to pharmaceutical packaging samples. Finally, studies showing the applicability of μGC for the simultaneous measurement of headspace oxygen/moisture in blister packaging and other common pharmaceutical packaging are presented.

2. Experimental

2.1. Materials

2.1.1. Headspace oxygen standard preparation

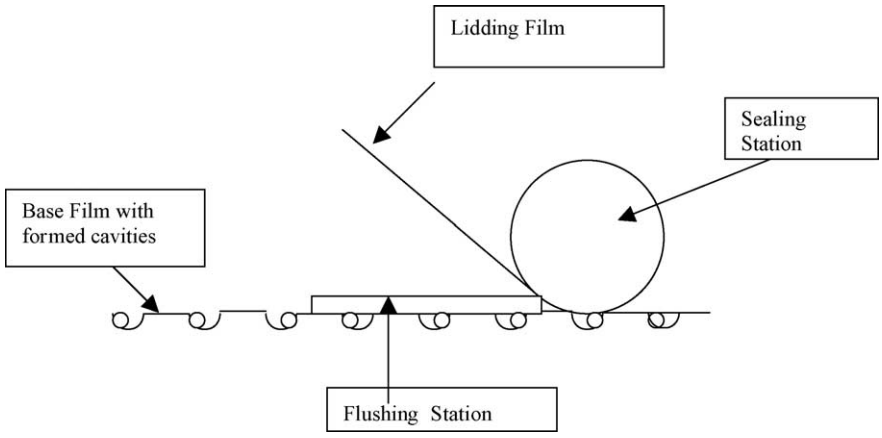
Standards containing various concentrations of oxygen in nitrogen were prepared from double-gravimetrically certified oxygen gas cylinders (Scott Specialty Gases, Plumsteadville, PA). Concentrations of oxygen standards employed were: 0.00, 1.0, 5.0, 10.0, and 20.0% oxygen in nitrogen. Gas from each respective cylinder was slowly fed into a portable glove bag (Spilfyter®, Thomas Scientific, Swedesboro, NJ) via a short length of Tygon® tubing. After purging ∼1 h to remove residual atmosphere, 10-mL clear glass vials (25 mm × 54 mm Type I untreated, Kimble, Vineland, NJ) were each filled under a given atmosphere and 20-mm gray rubber stoppers (S-87J, 4405/50, West Pharmaceutical Services, Lionville, PA) immediately put in place. After filling 30 vials, the vials were removed from the bag and an aluminum flip-top cap was immediately crimped into place on each. Vials from each prepared lot were analyzed immediately using a PBI Dansensor CheckMate® 9900 O_2/CO_2 (PBI Dansensor A/S, Ringsted, Denmark) analyzer to confirm the oxygen concentration. The validation of this measurement approach was presented elsewhere [1]. Results indicated that the concentration of oxygen in the prepared standard vials was the same as that provided in the corresponding certified cylinder. Previous studies showed that the standard vials maintained integrity against the leakage of atmospheric oxygen for at least three months [1]. Measurement of the vial-to-vial content uniformity using the CheckMate 9900 oxygen analyzer indicated no measurable differences among five randomly pulled vials.

2.1.2. Headspace moisture standard preparation

Standards containing various concentrations of headspace moisture were selected and prepared at room temperature. Headspace moisture standards employed in the study were from saturated aqueous solutions: ∼6% RH (lithium bromide), ∼11% RH (lithium chloride), ∼33% RH (magnesium chloride), ∼43% RH (potassium carbonate), ∼58% RH (sodium bromide), and ∼75% RH (sodium chloride). All salts employed were obtained from Fisher Scientific (Pittsburgh, PA). In brief, saturated salt solutions were prepared and filled into 1.8-mL clear HPLC sample vials (12 mm × 32 mm, Agilent Technologies, Wilmington, DE). The uncapped HPLC sample vials were then placed into 50-mL clear glass tubing vials (Verretubex Flacons, Paris, France) and the 50-mL clear glass tubing vials capped with gray rubber stoppers (28IV, West Pharmaceutical Services, Lionville, PA). The thus prepared headspace moisture standards were allowed to equilibrate at room temperature for at least 24 h before being analyzed. Once equilibrated, three random vials from each lot were analyzed using the Lighthouse Instruments Headspace Moisture Analyzer (FMS 1400H, Charlottesville, VA) to confirm both the moisture concentration and uniformity of the prepared standards.

2.1.3. Glass vial sample preparation

20-mL clear glass vials (23 mm × 75 mm, Agilent Technologies, Wilmington, DE) were each filled with pre-equilibrated placebo tablets or capsules under various humidity conditions. These vials were immediately crimped with the crimp caps (20 mm silver aluminum, 20 mm PTFE/silicone septa, Agilent Technologies, Wilmington, DE). Then, the prepared samples were allowed to equilibrate under room temperature for 1 week before analysis.



Scheme 1. Schematic representation of equipment used for modified atmosphere packaging of cold form aluminum blisters.

2.2. Instrumentation

2.2.1. μGC

μGC was carried out using an Agilent 3000 micro-GC (Agilent Technologies, Wilmington, DE) equipped with two gas chromatographic modules. Each module is equipped with an injector, separations column, and thermal conductivity detector. A built-in diaphragm pump was used to withdraw samples for presentation to the analysis module injectors. Analysis module A contained a PLOT 5 Å molecular sieve column (10 m length × 0.32 mm i.d., 12 μm film thickness) and analysis module B contained a co-polymer PLOT U column (6 m length × 0.32 mm i.d., 30 μm film thickness). PLOT U consists of a co-polymer of divinylbenzene/ethylene glycol dimethacrylate [2]. Simultaneous analysis of headspace oxygen and moisture on module A and B, respectively, was completed in slightly under 90 s. Argon was selected as the carrier gas for module A in order to match conductivities with residual atmospheric argon, thus making the instrument blind to residual atmospheric argon that could not be separated from oxygen on the short column. Helium was selected as the carrier gas for module B for the determination of moisture. To eliminate moisture from the carrier gas, a moisture trap was installed in-line with the helium carrier gas feed.

2.2.2. Headspace oxygen measurements by electrochemical methods

A PBI Dansensor CheckMate® 9900 O_2/CO_2 (PBI Dansensor A/S, Ringstëd, Denmark) analyzer equipped with a solid-state zirconia ion-selective electrode for oxygen determination was employed. The instrument was allowed to warm up for 10 min prior to taking measurements and was calibrated according to vendor specifications. The instrument was set to withdraw 2 mL of headspace using a small internal diaphragm pump, which fed the headspace sample into a small cell containing the measurement electrode.

2.2.3. Headspace moisture measurements by frequency modulation spectroscopy

A Lighthouse Instruments FMS-1400H (Lighthouse Instruments, Charlottesville, VA) frequency modulation spectrophotometer equipped with a tunable diode laser source (1410 nm) and photodiode detector was used for headspace moisture measurements. The instrument was allowed to equilibrate for 30 min prior to taking measurements. The sample holder was constantly purged with dry nitrogen set at a flow rate of 3 standard L/min and measurements were acquired at a sampling rate of 100 Hz. The instrument was calibrated with saturated sodium chloride solution (75% RH) prior to measurement.

2.3. Blister package samples preparation

The modified atmosphere packaging (MAP) blister samples containing placebo tablets were prepared using a custom-designed blister flushing machine. The base film consisted of standard 45-micron composite cold form aluminum film. The lidding foil consisted of 20-micron hard tempered aluminum foil. The nitrogen flushing station was located past the cavity forming station just prior to the sealing station and oriented such as to flush the formed cavities on the base film (see Scheme 1). Pure nitrogen (<0.01% O_2) was used to flush the blisters at a machine speed of 30 cycles per minute prior to blister card formation. Following the nitrogen flush, 50 blister cards were produced in the each run. The volume of each blister cavity was approximately 1520 μL, while that for the placebo tablet was 320 μL. The blister card was labeled in the order of production starting from 1 to 50.

3. Results and discussion

3.1. Method development

There are a number of similarities and differences between conventional and μGC that should be noted. The basic

principle for the techniques is the same in terms of fundamental operation and both share the same technology platform in terms of available separation columns and detectors. Due to the design of the injection port system, μGC instrumentation provides no means to volatilize analyte species and thus cannot handle liquid samples. While sampling with a conventional GC is either performed via manual syringe injection or by use of an autosampler, with a μGC the sample is introduced by use of a diaphragm pump. Because μGCs are constructed from micromachined parts, the instruments are typically small enough to be portable. Thus, much of the application of μGCs has been focused on field analysis for environmental and industrial use. For example, Crume [5] reported the rapid and continuous monitoring of volatile organic compounds (VOC) and carbon dioxide in air using μGC, and Lambert and Owens [3] utilized μGC to obtain VOC emission profiles in various manufacturing facilities to help control fugitive emissions in a pharmaceutical plant.

Fig. 1 shows the schematic for the μGC employed in the present study. The inlet can be fitted with tubing for on-line applications, such as petrochemical fractionation [10]. On the other hand, the inlet can be outfitted with a short piece of tubing and a syringe needle placed on the end to interface the sample inlet with packaging samples or for general static headspace gas analysis. In either of the described configurations, sample is introduced into the instrument by use of a small internal diaphragm pump. The pumping time is usually adjusted to allow adequate time to purge the injector and internal tubing (∼350 μL) that connects the inlet and injector. The μGC employed in the present case was of modular design with replaceable sample analysis modules consisting of injector, column, and detector on a single card. Depending on the desired separation, various sample module cards can be purchased and easily switched into the instrument. Two sample modules were employed in the present case (vide infra).

Following a purge step, the sample in each sample analysis module (∼1–10 μL) is swept onto the column with specified carrier gas for the separation step. A different carrier gas may be employed for each sample module. μGC detector options are typically limited to thermal conductivity detection when compared to conventional GC. Due to the significant differences in their polarities and overall properties, the quantitation of oxygen and moisture is difficult to achieve on a single stationary phase; thus, the two-module design proved pivotal in the present case for the simultaneous analysis of oxygen and moisture. Owing to the excellent flexibility of the μGC employed, attention turned toward developing an appropriate set of methods for the analysis.

To separate oxygen from argon and nitrogen in an air sample, a μGC analysis module (A) consisting of a thin-film PLOT capillary column coated with a 12-μm thick zeolite molecular sieve (50 μm pore size) film was employed. This column was selected from previous work that indicated that such a separation was feasible [1]. The mode of separation is based on the size of the analyte molecule or atom; retention time is as follows: nitrogen > oxygen > argon. For the module employed, oxygen and argon (natural abundance 0.93%) could not be separated and argon was thus used as a carrier gas to circumvent this interference through subtraction of argon signal due to the match in conductivity between the mobile phase and interfering species.

To separate moisture from air (argon, oxygen, nitrogen) in a headspace sample, a μGC analysis module (B) consisting of a polar co-polymer thin-film PLOT U capillary column coated with a 30-μm thick film was employed. The mode of separation is based on the polarity of the analyte, with moisture eluting later relative to air.

In the present study, a series of experiments were explored in order to develop and optimize the separation of oxygen and moisture on each μGC analysis module. First, we describe experiments for oxygen analysis. A generic inlet and injector temperature of 90 °C was employed under conditions of varying column temperature. Over the entire column temperature range of 50–70 °C explored, the oxygen peak was always well separated from nitrogen and maintained sufficient retention to be quantified relative to the front of the chromatogram. Based on the above studies, the inlet and injector temperatures were fixed at 90 °C with a column temperature of 60 °C. An example chromatogram illustrating the separation of oxygen from nitrogen is shown in Fig. 2.

Secondly, the experiments for the optimization of headspace moisture are described. With constant inlet (120 °C) and injector (95 °C) temperatures, the temperature of the column was varied from 100–130 °C and three samples of lab air were analyzed at each temperature. The reason for selecting a higher inlet temperature is to prevent retention of moisture in the inlet during sampling. The Table 1 data shows that retention time expectedly decreased with increased column temperature, but analysis S.D. decreased with higher column temperature. The data suggests operating at a higher

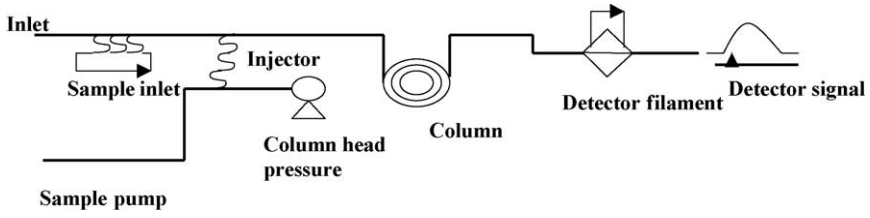


Fig. 1. Simplified schematic of a typical μGC.

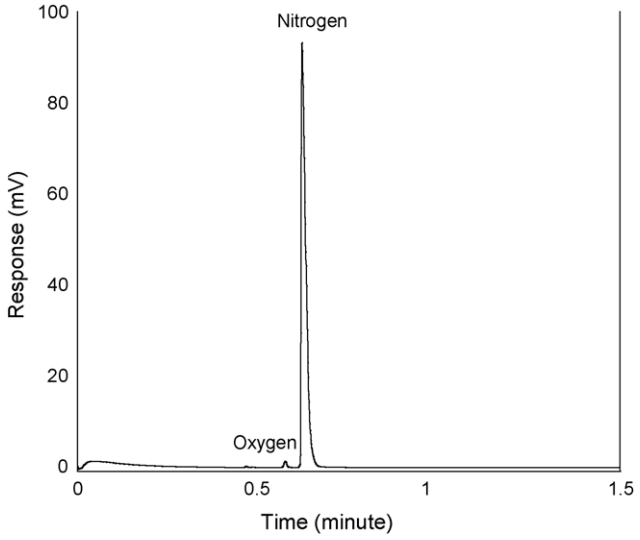


Fig. 2. Example chromatogram illustrating the separation of oxygen and nitrogen in the blister sample. Column: PLOT 5 Å molecular sieve, 10 m × 0.32 mm; column temperature: 60 °C; flush volume: approximately 600 μL; injection volume: approximately 1 μL.

Table 1
Moisture retention and peak area S.D. as a function of column temperature (average of $N = 3$)

Column temperature (°C)	Retention time (min)	Peak area S.D. (%)
100	1.182	0.61
110	0.965	0.44
120	0.808	0.24
130	0.697	0.13

column temperature will provide results with slightly less variability. Based on these results, a column temperature of 130 °C was selected. An example chromatogram illustrating the separation of moisture from air is shown in Fig. 3.

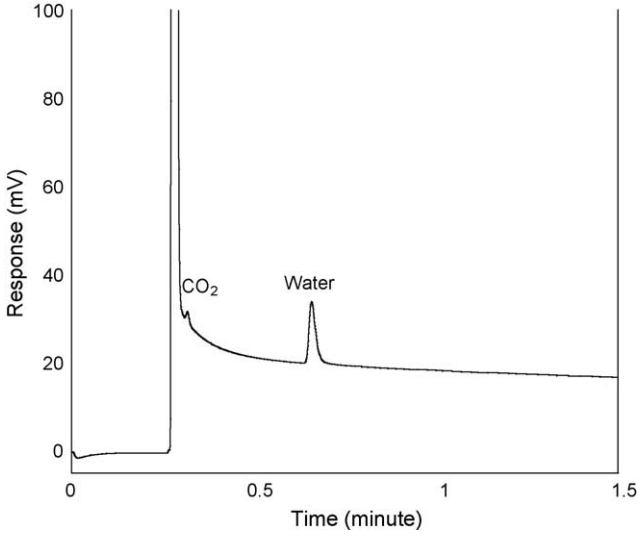


Fig. 3. Example chromatogram illustrating the separation of air and moisture in a blister. Column: PLOT U, 6 m × 0.32 mm; column temperature: 130 °C; flush volume: approximately 600 μL; injection volume: approximately 4 μL.

With the μGC employed, both sample analysis modules employ a common inlet and thus only one temperature can be set. Each module consists of its own injector, column, flow control valve, and a thermal conductivity detector; therefore, the chromatographic parameters such as the carrier gas, injector temperature, and column pressure can be independently controlled and optimized for each module. An inlet temperature of 120 °C was chosen to reduce the possibility of moisture being trapped in the inlet. Optimized chromatographic conditions are as follows:

	Oxygen	Moisture
Carrier gas	Argon	Helium
Sample inlet temperature (°C)	120	120
Injector temperature (°C)	90	95
Column temperature (°C)	60	130
Sampling time (s)	15	15
Inject time (ms)	50	50
Run time (s)	90	90
Column pressure (psi)	30	25

With methods in hand to rapidly (90 s) and simultaneously separate and quantitate both headspace oxygen and moisture using μGC, attention turned toward understanding the minimum sample volume required for analysis in order to understand the capabilities of the instrument for measuring extremely small volume samples. The sampling time was examined to evaluate the potential for sample carryover from run-to-run. As noted previously, the μGC uses a diaphragm pump to remove a portion of sample to purge the inlet and injector before filling the injector loop. Based on the dimensions of tubing and length of sample transfer line connecting the inlet with puncture needle, the estimated dead volume of the μGC system is on the order of 50–75 μL. To test the minimum quantity of sample required for accurate measurement of headspace oxygen and moisture, sampling time was gradually increased in 2-s intervals (170 μL) in an experiment to explore sample volume requirements. Sampling was performed from scintillation vials (50 mL) to ensure that an adequate volume existed to minimize depletion of the package headspace. An air sample was run before each injection of test sample (1% oxygen standard) so that the system would have to purge from relatively high oxygen conditions. For the analysis of moisture, a 75% RH standard (saturated NaCl solution) was analyzed prior to the injection of 6% RH sample (saturated LiBr solution). All the measurements were performed in duplicate.

The results, displayed in Fig. 4, show that sample carryover from air during oxygen analysis is significant when the sampling time is less than 4 s. The oxygen approaches within 0.05% of the nominal 1.0% O_2 value with a sampling time ≥8 s. The carryover for the moisture measurement slowly decreases with the increase of sampling time. The moisture approaches within 0.5% of the nominal 6.0% RH

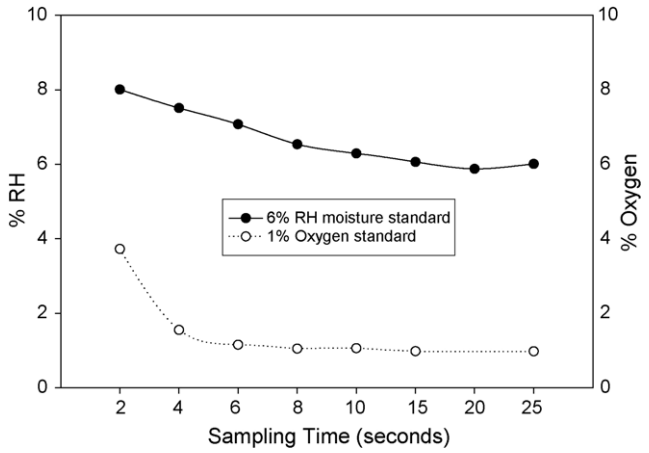


Fig. 4. Results of experiments designed to assess sample carryover and minimum sample volume requirements determined in a 50-mL scintillation vial. Headspace oxygen: column: PLOT 5 Å molecular sieve, 10 m × 0.32 mm; column temperature: 60 °C; injection volume: approximately 1 μL. Headspace moisture: column: PLOT U, 6 m × 0.32 mm; column temperature: 130 °C; injection volume: approximately 4 μL.

value with a sampling time ≥8 s. The results indicate that a sampling time of 8 s is enough to eliminate the carry-over from previous injections for both headspace oxygen and moisture measurements. For both analytes a purge time of 8 s (∼750 μL) was found to be sufficient to produce analyses without significant carryover from run-to-run.

3.2. Evaluation of method performance

In the present study, the linearity of μGC method for the determination of oxygen over the range of 0.00–20.0% was evaluated. Oxygen standard vials containing 0.00, 1.0, 5.0, 10.0, and 20.0% oxygen were assayed (see Section 2 for details on sample preparation). As mentioned previously, for a given concentration, vials from the same lot of prepared samples were analyzed for comparative purposes by the PBI Dansensor CheckMate® 9900 O_2/CO_2 analyzer. The technique displayed excellent linearity across the concentration range explored ($R^2 = 0.99999$). Precision was evaluated by performing 10 replicate analyses of 20.9% (air, high) and 1.00% (low) standards. These experiments yielded an R.S.D. of 0.3 and 0.9%, respectively. The limit of quantitation (signal-to-noise, $S/N > 10$) of oxygen for the technique is estimated at ∼0.03% (Tables 2 and 3).

Table 2
Comparison of headspace oxygen measurement by μGC and PBI Dansensor approaches (average of $N = 3$)

O_2 standard (%)	Measured (μGC) (%)	Measured (Dansensor) (%)
0	0.0	0.1
1.0	0.9	1.1
5.0	5.0	4.9
10.0	9.9	9.9
20.0	20.0	19.9

Table 3
Comparison of headspace moisture measurement by μGC and FMS-1400H approaches (average of $N = 3$)

Moisture standard (%)	Measured (μGC) (%)	Measured (FMS-1400H) (%)
6	6.7	7.7
11	10.7	14.1
33	32.7	35.9
43	43.1	47.9
58	57.3	59.1
75	75.7	76.2

Likewise, similar experiments were performed to evaluate the performance of the μGC method for moisture analysis. The linearity was determined in duplicate from 6 to 75% RH by analyzing the headspace over saturated salt solutions (see Section 2 for details on sample preparation). Excellent linearity, demonstrated by a correlation coefficient $R^2 > 0.999$ was achieved for duplicate sample analyses. The precision of the method, as gauged by the reproducibility of 10 replicate injections of 43 and 75% RH standards were also excellent, yielding R.S.D. of 1.4 and 1.5%, respectively. The LOQ of moisture for the technique is estimated at ∼0.1% RH.

3.3. Application of analytical approach for the determination of headspace moisture and oxygen in pharmaceutical packaging

As mentioned earlier, sample introduction is one of the more problematic aspects of headspace oxygen measurements. Prior experience showed that manual sample introduction at a conventional GC proved problematic in that sample contamination was possible from sample withdrawal, transfer, and injection steps. Gas-tight locking syringes, as well as great care, were required to avoid contamination. Additionally, another source of error proved to be the volume of residual atmospheric gas remaining in the syringe needle. Such a volume of gas proved to be a significant contributor to the bias and overall accuracy of the technique at low oxygen levels and in small headspace volumes. In the present case, use of the μGC eliminates many sources of error found with conventional GC. The sample needle was connected to the diaphragm pump via a short piece of tubing. To perform sample injections, a self-adhesive rubber septum was placed on the packaging seal of interest and punctured with the sampling needle. Sample was immediately withdrawn using the sample pump for a fixed interval of time. A portion of the sample was used to purge the syringe needle volume and sampling lines of residual atmospheric gases. Following purging, a portion of sample was split and sent to the injection ports of each of the analysis modules for separation. In the procedure employed, the sources of contamination are minimized to only the sample/sampling needle interface and transfer; manual injection, and syringe barrel volume were eliminated.

Blister packaging is widely used in the pharmaceutical industry. Some common blister packaging materials include

Table 4
Headspace oxygen and moisture in cold form aluminum blister ($N = 1$)

Blister card number	Headspace oxygen (%)	Headspace moisture (% RH)
4	1.00	49.0
7	0.97	43.4
8	0.97	48.5
20	0.74	48.6
27	0.63	50.6
31	0.81	48.1
42	0.74	46.8
44	0.58	51.6

polyvinyl chloride, polyvinyl dichloride, Aclar®, and aluminum. Among these blisters, cold form aluminum is considered one of the most impermeable against moisture and oxygen ingress. Typical small volumes in blister cavities (estimated 200–1600 μL) and their geometrical shape present challenges for headspace analysis in terms of sample volume requirements for analysis and sample removal. The utilization of μGC to analyze oxygen and moisture overcomes such limitations for the larger blister cavities (e.g., >400 μL, see Table 4) and offers several advantages, such as rapid analysis time and the capability to simultaneously quantify oxygen and moisture in a single analysis run. Headspace moisture and oxygen data from a set of cold form aluminum blister samples (∼1500 μL cavities) is reported in Table 4. The blister card samples were prepared as described in the experimental section using a prototype modified atmosphere packaging system to flush the blister cavities with nitrogen (<0.01% O_2) prior to sealing. The measurements were performed by analyzing six blister cavities on each individual card listed in Table 4. As expected, the headspace moisture levels are fairly constant across the various blister cards measured and is reflective of the ambient relative humidity in the packaging room, which was uncontrolled. Overall, the headspace oxygen level in the blisters gradually decreases across the process of production from the start to the finish, consistent with residual atmospheric gases being removed with continued flushing. The data suggests that pre-flushing the MAP unit tooling will be necessary prior to start of production to ensure uniformity.

A series of 20-mL glass vials containing tablets and capsules at various humidity conditions were measured for headspace moisture to further examine the feasibility of μGC for different packaging types. The vials were well-stoppered and sealed to prevent leaking. The vials were first tested by the Lighthouse FMS-1400H and then the same vials were then measured by μGC. The results of the experiments are reported in Table 5. As a comparison, the headspace moisture data obtained by Lighthouse headspace moisture analyzer (FMS-1400H) are also included. The results between the two techniques are comparable within the error of the measurements. The data indicates that μGC is a rapid, accurate means to determine headspace moisture values.

Table 5
Headspace moisture in various vial packages as determined by μGC and FMS-1400H ($N = 1$)

Sample	μGC (% RH)	FMS-1400H (% RH)	Δ
A	17.2	19.0	1.8
B	85.3	78.1	7.2
C	17.7	19.8	2.1
D	48.6	48.1	0.5
E	29.6	32.2	2.6
F	51.2	50.5	0.7
G	19.3	19.0	0.3

4. Conclusions

The use of micro-gas chromatography provides a convenient way to determine both headspace oxygen and moisture simultaneously. The headspace oxygen and moisture were analyzed in two separate modules of μGC simultaneously in less than 90 s. The method was shown to exhibit excellent accuracy, linearity, and sensitivity. Application of the method was demonstrated in the analysis of headspace oxygen and moisture in various pharmaceutical packaging types. Extension of the technology to measure smaller blister cavities (i.e., <400 μL) would require minimization of purge volumes

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