# The determination of extractables and leachables in pharmaceutical packaging materials using headspace GC/MS

## Application Note

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**Abstract**

Using the Agilent G1888 Network Headspace/6890N GC/5975 inert MSD system several primary packaging materials for pharmaceuticals were evaluated in a study. In this Application Note results for two of these materials, a labeled HDPE bottle and a soft elastomer liner from the inside of the screw cap are presented. A multiple headspace extraction technique (MHE) was used and the highest attainable amount of extractables that could ever be concentrated in the drug product was calculated. Further, the extraction efficiency of the MHE procedure was studied using benzaldehyde and phenol as target compounds. The analytical results obtained from the inert 5975 headspace-GC/MS provide excellent sensitivity when utilizing SIM/Scan data acquisition with multiple headspace extraction (MHE). The synchronous SIM/Scan feature of the 5975 MSD allows for very low level SIM detection while also searching for unkowns using scan data.

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## Introduction

The containers used for pharmaceutical packaging are regulated by many different government and non-government bodies. For examples, FDA guidances and USP procedures provide some of the requirements to help drug manufacturers in the USA develop the necessary procedures. For international distribution, the situation becomes complicated by inconsistencies in requirements in different countries. However, the FDA and USP work with other countries and the International Conference on Harmonization (ICH) to harmonize monographs and procedures.

Evaluation of packaging materials for potential extractables and leachables is critical to guarantee the integrity of the drug product and assure compliance with CFR Title 21, Part 211.65 which states: Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond official or other established requirements[1]. The US FD&C Act also states that a drug or device shall be deemed to be adulterated if its container is composed in whole or part of any poisonous or deleterious substance which may render the contents injurious to health[2]. A good summary of regulatory and scientific considerations on testing for extractables and leachables can be found in reference [3].

A container or drug delivery device, often referred to as a container closure system (CCS), for pharmaceutical products may release low molecular weight chemicals into the product and possibly compromise the biological safety and efficacy of the drug product. These chemicals include both extractable and leachable components. Extractables are chemical substances that are obtained by exposing the packaging to a variety of solvents under exaggerated incubation conditions of time and temperature. Leachables differ from extractables in that they are chemical substances that migrate under normal conditions of use from the CCS into a drug product. Leachables are therefore a subset of extractables; all extractables are potential leachables of toxicological concern.

Pharmaceutical container closure systems are usually fabricated from glass, plastic, or a variety of metals including aluminum and stainless steel. Extractables may come from these primary packaging materials or from secondary packaging components. For example, plastics consist of the polymer, residual monomers or low molecular weight oligomers, additives such as plasticizers, phenolic antioxidants, UV stabilizers, colorants, catalysts, raw material impurities and many other production aids. Secondary packaging may include laminates such as adhesives and release agents, inks, epoxides, urethanes, acrylates and polyesters. Residual solvents that originate from the packaging materials would have to be classified as extractables

## Experimental

Mass Spectrometry (MS) is perhaps the most widely applied technique to detect, identify and quantify organic extractables. For this application an Agilent G1888/6890/5975 Headspace/GC/MSD system is used to characterize extractables. Headspace vials of 10 mL volume were used and the headspace sampler was equipped with a 1 mL sample loop. Sufficient flow must be maintained through the system to avoid excessive peak broadening, therefore split injection is used. At the chosen split ratio of 1:1, the headspace sample loop is swept fast enough to produce good peak shapes. Headspace vials containing 10 micro liters of a standard in DMSO or methanol were equilibrated for 60 minutes whereas the milled samples of high density polyethylene (HDPE) and liner polymer from the closure system were equilibrated for 300 and 120 minutes, respectively. The headspace temperature was selected to be just below the melting point but above the glass transition temperature of the polymer: 125°C for the HDPE and 100 °C for the liner material.

In static headspace extraction an analyte is partitioned between the condensed phase and the gaseous phase until equilibrium is reached. However, since a single extraction will never force all of the analyte contained in the solid sample to migrate into the gaseous headspace, a multiple headspace extraction technique (MHE) is used and the highest attainable amount of extractables that could ever be concentrated in the drug product is calculated. This is the equivalent of doing an exhaustive extraction on the sample that gives the highest concentration for the analyte. This is the worst-case scenario with the highest associated risk attributed to the analyte.

Reference 4 gives an extensive description of the MHE technique. Appendix 1 from that Application Note has been duplicated at the end of this note and gives the salient features of the MHE technique and an example for calculating the concentration of an analyte. Since standard chromatography software does not usually include a quantitation procedure for MHE, an Excel template (table 2 and figure 8) was designed to calculate properties derived from the semi-logarithmic plot: the correlation coefficients, slopes, total peak areas and the concentration of the analyte in the sample. The sample weight and the amount of standard added to the headspace vials is also entered in the spreadsheet. Note that the standard of the analyte does not have to be prepared in the sample matrix and is usually prepared in solution using a high boiling point solvent such as DMSO. Matrix effects do not influence the concentration calculated with the MHE techniques. This is the beauty of a matrix-independent MHE calculation.

In order for the MHE technique to work efficiently with solid samples, the sample must be reduced to a fine powder to maximize the surface area to volume ratio. This was accomplished with a 6750 SPEX SamplePrep Freezer/Mill that cools the sample to cryogenic temperatures and pulverizes it by magnetically shuttling a steel impactor back and forth against two stationary end plugs. Since the vial is closed, the integrity of its contents is maintained: hazardous or critical samples are easily controlled, cleanup is simplified, and cross-sample contamination is eliminated. Because the container holding the sample is immersed in liquid nitrogen throughout the milling cycle, the sample is kept at cryogenic temperatures and its key aspects are preserved. In contrast, conventional room-temperature grinding may alter the sample composition by the heat generated during grinding and some of the volatile components may escape.

The packaging materials extensively evaluated in this study include a HDPE (high-density polyethylene) bottle with the printed label still attached and a soft elastomer liner from the inside of the screw cap. A blister pack, an insulin syringe, and a polypropylene (PP) container were also tested but the results are not reported here. All these containers except the syringe had contained pharmaceutical drug products. The insides of these containers were carefully cleaned to ensure that no drug residue remained. All the samples produced good chromatograms with an abundance of peaks.

| **6890N GC** | |
|---|---|
| Injection port | Volatiles interface |
| Temperature | 225 °C |
| Split ratio | 1:1 |
| Carrier gas | Helium |
| Constant flow mode | 1.2 mL/min |
| **GC oven program** | |
| Initial temperature | 40 °C |
| Initial time | 4 min |
| Rate | 20 °C/min. |
| Final temperature | 300 °C |
| Final time | 5 min |
| Columns: | 30 m x 0.25 mm x 0.5 µm DB-5MS, part# 122-5536 |
| **G1888A Headspace sampler** | |
| Loop size | 1 mL |
| Vial pressure | 25 psig |
| Headspace oven | 125 °C for HDPE, 100 °C for liner |
| Loop temperature | 150 °C |
| Transfer line temperature | 150 °C |
| Advanced function 8 | MHE on, 8 |
| Equilibration time | 300 min., no shake |
| GC cycle time | 30 min |
| Pressurization | 0.3 min |
| Vent (loop fill) | 0.3 min |
| Inject | 3 min |
| **5975 Inert MSD** | |
| Synchronous SIM/Scan mode on | |
| SIM 1 group, 3 ions | |
| Scan 35 to 350 amu, samples 2 ^2 | |
| Threshold | 100 |
| EM offset | +300 |
| Source temperature | 230 °C |
| Quad temperature | 150 °C |
| Tune | atune.u |
| ChemStation software | G1701DA D.02.00 |

**Table 1**
**Instrument conditions.**

## Experimental results and discussion

Figure 1 shows the chromatograms acquired in synchronous SIM/Scan mode from a 0.208 g sample of cryo-milled HDPE. An enlargement of the scan data is shown in figure 2. The chromatogram shows many peaks most of which are from siloxanes (probably from the column) and alkenes. The chromatogram is very complex and many peaks are composed of multiple overlapping components and the apex spectrum is actually a composite of these constituents. A mass spectral library search would give a poor match, at best, and certainly would not identify all of the individual components that make up the composite spectrum. Deconvolution produces "clean" spectra for each overlapping component. These individual spectra can then be library searched with a high expectation for good results. A simplified illustration of this deconvolution process is shown in figure 3.

When the data for HDPE was processed with the Automated Spectral Deconvolution and Identification System (AMDIS) from NIST, the program found 229 component spectra and identified 15 targets from a database of 731 hazardous chemicals, the Agilent Hazardous Chemical Database Library (HCD)[5,6]. A typical output from AMDIS is shown in figure 4. Among the compounds identified were phenol, di-n-butyl phthalate and bis-2-ethylhexyl phthalate. Actually, a number of phthalates were found between 12 and 19 minutes and have been indicated on figure 2 as the phthalate region.

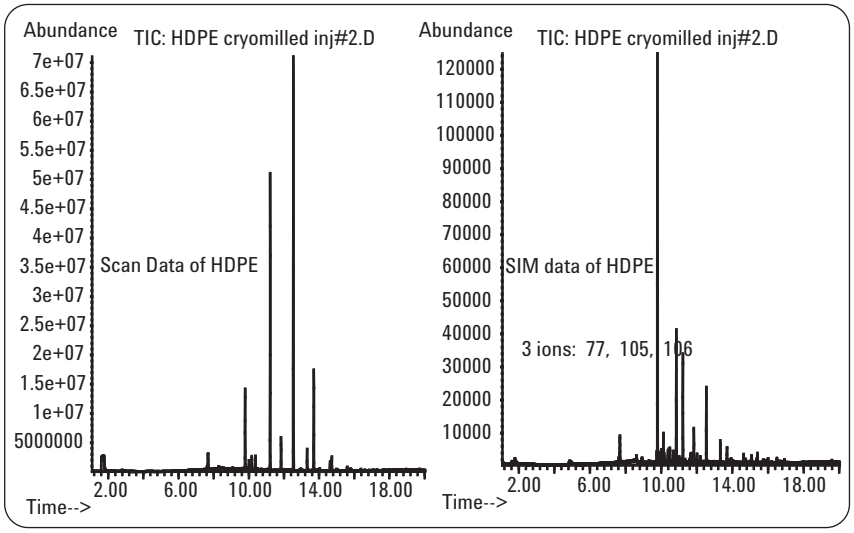


**Figure 1**
**Synchronous SIM/Scan data from a 0.208 gram sample of cryo-milled HDPE polymer.**

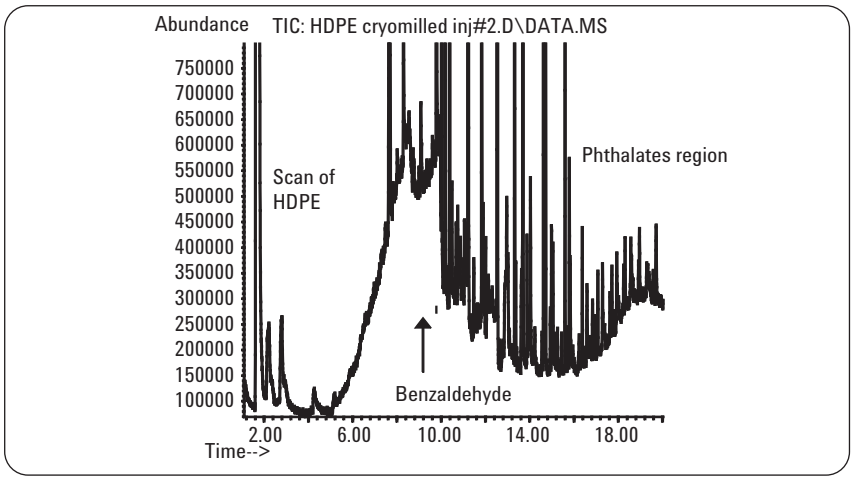


**Figure 2**
**Enlargement of the Scan data from figure 1.**

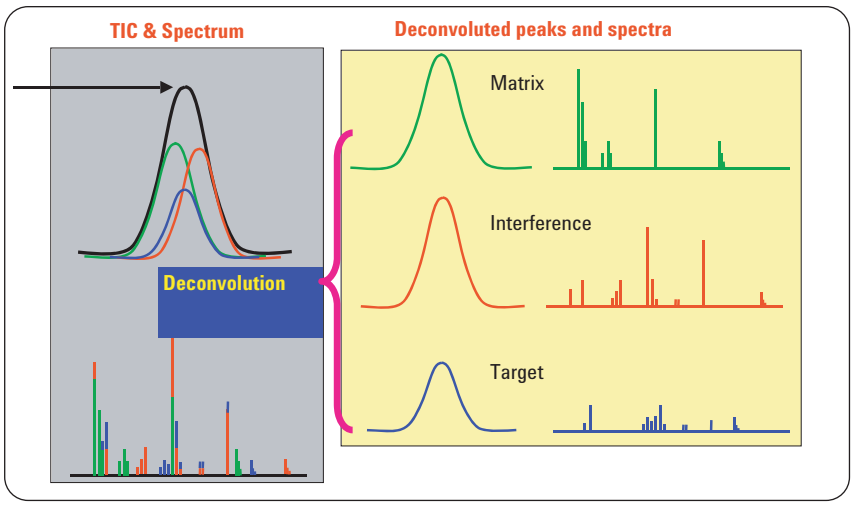


**Figure 3**
**AMDIS deconvolution pulls out individual components and their spectra.**

Since most of the electron ionization spectra of phthalates look the same and unequivocal identification of the phthalates is difficult, positive identification of the phthalates may only be accomplished by looking at chemical ionization data which gives molecular weight information. Also identified in figure 2 is the location of the benzaldehyde peak that is used for the MHE study of HDPE.

SIM data was collected for benzaldehyde using the 77,105 and 106 ions that are characteristic of benzaldehyde. The area data given in fables 2 – 4 are for the extracted 106-ion chromatograms.

Figures 5 and 6 illustrate how matrix interference can complicate the mass-spectral identification of peaks. A very large siloxane peak with an intense 281 ion coeluted with the benzaldehyde. To eliminate the siloxane interference from the spectrum, extracted ion chromatograms of 281, 105 and 106 were generated. The three chromatograms were normalized so that the peaks maxed out at 10000 counts. A good background spectrum with the proper ion abundance was now easily selected from the left of the benzaldehye peak maximum. Figure 6 shows the spectrum before and after background correction. The corrected spectrum when search against the Wiley library of spectra produced an unequivocal hit for benzaldehyde. However, the AMDIS did all this work for every peak in the chromatogram in less than a minute.

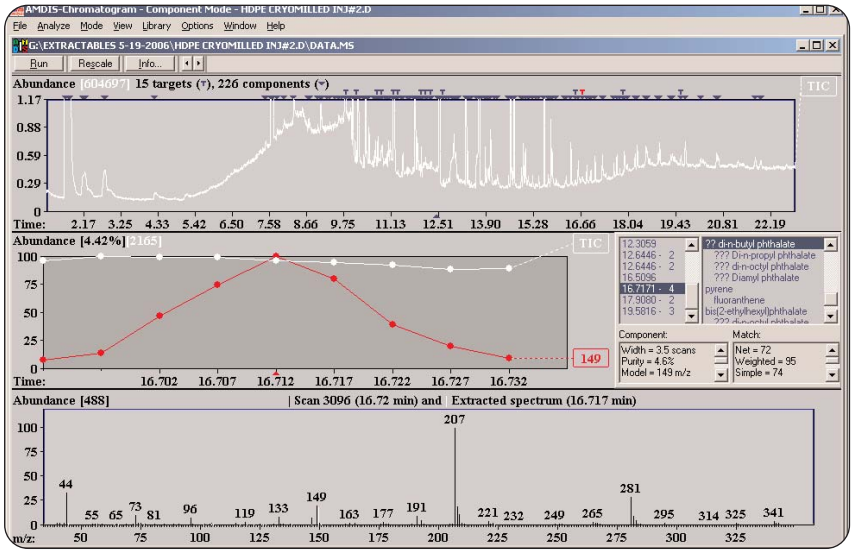


**Figure 4**
**AMDIS results for the scan data of HDPE with the target at 16.71 min identified as di-n-butyl phthalate.**

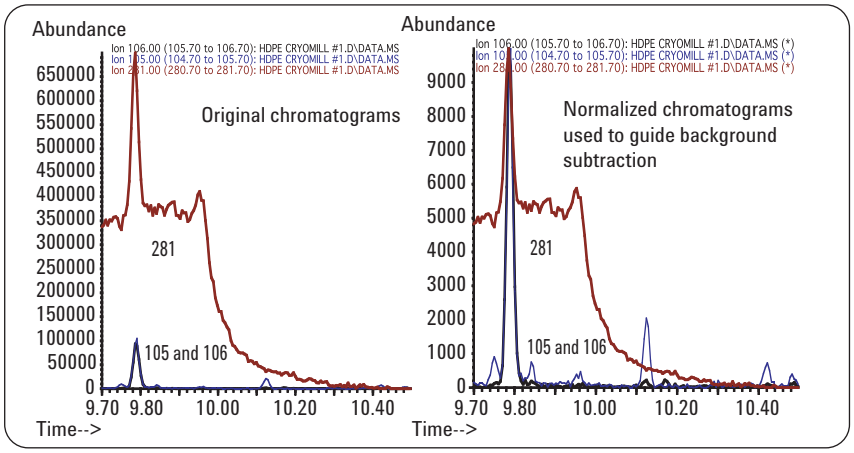


**Figure 5**
**Manual MS deconvolution attempted for the peak at 9.8 min.**

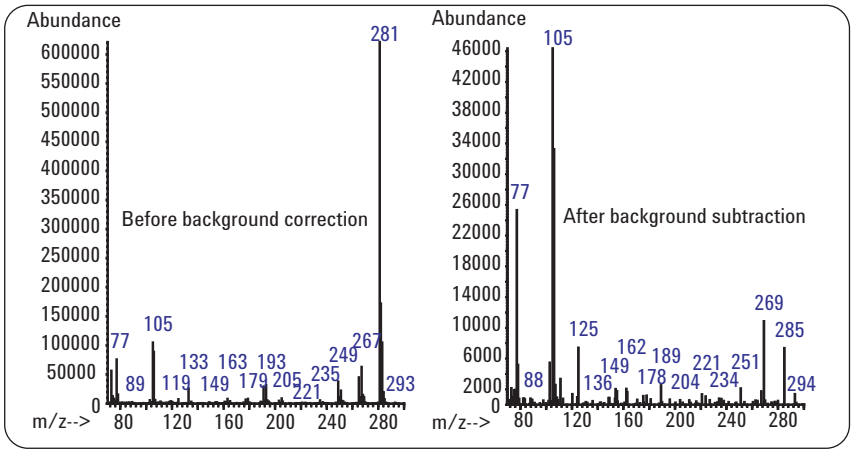


**Figure 6**
**The spectrum for the peak at 9.8 min before and after doing a background subtraction.**

Figure 7 shows the changes in the benzaldehyde peak as a function of the number of extractions during the MHE. The peak area should decreases exponentially with the extraction number. However, sometimes during MHEs some analytes may exhibit a smaller peak area from the first extraction than what is observed from the second extraction, while the remaining extractions show the expected exponential decrease in the peak areas. Such behavior was also observed for benzaldehyde in HDPE (figure 7, 8 and table 2).

Since headspace analysis involves a gas-phase extraction, we should be aware that the first extraction is always done with air for the extraction fluid because that is in the vial when the sample is placed in the vial and capped. Subsequent extractions are done primarily with helium because that is the gas used to pressurize the vial after equilibration. The extraction efficiency with air is probably less than with helium which causes the peak area of the first extraction to be lower than what the graphical extrapolation would indicate (figure 8). In such cases a modified form of the equation may be used to calculate the total area for the analyte (see Appendix for the original equation). Now the Total Peak Area is

$$Total\ Peak\ Area = A_1 + \frac{A_2}{(1 - e^{-K})}$$

where the second half of the equation (the ratio) gives the total peak area as derived from the regression analysis using the results from the second and subsequent extractions.

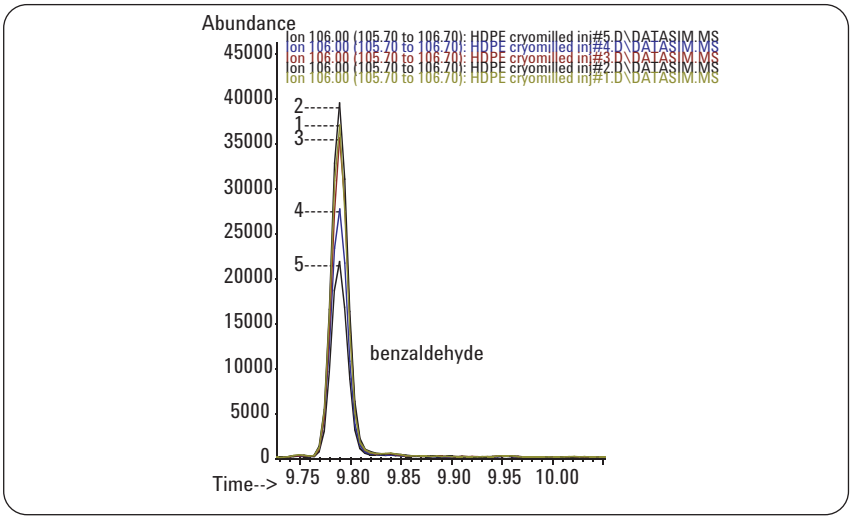


**Figure 7**
**Multiple headspace extraction data for the benzaldehyde peak from HDPE. The numbers next to the peak indicate the extraction number.**

| Benzaldehyde in 0.208 grams of HDPE polymer (cryomilled) | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| **extraction #** | **sample** | **standard** | | standard | stats |
| 1 | 126081 | 90157 | | 0.821008 | 108302.5 |
| 2 | 129433 | 72611 | | 0.004898 | 0.016243 |
| 3 | 118095 | 58834 | | 0.998153 | 0.015487 |
| 4 | 98261 | 49099 | | 1621.638 | 3 |
| 5 | 84345 | 40898 | | 0.388965 | 0.00072 |
| 6 | 68811 | 32992 | | | |
| 7 | 56676 | 27095 | | sample | stats |
| 8 | 45872 | 22746 | | 0.897668 | 151819.2 |
| | | | | 0.023684 | 0.078551 |
| regression correlation (E4 or E11) | 0.873825502 | 0.998153435 | | 0.873826 | 0.074896 |
| slope (k) = ln(E2 or E9) | -0.107955422 | -0.197222062 | | 20.7766 | 3 |
| | | | | 0.116544 | 0.016828 |
| total area = (A(1)/(1-e(-k))) | 1232073 | 503694 | | | |
| | | | | | |
| analyte in vial (mg) | 0.026906838 | 0.011 | | | |
| sample amt (mg) in vial | 208 | | | | |
| | | | | | |
| concentration (ppm) in wt/wt | 129.36 | | | | |
| concentration (wt-%)=ppm * (10 ^ -4) | 0.0856 | | | | |

**Table 2**
**Excel template used for entering area data, sample weight and standard amounts used for the calculations needed for the MHE procedure. Table contains raw data for benzaldehyde in HDPE.**

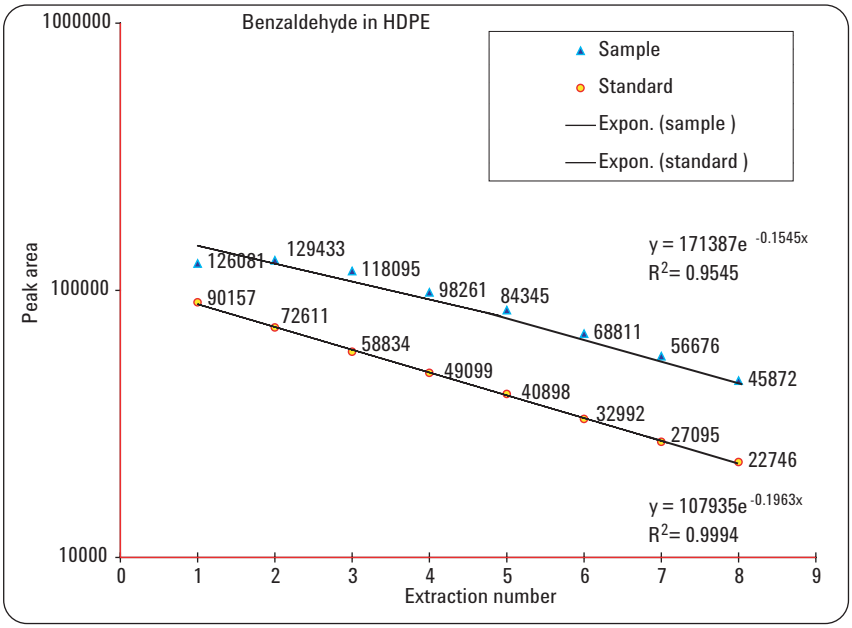


**Figure 8**
**Semi-logarithmic plot of the MHE raw data for benzaldehyde in HDPE.**

Should the above argument for extraction efficiency be indeed validated by purging the headspace vial with helium before sample introduction, another option would be to select the point associated with the first extraction in the Excel semilogarithm plot and drag that point onto the regression line generated by the subsequent extraction points. The results for such a data treatment is shown in figure 9 and table 3. When the data point is dragged onto the regression line, the peak area linked to the table is no longer an integer value but now has decimal points. Clearly the $R^2$ of the regression line, the correlation coefficient, has improved from 0.9546 (figure 8) to 0.9931 (figure 9). Note that the data point for the 2nd extraction also appears a little below the regression line.

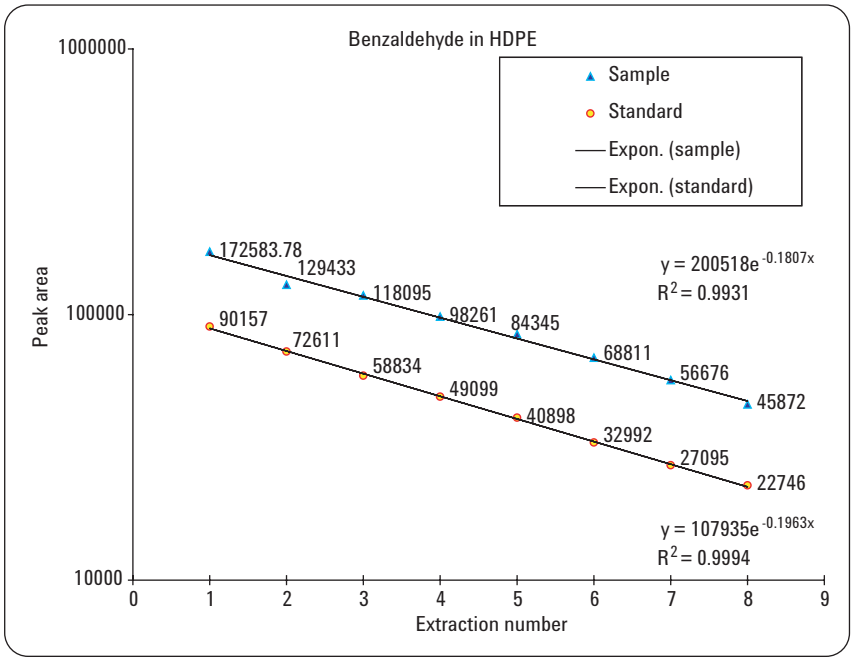


**Figure 9**
**Semi-logarithmic plot of the MHE data for benzaldehyde after forcing the area associated with the 1st extraction to fall on the regression line.**

| Benzaldehyde in 0.208 grams of HDPE polymer (cryomilled) | | | | | |
|---|---|---|---|---|---|
| | | | | samp before fix | |
| **extraction #** | **sample** | **standard** | | standard | stats |
| 1 | 172583.78 | 90157 | 126081 | 0.821008 | 108302.5 |
| 2 | 129433 | 72611 | 129433 | 0.004898 | 0.016243 |
| 3 | 118095 | 58834 | | 0.998153 | 0.015487 |
| 4 | 98261 | 49099 | | 1621.638 | 3 |
| 5 | 84345 | 40898 | | 0.388965 | 0.00072 |
| 6 | 68811 | 32992 | | | |
| 7 | 56676 | 27095 | | sample | stats |
| 8 | 45872 | 22746 | | 0.843035 | 195167.2 |
| | | | | 0.015703 | 0.052081 |
| regression correlation (E4 or E11) | 0.975253934 | 0.998153435 | | 0.975254 | 0.049658 |
| slope (k) = ln(E2 or E9) | -0.170747071 | -0.197222062 | | 118.2314 | 3 |
| | | | | 0.291546 | 0.007398 |
| total area = (A(1)/(1-e(-k))) | 1099503 | 503694 | | | |
| | | | | | |
| analyte in vial (mg) | 0.024011686 | 0.011 | | | |
| sample amt (mg) in vial | 208 | | | | |
| | | | | | |
| concentration (ppm) in wt/wt | 115.44 | | | | |
| concentration (wt-%)=ppm * (10 ^ -4) | 0.0856 | | | | |

**Table 3**
**Data for benzaldehye in HDPE but with a correction made to the area associated with the 1st extraction.**

Probably not all the air in the headspace vial had been replaced with helium after the first extraction and the 2nd extraction was done with a mixture of air and helium. If that data point is also moved onto the regression line (figure 10 and table 4), the R2 value for the graph becomes 0.9989 and the calculated amount of benzaldehyde in the sample goes from 0.0261 grams for the original virgin data to 0.0229 grams after manipulation, i.e., the calculation gives 14 % more analyte without the correction.

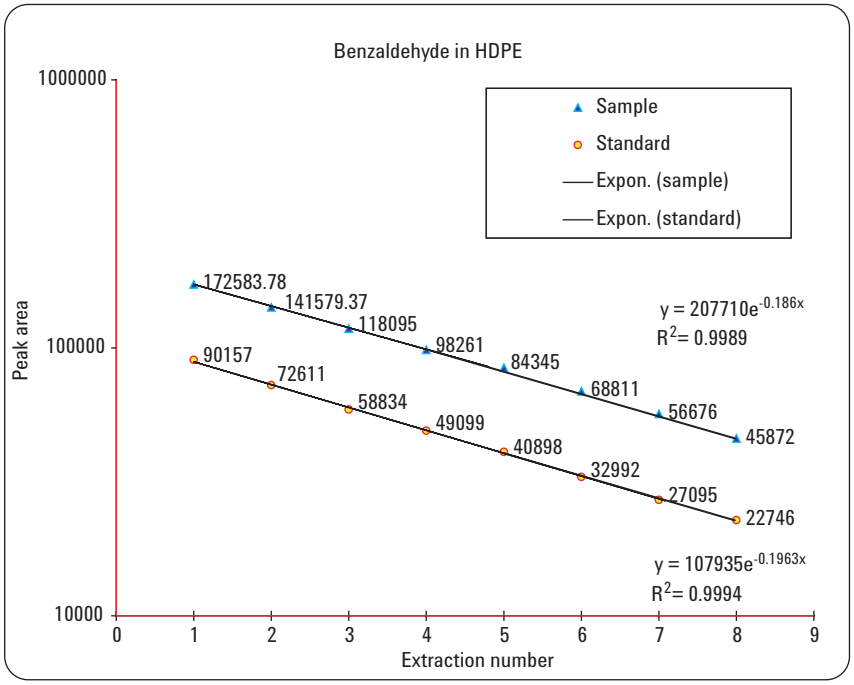


**Figure 10**
**Semi-logarithmic plot of the MHE data for benzaldehyde after forcing the areas associated with the 1st and 2nd extraction to fall on the regression line.**

| Benzaldehyde in 0.208 grams of HDPE polymer (cryomilled) | | | | | |
|---|---|---|---|---|---|
| | | | samp before fix | | |
| **extraction #** | **sample** | **standard** | | standard | stats |
| 1 | 172583.78 | 90157 | 126081 | 0.821008 | 108302.5 |
| 2 | 141579.37 | 72611 | 129433 | 0.004898 | 0.016243 |
| 3 | 118095 | 58834 | | 0.998153 | 0.015487 |
| 4 | 98261 | 49099 | | 1621.638 | 3 |
| 5 | 84345 | 40898 | | 0.388965 | 0.00072 |
| 6 | 68811 | 32992 | | | |
| 7 | 56676 | 27095 | | sample | stats |
| 8 | 45872 | 22746 | | 0.835507 | 204119.5 |
| | | | | 0.00453 | 0.015024 |
| regression correlation (E4 or E11) | 0.998097615 | 0.998153435 | | 0.998098 | 0.014325 |
| slope (k) = ln(E2 or E9) | -0.179716781 | -0.197222062 | | 1573.967 | 3 |
| | | | | 0.322981 | 0.000616 |
| total area = (A(1)/(1-e(-k))) | 1049185 | 503694 | | | |
| | | | | | |
| analyte in vial (mg) | 0.022912801 | 0.011 | | | |
| sample amt (mg) in vial | 208 | | | | |
| | | | | | |
| concentration (ppm) in wt/wt | 110.16 | | | | |
| concentration (wt-%)=ppm * (10 ^ -4) | 0.0856 | | | | |

**Table 4**
**Data for benzaldehyde in HDPE but with corrections made to the areas associated with the 1st and 2nd extractions.**

The synchronous SIM/Scan data for the liner material and the spectrum of phenol at 9.83 min are shown in figure 11. AMDIS results are shown in figure 12. 213 components and 15 targets are identified. The graphics show the phenol target at 9.83 min and the deconvoluted spectrum.

Table 5 lists the MHE-area data for phenol extracted from the liner material and the standard prepared in methanol. DMSO could not be used in the preparation of this standard because a solvent impurity with a strong 94 ion co-eluted with the phenol peak. The concentration of phenol was calculated at 0.63 ppm in wt/wt units. Figure 13 gives the Excel MHE graphics for the sample and standard.

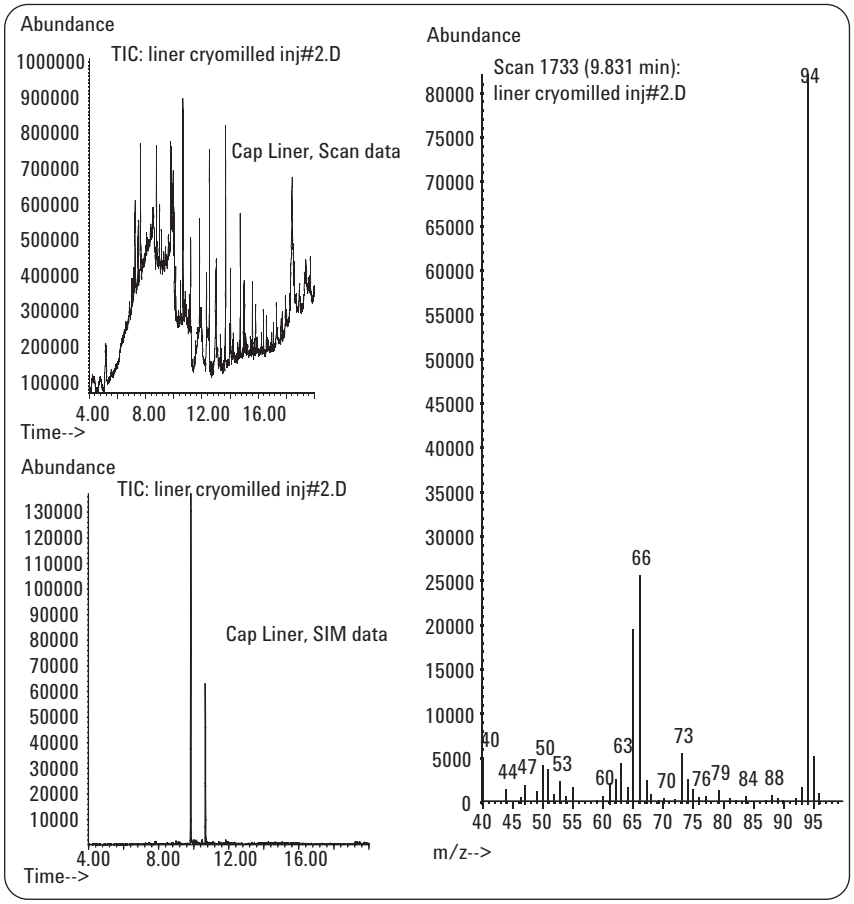


**Figure 11**
**Synchronous SIM/Scan data for 0.084 grams of cryo-milled liner polymer and the background-subtracted spectrum at 9.83 min.**

| phenol in 0.084 grams of liner polymer (cryomilled) | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |
| **extraction #** | **sample** | **standard** | | standard | stats | |
| 1 | 25882.12 | 33028 | | 0.630118 | 54417.16 | |
| 2 | 19906.73 | 22052 | | 0.013536 | 0.044895 | |
| 3 | 15631.47 | 14377 | | 0.99743 | 0.042806 | |
| 4 | 11977 | 8406 | | 1164.101 | 3 | |
| 5 | 9017 | 5314 | | 2.133035 | 0.005497 | |
| 6 | 7093 | 3389 | | | | |
| 7 | 5729 | 1881 | | sample | stats | |
| 8 | 4643 | 1223 | | 0.769746 | 33794.04 | |
| | | | | 0.004119 | 0.013662 | |
| regression correlation (E4 or E11) | 0.999257247 | 0.997429527 | | 0.999257 | 0.013026 | |
| slope (k) = ln(E2 or E9) | -0.261695112 | -0.461847924 | | 4036.026 | 3 | |
| | | | | 0.684843 | 0.000509 | |
| total area = (A(1)/(1-e(-k))) | 112407 | 89293 | | | | |
| | | | | | | |
| analyte in vial (mg) | 5.31233E-05 | 0.0000422 | | | | |
| sample amt (mg) in vial | 84 | | | | | |
| | | | | | | |
| concentration (ppm) in wt/wt | 0.63 | | | | | |
| concentration (wt-%)=ppm * (10 ^ -4) | 6.32421E-05 | | | | | |

**Table 5**
**Data for phenol in liner polymer.**

## Conclusion

Analytical results obtained from the inert 5975 Headspace-GC/MS provide excellent sensitivity when utilizing SIM/Scan data acquisition with multiple headspace extraction (MHE). The synchronous SIM/Scan feature of the 5975 MSD allows for very low level SIM detection while also searching for unkowns using scan data. AMDIS in conjunction with the Agilent Hazardous Chemicals Database Library made identification of components and targets in complex matrices very easy and fast. The matrix-independent MHE technique can generate quantitative values for target extractables for risk evaluation in a worst-case scenario. A very good discussion of how the numbers generated for extractables and leachables may be evaluated

relative to ICH concentration limits is given in reference 7. Here Goldstein et. al. describe a hypothetical extractable study for acetonitrile and acetic acid and compares the results to ICH guidelines for Class I, II, and III residual solvents. In a similar approach, the values for benzaldehyde and phenol as determined by MHE could be compared to Permitted Daily Exposure (PDE) limits.

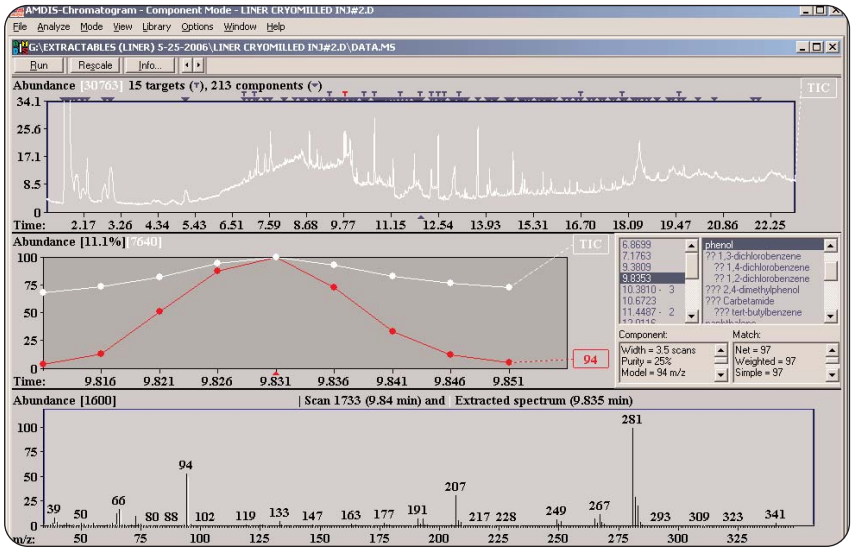


**Figure 12**
**AMDIS results for the scan data of the liner with the target at 9.83 min identified as phenol.**

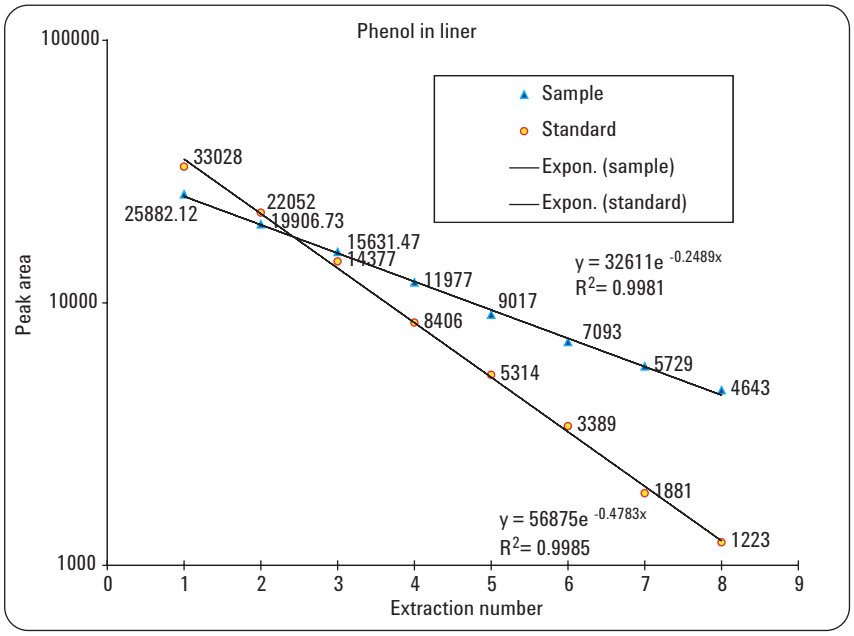


**Figure 13**
**Semi-logarithmic plot of the MHE data for phenol in liner polymer.**

## References


1.
Code of Federal Regulations, Food and Drugs Title 21, Part 211.65; *U.S. Government Printing Office, Washington, DC, rev. 1 April* **2004**.

2.
Chapter V Drugs and Devices, Section 501(a) (*3) Federal Food, Drug, and Cosmetic Act as Amended through December 21, 2000, U. S. Government Printing Office, Washington D.C.*, **2001.**

3.
C. Jeanne Taborsky and Eric B. Sheinin, *American Pharmaceutical Review, Volume 9 Issue 4, pp. 10 – 15, May/June*, **2006.**

4.
Albert E. Gudat and Susan M. Brillante, "Multiple Headspace Extraction – Capillary Gas Chromatography for the Quantitative Determination of Volatiles in Solid Matrices." *Agilent Application Note, Publication number 5965-0978E*, **2000.**

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## Appendix

In the Multiple Headspace Extraction technique the sample is equilibrated at some temperature for a given amount of time and the headspace above the sample is analyzed. This equilibration and measurement process is repeated multiple times and an exponential decrease in the peak areas is observed. If we perform an infinite number of extractions, all the volatile impurities will be converted into the gas phase and the total peak area (eqn. 1) will correspond to the total content of the analyte in the sample:

$$Total\ Peak\ Area = \sum_{n=1}^{\infty} A_n = A_1 + A_2 + A_3 + \ldots + A_n \qquad (1)$$

However, such a large number of extractions per sample becomes impractical and we are forced to use arguments from kinetics to get the total peak area.

The rate of conversion of the the analyte from the solid matrix into the gas phase is assumed to follow 1st order kinetics

$$-\frac{dc}{dt} = k\,c \qquad (2)$$

which upon integration becomes

$$c = c_0\, e^{-k\,t} \qquad (3)$$

If the gas extraction is carried out carefully and for equal times, and equal portions of the headspace gas are introduced into the chromatograph, then the peak areas of a given analyte in the chromatogram will follow the same exponential law since at equlibrium the distribution coefficient $K_d$ is a constant, $K_d = c_c/c_g$ where $c_c$ and $c_g$ are the concentrations of the analyte in the condensed and gas phase, respectively. For a discontinuous or stepwise gas extraction performed at equal time intervals, eqn. 3 now becomes

$$A_n = A_1\, e^{(1-n)K} \qquad (4)$$

*Note:* n = 1 at t = 0 since t = n - 1

$A_n$= the peak area of the $n^{th}$ injection $A_1$= the peak area of the $1^{st}$ injection

For an inifinitely large number of extractions, the total peak area for an analyte thus becomes

$$\sum_{n=1}^{\infty} A_n = A_1 \left( 1 + e^{-K} + e^{-2K} + e^{-3K} + \ldots \right) \qquad (5)$$

This decreasing geometric progression in eqn. 5 converges to

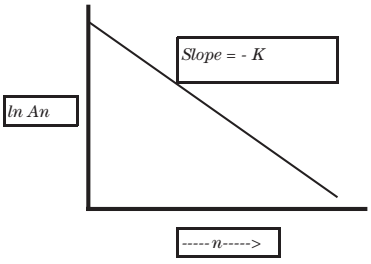
$$\sum_{n=1}^{\infty} A_n = \frac{A_1}{(1 - e^{-K})} \qquad (6)$$

We therefore do not need to do a complete gas extraction to obtain the total peak area but we must obtain values for $A_1$ and K. The $A_1$ value is the measured peak area of the analyte after the 1st gas extraction and K is the slope obtained from a regression analysis of the semilogrithmic plot of eqn. 4:

$$\text{In } A_n = \text{In } A_1 + ( 1 - n ) K \qquad (7)$$

or

$$\text{In } A_n = - K ( n - 1 ) + \text{In } A_1 \qquad (8)$$




For two measurements eqn. 6 simplifies to:

$$\sum_{n=1}^{\infty} A_n = \frac{A_1^2}{(A_1 - A_2)} \qquad (9)$$

**Example Calculation:**

**Solid Sample** ( 337 mg in vial)

$$\sum_{n=1}^{\infty} A_n = \frac{A_1}{(1 - e^{-K})} = \frac{6072}{(1 - e^{0.4615})} = 16423$$

**Analyte Standard** ( 0.00866 mg in vial)

$$\sum_{n=1}^{\infty} A_n = \frac{15609}{(1 - e^{0.6654})} = 32120$$

$$\frac{Total\,Area_{analyte}}{Amount_{analyte}} = \frac{Total\,Area_{standard}}{Amount_{standard}}$$

$$Amount_{analyte} = \frac{16423}{32120} * 0.00866 = 0.00443 \text{ mg}$$

$$\text{Analyte conc. (ppm by wt/wt)} = \frac{Amount_{analyte}}{Weight_{sample}} * 1\,e^{6} = \frac{0.00443}{337} * 1\,e^{6} = 13.1 \text{ ppm}$$

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