

Residual Volatiles Quantification for Novel Matrices

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Statement of Purpose: The production and processing of absorbable, polymeric devices frequently includes the removal of residual contaminants such as solvents and other low molecular weight species that must be quantified to efficiently develop safe materials, constructs and devices. Models to describe and predict the removal of volatiles when developing new specifications and processes require quantitative results to be generated and applied. Analysis of a single sample by USP <467> Residual Solvents only determines if the Residual Solvent Content (RSC) is above or below the tabulated concentration limits. The USP recommended general methodologies of Headspace (HS) analysis with a Gas Chromatograph (GC), the column type, G43 or type 624, and a flame ionization detector (FID) were utilized¹ to develop a RSC HS-GC method. Slight adjustments to a residual solvent HS-GC method should allow for other residual compounds such as monomers and degradation products to be quantified as well.

Methods: A Perkin Elmer Clarus® 580 Gas Chromatograph was used in conjunction with a Perkin Elmer TurboMatrix® 40 to perform analysis. Multiple Headspace Extraction (MHE) allowed for a single sample to be analyzed and produce a quantitative result in weight percent. From Kolb's literature, "[MHE] is dynamic gas extraction carried out stepwise."² MHE eliminated the effect of the matrix on the analysis². A method specific to the analyte was needed with little to no sample manipulation. The focus material (ESM) for the development of the method was an absorbable, polymeric composite electrospun from a hexafluoroisopropanol (HFIP) solution. Removal of matrix effects allowed for an external standard calibration over an extreme range of analyte concentrations, 15 ppm to 10% by weight. Standards were prepared by diluting HFIP in water. Standard addition was used to confirm the accuracy of the test when applied to the ESM. The HFIP diluted with water was added to the ESM, and the mass of the sample as well as the addition was recorded. Each addition was performed in triplicate (Non-spiked ESM, n=6).

Results: The correlation coefficient of the standard curve shown in Figure 1 demonstrated the vast range and effectiveness of the residual solvent test method.

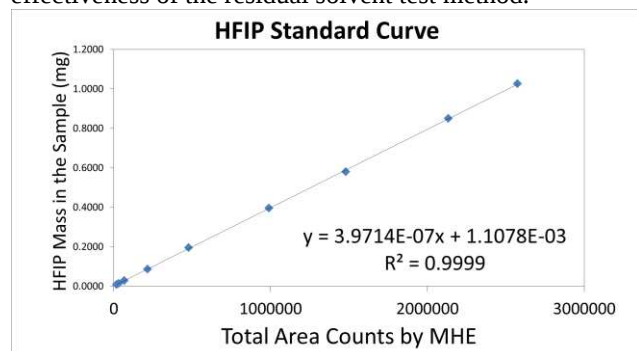


Figure 1. External Standard Curve Generated by Diluting HFIP in Water

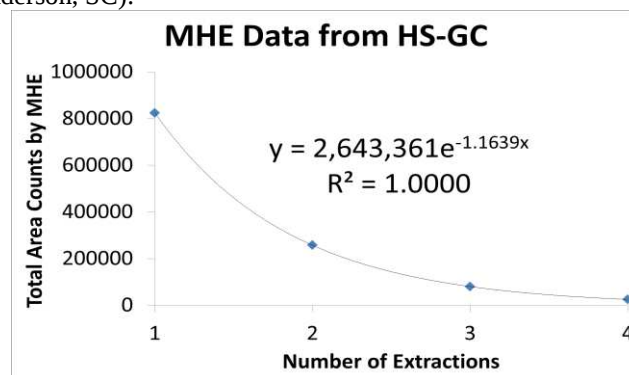


Figure 2. MHE Curve Generated via Analysis of ESM Despite visibility in Figure 1, linearity did hold through the low concentration range. Sample size was varied from 10 mg to 500 mg to achieve the displayed range. The exponential decay and associated correlation coefficient generated by MHE when analyzing ESM, Figure 2, confirmed that equilibrium was being achieved between each extraction, and the risk associated with extrapolation of the trendline when performing the MHE calculations was minimal.

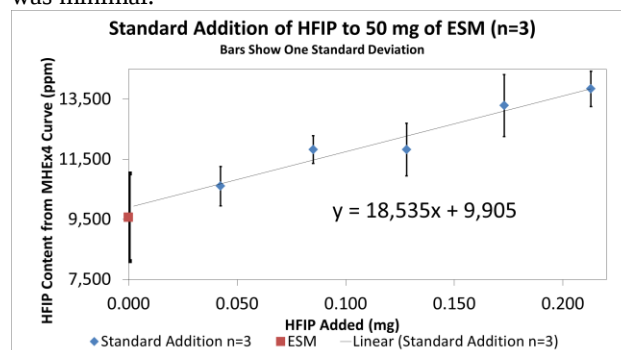


Figure 3. Standard Addition of HFIP to ESM

The trend shown by standard addition in Figure 3 confirmed the accuracy when utilizing MHE with the other aspects of the testing method. This was shown by the trendline associated with the addition samples having a y-intercept value that fits the data collected for material that was not spiked with HFIP. The variability observed in Figure 3 was believed to be associated with the inconsistency of the ESM, not the testing method.

Conclusions: This MHE methodology reduces the number of samples required for quantitative analysis of volatile residuals in novel material constructs and is accurate and effective. Recommendations for future work include using the same method developed to generate standard curves for other solvents that could be present in other materials and devices at residual levels. The method could also be slightly adjusted to determine contents of monomer and other residual contaminants by optimizing the GC oven profile as well as the headspace extraction.

References:

1. USP <467> Residual Solvents. 2007.
2. Kolb, Bruno and Ettre, Leslie S. Static Headspace-GC. 2006; 213-238.