

Detection and Identification of Extractable Compounds from Polymers

GOAL

To detect and identify unknown polymer extractables not found using conventional GC/MS techniques. To apply the well-established QToF accurate mass measurement workflow to GC/MS analysis.

BACKGROUND

Containers specified for packaging pharmaceutical products are required to be tested for extractables to verify the absence of toxic impurities that could transfer to the drug. Often the monomer and polymer manufacturers do not provide all necessary compound information. Additional compounds may also be formed in the molding process. Therefore, there is need for identification of substances in the polymer that can potentially contaminate the drug product. Typically, this is accomplished by extracting the component with three different solvents and analyzing the extracts by LC/MS and GC/MS*. With EI on a single quadrupole GC/MS, sufficient sensitivity for library identification often cannot be accomplished for all prospective analytes.

Initial analyses of the nylon sample by single quadrupole GC/MS using conventional EI and CI were unable to provide data of sufficient intensity and quality to identify impurities. However, once this EI data revealed the presence of an impurity, it was important to establish its identity to ensure that this extractable would not impart undesirable qualities to the drug product through contact with the nylon.

APGC/QToF with MS^E allows elemental composition determination of compounds that could not otherwise be identified.

THE SOLUTION

For the analysis, sample preparation was performed using 2 g nylon resin microwave extracted 3h/70 °C in 10 mL isopropanol. The GC/MS system was a Waters Xevo® G2 QToF with an Atmospheric Pressure Gas Chromatography (APGC) source and 7890A GC.

APGC provides soft ionization resulting in a large peak for the molecular ion leading to improved sensitivity. In addition, the analysis can be performed with concurrent acquisition of both high and low collision energy data (MS^E). This facilitates structural elucidation by providing accurate mass data for both intact molecular ions as well as structurally significant fragment ions.

Figure 1 shows the EI TIC (A) compared with the two simultaneously acquired MS^E TICs from the APGC QToF experiment. The peak for the analyte at 15.75 min is readily observed in both APGC traces despite the fact that using conventional CI there was no

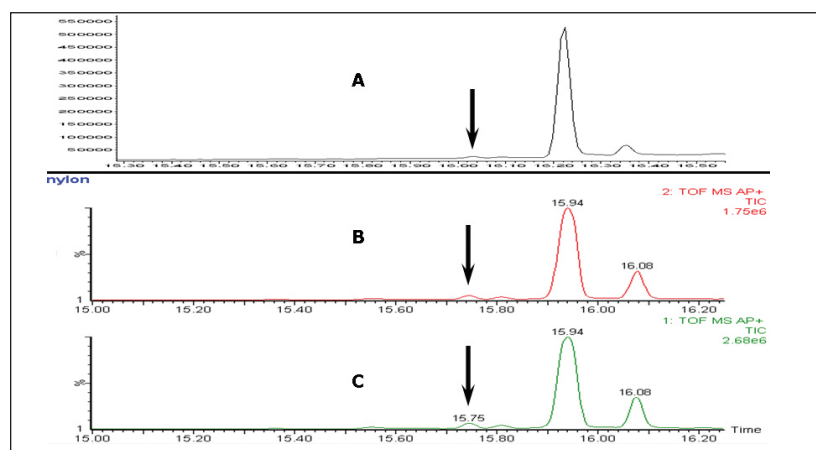


Figure 1. A = EI TIC, B = high energy/fragmentation APGC TIC, C = low energy/molecular ion APGC TIC.

discernable peak. As a result of the sensitive detection of the analyte in both traces, high quality spectra for the intact molecular ion as well as a full range of fragment ions (Figure 2) is available for interpretation using accurate mass measurement and structural elucidation software.

In order to better qualify the sensitivity of the technique, the XIC for 222.2222 Da was plotted with a portion of the background magnified, as shown in Figure 3. This clearly demonstrates signal-to-noise in excess of 1000:1 for a compound undetected using convention vacuum source CI. Furthermore, upon plotting this XIC additional peaks of the same mass are observed. One of these, at 15.91 min, coelutes with the main extractable component of the nylon and would fail to be detected without the sensitivity and the high resolving power, at 22,500 FWHM, of the QToF. The stability and resolving power of the QToF together provide excellent mass accuracy (Figure 3), which allows determination of the elemental composition of the analyte not possible with previously acquired EI and CI data.

The comparison of the acquired data to the theoretical isotope pattern in Figure 3 helps show the dynamic range of the QToF as well as its ability to accurately measure and represent the naturally occurring isotope abundances. The proposed molecular formula and fragments support a structure that is a degradant of a proprietary processing aid identified by the resin manufacturer. The exact structure is not included here due to the proprietary nature of the formulation.

SUMMARY

The soft ionization of APGC provides an orthogonal technique to conventional EI and CI revealing previously undetectable compounds of interest and providing spectra with a controllable extent of fragmentation. This provides greater confidence in product purity for drugs that contact polymers during storage and delivery.

In this study, EI GC/MS on a single quadrupole was demonstrated to lack sufficient sensitivity to provide reliable library matches. Additionally, there is a high

likelihood that polymer extractables will not be present in commercially available libraries making a Xevo G2 QToF with an APGC for accurate mass information a more fit-for-purpose solution in the determination of unknowns. As a result, APGC/QToF with MS^E allows elemental composition determination of compounds that could not otherwise be identified even with sufficiently intense EI spectrum.

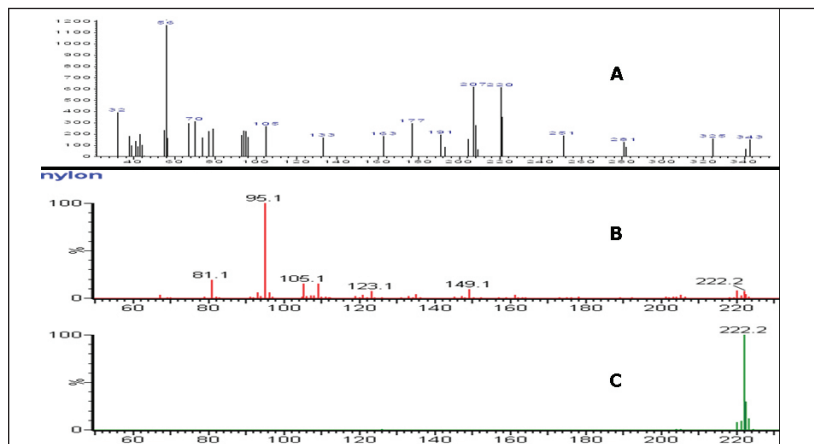


Figure 2. A = EI spectrum, B = high energy/fragmentation APGC spectrum, C = low energy/molecular ion APGC spectrum.

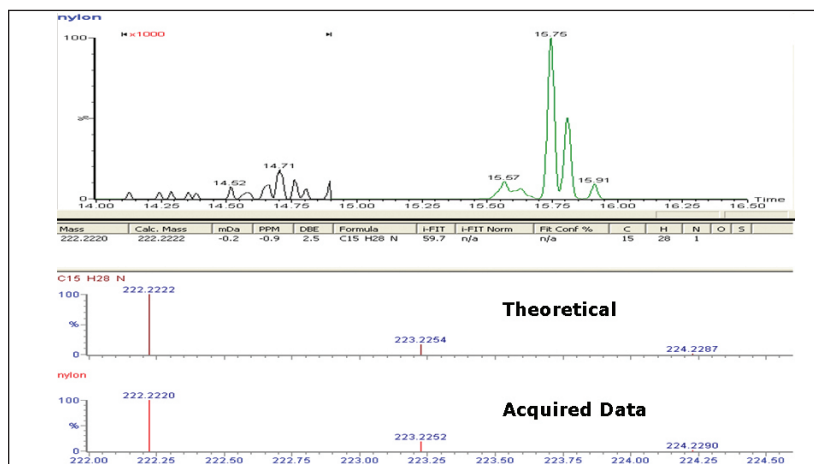


Figure 3. Upper, accurate mass XIC of 222.2222 Da. Lower, accurate mass spectrum from low energy MS^E data along with the theoretical isotope model for the calculated elemental formula.

* Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, Leachables and Extractables Working Group, Product Quality Research Institute (PQRI), 2006 (www.pqri.org).

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