Cambridge Polymer Group

Did Your Device's Biocompatibility Study Fail?

Trace Level Analysis to the Rescue

By Norma Turner, Director of Analytical Services

Summary

You have designed and manufactured your device; it has passed all the screening tests but has failed cytotoxicity! What do you do now? Look for trace level contaminants that may have caused the cytotox failure. Analyzing the test media from the failed cytotoxicity can be extremely enlightening in some cases. By tracing the analysis back to the bill of materials (BOM) and processing aids, you can identify the reason for the failed test. If the compounds identified are determined not to pose a toxicological risk for the intended application, this information may provide a rationale for releasing the product.

This application note describes the investigation of trace level contaminates in samples of minimum essential media (MEM) solution after extraction of orthopedic medical devices for a cytotoxicity assessment.

Introduction

A cytotoxicity test involves preparing an extract from a medical device using a MEM solution, and then exposing that extract to living cells. The extent of cell reactivity to the extract exposure is categorized on a scale from 0-4 (4=severe reactivity). Failed cytotoxicity (score of 3-4) is usually caused by a residual material on the surface of a medical device. After such a failure, the cleanliness of a device can be determined by performing an extraction of the medical device and initially analyzing the resulting extracts by traditional methods such as total organic carbon, total hydrocarbon content or a gravimetric assessment of the residues. Additionally, the test media can be inspected for possible sources of the contaminants to assess if the residues truly present a toxicological risk. In the study presented here, several samples of MEM solution were examined, both those that passed and failed a cytotoxicity assessment as well as neat samples of MEM solution.

Experimental and Results

Trace level residue analysis can involve many techniques but in this study the testing was performed by gas chromatography mass spectrometry (GC-MS), liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) and inductively coupled plasma mass spectrometry (ICP-MS). Analysis of the neat test media provided a baseline for the study and the framework for looking for differences between spectra of extracted test media. The MEM solutions

were extracted with suitable solvents (hexane, ethyl acetate, etc.) and these extracts were analyzed and compared to the extracts from a fresh test media. Analyzing the extracts rather than the neat test media allows for a cleaner system where differences in the spectra will be more noticeable.

For the analysis by GC-MS, notable peaks in the mass spectrum were compared to a NIST reference library to determine the identity of compounds that may be contributing to the failed cytotoxicity. For the LC-QTOF analysis, an exact mass for each compound was determined and software packages were used to generate a likely empirical chemical formula.

In this study, the compounds that were identified included a surfactant in a cleaning agent, quaternary amines, chelating agents, residual acids and glycols. With this additional information, toxicologists analyzed the specific compounds identified to determine if they were present at levels that could constitute a toxicological concern. Finding that they were not above these thresholds, the client was able to release the held product.

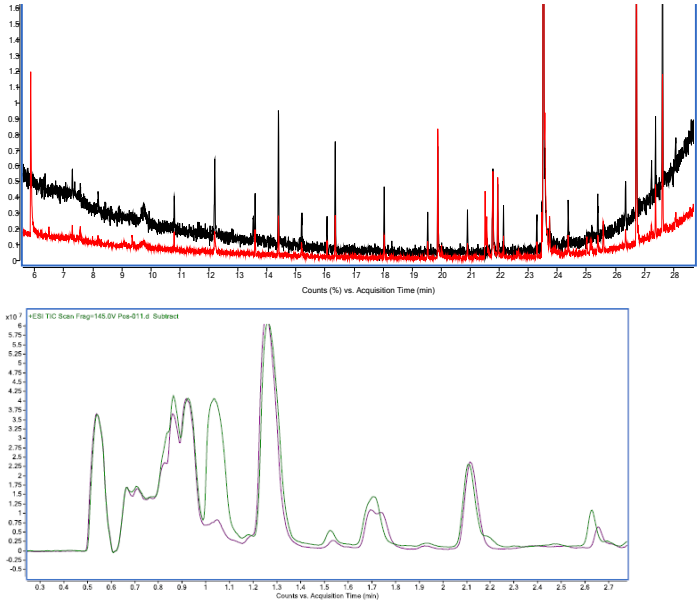

Figure 1: GC-MS analysis of extracts from MEM solution (red failed cytotoxicity, black passed)

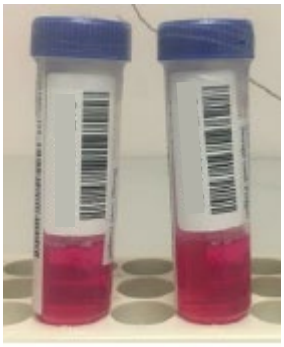

Figure 2: LC-QTOF-MS ESI+ analysis of extracts from MEM solution (green failed cytotoxicity, red passed)

Conclusions

In many cases, a failed cytotoxicity result can be attributed to a processing aid, such as a cleaning agent, machine oil, or passivation step.

Trace level analysis can detect compounds that can be attributed to failed biocompatibility studies. These analyses, conducted on the test media, can provide a less complicated spectrum where only compounds that may affect the cytotoxicity result are present rather than performing a full cleanliness assessment on the device.

A failed cytotoxicity test does not necessarily mean the lot must be scrapped. Instead, additional chemical analysis can often identify the cause of the test results, allowing for further review to determine if the lot is safe to release.

This trace level analysis expands to other areas as well:

- Why does your seal fail? Trace levels of oils present can compromise the integrity of the closure.
- Has your polymeric device completely degraded? Looking for trace levels of the material in a matrix can provide you with the answer.

Other test methods that can help with trace level analysis include pyrolysis GC-MS, ion chromatography, scanning electron microscopy with energy dispersive spectroscopy (SEM-EDS), and Fourier-transform infrared spectroscopy (FTIR), all services that are provided by Cambridge Polymer Group.

About Norma Turner

Norma Turner brings 20 years of experience in polymer characterization and development within the medical device industry. Her career began with a focus on polyesters for tissue scaffolding applications. Since joining Cambridge Polymer Group, Norma has enjoyed a progressive career path, working across a diverse range of materials throughout the entire manufacturing process, from raw materials to final finished devices. Her expertise encompasses key medical device materials such as bone cement, UHMWPE, and hydrogels. In recent years, Norma has shifted her focus towards risk assessments and navigating regulatory agency interactions for medical devices. This deep understanding of both material science and regulatory requirements allows her to effectively guide clients in achieving successful product development and commercialization. Norma received her B.Sc. in Chemical Engineering from University of Alberta, Edmonton and her M.S. from Queen's University at Kingston, Ontario.

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