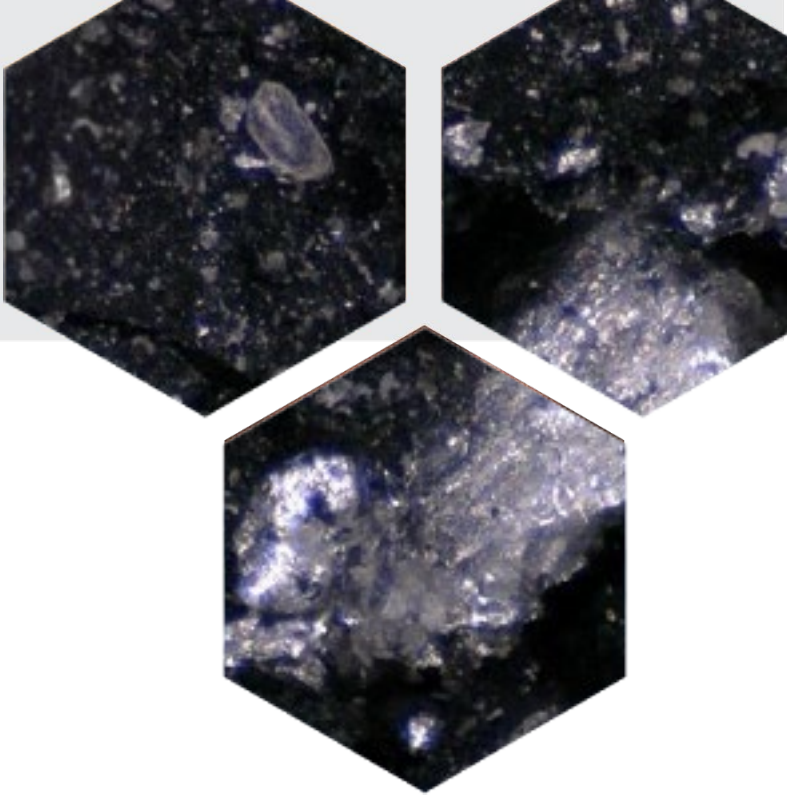
Cambridge Polymer Group



Root Cause of Discolored Drug Product

By Jaimee Robertson, Director of Consulting Services

Summary

Root cause analysis is the process by which the source of a problem is identified. The complex nature of problems requiring in-depth root cause analysis necessitates multidisciplinary expertise. At CPG, we utilize our vast analytical capabilities to gather data on the problem at hand, and we draw on our fundamental materials science, engineering, and chemistry knowledge to interpret our findings. A detailed understanding of the product and manufacturing processes is also necessary, so we typically work closely with our clients throughout the process. In this real example, CPG employed microscopy and elemental analysis to inspect and analyze a discolored drug product.

Introduction

CPG was approached with an urgent request to determine the cause of a color change in an aqueous drug product. One unit in the production lot failed inspection due to a purple hue in the normally colorless solution, and the lot was placed on hold until the reason for the color change was determined. The drug solution was contained in a glass vial with a rubber septum, and in addition to the purple hue in the drug solution, the client identified a discolored region on the vial wall near the septum. CPG performed an expedited root cause analysis to determine the cause of both discolorations.

Root Cause Analysis

The client provided the discolored drug product and a control for comparison. Digital optical microscopy and scanning electron microscopy with energy dispersive spectroscopy (SEM-EDS) were employed for the analysis.

Optical Microscopy

Barrier properties are evaluated by standardized/instrumented test methods such as those listed in the table below. Different materials range in their ability to protect against the influx of potential contaminants. Ethylene vinyl alcohol (EVOH), for example, is a superior oxygen/gas barrier and is often used in packaging for products susceptible to oxidative degradation, such as polyethylene orthopedic implants. EVOH's complex crystal structure creates a tortuous pathway for molecular diffusion, thereby slowing the rate

of gas transport across the film. However, due to its hygroscopic nature, EVOH is not a functional moisture barrier. Water absorbed by EVOH plasticizes the polymer, causing a loss of oxygen barrier properties. For this reason, EVOH is often used in multilayer packaging, in which an outer layer serves as a moisture barrier to both protect the product and preserve EVOH's performance.

Figure 1: Left: The discoloration on the vial wall was identified as radiant particulates clustered near the rubber septum. Right: Adjacent to the particulate, the rubber septum was torn and discolored.

SEM-EDS

The embedded metallic particle, dried residues from the drug solutions (discolored product and a control), and the particulate cluster from the vial wall were analyzed using SEM-EDS to determine the elemental composition.

The embedded metallic particle was identified as galvanized steel due to the iron, chromium, and carbon content and the presence of a zinc coating on one surface of the particle. The particle was a foreign contaminant, likely introduced into the septum during the molding process.

Relative to the control, the discolored drug residues had reduced sulfur, sodium, and oxygen content, all of which were associated with an antioxidant in the drug solution. Conversely, the discolored surface of the rubber septum around the embedded particle was rich in these elements. The septum surface also had elevated zinc content; as there was no zinc in the drug formulation or vial materials, the galvanized steel particle was identified as the source of the zinc. A small percentage of iron was also detected in the discolored drug residues, suggesting the presence of metallic ions from the steel particle in solution.

Figure 2: A galvanized steel particle was embedded in the rubber septum near the particulate on the vial wall.

The particulates from the vial wall were primarily composed of zinc and sulfur. Again, the zinc was traced to the galvanized steel particle, and the sulfur was from the antioxidant additive in the drug solution; the particulate was the product of a reaction between the zinc from the coating on the metal particle and the antioxidant. Precipitation of the particulates from solution explained the reduced signal for elements associated with the antioxidant in the discolored drug residues.

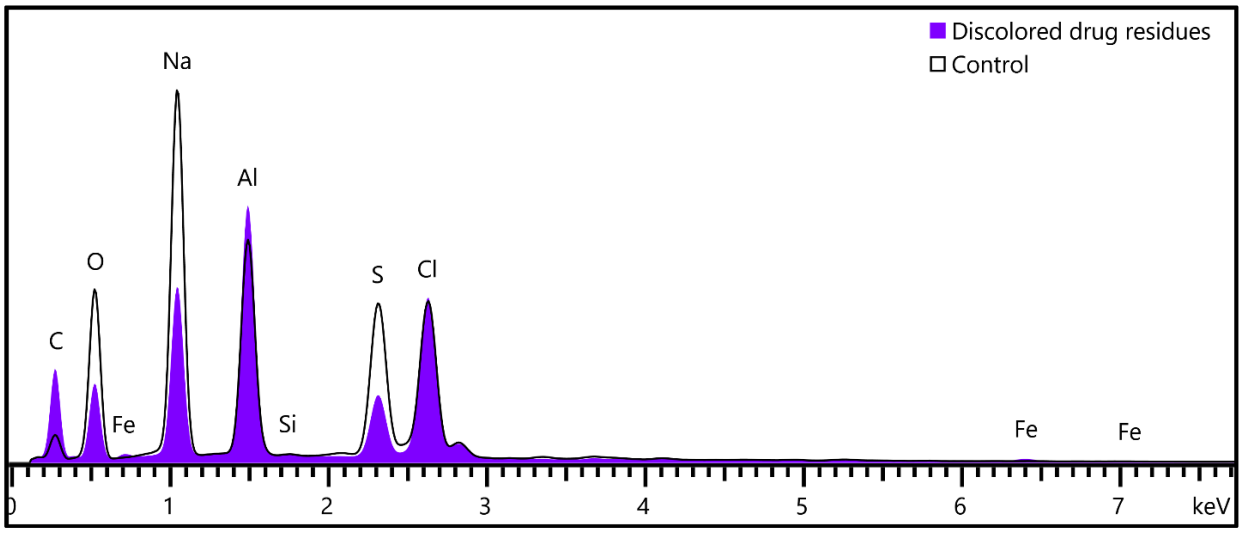


Figure 3: Comparison of the SEM-EDS spectra collected from the discolored drug residues and a control identified reduced sulfur, sodium, and oxygen content in the discolored residues. A small percentage of iron in the discolored residues indicated the presence of metallic ions in solution.

Conclusions

CPG determined the root cause of the color changes observed in the drug product. A galvanized steel particle was inadvertently incorporated into the rubber septum during molding. In the presence of the acidic drug solution, the zinc coating on the metallic particle was corroded, and the zinc reacted with the sulfur-containing antioxidant in solution, producing zinc sulfide, a water-insoluble, phosphorescent compound. The phosphorescence explains the radiant appearance of the particulates on the vial wall. While not directly confirmed by SEM-EDS due to sensitivity limits, the purple color change was attributed to chromium (III) ions in solution. Chromium (III) can complex with water molecules, forming hexaaquachromium (III) ion, which is purple in color.

The root cause analysis performed by CPG identified the cause of the discolorations, enabling release of a production hold placed on the drug product.

About Jaimee Robertson

As Director of Consulting Services at Cambridge Polymer Group, Jaimee Robertson develops new medical devices from initial specifications through concept refinement and product manufacturing, helping clients turn their product visions into reality. Drawing on her years of experience in medical device innovation, she develops custom analytical techniques to characterize polymeric materials, including in-vitro test assays for screening product performance in simulated end-use conditions. Jaimee performs root-cause analysis on medical devices to assess potential and actual failure modes. She received her B.S. in Chemical Engineering and Mathematics and her M.S. in Chemical Engineering at Syracuse University.

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