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FOREIGN PARTICULATE AND GLASS DELAMINATION INVESTIGATIONS USING AUTOMATED RAMAN/LIBS

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PURPOSE

Foreign particulate matter in drug products is a common problem in the pharmaceutical industry that can have major impacts on pharmaceutical companies, from both financial and safety aspects. While manual particulate characterization is best suited for many investigations, automated Raman / LIBS analysis can offer additional insight and investigative solutions to contamination issues, including foreign particulate matter and glass delamination. The purpose of this poster presentation is to describe the methodologies and effectiveness of utilizing automated Raman/LIBS analysis techniques versus routine manual testing methodologies. When launching an investigation, it is important to determine the scope of the project, so that one can best determine which method will provide the most informative results.

METHODS

Current methods of foreign particulate characterization include, but are not limited to optical microscopy, Scanning Electron Microscopy/ Electron Dispersive Spectroscopy (SEM-EDS), Fourier Transform Infrared Spectroscopy (FTIR), and Raman spectroscopy. These methods offer a complete and detailed identification of a material; however, sample preparation for multiple techniques, along with carrying out various tests can be impractical when dealing with extremely large populations of particles. The Single Particle Explorer (SPE)-raman.ID+metal.ID (Laser Induced Breakdown Spectroscopy, LIBS) system offers the ability to establish the size and chemical composition of hundreds of particles, whether the chemical makeup is metallic, organic or inorganic [3]. The system combines image analysis (to determine particle count, size and shape) with spectroscopy (to determine identity), resulting in the ability to analyze hundreds of particles in hours, as shown in Figure 1.

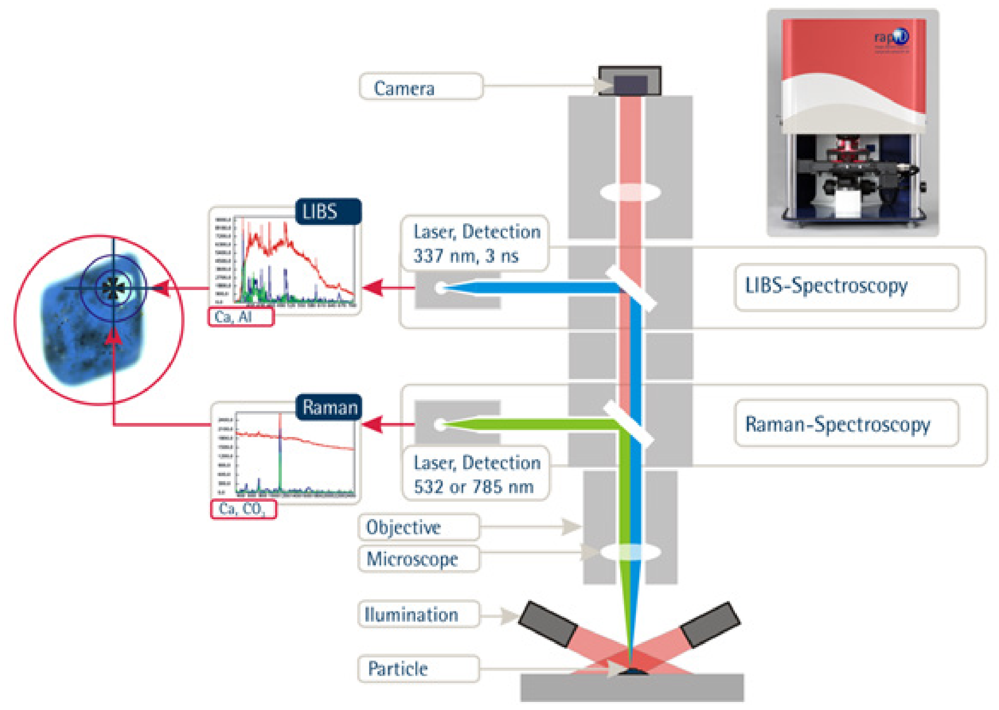

FIGURE 1: Single Particle Explorer (SPE)-raman.ID + metal.ID system schematic.

RESULTS

Contamination can involve different types of failures, whether related to particulate or sterility. Particulate is related to the presence of foreign particles, and sterility is related to the presence of microorganisms. These contaminants, which are seen in the final products, can be introduced from various sources. Particulate contamination and glass delamination analysis are completed using manual and/or automated methods, depending on the investigation's requirements.

FOREIGN PARTICULATE INVESTIGATIONS

Manual particulate characterization analysis is useful when a limited number of unknown particles need to be identified. Sample isolation and preparation of particulate is very critical, as particulate tends to be very small in size and limited in number. Best practice includes a forensic approach to analytical testing, as source determination of the foreign particulate is typically the goal. A multi-analytical approach, including optical microscopy, SEM-EDS, FTIR and Raman spectroscopy was used to determine the identification of the particulate. Utilizing multiple technologies can fully characterize materials, because certain methods can make up for the shortcomings of other methods; that is, the group of methods almost work together like a team in order to attain a comprehensive identification of the material. Utilizing a multi-level approach, along with the specialized expertise of a trained forensic scientist adds great value to nonconformance investigations and sourcing failures [2]. SEM-EDS analysis provides elemental composition of a sample (particularly useful with metals and inorganic materials) and high resolution/high magnification images, as shown in Figure 2. FTIR analysis classifies and identifies organic compounds based on vibrational modes in their structure. Raman spectroscopy is a complementary technique to FTIR and is based on molecular vibrations in a structure based on scattering of light, rather than absorption, as shown in Figure 3. Raman is also a useful technique for obtaining various types of information including chemical identification, crystalline structure determination, and polymorphism detection. Raman analysis is also particularly useful in mineral identification and in instances where particle isolation is not possible (such as an inclusion in a piece of glass). And so, by utilizing microscopy, coupled with elemental and spectroscopic examination, one can really start to achieve a detailed identification of a material.

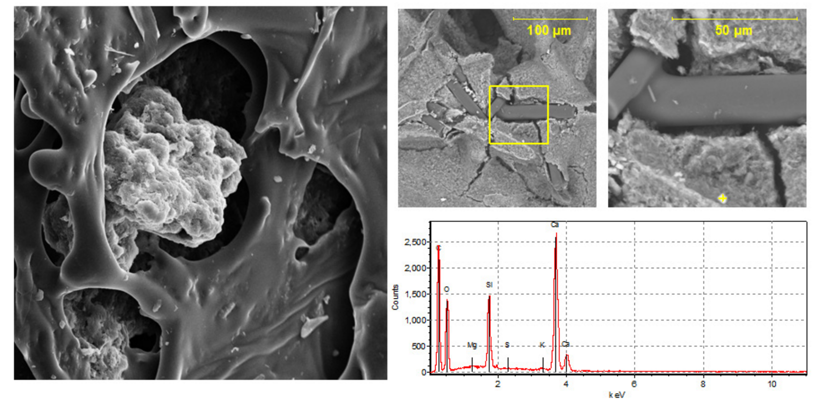

FIGURE 2: High resolution image (left) and elemental compositional data (right) collected using manual SEM-EDS.

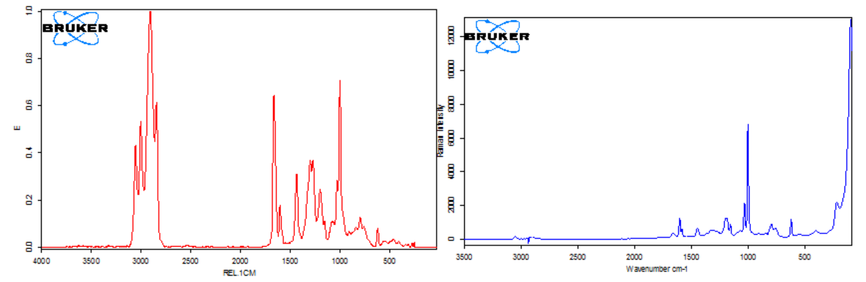

FIGURE 3: A FTIR spectrum of polystyrene (red) vs. a Raman spectrum of polystyrene (blue).

Automated particulate characterization analysis becomes useful when the general characterization, size distribution and count of a large population of known or unknown materials are of interest. Sample preparation is minimal, only involving filtration onto filter membranes specific to the desired analysis. Automated SPE (Raman and LIBS) and automated SEM-EDS techniques were used for analysis. Automated Raman analysis completes image analysis (particle count, size and shape) on particles 2µm and greater, along with the chemical identification, as shown in Figure 4. Automated LIBS also provides image analysis, as well as spectra of metallic and inorganic particles 10µm and greater, as shown in Figure 5. The SPE provides automated data searching, along with the ability for manual confirmation of specific particles. Automated SEM-EDS is a complementary technique used to classify particles (most commonly metallic and inorganic particles) 2µm and greater, as shown in Figure 6. This becomes especially useful, since the LIBS is generally not applicable to particles in the 2-10µm size range.

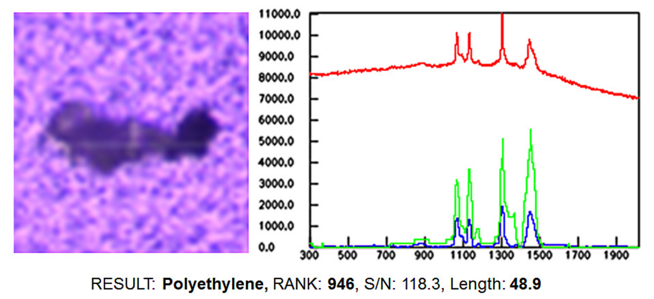

FIGURE 4: An automated particle image, Raman spectrum, classification and size information of a polyethylene particle, using the SPE system.

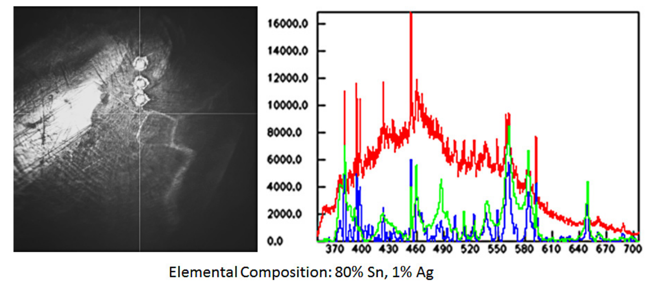

FIGURE 5: An automated particle image, LIBS spectrum and elemental composition data using the SPE system.

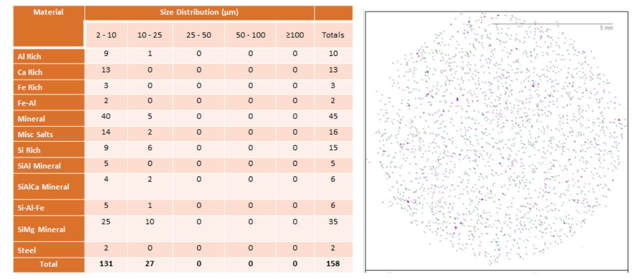

FIGURE 6: Elemental composition data, along with a particle summary map using automated SEM-EDS analysis.

GLASS DELAMINATION INVESTIGATIONS

Contamination concerns in parenteral drug products are of special concern, due to the use of the final products. Contamination can have critical health implications such as: venous thrombosis (blood clots), infusion (inflammation of the vein), pyrogenic reactions (fever), systemic sepsis (infection), tissue infarction (death of tissue) or death [1, 4]. Glass vials can be a possible source of contamination due to glass delamination, which is a phenomenon that occurs when the top layers of the interior glass surface flake off due to a chemical breakdown of the glass surface.

Glass delamination investigations were completed using manual and automated techniques. Optical microscopy, SEM-EDS (manual and automated) analysis of the liquid contents from the glass vials, along with high resolution imaging of the interior surfaces of the glass, assist in glass delamination investigations. Identifying the presence or absence of glass lamellae (thin flakes of glass), pitting (small hole-like defects present on glass surfaces; pitting can be indicative of, and a precursor to glass delamination) and/or surface abnormalities on the vials are crucial steps in these investigations, as shown in Figure 7. Automated LIBS has the ability to identify glass particles, as shown in Figure 8. Therefore, this technique has the potential to be an efficient method to detect, size and enumerate glass lamellae.

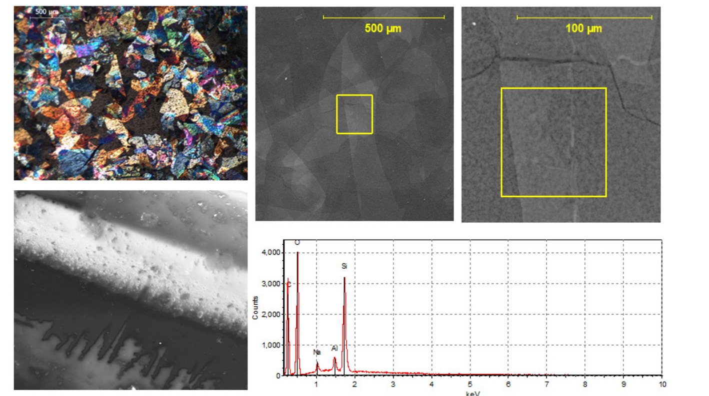

FIGURE 7: Glass delamination investigation using optical and manual SEM-EDS analysis.

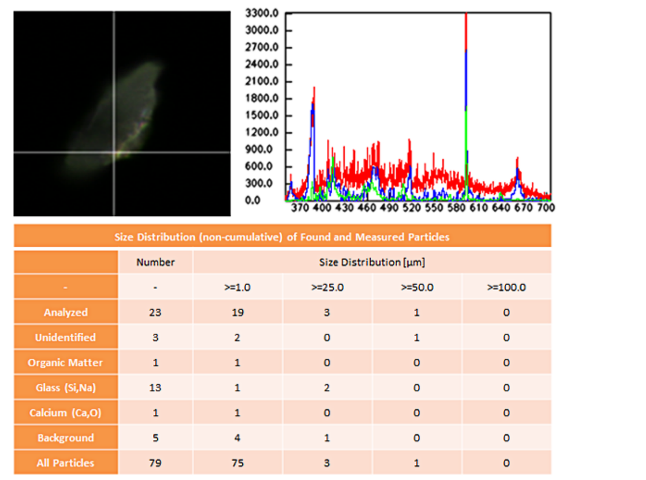

FIGURE 8: Automated LIBS analysis data after detection for the presence of glass material using the SPE system.

CONCLUSIONS

In some instances, manual methods of particle analysis proved to be more successful. This was especially the case, when particles were large enough for manipulation and manual analysis and when a limited number of particles were of interest in an investigation. Certain investigations require characterization, particle size distribution, and enumeration for a large population of particles; the value of the automated Raman and SEM-EDS analyses is evident in these types of investigations. Both manual and automated techniques prove to be useful in investigations specifically related to glass delamination. Automated LIBS has potential for providing sizing and enumeration of lamellae in glass delamination investigations; this type of technique will require additional studies before it can be introduced to nonconformance investigations and stability studies related to delamination.

REFERENCES

1. Lacocca R. G. (2011, November 1) The Causes and Implications of Glass Delamination. Pharmaceutical Technology. Retrieved from http://www.pharmtech.com/pharmtech/Analytics/The-Causes-and-Implications-of-Glass-Delamination/ArticleStandard/Article/detail/747427.
2. Byrne R. L. , Exline D. E. (August 2013) A forensic approach to particulate contamination in inhalable drug products. Inhalation Magazine. Pg. 1-5.
3. SPE Operators Guide raman.ID+metal.ID. (2013) RapID Particle System GmgH. Edition 1.8.
4. Tran T., Kupiec T., Trissel L., (2006, May/June)Quality-Control Analytical Methods: Particulate Matter in Injections: What is it and What are the Concerns? International Journal of Pharmaceutical Compounding. Vol. 10, No. 3.
5. B. Braun (2011, March) Particulate Contamination: Risk Prevention in Infusion Therapy. B. Braun Melsungen AG. Nr. 0669091.