A forensic approach to particulate contamination in inhalable drug products

The FDA's actions indicate identification and source determination of contaminants is necessary

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Contamination 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. Inhalable drug products are unique with regards to the affects of contamination, due to end-use design. Inhalation of foreign particles can lead to particle settlement in the alveolus, which (depending on the size and distribution of the particles) can lead to such contraindications as allergic reactions, pain, inflammation, adverse immune responses, aggravated asthma, chronic bronchitis and acute respiratory affects.[1-3]

The US Food and Drug Administration (FDA) has taken action against companies specifically for violations involving inadequate investigations of contamination failures within products. Warning letters include verbiage such as "…the black particles were not identified and source was not determined. In addition, there was no attempt to determine if the black particles originated from the manufacturing process, or if additional lots were affected…" and "Reddish-brown particulate matter has been a recurring problem…The cause of the particulate matter problem has not been determined."[4,5] These statements indicate that merely the detection of foreign particulate contamination is not sufficient in itself, but that the identification and source determination of the contaminants is necessary.

Some companies may utilize a reactive style of quality control, rather than a proactive approach. According to the International Conference on Harmonisation (ICH) guidance (Q8 Pharmaceutical Development), "It is important to recognize that quality cannot be tested into products; i.e. quality should be built in by design."[6] The focus of Quality by Design is on product and process understanding, which involves having knowledge of raw material quality, process parameters and control sources for process variability, in order to accomplish prevention of contamination. This is where utilizing a forensic approach to foreign particulates in drug products can play a unique and important role in quality control.

Usually, the first step in understanding contamination within inhalable drugs is to be aware of causes

of contamination and potential sources within a process. Historically, particle size within inhalable drug products has been of particular interest, due to the correlation of particle size to pulmonary effects.[7] Methods utilizing techniques such as light obscuration, laser diffraction and light scattering have value when considering a need for particle counting and sizing. However, they are limited in the sense that they do not provide identification of foreign particulates, nor do they provide the possibility of sourcing the contaminants. In order to source contamination and thereby design a controlled environment to avoid contamination in the future, one must begin with an identification of the material, not just the detection of it.

A multi-level approach to foreign particulate testing and source determination

Prior to performing testing, one must consider acceptable limits. Acceptance criteria for impurities should be determined with a validation protocol. Foreign particulates are generally organized into size ranges of <10 µm, 10-25 µm and >25 µm. The size of foreign particulates is of significant concern for inhalable drug products, because particles that are minute enough are inhalable and, depending on various factors, may potentially get trapped in the alveolus.[8] Characterization of foreign particulates involves various aspects, including identification, sizing, counting and sourcing of the contaminants. Since the toxicological impact of foreign particulates in inhalable drug products has not been thoroughly evaluated, there is little guidance for the presence of foreign particles in inhalable drugs. One may consider the guidance in place for parenteral drug products when approaching inhalable pharmaceuticals, since both types of drug products present unique dosing methods (inhalation and injection).[3]

Once acceptance criteria are determined and a nonconformance issue is found, the next step is to perform isolation and analysis of materials. For larger observed particulates wherever they originate (e.g. raw materials, batch of final formulation, etc.), manual isolation procedures can be utilized. If, however, particulates are too small for manual isolation, a more in-depth sample preparation will be necessary. Typically, an emitted dose of the inhalable product is collected in a particle-free environment, followed by dissolution of the active pharmaceutical ingredient and excipients with solvents. The sample can then be prepared using vacuum filtration. Depending on the particulate size range, analysis can either be performed after isolating the particulates from the filter or it can be analyzed directly from the filter substrate. Methods of sample preparation will largely determine the methods of analysis used. If complete manual isolation is accomplished, a variety of analyses are available for characterization. These include scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM-EDS), Raman spectroscopy, Fourier transform infrared (FTIR) spectroscopy, optical microscopy, microspectrophotometry, fluorescence microscopy, liquid particle counting, etc. When analysis is to be performed directly from a filter substrate, analyses are more limited to methods that don't require additional sample preparation (i.e. SEM and Raman).

Table 1 lists some technologies used in foreign particulate analysis, along with the capabilities and limitations of each. Utilizing multiple technologies can add the capabilities needed to fully characterize materials, by using various methods to make up for the shortcomings of other techniques. Utilizing a multi-level approach, along with the specialized expertise of a trained forensic scientist, adds great value to nonconformance investigations and sourcing failures.

Table 1

Technologies used in foreign particulate analysis

Method	Sizing & counting	Elemental	Chemical	Automation	Specific	Level of expertise	Cost	Speed
Optical microscopy	Yes	No	No	Possible	No	High	Low	Slow
Liquid particle counting (HIAC)	Yes	No	No	Yes	No	Low	Low	Fast
Raman manual spectroscopy	No	No	Yes	Possible	Yes	High	Moderate	Fast
Name of technique (RapID)	Yes	No	Yes	Yes	Yes	High	Moderate	Fast
FTIR	No	No	Yes	Possible	Yes	High	Moderate	Fast
SEM-EDS	Yes	Yes	No	Possible	Yes	Moderate	High	Fast

Forensic science as it relates to foreign particulate sourcing

Forensic science is essentially the application of scientific techniques to law. Forensic scientists evaluate physical evidence not only to identify material, but also to determine if an association exists between a questioned sample (e.g. a fiber found on a victim) and a known potential source (e.g. a carpet from a suspect's car). This goal in forensic trace evidence analysis can be related to sourcing contamination issues in the production of pharmaceutical products. Just as criminal and civil law are monitored by the use of technology and science, so is quality used to monitor within the pharmaceutical industry.[9]

Utilizing a forensic approach to foreign particulate identification and source determination offers a unique advantage. Forensic scientists have specialized training in their particular field of expertise, and trace evidence examiners have focused, in-depth training on the analysis of fibers, textiles, hairs, paint, glass, etc. This allows them to make associations regarding these materials. For example, a pharmaceutical company may have a quality department that has an analytical laboratory capable of determining that a detected contaminant is a hair. An analyst that has specific training in forensic hair analysis, however, can go further in the examination of the contaminant; he or she may be able to determine if the hair is human or animal, the racial origin (if human), the species (if animal), etc. In addition, DNA analysis of the hair can aid in species determination. These advanced analytical methods can help with the challenge of sourcing the contaminant. If a hair, for example, would be determined to be a feline hair, one could quickly eliminate other possible hair sources such as textile wools or human hair.

When forensic scientists analyze samples, they generally compare results to a known possible source. For instance, if a hit-and-run accident had occurred and no obvious suspects were accounted for, the use of a paint database would become imperative. Databases exist within the forensic community, which relate chemical properties of paint to specific makes and models of vehicles. If an investigator knows the characteristics of the questioned paint chip, he or she can enter that information into a database and a list of possible sources will be presented, thereby narrowing the search considerably.

Likewise, quality personnel within the pharmaceutical industry can use the same concept in their investigations. The idea of taking a proactive, rather than reactive, approach to the management of foreign particulate contamination involves having in-depth knowledge of most (if not all) of the materials present within a process. Foreign particulates can be introduced into a drug product from numerous sources and various stages in the production process. When considering the source of a contaminant that appears in a batch of a pharmaceutical product, one must consider every aspect of the process. This includes raw materials (e.g., packaging, labeling, solvents, etc.), equipment (e.g. milling and mixing equipment), cleaning protocols, specific methods (e.g. pyrolysis), packaging and labeling materials for the final formulation and environmental concerns (stemming from personnel, personal protective equipment, facilities.[10] Building a database can be very useful when attempting to narrow the possibilities, allowing for quick identification of possible sources for contaminants. This increased efficiency in handling foreign particulates decreases both safety and financial risks to the manufacturer. In addition to developing databases, utilizing multiple technologies for material characterization is imperative.

A case study

Fibers are often found in a raw material, such as polysorbate, used to make various drug products. In instances where overall analysis is limited to spectroscopy of the fibers (using FTIR), the conclusions would indicate the fiber is consistent with cellulose and additional analysis may be omitted, possibly leading to the loss of valuable information. Acquiring more information about a sample allows for quicker and more cost-effective problem resolution. For example, the fiber may be natural cellulose (e.g. cotton) or manufactured cellulose (e.g. rayon). A scientist with specific training in fiber analysis can utilize technologies such as optical and polarized light microscopy to attain more in-depth information regarding the fiber (natural vs. synthetic, diameter, or presence of manufacturing characteristics). Additionally, performing a cross-section on the fiber to determine the cross-sectional shape of the fiber (e.g. trilobal, round, etc.) may aid in source determination. The ability to derive specific information related to the fiber's origin is critical during the source apportionment of the investigation, to determine the root cause and assist in determining impact on the product and, ultimately, remediation of future sources of the particulate from the manufacturing process.

An example is shown in Figure 1. This fibrous material was collected and examined using optical microscopy and polarized light microscopy (Figures 1 and 2). FTIR analysis indicated it was a cellulose

fiber (Figure 3). Fibers composed of cellulose, as previously mentioned, can be categorized into two main groups: natural and synthetic. Evaluation of the differences seen in the FTIR spectra of natural vs. synthetic (regenerated) cellulose reveals the ability to make distinctions, as seen in an FTIR spectral overlay (Figure 4). The fiber in question showed consistency with regenerated cellulose, however, when taking the multi-level approach, an analyst utilized an additional stage of analysis for confirmation. Regenerated cellulose and natural cellulose also exhibit major differences in optical qualities. As seen in the side-by-side images of Figure 5, regenerated cellulose displays a fairly uniform appearance while natural cellulose exhibits properties such as undulation and cross-hatching. In addition, regenerated cellulose displays different qualities than natural cellulose when viewed under polarized light. While

Figure 1

Optical micrograph of recovered fiber

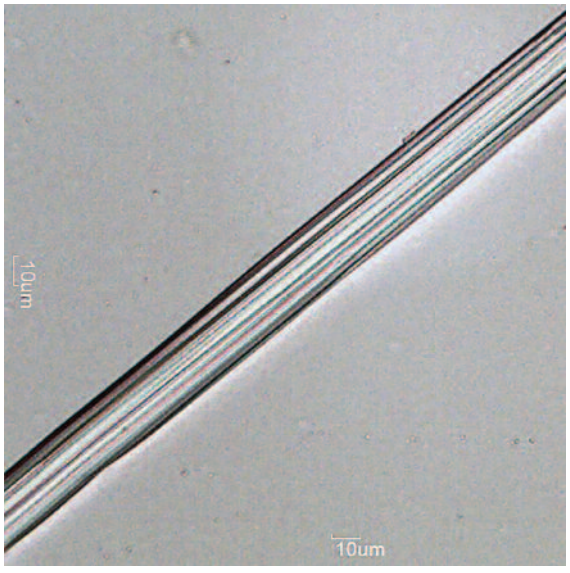


Figure 2

Polarized light image of recovered fiber

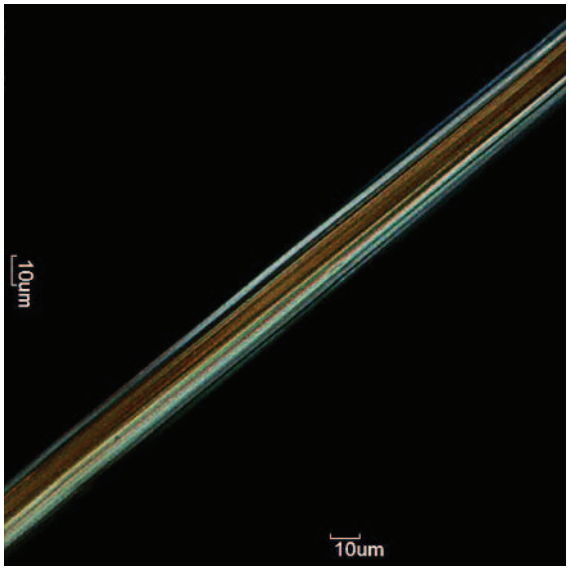


Figure 3

FTIR spectrum of recovered fiber indicating a regenerated cellulose fiber

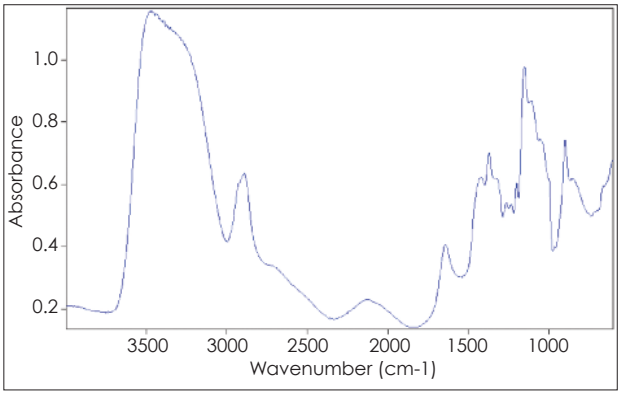


Figure 4

FTIR spectrum of recovered fiber indicating a regenerated cellulose fiber

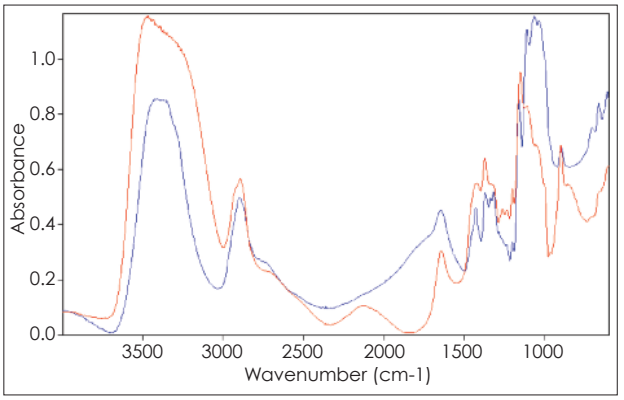
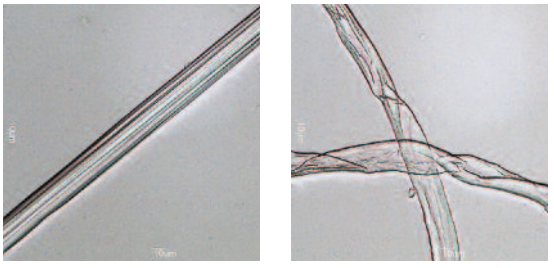


Figure 5

Optical comparison of regenerated cellulose fiber (left) and natural cotton (right)



regenerated cellulose may go to extinction, natural cellulose does not. Optical and polarized light microscopy confirmed the FTIR results, showing that the question fiber was indeed regenerated cellulose, rather than natural cellulose. Therefore, the ability to eliminate potential sources of natural cellulose (e.g. Kimwipes, paper, etc.) was developed. Potential sources of the fiber were collected, based on the initial characterization of the fiber. Figure 6 depicts the side-by-side comparison of the optical micrograph of the questioned fiber with a potential source material. An FTIR spectral overlay of the two fibers is shown in Figure 7, indicating the same chemical composition for the recovered fiber and the source material. This example demonstrates a basic analytical approach to characterizing an unknown particulate but also provides a means of investigative information to determine possible sources of the particulate and ultimately to identify the actual source of the foreign particulate matter.

Figure 6

Side by side comparison of recovered fiber (left) with a potential source material (right)

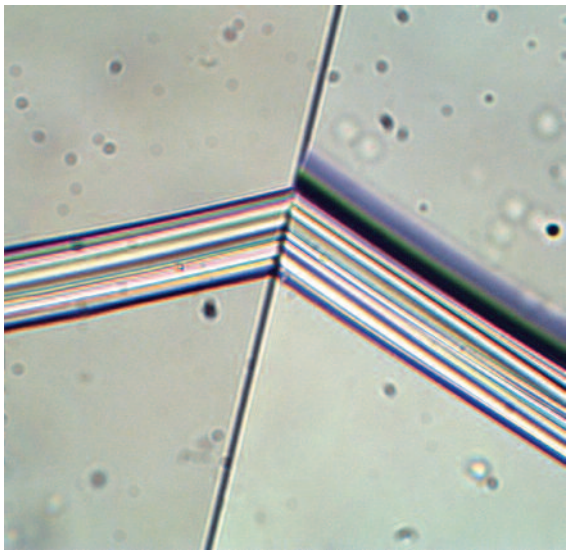
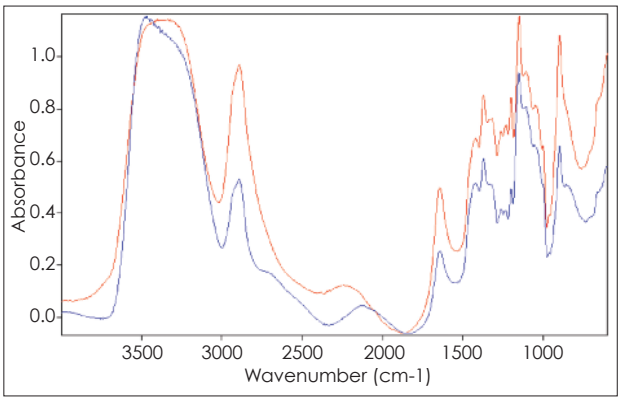


Figure 7

FTIR spectral overlay of recovered fiber (blue) and source fiber material (red)



Conclusion

While foreign particulate contamination of drug products can have major implications for pharmaceutical companies, the specialized training that forensic trace evidence examiners possess can help to quickly source and remedy contamination issues. Inhalable drug products may encounter contamination from various sources, from raw materials to device wear. A systematic forensic approach aids not only with source determination but also from financial and quality perspective. This in turn helps to engineer more efficient systems that create a safer product for the end user.

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