Detecting Siliceous Flakes in Glass Containers using Microscopic Techniques

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Introduction

Flakes were observed in a product in a glass container of the type that may be used for nebulized products. Water and other solvents can degrade glass, probably by attack of hydroxide ions on the glass matrix. The hydroxide ion can penetrate the glass surface to a sufficient depth to initiate significant attack on the silicate structure. As the silica matrix dissolves, the glass interface will degrade causing delamination from the glass surface. The resulting flakes are often essentially transparent and so a special procedure is needed to successfully monitor for this condition.

Unused containers were examined using Differential Interference Contrast microscopy combined with Extended Depth of Field (EDF) image processing to nondestructively image the inside surface of the glass.

The glass containers were then challenged with a high pH aqueous solution while being autoclaved at 121 deg. C for 1 hour. After the containers cooled, they were emptied and the inside of the containers after drying were inspected. If delamination has occurred the surface will have a mottled appearance. In the case of filled containers, the siliceous flakes can be observed by swirling the container while illuminating with a fiber optic light source. The containers can then be rinsed and dried to allow microscopic examination of the inner surface.

The results were compared.

Background and Theory

Special optical microscope technique

The optical microscopic technique most effectively used to assess the inner surface of the vials integrated Nomarski Differential Interference Contrast (DIC), Z-stack Extended Depth of Field (EDF), and long working distance microscope objective techniques. The long working distance microscope objective was needed to observe the inner curved surface of the vial. EDF was needed to present a clear, in-focus image of the curved inner surface, since otherwise the curvature would have taken the two edges of the image out of focus. DIC was needed to observe the changes in the transparent glass.

DIC

DIC is known to be an excellent mechanism for rendering contrast in transparent specimens. It is a beam-shearing interference system in which the reference beam is sheared by a minuscule amount, generally somewhat less than the diameter of an Airy disk. The technique produces a shadow-cast image that effectively displays the gradient of optical paths for both high and low spatial frequencies present in the specimen. Those regions of the specimen where the optical paths increase along a reference direction appear brighter (or darker), while regions where the path differences decrease appear in reverse contrast. As the gradient of optical path difference grows steeper, image contrast is dramatically increased.

The spatial relationship and phase difference between ordinary and extraordinary wavefronts is governed by the position of the objective prism. The beam of linearly polarized light (see illustration 1) emerging from the polarizer first enters the lower Wollaston prism (labeled the Condenser Prism) before being separated into two orthogonal components and sheared at the quartz wedge interface.

The image of the light source and condenser prism is transferred by the optical system (condenser and objective) onto the inverted second Nomarski prism located at the objective rear focal plane. The linear phase shift across the face of the condenser prism is precisely compensated by an opposite phase shift in the objective prism. Translation of the objective prism along the shear axis does not alter the phase shift distribution, but instead, adds or subtracts a constant phase difference across the entire microscope aperture. The matched prism system enables image formation to occur with the same bias retardation for every wavefront pair projected from the condenser aperture, irrespective of the route through which it traverses the specimen to reach the objective.

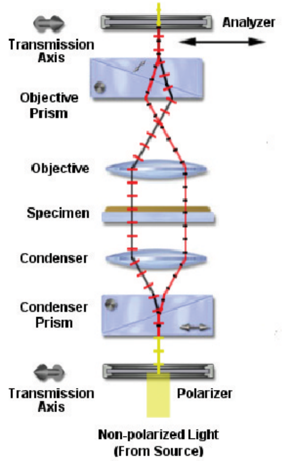

Illustration 1

Microscope Configuration for DIC

The optical path difference between wavefronts is determined by the objective prism position and the optical thickness of the specimen. Bias is introduced into the differential interference contrast microscope by translating the objective Nomarski prism back and forth along the optical axis using a fine adjustment knob.

EDF

EDF combines pixels from the various source image planes using the areas that are most in focus (i.e. constructs a composite image from the portion of each "slice" that was in focus. Areas are selected so as to maximize local contrast.

Images are selected by using the computer-controlled focus to choose the focal plane so that the center is in focus (which is the highest plane), and then choosing the focal plane so that the two edges of the field of view are in focus, (which is the lowest plane). Fifty images are then acquired and then processed according to the pre-selected process. This yields a single combined image with maximum local contrast.

Long working distance microscope objective

A 20X U Plan Objective with a numerical aperture, (NA), of 0.45 and a stated working distance (wd) of 6.4-7.6 mm was used.

The Chemistry of Siliceous Flake Formation in Glass Containers

Separation of surface glass can occur resulting in thin siliceous flakes of reacted glass sloughing off into the product. This delamination may contaminate the drug product to an unacceptable degree. Glass delamination occurs when the surface reacts with materials which remove elements from the glass matrix. It is believed that aqueous solutions, particularly basic solutions, enable this process. Certain manufacturing conditions may also predispose containers to delamination. Initial stages of delamination may be observed at the time of production or may occur over a long period of time in storage or after being in contact with product. Water and other solvents can degrade glass, generally by attack of hydroxide ions on the glass matrix. The hydroxide ion can penetrate the glass surface to a sufficient depth to initiate significant attack on the non-silicate structure. As the matrix dissolves, the glass interface will degrade producing the silica rich microscopic flakes.

To ensure the integrity of glass containers, a screening test can be designed based on experiments to indicate the likelihood of siliceous flake occurrence in a container. For unused containers, microscopic examination of the inner glass surfaces as received and after being challenged with stressed conditions can predict or detect containers which will or have been delaminated. This should reduce incidents of possible contamination of drug product with siliceous flakes, building quality into the process.

It has long been understood that soda-lime and borosilicate glass containers can be attacked by the solutions that they contain. Acidic solutions attack the glass surface only slightly whereas neutral and alkaline solutions are more aggressive. Glass scientists commonly refer to the leaching process as Stage 1 and Stage 2 corrosion.

In Stage 1 corrosion, the sodium ions in the glass diffuse into the solution and are replaced by hydrogen ions which are provided by the dissociation of water. As the leaching process continues, the alkalinity increases. The reactions are shown in the following equations:

$$H_2O \rightleftarrows H^+ + OH^-$$

$$\text{SiONa (glass)} + H_2O \rightleftarrows \text{SiOH (glass)} + \text{NaOH}$$

As the pH of the solution reaches 9 or greater, Stage 2 corrosion begins. At this pH, the hydroxide ion concentration is sufficient to attack the silicate network. This degradation process begins to dissolve the glass allowing siliceous flakes to be produced. The reaction is shown in the following equation:

$$\text{Si-O-Si (glass)} + \text{NaOH} \rightleftarrows \text{Si-OH (glass)} + \text{Na-O-Si (dissolved glass)}$$

Test Method

The containers were examined in the "as received" condition by various techniques. Then the containers were challenged by filling with liquid and autoclaving. After the filled containers cooled, the liquid was filtered and the containers dried in an oven. The containers that had been challenged were then examined using several microscopic techniques.

Results

Microscopic examination

Stereo microscope technique

The containers "as received" and after being challenged were viewed using a stereomicroscope, but the results were inconclusive.

Compound microscope technique

The containers "as received" and after being challenged were viewed using a compound, but the results were inconclusive.

Scanning Electron Microscope

An attempt was made to examine portions of the containers in the "as received" condition by a sequence of controlled fractures of the container. This was unsuccessful, in that the fracturing did not occur as intended.

Special optical microscope technique

The special optical microscope technique was used to examine the containers in the "as received" condition. Then the containers were challenged by filling with a high pH aqueous solution and autoclaving. After the filled containers cooled, the liquid was filtered and the containers dried in an oven. The containers that had been challenged were then examined using the special optical technique.

Part I, containers were examined in the "as received"

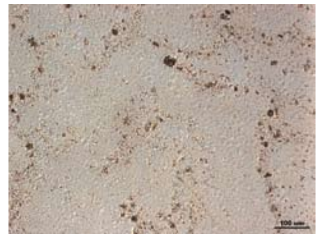

Image 1: Vendor A - Composite Image of Container "as received" from "suspect" lot.
In the case of the "suspect" container, this showed an interlocking lattice network of small defects, suggestive of cracks, outlining areas suggestive of flakes.

Image 2: Vendor A - Composite Image of Container "as received" from another lot produced similarly to the "suspect" lot.
In the case of another lot produced similarly to the "suspect" container, this showed an interlocking lattice network of small defects, suggestive of cracks, outlining areas suggestive of flakes.

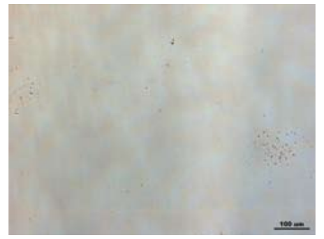

Image 3: Vendor B - Composite Image of Container "as received" from another lot produced differently from Vendor A.
Container showed a smoother surface appearance upon comparison to Vendor A's containers.

Part II, containers were examined after being challenged with a high pH aqueous solution at 121 deg C for one hour.

Image 4: Vendor A - Composite Image of Container after being challenged from "suspect" lot.
In the case of the "suspect" container, this showed a mottled surface appearance.

Image 5: Vendor A - Composite Image of Container from another lot produced similarly to the "suspect" lot after being challenged.
Container showed little change in surface appearance.

Image 6: Vendor B - Composite Image of Container from another lot produced differently from the "suspect" lot after being challenged.
Container showed a smooth surface appearance with little or no change.

Analysis

Defects were observed on the inner surface of containers in the "as received" condition from a "suspect" lot of containers and another lot of containers produced by the same process, but was not observed on the surface of similar containers produced by a different process.

Containers from those three lots were challenged with a high pH aqueous solution at 121 deg. C for one hour.

After the challenge, the inner surface of the container from Vendor A "suspect" lot showed extensive degradation, and obvious depressions. The container from the other lot produced by Vendor A showed little change from before the challenge. The container produced by Vendor B showed no obvious change from before the challenge.

Interpretation

Flakes were observed in a product in a glass container of the type that may be used for nebulized products. The resulting flakes are often essentially transparent and so a special procedure is needed to successfully monitor for this condition.

A special optical microscope technique was developed that allowed for the inspection of the containers in the "as received" condition.

Defects were observed on the inner surface of containers from a "suspect" lot of containers and another lot of containers produced by the same process, but was not observed on the surface of similar containers produced by a different process.

The extent of the defects observed using the special optical microscope was related to the degree of degradation caused by the challenge.

Conclusion

This project evaluated the glass containers for likelihood of failure due to glass delamination and confirms that evaluation with a challenge.

To ensure the integrity of glass containers a screening test can be designed based on experiments to indicate the likelihood of siliceous flake occurrence in a container. For unused containers, microscopic examination of the inner glass surfaces as received and after being challenged with stressed conditions can predict or detect containers which will or have been delaminated. This should reduce incidents of possible contamination of drug product with siliceous flakes, building quality into the process.

In conclusion, special considerations for container integrity and interaction with drug product should be given when selecting glass for an inhalation or intranasal system to ensure a quality product.

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