Characterization of Glass Particles in Biopharmaceutical Drug Products by Microscopic and Spectroscopic Methods

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Glass vials are a commonly used primary container for parenteral drugs including biopharmaceuticals. Different types of glass related particles (GRP), although in low occurrence rate, may be present in drug products. Proper classification and investigation of these glass related particles will help to understand GRP formation mechanism, improve process control, reduce GRP occurrence rate, and deliver safer parenteral drugs to patients. In this manuscript, we introduce a classification scheme and characterization tools for GRP. We propose to classify GRP as glass chip, glass lamella/flake, and silica gel particles. Using representative samples from each type of glass particles, this study summarized their forensic differentiations based on Scanning Electron Microscopy and Fourier Transform Infrared Spectroscopy.

Glass chips are solid glass pieces broken off from the glass container due to mechanical forces. They are often thick, have three dimensions with irregular contours, and exist in sparse numbers when observed. The mechanical forces can be from the shaking during transportation, or from the capping and de-capping of the vial stoppers. In case of shaking, the affected "chip" site is often located at the vial shoulder area. This area has residual stress as a result of elevated temperature to form the shape of mouth from glass tubes during vial formation. Capping and de-capping of vial stoppers may also damage the mouth area from the abrasion force between the vial stopper and the vial.

Glass lamellae, also called glass flakes, are typically very thin, polydisperse in length and width, fragile, light-reflecting, and existing in relative abundance when observed. They are thin glass sheets peeled off from the inner surface of the glass container through the process of delamination. Delamination occurs due to the weakening of the glass network by mechanical stress, or by interaction with drug product solutions. Delamination risk factors include neutral pH drug product formulation and high alkalinity glass types. These particles have been historically called glass flakes as a result of chemical delamination [1]. It has been used the term "lamellae" interchangeably with glass flakes in the product recall of Epogen and Procrit [2].

Silica gel particles are typically amorphous, translucent to white, existing in abundance when observed. The particles have powder-like appearance and loosely formed surface. The formation of silica gel particle is a two-step chemical phenomenon: Firstly the glass's Si-O-Si network disintegrates and dissolves into free silicic acids, then these free silicic acids polymerize and form loosely networked silica gel particles. This process is facilitated by unfavorable conditions such as freeze-thaw and neutral/basic pH formulations. The disintegration of Si-O-Si network, or glass dissolution, happens under unfavorable formulation and storage conditions of glass vials, such as neutral to basic pH solution and stored for a longer time at room temperature [3].

These three glass particle types have very distinctive SEM features, as demonstrated by their

representative SEM images in Figure 1. Glass chips (Figure 1 A) have distinct three-dimensional contour line with an irregular shape due to its breakage from the vial. Glass lamellae have a two-dimensional flat structure (Figure 1 B) and the larger ones could be even folded (data not shown). Silica gel particles (Figure 1 C) show the morphology of dried fluffy gel with an uneven surface. The small black holes on the filter of silica gel are the filter pores with a size of about 0.8 μm.

FTIR spectra of glass chips, glass lamellae and silica gel particles all have the Si-O related peaks in the 800-1300 cm^{-1} region (Figure 2). The most characteristic peaks for all three types of glass particle types are the Si-O asymmetric stretching between 1050 and 1100 cm^{-1}. The peak positions of the Si-O for the typical GRP in this study are in the order of 1096 cm^{-1} for glass lamella, 1079 cm^{-1} for glass chips and 1059 cm^{-1} for silica gel particles. Higher wavenumbers of Si-O peak in the glass lamella and the glass chip are a reflection that they have stronger or shorter Si-O bond compared with silica gel. The peak at 803 cm^{-1} is from symmetric stretching of Si-O and the peak at 953 cm^{-1} from silanol Si-O stretching [4]. The shoulder peak at 1212 cm^{-1} is from polymerized SiO_4 tetrahedral units. The absorption peak for polymerized unit at 1212 cm^{-1} is the strongest in glass chip, the weakest in glass lamellae, and intermediate in silica gel particles. This indicates that there is less tetrahedral SiO_4 structure in the glass lamellae than in the glass chips.

REFERENCES

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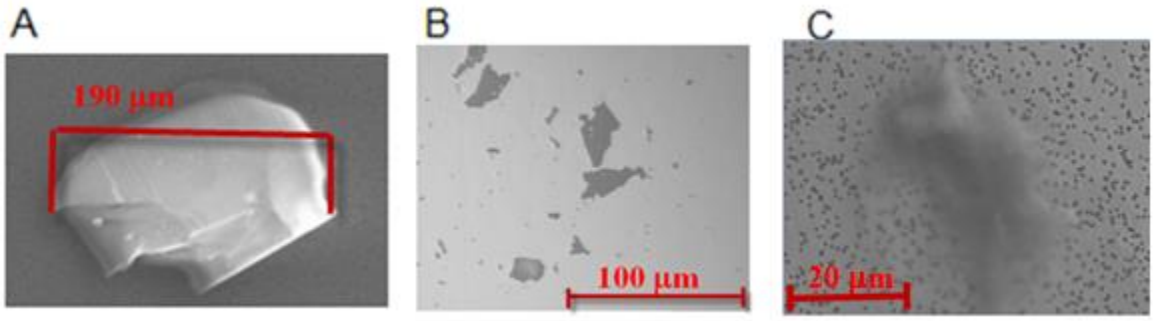

Figure 1. SEM images of a glass chip (A), glass lamellae (B) and silica gel (C).

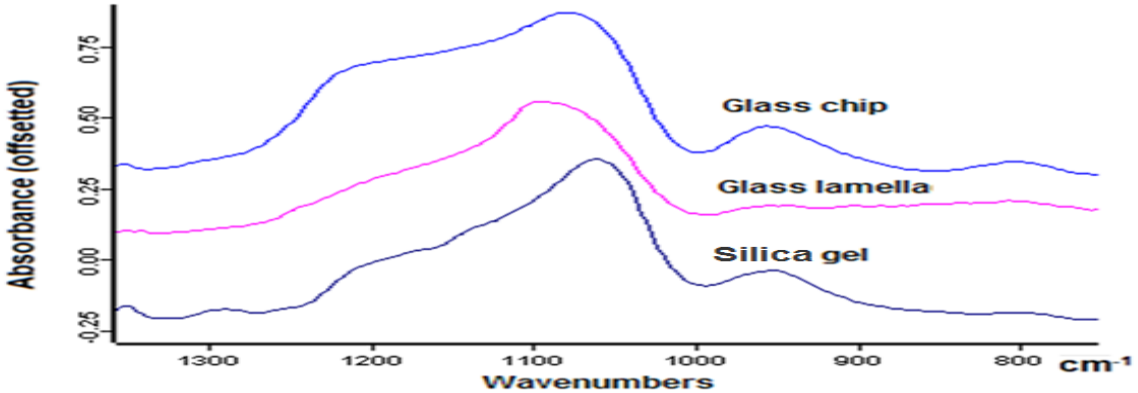

Figure 2. FTIR spectra of glass chip, glass lamella and silica gel.