

# Advantages of Broad Ion Beam Milling for Studying Interactions of Container and Drug Formulation

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## Abstract

Focused ion beam (FIB) is an advanced technique to prepare high-quality cross-sections of various pharmaceutical materials for further investigation. However, cross-sectional sample preparation using FIB may be expensive, time consuming and labor intensive. We employed broad ion beam (BIB) milling system instead of FIB to prepare high-quality cross-sections to investigate pharmaceutical materials such as glass vials. BIB may be used for a larger cross-section with lesser damage to the sample surface compared to FIB. The purpose of this study was to investigate the utility of BIB milling technique for studying the interactions of primary container with drug formulation of two injectable drug products a and b.

## Introduction

Particulates in parenteral solutions may impact drug product quality. It is of great importance to evaluate the interactions of drug formulation with its primary container which requires to prepare cross sections of the container. In recent years, broad ion beam (BIB) milling has been employed for preparing high-quality cross-sectional samples to investigate pharmaceutical materials [1]. Compared to focused ion beam (FIB), BIB produces a cross-sectional surface with lower level of milling damage [2]. In addition, BIB can process larger sample surface area and up to ~4mm depth compared to FIB [3, 4]. In this study, BIB milling has been used as a novel technique to facilitate the evaluation of primary containers of two injectable drug products.

## Materials and Methods

The study design included sample lots from a complex injectable generic drug product and the referenced listed drug product. Vials of sample having particulates were prepared with BIB and characterized with a field emission scanning electron microscope (FE-SEM) coupled with energy dispersive spectroscopy (EDS)..

## Results and Discussion

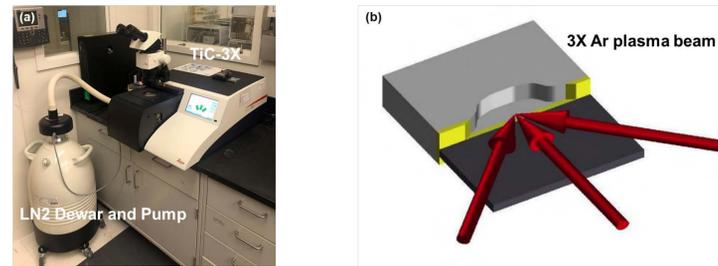


Figure 1. (a) The Leica TiC-3X Broad ion beam (BIB) milling system with cryo-stage at DPQR/OTR; (b) the BIB system has three Ar plasma beams to bombard the sample to create a smooth cross-sectional surface.

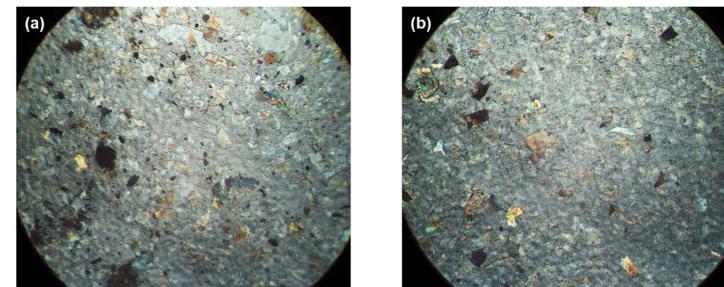


Figure 2. Microscopic images showing particulates in the complex drug products as revealed on the membrane filter (a) Product A and (b) Product B.

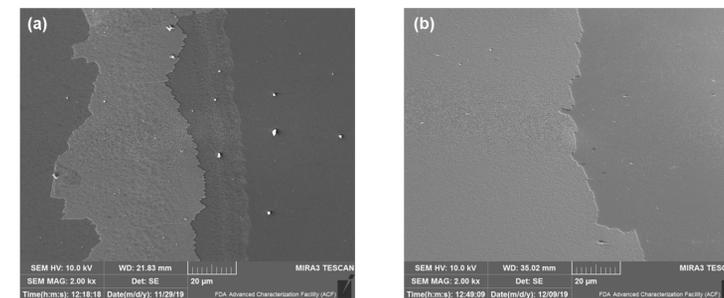


Figure 3. FE-SEM imaging: Deposition on the inner surfaces of vials were observed that may be a possible source of particulates in (a) Product A and (b) Product B.

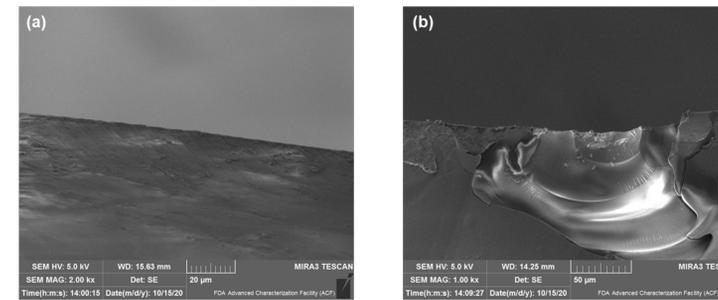


Figure 4. FE-SEM imaging of non-ion milled samples showing artifacts (a) chipped and (b) nicked edge in vials with random breaks.

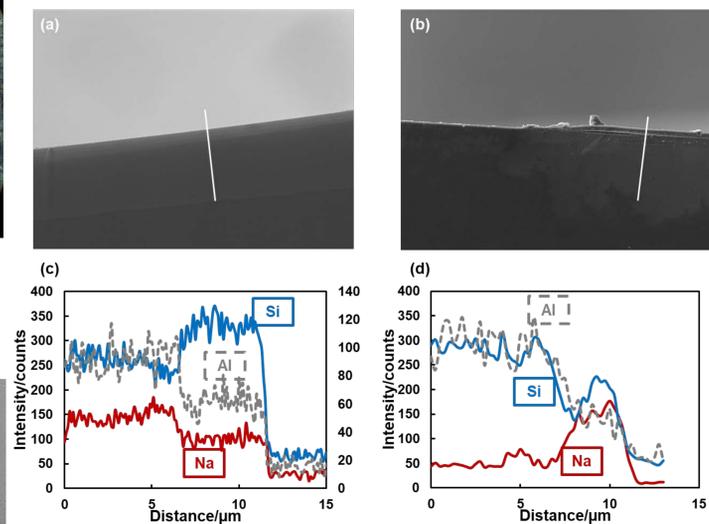


Figure 5. (Top) FE-SEM images after ion-milling. BIB prepared cross-sectional samples revealed smoother surfaces (a) Product A and (b) Product B. (Bottom) EDS spectra reveal the differences between the samples. The white line in (a) and (b) represent the scanned-line in (c) and (d), respectively.

## Conclusion

- BIB technique provided several advantages over traditional FIB technique. This new approach is rapid, less expensive, and highly automatic to create cross-sectional sample with minimal level of artifacts (e.g., chipped and nicked edges).
- The use of BIB milling allowed the preparation of high-quality cross-sectional samples for investigating the source of particulate formation using SEM-EDS while analyzing its composition at the same time, especially for products
- In summary, the development and application of BIB technique for evaluation of glass samples may provide necessary information for regulatory science-based decisions for injectable drug product.

## References

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## Disclaimer

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