1642 CD
DOI: 10.1017/S1431927606061320
Microsc Microanal 12(Supp 2), 2006

An SEM and EDS investigation of the formation of insoluble residues in a developmental pharmaceutical liquid formulation

Bethany L Bustard, Craig A.J. Kemp

Eli Lilly and Company, Indianapolis, IN 46285

The progressive formation of insoluble residues in a pharmaceutical liquid formulation under development was investigated using scanning electron microscopy (SEM), energy dispersive spectroscopy (EDS), and automated feature analysis (AFA). Analysis of the filtered particulates indicated that a diversity of sizes, morphologies and compositions were present. There appeared to be a correlation between the particle size, the number of particulates per category and the stand-time prior to filtration.

An ASPEX Rx automated scanning electron microscope with automated feature analysis was used to capture the changing populations of particulates. Vials of lyophilized formulation were reconstituted in WFI (water for injection) and then allowed to stand for a pre-determined amount of time before they were filtered through nylon filters. The dry membranes were then analyzed in variable pressure mode, scanning for particles from 3.0 to 200.0 μm in maximum diameter. Size measurements were recorded for each individual particle detected and EDS analysis was conducted to determine the relative composition. In addition to the inorganic constituents, active pharmaceutical ingredient (API)- related materials could also be identified through the simultaneous detection of Br, Cl, and S, which are specific to the API chemical structure.

Figures 1 and 2, show that the number of particles present on a filter increases as the stand-time after reconstitution increases. By classifying the particles based on their relative composition, a trend could be observed in the amount of particles in certain classes increase with increase in time, while others appeared to decrease. Figure 3 gives the percentage of particles detected per filter in terms of the distribution of particle composition category populations. From this histogram it is easy to observe the increase in Ca-P, API-Si and API-Ca-P particles that are present. It also shows the decrease in the percent of Si-Rich particles; however Figure 2 shows that the absolute number of Si-Rich particles does not significantly decrease overtime. The field images also revealed a presence of larger particles at later time periods. Three dimensional plots were created to show the total number of particles by size range and category for each of the filters, Figure 4. SEM micrographs of representative API-Si and Ca-P particles are shown in Figure 5. A morphological difference is observed between these two classes of particle. The API-Si particle appears more gel-like with less defined borders, while the Ca-P particle is more crystalline in appears with well defined edges. The results show that as the stand-time prior to filtration is increased, the amount of particles in the 25.0 micron or greater range increases, especially in the API-Si, API-Ca-P and Ca-P categories.

Possible incompatibilities between the API and equipment materials; and between the reconstitution diluent and impurities in the inactive ingredients were thus identified. Automated SEM detection and analysis of many hundreds of microscopic features provided a convenient means of measuring the evolution of the particulates over time. By following the compositional variations and temporal trends, an insight into the underlying mechanism was provided without resorting to labor-intensive preparative isolation.

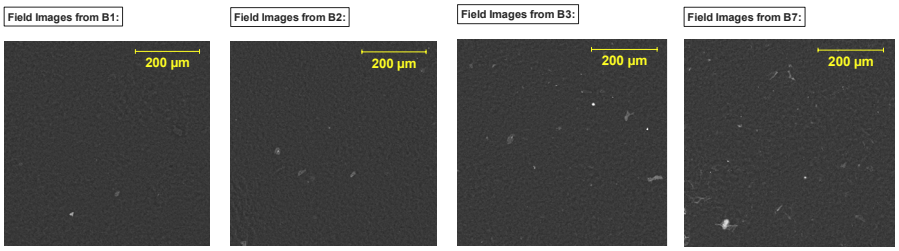

Figure 1. Representative SEM field images from filters B1 (filtered 1 day after reconstitution), B2 (2 days after reconstitution), B3 (3 days after reconstitution) and B7 (7 days after reconstitution).

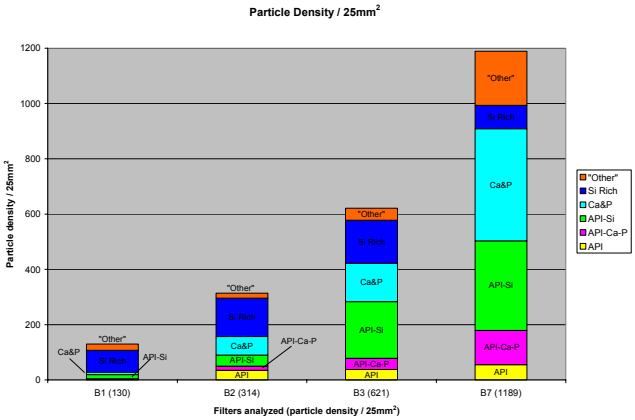

Figure 2. Histogram of data showing distribution of particle composition category populations in terms of absolute numbers of particles normalized by area.

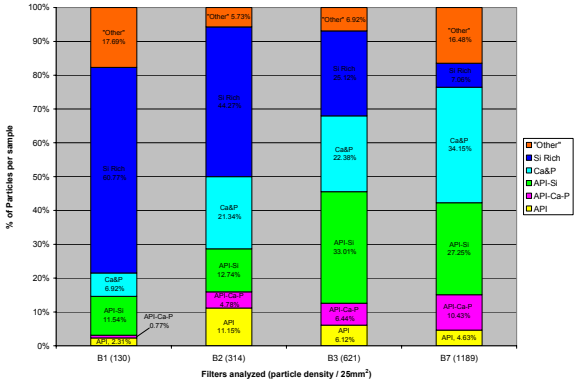

Figure 3. Histogram showing distribution of particle composition category populations expressed as a percentage of particles detected per filter.

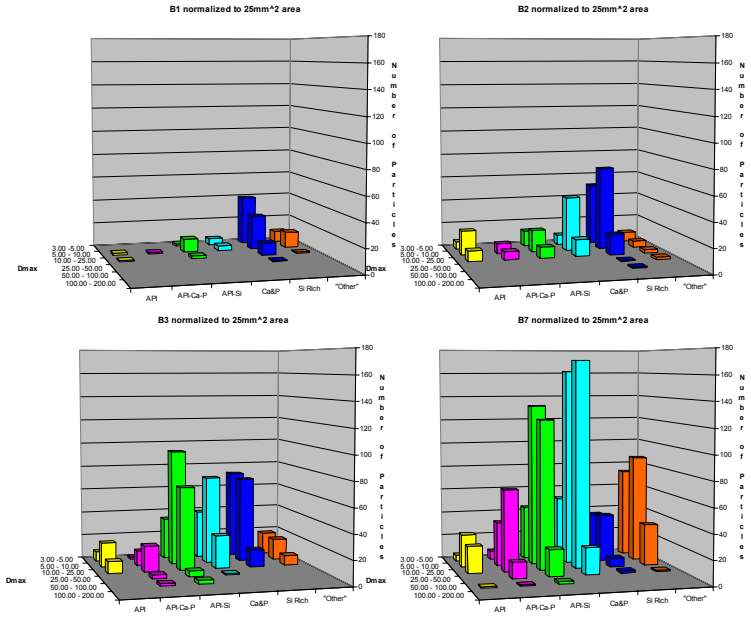

Figure 4. Histograms plotting total number of particles by size range and category for the time-study filters. B1 (top left), B2 (top right), B3 (bottom left), and B7 (bottom right).

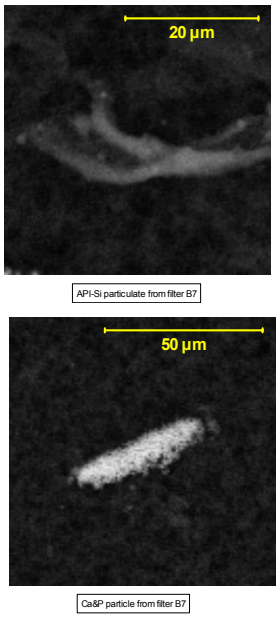

Figure 5. SEM micrographs of API-Si particulate (top) and Ca-P particulate (bottom).

https://doi.org/10.1017/S1431927606061320 Published online by Cambridge University Press